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Curcumin: A Comprehensive Review of Its Bioactivities, Therapeutic Potential, and Safety in Functional Food and Health Applications

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ABSTRACT: Curcumin, the principal polyphenol derived from *Curcuma longa*, has evolved from a traditional culinary pigment to a promising functional-food ingredient with extensive physiological applications. This review synthesizes six decades of research elucidating this transformation. Initially, we summarize curcumin's ethnomedical origins, followed by an analysis of its pharmacokinetic profiles in rodents and humans. Native curcumin predominantly resides within the intestinal lumen and mucosa; however, contemporary delivery systems—including solid-lipid nanoparticles, micelles, protein–polysaccharide complexes, and piperine co-crystals—can significantly enhance systemic bioavailability by up to two orders of magnitude. We subsequently examine mechanistic evidence across nine major health domains, highlighting cardiovascular, neuroprotective, respiratory, gastrointestinal, anti-tumor, and metabolic effects, supported by more than 250 primary studies published between 2020 and 2024. Animal toxicology and clinical safety data confirm a wide safety margin, supporting the currently established acceptable daily intake of 0–3 mg kg^{-1} body weight. Nonetheless, potential interactions with anticoagulants and hormetic pro-oxidant effects observed at very high doses merit continued monitoring. Ongoing challenges encompass dose standardization, metabolite characterization, and precision-nutrition clinical trials stratified by microbiome and genetic factors. Addressing these research gaps and integrating curcumin into optimized food matrices are essential steps toward translating laboratory findings into evidence-based dietary strategies that safely enhance human health.

Keywords: curcumin, functional food, bioavailability, pleiotropic bioactivity, safety

1. Introduction

Curcuma longa L., commonly known as turmeric, is a perennial herbaceous plant belonging to the *Zingiberaceae* family. The rhizome of *Curcuma longa* has long been used as a traditional medicinal herb in Asia, particularly within the Ayurvedic system of India, where it is revered as a "universal remedy" due to its wide range of therapeutic effects. Traditionally, turmeric has been used to relieve arthritis, jaundice, skin disorders, indigestion, and wound healing. It is also believed to enhance immunity and promote overall wellness through its anti-inflammatory, antioxidant, blood-purifying, and circulatory-stimulating properties [1].

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In traditional Chinese medicine (TCM), turmeric has been historically valued for its functions in invigorating qi and blood circulation, alleviating pain, clearing heat and toxins, and reducing swelling. Its earliest documented use in China dates back to the Song Dynasty, notably in the classical formulation "Wubi Decoction" recorded in Tai Ping Hui Min He Ji Ju Fang [2]. In TCM practice, turmeric is commonly prescribed for conditions such as palpitations, convulsions, headaches, blood deficiency, blood stasis, wind-heat symptoms, and localized inflammation [3,4].

The major bioactive constituents of *Curcuma longa* are curcuminoids and volatile turmeric oils [5–7]. Among the curcuminoids, curcumin is the most abundant, accompanied by demethoxycurcumin and bisdemethoxycurcumin. Curcumin typically accounts for approximately 2%–5% of the total dry weight of turmeric rhizomes [8,9]. In addition to its presence in turmeric, curcumin is also found in the rhizomes of other species within the Zingiberaceae and Araceae families. Notably, curcumin serves as the principal natural pigment responsible for the distinctive yellow color of curry powder, a widely used spice across Asia.

Curcumin was first isolated in 1815 [10], crystallized in 1870 [11], and its chemical structure was elucidated by Lampe in 1910 [12]. Chemically, curcumin ($C_{21}H_{20}O_6$) has a molecular weight of approximately 368.38 g/mol and a melting point of 183℃ [13]. Please refer to **Figure 1**. It is poorly soluble in water but readily soluble in organic solvents such as ethanol, dimethyl sulfoxide, acetone, and chloroform [14]. Curcumin remains relatively stable under acidic conditions (pH < 7), but undergoes rapid degradation in neutral and alkaline environments [15,16].

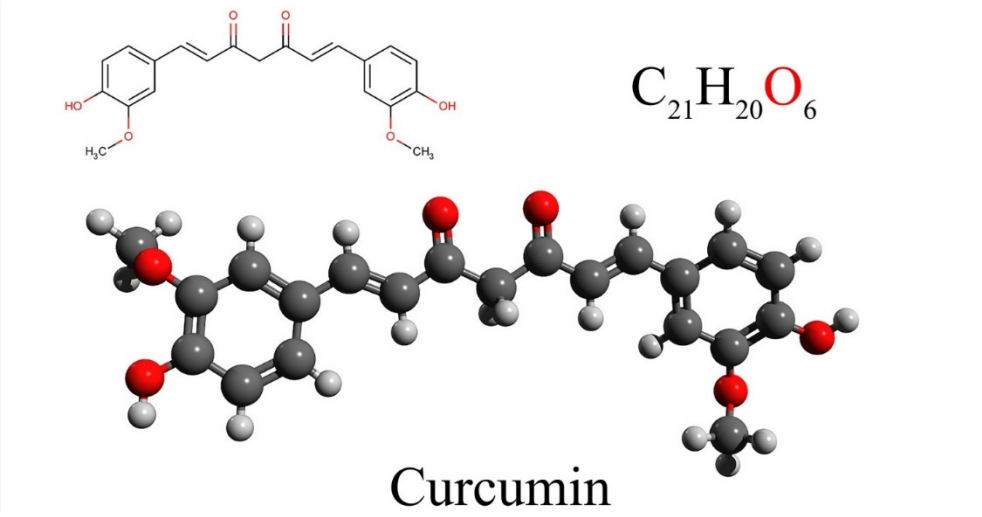

Fig.1. Curcumin spatial structure and molecular formula.

The primary metabolites of curcumin include tetrahydrocurcumin and hexahydrocurcumin. Among these, tetrahydrocurcumin exhibits greater chemical stability under physiological conditions and improved aqueous solubility compared to curcumin, while curcumin itself demonstrates better solubility in lipid-based media. Notably, tetrahydrocurcumin also exhibits favorable stability in plasma [17,18].

In recent years, curcumin has garnered worldwide interest for its pleiotropic pharmacological profile and capacity to modulate an array of molecular targets. An expanding body of evidence shows that it exerts potent antioxidant and anti-inflammatory activity; confers cardio-, neuro-, respiratory-, digestive- and

hepatoprotective effects; and displays antitumour, anticoagulant, and antimicrobial properties. Beyond these, curcumin favourably regulates glucose and lipid homeostasis, inhibits fibrotic remodelling, fine-tunes immune responses, promotes gastrointestinal motility, and even attenuates biological ageing. The convergent molecular pathways that underpin these benefits are summarised in **Figure 2**, while their major organ-system and clinical manifestations are mapped in **Figure 3**. Against this backdrop, the present review synthesises recent advances in curcumin pharmacology and explores their implications for future translational and clinical applications.

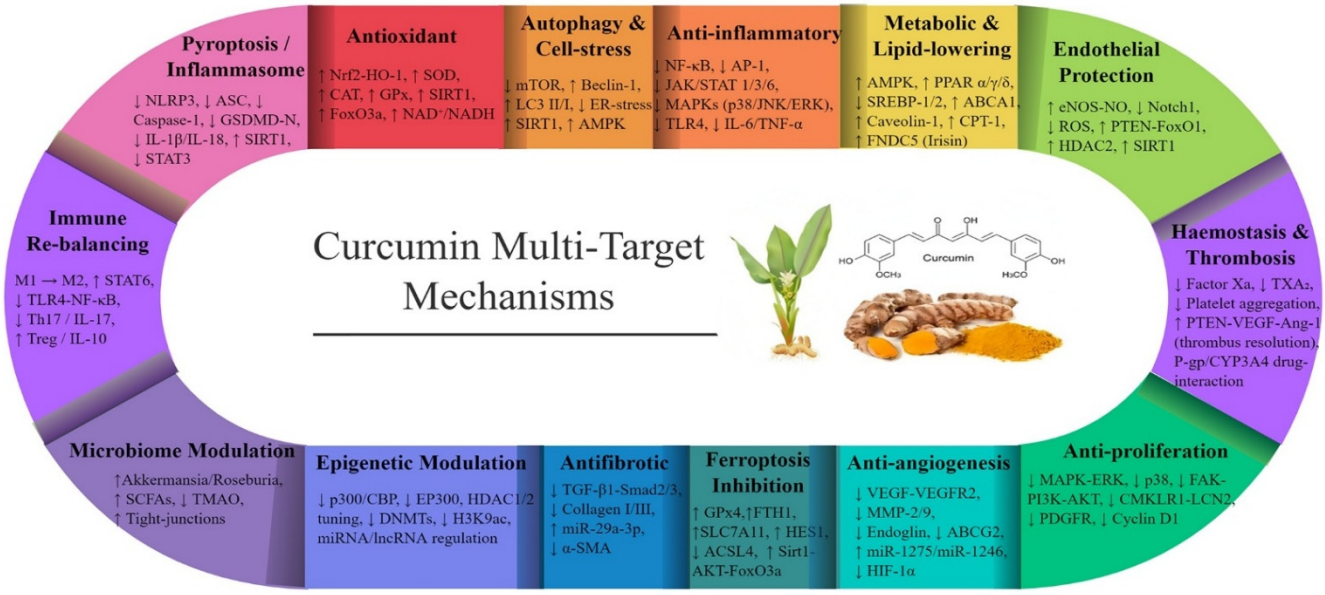

Fig. 2. Curcumin Multi-Target Mechanistic Wheel: 14 Integrated Pathways.

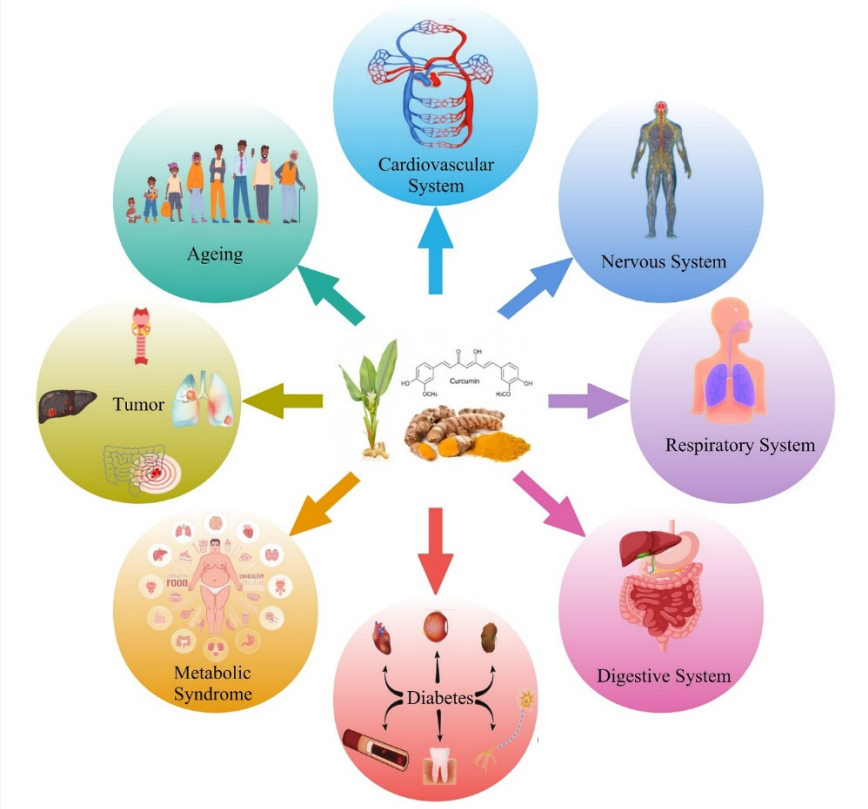

Fig. 3. Pharmacological Effects of Curcumin and Its Major Clinical Applications.

2. Literature search strategy and study-selection criteria

We systematically searched PubMed, Web of Science Core Collection, Scopus, Embase, the Cochrane Library, and CNKI for papers published between 1 January 2020 and 31 December 2024 using the Boolean string ("curcumin" OR "Curcuma longa" OR "turmeric") AND ("bioavailability" OR "functional food" OR "nutrition" OR "immunology" OR "safety" OR "toxicology"). Only full-length primary studies available in English or Chinese were considered. Both authors independently screened titles/abstracts and then full texts, resolving any disagreements by consensus. The search yielded 876 records; after removing 142 duplicates, 734 unique articles remained. Title/abstract screening excluded 399 papers, and full-text review removed a further 82 that involved non-oral administration, suprapharmacological doses, or lacked food-relevant outcomes. Consequently, 253 oral, food-related primary studies were included and provide the evidentiary foundation for this review.

3. Pharmacokinetic Profile of Curcumin

Over the past six decades, extensive studies have demonstrated that curcumin exhibits low systemic absorption and is rapidly metabolized in vivo, resulting in poor bioavailability. This pharmacokinetic limitation poses a major challenge for its clinical application. However, recent research has focused on various strategies to enhance the bioavailability of curcumin, offering promising solutions to overcome these barriers.

3.1 Preclinical Pharmacokinetic Studies

Early studies have demonstrated that curcumin exhibits poor oral bioavailability in rodents. Following oral administration of curcumin at a dose of 1 g/kg in rats, approximately 75% of the compound was excreted in feces, while only trace amounts were detected in urine [19]. Ravindranath et al. investigated the pharmacokinetics of [^{3}H]-labeled curcumin at doses of 10, 80, and 400 mg in rats, and found that radioactivity was detectable in the blood, liver, and kidneys, with fecal excretion being the predominant elimination route. Urinary excretion remained minimal, and although most of the radioactivity was eliminated within 72 hours at lower doses, substantial amounts persisted in tissues up to 12 days post-administration at 400 mg. Notably, approximately 60%–66% of the labeled curcumin was absorbed, regardless of dose level [20]. Ireson et al. reported that curcumin undergoes extensive metabolism in rats, primarily via reduction reactions. It is initially reduced to dihydrocurcumin and subsequently to tetrahydrocurcumin and hexahydrocurcuminol. In addition, curcumin is subjected to conjugation reactions in the liver and intestinal mucosa, forming glucuronide and sulfate conjugates. Among these, curcumin glucuronide and curcumin sulfate were the predominant metabolites detected in rat plasma, whereas levels of tetrahydrocurcumin and hexahydrocurcuminol were relatively low [21]. Other studies have shown that intraperitoneal injection of curcumin at 0.1 g/kg in mice led to its rapid conversion into dihydrocurcumin, tetrahydrocurcumin, and their corresponding monoglucuronide conjugates [22]. High-performance liquid chromatography-mass spectrometry analyses revealed that after oral administration, curcumin appears in plasma primarily in the form of its glucuronide and sulfate derivatives, with only minimal amounts of the parent compound detected [23]. Even under high-dose oral

administration (approximately 1.2 g/kg), curcumin concentrations in plasma, liver, and colonic mucosa remained extremely low [24].

Several strategies have been explored to improve curcumin's oral bioavailability. For instance, Suresh et al. demonstrated that co-administration of curcumin with piperine, an inhibitor of hepatic and intestinal glucuronidation, significantly enhanced its systemic availability in rats [25]. Vijayan et al. developed self-microemulsifying drug delivery systems incorporating turmeric oils (from *C. longa* and *C. aromatica*) to improve the oral delivery of curcumin. In rat pharmacokinetic studies, the modified formulations S-CL1 and S-CA1 enhanced curcumin bioavailability by 26-fold and 29-fold, respectively, compared to curcumin suspension [26].

Recent studies have also highlighted the regulatory effects of curcumin on the gut-liver axis. Gao et al. reviewed the potential mechanisms by which curcumin modulates gut microbiota composition, thereby exerting therapeutic benefits in hepatobiliary diseases [27]. Given the significant first-pass metabolism and enterohepatic circulation of curcumin, its poor oral absorption and extensive biotransformation in rodents underscore the need for formulation optimization to enhance its pharmacokinetic performance.

3.2 Clinical Pharmacokinetic Studies

In a phase I clinical trial, Sharma et al. evaluated the pharmacokinetics, biomarker activity, and patient compliance associated with oral administration of curcumin in humans. Fifteen patients with advanced colorectal cancer received daily oral doses of curcumin ranging from 0.45 g to 3.6 g for up to 4 months. Plasma, urine, and fecal samples were collected to determine the concentrations of curcumin and its metabolites, while changes in three biomarkers were assessed: GST activity, levels of M_1G DNA adducts, and prostaglandin E_2 (PGE_2) production. The results revealed that curcumin and its glucuronide and sulfate conjugates were detectable in plasma at concentrations of approximately 10 nmol/L, and were also present in urine. Notably, a daily dose of 3.6 g significantly suppressed inducible PGE_2 production in peripheral blood samples as early as 1 hour post-administration, and this inhibitory effect persisted after 29 days of treatment ($P < 0.05$). No dose-limiting toxicities were observed throughout the study. These findings suggest that a 3.6 g/day dose of curcumin is well tolerated and may be appropriate for subsequent phase II trials, particularly for the prevention or treatment of malignancies beyond the gastrointestinal tract [28].

Additional clinical studies have further elucidated the pharmacokinetic characteristics of orally administered curcumin and its metabolites in humans. Cheng et al. conducted a pharmacokinetic/pharmacodynamic study in 12 healthy volunteers who received a single 4 g dose of curcumin capsules. Plasma samples revealed no detectable levels of the parent compound, while curcumin-O-glucuronide, the major metabolite, was quantifiable as early as 30 minutes post-dose, reaching peak concentration at approximately 2.7 hours. These results confirm that curcumin undergoes rapid intestinal metabolism, primarily forming glucuronide conjugates [29]. Similarly, Vareed et al. investigated the pharmacokinetics of curcumin in healthy subjects following oral administration of 10 g or 12 g of curcumin. Using high-performance liquid chromatography, they assessed serum concentrations of free curcumin, glucuronide, and sulfate conjugates from 0.25 to 72 hours post-dose. Free curcumin was detected in only one

subject, and only at isolated time points. However, all participants exhibited detectable levels of glucuronide and sulfate metabolites. The calculated area under the curve ($AUC_{0-\infty}$) values were (35.33 ± 3.78) μg·h/mL and (26.57 ± 2.97) μg·h/mL for the 10 g and 12 g doses, respectively, while the corresponding C_{max} values were (2.30 ± 0.26) μg/mL and (1.73 ± 0.19) μg/mL. The glucuronide-to-sulfate ratio was approximately 1.92:1, indicating predominant glucuronidation in human metabolism [30]. Dhillon et al. assessed the pharmacokinetics of curcumin in patients with advanced pancreatic cancer who received 8 g of curcumin daily until disease progression. Despite low systemic availability, plasma levels of curcumin remained stable over the first four weeks of treatment, ranging from 22 to 41 ng/mL. Although curcumin itself was minimally present, its glucuronide and sulfate conjugates were consistently detected, suggesting limited absorption and rapid metabolism. Interindividual variability was observed in pharmacokinetic profiles, but some patients still demonstrated pharmacodynamic responses, indicating biological activity [31]. To further investigate tissue distribution, Garcea et al. examined curcumin levels in colorectal cancer patients. Twelve individuals were divided into three groups receiving 0.45, 1.8, or 3.6 g of curcumin daily for 7 days before surgery. Analysis of tumor and adjacent normal tissues revealed that at the 3.6 g dose, curcumin concentrations reached (12.7 ± 5.7) nmol/g in normal mucosa and (7.7 ± 1.8) nmol/g in malignant tissue. Trace amounts of curcumin sulfate and glucuronide were also detected, while plasma levels remained negligible. These findings suggest that oral curcumin can accumulate in intestinal tissues but shows poor systemic distribution beyond the gastrointestinal tract [32]. In a related study, Garcea et al. evaluated curcumin distribution in hepatic tissue of 12 patients with colorectal cancer metastases to the liver. Participants received 0.45, 1.8, or 3.6 g of curcumin daily for 7 days, followed by liver resection. HPLC analysis of peripheral and portal venous blood, bile, and liver tissue revealed only trace levels of the parent compound and its conjugates in plasma. Curcumin was undetectable in liver tissues collected 6–7 hours after the final dose, and metabolite concentrations were also minimal, further supporting the conclusion that orally administered curcumin has limited hepatic distribution [33].

In summary, oral administration of curcumin results in extremely low systemic bioavailability. Only at high daily doses (≥3.6 g) can curcumin be detected at nanomolar concentrations within intestinal tissues, whereas the parent compound remains virtually undetectable in peripheral circulation and hepatic tissues. The presence of glucuronide and sulfate conjugates in the intestine, blood, and liver further confirms that curcumin undergoes extensive first-pass metabolism and limited absorption, preventing it from reaching pharmacologically relevant concentrations in extraintestinal tissues. Therefore, oral curcumin may be more suitable for the prevention or treatment of gastrointestinal diseases, while its use for conditions such as hepatocellular carcinoma may require alternative routes of administration to ensure adequate tissue exposure.

3.3 Strategies to Improve the Bioavailability of Curcumin

The clinical translation of curcumin has been largely hampered by its intrinsically poor oral bioavailability. To address this limitation, a variety of formulation and delivery strategies have been investigated to enhance its absorption, metabolic stability, and systemic exposure.

One promising approach involves formulation modification. Choongjin Ban et al. developed solid lipid nanoparticles (SLNs) using tristearin and polyethylene glycol (PEG)-based surfactants to improve the oral

bioavailability of curcumin. By modulating emulsifier type and concentration, they tailored the digestion behavior and micellar properties of SLNs. Simulated gastrointestinal digestion revealed that all SLNs yielded high curcumin bioaccessibility (> 91%). Notably, SLNs modified with long-chain PEG exhibited neutral surface charge and favorable intestinal epithelial permeability, leading to over a 12-fold increase in bioavailability. These findings suggest that interfacial engineering of SLNs offers a promising strategy for curcumin delivery in functional foods and pharmaceuticals [34].

Another approach involves the use of bioenhancing excipients or adjuvants [329]. Guangrui Xu et al. formulated ternary composite nanoparticles composed of curcumin, casein, and soybean soluble polysaccharides. These nanoparticles, prepared via high-pressure homogenization and pH-driven self-assembly, showed high encapsulation efficiency (~97%) and maintained physical stability over 30 days. In vitro digestion studies demonstrated a curcumin release rate of 52.3%, while in vivo pharmacokinetic studies in mice revealed a 3.4-fold increase in oral bioavailability. The study highlights the potential of protein–polysaccharide composite carriers in curcumin delivery [35]. Similarly, Ruoning Wang et al. designed a co-crystalline solid dispersion system of curcumin and piperine without excipients, using melt-quenching techniques. Piperine acts as a metabolic inhibitor, reducing glucuronidation and enhancing membrane permeability. This system showed improved dissolution and at least 3-month stability, with AUC values 2.16-fold and 1.92-fold higher than crystalline and amorphous curcumin, respectively. The results demonstrate that co-crystal engineering, coupled with metabolic inhibition, effectively improves curcumin bioavailability [36].

Nanotechnology-based delivery systems have also gained increasing attention. Prakash Ramalingam et al. developed chitosan-coated SLNs to enhance the stability and oral absorption of curcumin. The use of food-grade lipids ensured safety, while chitosan coating improved mucoadhesion and residence time in the gastrointestinal tract. The system exhibited long-term stability under both room and refrigerated conditions and significantly enhanced oral bioavailability compared to curcumin suspension. These findings provide new opportunities for incorporating curcumin into functional food and nutraceutical applications [37].

In addition, novel powder and micellar technologies have shown remarkable potential. Christina Schiborr et al. conducted a randomized crossover study in 23 healthy volunteers (13 women and 10 men) to compare the bioavailability of three oral curcumin formulations: unformulated powder, micronized powder, and liquid micelles. Micronized curcumin showed 14-fold, 5-fold, and 9-fold increases in women, men, and the total cohort, respectively, compared to raw powder. Remarkably, the micellar formulation enhanced bioavailability by 277-fold in women, 114-fold in men, and 185-fold overall. All formulations were well tolerated, and gender-based differences in absorption were observed, warranting further investigation [38].

Collectively, these strategies have partially overcome the barriers associated with curcumin’s low oral bioavailability and offer a range of options for clinical and functional use. Nonetheless, further studies are warranted to optimize these delivery systems for maximal efficacy and consistent pharmacokinetics.

Taken together, preclinical studies have consistently shown that curcumin has poor oral bioavailability in rodents, largely due to extensive first-pass metabolism and enterohepatic circulation. Clinical data corroborate

these findings, indicating that only high doses (e.g., ≥3.6 g/day) result in detectable levels of curcumin in intestinal tissues, while levels in peripheral circulation and the liver remain minimal. These findings suggest that curcumin is best suited for the treatment of gastrointestinal diseases via oral administration, while systemic diseases such as hepatocellular carcinoma may require alternative delivery routes. The strategies outlined above provide a foundation for dose selection, formulation development, and route optimization in future clinical applications of curcumin.

4. Bioactive Properties, Therapeutic Applications, and Health Benefits of Curcumin

4.1 Protective and Therapeutic Effects of Curcumin on Cardiovascular System

Curcumin exhibits a wide range of protective and therapeutic effects on the cardiovascular system. These include anti-atherosclerotic activity, lipid-lowering effects, attenuation of myocardial injury and hypertrophy, improvement of ischemia-reperfusion (I/R) injury, and prevention of stroke and related vascular disorders. These cardiovascular benefits are largely attributed to its modulation of multiple molecular signaling pathways involved in inflammation, oxidative stress, endothelial dysfunction, and lipid metabolism.

4.1.1 Anti-Atherosclerotic Effects

Atherosclerosis (AS) is a common cardiovascular disorder among the elderly, characterized by dyslipidemia, chronic inflammation, and endothelial dysfunction. Curcumin has been shown to inhibit the initiation and progression of AS through multiple mechanisms, including the regulation of lipid metabolism, suppression of inflammatory responses, and improvement of endothelial function. Ashraf et al. investigated the anti-atherosclerotic effect of microencapsulated curcumin formulated with gelatin and maltodextrin in a rat model of hypercholesterolemia. Dietary supplementation with this formulation significantly reduced low-density lipoprotein (LDL), triglyceride levels, atherogenic index (AI), and cardiac risk ratio (CRR), while markedly increasing high-density lipoprotein (HDL) concentrations. The improved bioavailability and stability conferred by microencapsulation contributed to its efficacy in modulating dyslipidemia and preventing atherogenesis [39]. Similarly, Momtazi-Borojeni et al. evaluated the therapeutic potential of intravenous curcumin administration in a high-cholesterol diet-induced atherosclerotic rabbit model. Curcumin injection significantly improved serum lipid profiles and mitigated atherosclerotic lesion development in a dose-dependent manner. At a low dose (1 mg/kg/week), reductions of 14.19% in total cholesterol (TC), 6.22% in LDL-C, and 29.84% in triglycerides (TG) were observed, along with a 14.05% increase in HDL-C. At a high dose (10 mg/kg/week), the improvements were more pronounced, with TC, LDL-C, and TG decreasing by 56.59%, 44.36%, and 25.92%, respectively, and HDL-C increasing by 36.24%. Histological analyses revealed that high-dose curcumin significantly reduced the severity of atherosclerotic plaques ($p = 0.03$), whereas the low-dose group showed no significant improvement [40]. Mechanistically, Yuan et al. demonstrated that curcumin attenuated cholesterol accumulation in vascular smooth muscle cells (VSMCs) by modulating the SREBP-1/caveolin-1 pathway. Oral administration of curcumin (20 mg/kg/day) for four months in $ApoE^{-/-}$ mice reduced atherosclerotic lesion area by 50% and upregulated caveolin-1 expression fivefold. In vitro studies showed that curcumin markedly decreased intracellular lipid droplet

formation and total cholesterol, cholesteryl ester, and free cholesterol levels in ox-LDL-treated VSMCs, accompanied by suppressed nuclear translocation of SREBP-1 and enhanced caveolin-1 expression. These effects were reversed by SREBP-1 inhibition, confirming that curcumin exerts its anti-atherogenic action through this pathway [41]. Zhong et al. further elucidated the molecular basis of curcumin's effect on foam cell formation using ox-LDL-induced THP-1 macrophages. Curcumin treatment inhibited TLR4 and miR33a expression, suppressed NF-κB pathway activation, and downregulated proinflammatory cytokines (TNF-α, MCP-1, IL-6), while restoring ATP-binding cassette transporter A1 (ABCA1) expression and cholesterol efflux. The effects of curcumin were mimicked by TLR4 antibodies, NF-κB inhibitors, and miR33a inhibitors, suggesting that its anti-foam cell and anti-inflammatory properties are mediated via the TLR4/NF-κB/miR33a axis [42]. In a clinical context, Dastani et al. reported that nano-curcumin administration (80 mg/day for 3 months) significantly reduced high-sensitivity C-reactive protein (hs-CRP) and lipoprotein(a) levels in patients with type 2 diabetes and mild-to-moderate coronary artery disease. Notably, the proportion of patients with low and moderate inflammation increased to 34.35% and 62.5%, respectively, while the prevalence of severe inflammation decreased to 3.125% ($P = 0.016$), underscoring the dual lipid-lowering and anti-inflammatory potential of curcumin in attenuating atherosclerosis progression [43].

Curcumin has also been demonstrated to exert potent antioxidant and endothelial-protective effects. Yang et al. investigated the role of curcumin in attenuating oxidative stress injury (OSI) via the inhibition of Notch1 signaling in H_2O_2-treated human umbilical vein endothelial cells (HUVECs) [44]. Both DAPT (a γ-secretase inhibitor) and Notch1 siRNA significantly reduced the expression of Notch1 and its downstream target Hes1, alleviating oxidative stress-induced cellular damage. Curcumin treatment markedly improved cell viability, adhesion, and migration, while decreasing ROS levels, apoptotic index, and the expression of Caspase-3, Bax, and cytochrome c. Notably, curcumin upregulated the anti-apoptotic protein Bcl-2. These findings suggest that curcumin confers endothelial protection at least partly through the suppression of Notch1 signaling. Tubsakul et al. further demonstrated that curcumin mitigated hypertension and oxidative stress induced by chronic lead (Pb) and cadmium (Cd) exposure in rats [45]. Pb and Cd impaired endothelium-dependent vasorelaxation and elevated NADPH oxidase-derived ROS production. Curcumin restored endothelial function by upregulating endothelial nitric oxide synthase (eNOS) expression, enhancing plasma nitrite/nitrate levels, and reducing oxidative burden via NADPH oxidase inhibition. The synergistic antioxidant effects of curcumin in combination with other polyphenols have also been explored. In H_2O_2-challenged EA.hy926 endothelial cells, a curcumin-resveratrol (CR) mixture at an optimal ratio of 8:2 significantly improved cell survival, inhibited ROS production and caspase-3 activation, and enhanced nuclear translocation of Nrf2 and expression of downstream HO-1 protein [46]. The CR combination also elevated SOD activity and intracellular NAD levels, suggesting activation of the Nrf2-HO-1 antioxidant pathway. This study highlights a promising combinatory strategy for the management of endothelial oxidative injury. Moreover, Wang et al. reported that curcumin combined with baicalein (Cur+Bai) synergistically protected against macrovascular dysfunction in models of diabetic vasculopathy [47]. In H_2O_2-damaged endothelial cells and diabetic rats, the Cur+Bai combination (1:1) outperformed monotherapies in restoring

endothelial cell viability, and significantly reduced fasting blood glucose and lipid levels. Histological analysis revealed improved vascular integrity in the aortic arch and thoracic aorta. Mechanistic investigations confirmed that this protective effect was mediated by activation of both the Nrf2 and MAPK/JNK signaling pathways.

Curcumin and its major metabolite, hexahydrocurcumin (HHC), have been shown to inhibit the pathological proliferation and migration of vascular smooth muscle cells (VSMCs), thereby exerting anti-atherosclerotic effects. He et al. demonstrated that curcumin attenuated VSMC hyperactivity by suppressing the chemerin/CMKLR1/lipocalin-2 (LCN2) signaling axis in atherosclerosis (AS) [48]. In high-fat diet (HFD)-induced AS mouse models, the expression of CMKLR1 was markedly upregulated and positively correlated with aortic proliferation levels. Silencing CMKLR1 in VSMCs led to a significant reduction in proliferation and migration, as evidenced by decreased EdU incorporation, reduced wound healing ability, and lowered expression of PCNA and MMP-9. Mechanistic studies revealed that LCN2 acted as a key downstream effector of CMKLR1, with involvement of the p38/MAPK and Wnt/β-catenin pathways. Curcumin effectively suppressed this signaling cascade, thereby limiting VSMC dysfunction and delaying AS progression. These findings suggest that the chemerin/CMKLR1 axis may represent a promising therapeutic target for AS, with curcumin offering potential as a natural inhibitor. In a related study, Panthiya et al. found that hexahydrocurcumin (HHC) significantly mitigated angiotensin II (Ang II)-induced VSMC proliferation, migration, and inflammation [49]. In primary rat aortic VSMCs, HHC suppressed Ang II-induced upregulation of Cyclin D1 while restoring the expression of cell cycle regulator p21. HHC also markedly reduced ROS production and inhibited the expression of pro-inflammatory markers including NF-κB, TNF-α, IL-6, and MMP-9. Notably, these effects paralleled those of GKT137831, a NADPH oxidase (NOX1/4) inhibitor, and their combination further potentiated vascular protection. In addition, HHC reversed Ang II-induced suppression of peroxisome proliferator-activated receptor gamma (PPAR-γ) and its coactivator PGC-1α. These results suggest that HHC exerts vasoprotective effects by attenuating NOX-derived oxidative stress and restoring PPAR-γ/PGC-1α signaling, offering new insights for the prevention and treatment of hypertension and atherosclerosis.

Curcumin exerts anti-atherosclerotic effects in part by modulating macrophage polarization and gut microbiota-associated metabolic pathways. Zhang et al. demonstrated that cadmium (Cd) exposure promotes atherosclerosis (AS) progression through gut microbiota dysbiosis, enhanced trimethylamine N-oxide (TMAO) synthesis, lipid metabolism disruption, and M1-type macrophage polarization in $ApoE^{-/-}$ mice [50]. Cd exposure increased aortic plaque area, reduced gut microbial diversity, and elevated circulating TMAO levels. Notably, fecal microbiota transplantation from non-Cd-exposed donors attenuated AS in Cd-treated mice, confirming the role of microbiota-derived metabolites. Oral curcumin administration reversed these pathological changes by restoring gut microbiota composition, suppressing TMAO production, and reducing atherosclerotic plaque burden. These findings highlight a novel Cd–gut–TMAO–macrophage axis in AS and suggest that curcumin may protect against Cd-induced vascular injury through microbial and immunomodulatory regulation.

In a broader immunological context, Abdollahi et al. reviewed curcumin's regulatory effects on macrophage polarization, emphasizing its potential to shift macrophage phenotypes from pro-inflammatory M1 to anti-inflammatory M2 states in various inflammation-related diseases, including AS [51]. Curcumin suppresses M1-associated cytokines such as TNF-α and IL-1β, inhibits NF-κB and STAT1 signaling, and enhances the expression of M2-associated markers including IL-10 and arginase-1, thereby mitigating chronic inflammation and promoting vascular repair. Consistently, Chen Yushan et al. reported that curcumin significantly alleviated AS-associated inflammation by inhibiting M1 macrophage polarization and the expression of pro-inflammatory mediators such as iNOS, TNF-α, and CXCL9 [52]. The study further revealed that curcumin, alone or in combination with berberine, increased P-STAT6/STAT6 signaling activity, favoring M2 polarization. The combination treatment showed synergistic efficacy in suppressing inflammatory responses and macrophage polarization, suggesting that curcumin-mediated activation of the STAT6 pathway represents a promising immunomodulatory strategy for AS intervention.

Epidemiological studies have indicated a strong association between human cytomegalovirus (HCMV) infection and the development and progression of atherosclerosis. Curcumin has shown potential to suppress HCMV infection and improve host cellular microenvironments, thereby attenuating atherogenesis. Lv et al. demonstrated that oral curcumin administration significantly prevented atherosclerotic plaque formation in $ApoE^{-/-}$ mice by targeting cytomegalovirus-induced vascular inflammation [53]. In vitro, curcumin inhibited CMV replication and propagation in endothelial cells, reduced intracellular reactive oxygen species (ROS) production, and suppressed the expression of pro-inflammatory cytokines. Furthermore, it downregulated key components of the HMGB1–Toll-like receptors (TLRs)–NF-κB signaling axis, a critical pathway in viral-induced vascular inflammation. In vivo, curcumin treatment lowered serum levels of low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), and triglycerides (TG), reduced aortic plaque burden, and alleviated lipid accumulation and inflammatory damage in the liver, heart, lungs, and kidneys. These findings highlight a novel antiviral and anti-inflammatory mechanism by which curcumin confers vascular protection in the context of HCMV-associated atherogenesis.

4.1.2 Prevention and Treatment of Myocardial Infarction

Myocardial infarction (MI), a severe manifestation of coronary artery disease, is often accompanied by multiple complications and poses a significant threat to life. Curcumin and its nanoformulations have demonstrated promising therapeutic potential in both experimental and clinical models of myocardial infarction (MI), primarily through antioxidant, anti-inflammatory, and cardioprotective mechanisms. Boarescu et al. compared the cardioprotective effects of curcumin nanoparticles (CCNP) and conventional curcumin (CC) in isoproterenol-induced myocardial infarction in rats. Both treatments alleviated myocardial damage, but CCNP more effectively reduced creatine kinase-MB (CK-MB) levels, oxidative stress, inflammatory cytokines (TNF-α, IL-6, IL-1α, IL-1β, MCP-1, RANTES), and MMP-2/9 expression. Histological findings showed that CCNP better prevented necrosis, edema, and neutrophil infiltration, indicating enhanced efficacy via nanoformulation [54]. Yan et al. investigated the anti-inflammatory effects of curcumin in a mouse model of myocardial infarction (MI), revealing that curcumin attenuated early

inflammation and ventricular remodeling by modulating macrophage polarization. Curcumin downregulated M1 markers (iNOS, CCL2, CD86) and upregulated M2 markers (Arg1, CD163, CD206) in vivo, while flow cytometry confirmed reduced M1 and enhanced M2 macrophage infiltration. In vitro, curcumin suppressed LPS/IFNγ-induced M1 polarization and promoted M2 phenotype, partly via AMPK activation, suggesting its role in promoting post-MI resolution of inflammation through macrophage reprogramming [55]. Kang et al. developed heart-targeted extracellular vesicles to co-deliver curcumin and miR-144-3p, which enhanced cardiac targeting and therapeutic efficacy in myocardial infarction models [56]. Tabaee et al. conducted a randomized, double-blind, placebo-controlled trial to evaluate the effects of curcumin plus piperine supplementation (500 mg/day, 8 weeks) in patients with acute myocardial infarction (AMI). Compared to placebo, curcumin significantly reduced HbA1C, LDL, ALT, and ALP levels, while increasing HDL. No significant changes were observed in ejection fraction, cTnI, renal function, or electrolyte levels, suggesting metabolic but not direct cardiac functional benefits in AMI patients [57]. Chen et al. developed a smart exosome-mediated delivery system (ExoCTP) to enhance curcumin therapy in myocardial infarction. By avoiding mononuclear phagocyte system uptake, ExoCTP improved cardiac retention and targeted drug release. Compared to free curcumin, ExoCTP more effectively reduced oxidative stress markers (LDH, MDA, SOD, GSH) in ischemic myocardium and showed no systemic toxicity, highlighting its potential for precise cardiac therapy [58]. Pawar et al. demonstrated that curcumin protects diabetic mice from isoproterenol-induced myocardial infarction by activating CB2 cannabinoid receptors (CB2R). Curcumin restored hemodynamic parameters, improved antioxidant status, reduced inflammation and myocardial damage, and normalized biochemical markers. These effects were reversed by the CB2R antagonist AM630, suggesting CB2R involvement in curcumin's cardioprotective mechanisms in diabetic conditions [59].

4.1.3 Prevention and Treatment of Cardiac Hypertrophy and Heart Failure

Pathological cardiac hypertrophy is a key mechanism leading to the development of heart failure. Curcumin exerts multifaceted protective effects against cardiac hypertrophy and heart failure by modulating diverse molecular mechanisms. These include epigenetic regulation, suppression of pro-inflammatory signaling, enhancement of myocardial contractile function, upregulation of cardioprotective proteins, and inhibition of pathological remodeling pathways. One key mechanism involves the inhibition of the interaction between p300 and GATA4. Sunagawa et al. demonstrated that curcumin, acting as a p300 histone acetyltransferase inhibitor, effectively prevented hypertension-induced left ventricular (LV) hypertrophy in Dahl salt-sensitive rats. This cardioprotective effect occurred without altering blood pressure or systolic function, and was associated with reductions in myocardial wall thickness, LV mass index, cardiomyocyte size, perivascular fibrosis, and GATA4 acetylation [60]. Building on the importance of bioavailability, Takai and Morimoto compared the efficacy of ASD-Cur—an amorphous curcumin formulation—with Theracurmin® in myocardial infarction (MI)-induced heart failure. ASD-Cur achieved comparable therapeutic benefits at a lower dose, attributed to its superior pharmacokinetics [61]. In a clinical context, Funamoto et al. conducted a double-blind, placebo-controlled trial in patients with early-stage hypertensive heart disease. Although curcumin had no significant effect on the E/E′ ratio, it markedly suppressed plasma

BNP elevation, particularly in patients under 65 years, suggesting potential in reducing subclinical cardiac stress [62]. In contrast, a short-term trial by Panahi et al. found no significant changes in inflammatory or cardiac biomarkers in patients with acute decompensated heart failure, indicating that curcumin's benefits may depend on disease stage and treatment duration [63]. In addition to histone acetylation pathways, curcumin exerts cardioprotective effects via suppression of inflammatory signaling. Wang et al. reported that JM-2, a curcumin analog, significantly improved cardiac outcomes in diabetic cardiomyopathy (DCM) by inhibiting NF-κB activation. In both type 1 and type 2 diabetic mouse models, JM-2 alleviated inflammation and fibrosis while improving ventricular function, highlighting the therapeutic relevance of NF-κB pathway blockade in DCM [64]. Curcumin also contributes to improved cardiac contractility and vascular tone. Bai et al. showed that curcumin enhanced myocardial performance and endothelial-dependent vasodilation in a rat model of pressure overload-induced hypertrophy. These effects were associated with the upregulation of Na^+/Ca^{2+} exchanger (NCX) and endothelial nitric oxide synthase (eNOS), and were partially reversed by NCX inhibition, supporting the role of calcium handling in curcumin-mediated cardioprotection [65]. Furthermore, curcumin modulates stress-responsive signaling to mitigate chronic heart failure progression. Cao et al. demonstrated that curcumin treatment upregulated Dickkopf-3 (DKK-3) expression and suppressed the activation of p38, JNK, and ASK1 pathways in a rabbit model of volume- and pressure-overload-induced heart failure. This regulatory effect contributed to improved ventricular remodeling and decreased oxidative stress, suggesting a novel cardioprotective mechanism involving DKK-3-mediated inhibition of pro-apoptotic kinases [66].

4.1.4 Prevention and treatment of ischemia-reperfusion (I/R) injury

Curcumin exerts protective effects against ischemia-reperfusion (I/R) injury across multiple organs through antioxidative, anti-inflammatory, anti-apoptotic, and ferroptosis-inhibiting mechanisms, involving key regulatory pathways such as Nrf2, NF-κB, SIRT1, and PKC-θ. Mohamadian et al. systematically reviewed the protective effects and mechanisms of curcumin against I/R injury across multiple organs. I/R injury, commonly affecting the heart, kidneys, gastrointestinal tract, nervous system, and reproductive organs, is primarily caused by oxidative stress, inflammation, and cell death triggered by the restoration of blood flow following ischemia. As the principal bioactive component of turmeric, curcumin exerts multi-target protective actions through its antioxidant, anti-inflammatory, and anti-apoptotic properties. In the gastrointestinal tract, curcumin reduces oxidative damage, maintains mucosal barrier integrity, and inhibits bacterial translocation. In the liver, it suppresses NF-κB signaling and alleviates mitochondrial dysfunction. In reproductive organs such as the ovaries and testes, curcumin mitigates oxidative stress and enhances tissue repair. In the heart, it reduces infarct size and improves cardiac function by inhibiting inflammation and apoptosis. In renal tissues, curcumin protects against I/R injury induced by diabetes, nephrectomy, or nephrotoxic agents by lowering oxidative and inflammatory markers. Within the nervous system, including the brain and spinal cord, curcumin decreases neuronal apoptosis and glial activation through pathways such as BDNF/TrkB. These findings underscore curcumin's multi-organ protective capacity via modulation of signaling cascades like Nrf2 and SIRT1. Although further clinical validation is required, current evidence highlights curcumin as a

promising therapeutic candidate for I/R-related pathologies [67]. Supporting this, Cui et al. showed in a rat model that curcumin pretreatment (60 mg/kg, intraperitoneally) significantly reduced serum creatinine and BUN levels, attenuated oxidative stress and inflammation, and decreased renal tubular apoptosis, indicating dose-dependent renal protection [68]. Wu et al. demonstrated that curcumin alleviates spinal cord I/R injury (SCII) by reducing oxidative stress, inhibiting M1-type microglial activation, and suppressing neuroinflammation and neuronal apoptosis via modulation of the Nrf2/NF-κB axis, affirming its neuroprotective potential [69]. Lan et al. found that olfactory mucosa-derived mesenchymal stem cells pretreated with curcumin (CUR-OM-MSCs) mitigated cerebral I/R injury by attenuating neuronal PANoptosis and promoting M2-type microglial polarization through miRNA-423-5p–mediated inhibition of the NOD2/NF-κB/MAPK pathway, offering a novel strategy for ischemic stroke therapy [70]. In cerebral I/R injury models, Mo et al. reported that curcumin preserved blood-brain barrier (BBB) integrity and reduced intracellular Ca^{2+} overload through the PKC-θ signaling pathway, both in vitro and in middle cerebral artery occlusion/reperfusion (MCAO/R) rats [71]. Zhu et al. showed that curcumin alleviated hepatic I/R injury by inhibiting neutrophil extracellular trap formation via MEK/ERK pathway suppression; co-treatment with DNase-1 further enhanced this protective effect, suggesting a synergistic approach to liver IRI therapy [72]. Regarding myocardial I/R injury, Li et al. conducted a systematic review and meta-analysis encompassing 24 animal studies and 4 clinical trials, confirming that curcumin significantly reduces infarct size and improves cardiac function via antioxidant, anti-inflammatory, anti-apoptotic, and anti-fibrotic mechanisms[73]. Clinical data also suggested potential in reducing myocardial infarction and major adverse cardiovascular events, especially at higher doses and with longer treatment durations . Yuan et al. demonstrated that curcumin pretreatment inhibited ferroptosis, excessive autophagy, and apoptosis through upregulation of HES1, thereby reducing oxidative damage and maintaining mitochondrial and cellular homeostasis in myocardial I/R models [74]. Similarly, Zhao et al. found that curcumin alleviated myocardial I/R injury by suppressing autophagy-dependent ferroptosis via activation of the Sirt1/AKT/FoxO3a pathway, thereby preserving cardiomyocyte viability [75]. In a model of acute kidney injury-associated multi-organ I/R damage, Kar et al. revealed that curcumin reduced ferroptosis and oxidative stress in the liver, pancreas, and heart by restoring GPx4 levels and downregulating ACSL4 expression, with greater efficacy than the ferroptosis inhibitor LoxBlock-1 [76].

4.1.5 Prevention and Treatment of Stroke

Stroke, a common disorder of the central nervous system, encompasses both ischemic and hemorrhagic subtypes. Curcumin has been shown to exert significant preventive and therapeutic effects in the management of stroke. A growing body of preclinical and clinical evidence supports the neuroprotective role of curcumin in both ischemic and hemorrhagic stroke. Through diverse mechanisms—including anti-inflammatory, antioxidant, anti-apoptotic, and blood-brain barrier–preserving effects—curcumin demonstrates promising therapeutic potential in reducing stroke-induced neuronal injury and improving neurological outcomes. The following studies further elucidate these effects and delivery strategies. Marques et al. conducted a systematic search of PubMed, Scopus, and Web of Science databases, identifying 728 articles and selecting 53 rodent

studies for qualitative analysis to assess the neuroprotective effects of curcumin in stroke. Their findings revealed that high doses of free curcumin (e.g., 300 mg/kg) were necessary to significantly improve neurological deficits in both ischemic and hemorrhagic stroke models. In contrast, nanoformulations such as liposomes and micelles enhanced bioavailability, enabling low doses (e.g., 10 mg/kg) to achieve similar or superior efficacy. Mechanistically, curcumin exerted its protective effects via multiple pathways: it inhibited NF-κB signaling to reduce pro-inflammatory cytokines TNF-α and IL-6 (by 40%–60%), activated the Nrf2/HO-1 pathway to increase superoxide dismutase (SOD) activity (by 1.5–2 fold), and suppressed caspase-3 activity (by ~50%) to reduce neuronal apoptosis. Furthermore, curcumin preserved blood-brain barrier integrity, evidenced by a 70% reduction in Evans blue extravasation, and promoted a 30% increase in BDNF expression [77]. Extending these findings to clinical settings, Boshagh et al. performed a randomized controlled trial in ischemic stroke patients undergoing rehabilitation. A 12-week regimen of curcumin-piperine supplementation (500 mg/5 mg daily) significantly decreased hs-CRP, total cholesterol, triglycerides, carotid intima-media thickness, blood pressure, and body weight, while increasing total antioxidant capacity—highlighting curcumin's potential in modulating inflammatory and metabolic responses post-stroke [78]. Nanotechnology-based delivery systems also show great promise. Li et al. demonstrated that triblock copolymer nanomicelles loaded with curcumin (NC) significantly enhanced brain bioavailability and reduced NF-κB-p65 expression, pro-inflammatory cytokines (IL-1β, IL-6, TNF-α), and lipid peroxidation in a rat model of cerebral ischemia, indicating NC's potential as an anti-inflammatory therapeutic for stroke [79]. A comprehensive review by Subedi and Gaire further summarized the cellular and molecular neuroprotective mechanisms of curcumin in cerebral ischemia/reperfusion injury. curcumin was shown to: (1) reduce oxidative stress (ROS, MDA) while enhancing antioxidant markers (HO-1, Nrf2, SOD); (2) suppress inflammation via inhibition of NF-κB, MAPK, and NLRP3 inflammasome pathways, and promote M2 microglial polarization; (3) attenuate apoptosis by downregulating Bax and cleaved caspase-3, while upregulating Bcl-2; (4) maintain BBB integrity by increasing tight junction proteins (ZO-1, claudin-5) and inhibiting adhesion molecules (ICAM-1, VCAM-1); (5) regulate autophagy and ER stress (e.g., LC3-II/I, HIF-1α, GADD153); (6) ameliorate mitochondrial dysfunction and enhance mitochondrial biogenesis (UCP2, TFAM); and (7) promote neurogenesis and functional recovery by modulating BrdU/NeuN, NeuroD1, and Wnt/β-catenin signaling. Although curcumin demonstrated robust efficacy in preclinical models, the authors noted that clinical translation remains limited by its low bioavailability, underscoring the need for nanoformulations and combination therapies [80]. Further supporting these observations, Stadler et al. evaluated PAMAM dendrimer-encapsulated curcumin in a rat model of ischemic stroke. Compared to free curcumin or vehicle, the nanoformulated curcumin significantly improved neurological recovery, body weight restoration, and reduced GFAP expression. Interestingly, blank dendrimers alone also exhibited partial neuroprotective effects, suggesting intrinsic bioactivity that warrants further investigation [81]. Ahmadzadeh et al. highlighted the central role of autophagy in ischemic stroke and identified curcumin as a potent modulator of autophagy-related pathways. Specifically, curcumin was found to regulate PI3K/Akt/mTOR, Beclin-1, and AMPK axes, facilitating autophagic flux, clearing damaged organelles, preserving neuronal

homeostasis, and attenuating oxidative stress and inflammation. Moreover, curcumin influenced mitochondrial function and energy metabolism, thereby indirectly modulating autophagic activity and neuronal survival [82]. In the context of hemorrhagic stroke, Xu et al. demonstrated that curcumin mitigated early brain injury after experimental subarachnoid hemorrhage (SAH) by suppressing ferroptosis and neuroinflammation. Mechanistically, curcumin upregulated Nrf2 and HO-1 expression while inhibiting ferroptosis markers and downregulating p-p65 and inflammatory cytokines (TNF-α, IL-1β) in microglia. These effects led to reductions in brain edema, neuronal apoptosis, and improved neurological outcomes in behavioral assays, establishing Nrf2/HO-1 as a key axis for curcumin's protective action in SAH [83]. Yang et al. developed a polymeric nanoparticle formulation of curcumin (Cur-NPs) and tested it in a mouse model of intracerebral hemorrhage (ICH). Cur-NPs exhibited superior solubility and brain-targeting capability compared to free curcumin. These nanoparticles localized to lysosomes, ER, and mitochondria, effectively suppressed erastin-induced ferroptosis in vitro, and alleviated neurological deficits in vivo, validating Cur-NPs as a novel delivery platform for ICH therapy [84]. Similarly, Duan et al. formulated curcumin-loaded mPEG-PCL nanoparticles for intranasal delivery. In ICH mice, this strategy reprogrammed pro-inflammatory microglia toward an anti-inflammatory phenotype, reduced inflammation, neuronal death, and hematoma volume, and enhanced BBB integrity and functional recovery. This study provided the first evidence for non-invasive nasal delivery of curcumin nanoparticles to modulate the intracerebral immune microenvironment [85]. Further mechanistic insights were provided by Wang et al., who found that curcumin alleviated ICH-induced neuronal apoptosis and inflammation via inhibition of the JAK1/STAT1 signaling pathway. curcumin treatment improved neurological scores, reduced cerebral edema, and suppressed M1 microglial polarization. These protective effects were partly reversed by the JAK1 agonist RO8191, confirming the role of the JAK1/STAT1 axis in curcumin's action [86]. Finally, Ding et al. demonstrated that curcumin modulates microglial polarization through the TLR4/NF-κB pathway. In a C57BL/6 mouse ICH model, curcumin suppressed pro-inflammatory cytokine expression, reduced neuronal apoptosis, and promoted M2-type microglial activation. Immunohistochemistry and western blotting confirmed downregulation of TLR4 and NF-κB, highlighting this pathway as a key target in curcumin-mediated neuroinflammation attenuation [87].

4.1.6 Lipid-Lowering Effects

Curcumin has demonstrated lipid-lowering effects in both clinical and experimental settings. Multiple studies have shown that curcumin supplementation can improve serum lipid profiles by reducing triglycerides, total cholesterol, and LDL-C levels, while increasing HDL-C. These effects are observed across different formulations, including standard curcumin extracts and nanoformulations, and are supported by randomized clinical trials and meta-analyses. The mechanisms involve modulation of lipid metabolism pathways, such as fatty acid synthesis and β-oxidation, highlighting curcumin's potential as a natural adjunct in managing dyslipidemia and metabolic syndrome. Pamela et al. conducted a randomized, double-blind, placebo-controlled clinical trial to evaluate the effects of curcumin supplementation on lipid profiles in Brazilian women with elevated waist circumference. Participants received 500 mg of curcumin daily for 90

days. The results showed significant reductions in fasting glucose (FG), triglycerides (TG), and total cholesterol (TC) levels in the intervention group ($P < 0.001$ or $p = 0.001$) [88]. Similarly, Zohre Bateni et al. assessed the metabolic impact of nanomicellar curcumin in a randomized, double-blind, placebo-controlled trial involving 50 patients with metabolic syndrome. Participants received either 80 mg of nanocurcumin or a placebo daily for 12 weeks. The curcumin group showed a significant reduction in serum triglyceride levels [89]. On a mechanistic level, Mohammad Nosrati-Oskouie et al. reviewed curcumin's regulatory effects on fatty acid metabolism, particularly its influence on free fatty acids (FFAs), fatty acid synthesis (FAS), β-oxidation, and desaturase activity [90]. Since abnormal FFA and FAS activity is implicated in conditions such as insulin resistance, obesity, type 2 diabetes, hypertension, and various cancers, curcumin's ability to modulate these pathways—via its anti-inflammatory, antioxidant, anticancer, and lipid-lowering properties—offers a promising therapeutic strategy. Evidence from both animal and cell studies suggests that curcumin may reduce FFA levels and restore metabolic balance by modulating FAS, β-oxidation, and desaturase systems . Further supporting these findings, Vali Musazadeh et al. performed an umbrella meta-analysis to comprehensively evaluate curcumin's impact on lipid profiles in adults. This synthesis included 19 eligible systematic reviews and meta-analyses, concluding that curcumin significantly lowers TC, TG, and LDL-C levels while increasing HDL-C. These results affirm curcumin's potential as a lipid-lowering agent and highlight its utility as a nutritional adjunct in managing hyperlipidemia and cardiometabolic disorders [91]. Consistently, Mohammad Jafar Dehzad et al. conducted a systematic review and meta-analysis including 64 randomized controlled trials to assess the effect of curcumin/turmeric supplementation on lipid profiles. Using GRADE criteria to evaluate the quality of evidence, they confirmed that curcumin/turmeric supplementation significantly reduced TC, TG, and LDL-C levels while increasing HDL-C, reinforcing its role as an effective natural intervention for dyslipidemia management [92].

4.1.7 Inhibition of Angiogenesis

Angiogenesis is a fundamental physiological process required for embryonic development, tissue regeneration, and wound healing. However, excessive or aberrant angiogenesis contributes to the pathogenesis of numerous disorders, including retinal neovascularization, endometriosis, osteoarthritis, corneal neovascularization, and diabetic microvascular complications. Curcumin has demonstrated potent anti-angiogenic properties across diverse disease models, with mechanisms including VEGF signaling suppression, NF-κB inhibition, microRNA modulation, and dose-dependent endothelial regulation. These findings support its potential as a versatile therapeutic agent for preventing pathological neovascularization in ocular diseases, endometriosis, osteoarthritis, and diabetes-related angiogenic complications. Giménez-Bastida et al. found that curcumin and its metabolites—demethoxycurcumin (DMC) and bisdemethoxycurcumin (BisDMC)—at physiological concentrations (0.1–5 μmol/L) significantly inhibited human aortic endothelial cell (HAEC) migration and tube formation without affecting cell viability. The mechanism involved suppression of VEGF165-induced VEGFR2 phosphorylation and downstream ERK/Akt signaling [93]. In ocular models, Sinatrio et al. demonstrated that curcumin significantly reduced VEGF expression in human pterygium fibroblasts in a dose-dependent manner after 48 hours of treatment at

concentrations of 100 and 200 μmol/L. These findings suggest that curcumin may serve as a postoperative adjuvant to prevent recurrence by suppressing angiogenesis [94]. Bai et al. further elucidated the anti-angiogenic mechanism of curcumin in corneal neovascularization (CRNV), showing that it upregulated miR-1275 and miR-1246, which in turn suppressed VEGFB and NKAP expression. This inhibited HUVEC proliferation and angiogenesis, and interference with either miRNA or NKAP overexpression attenuated curcumin's effect, highlighting a miRNA-mediated regulatory mechanism [95]. In a systematic review, Arablou and Kolahdouz-Mohammadi evaluated curcumin's anti-angiogenic mechanisms in endometriosis. They found that curcumin reduced VEGF levels in serum and ectopic endometrial tissue, decreased microvessel density, and downregulated pro-angiogenic factors such as HIF-1α, VEGFR2, and PDGF-βR. Additionally, curcumin suppressed NF-κB–mediated inflammatory cytokines, further contributing to its anti-angiogenic effects. Curcumin also inhibited tube formation and invasiveness of HUVECs, reinforcing its therapeutic promise in controlling ectopic lesion vascularization [96]. Zhou demonstrated that porous gelatin scaffolds loaded with curcumin effectively inhibited angiogenesis and prevented cartilage ossification. In vivo experiments in rabbits showed reduced vascular ingrowth and sustained chondrogenic potential of bone marrow mesenchymal stem cells (BMSCs), thereby maintaining cartilage stability [97]. Similarly, Wang Sixiang et al. created chitosan–catechol nanoparticles conjugated with curcumin (Cur-CS-C NPs) for targeted osteoarthritis therapy. These nanoparticles demonstrated strong inflammation-responsiveness and ROS-scavenging activity, effectively suppressing subchondral angiogenesis and cartilage degeneration in a rat model. Mechanistically, the anti-angiogenic effects were mediated through modulation of the ROS-dependent NF-κB/PI3K-Akt pathway [98]. Dehghan et al. explored the anti-angiogenic effects of curcumin in a streptozotocin-induced diabetic rat model using the aortic ring assay. In the presence of exogenous VEGF, the diabetic group (D-V) exhibited the highest angiogenic response, which was significantly reduced in the curcumin-treated diabetic group (D-V-TC). This finding indicates that curcumin inhibits VEGF-driven angiogenesis under hyperglycemic and pro-angiogenic conditions, likely via suppression of VEGF, NF-κB, and related angiogenic factors [99]. Interestingly, Nigade et al. revealed a biphasic effect of curcumin on angiogenesis using CAM and zebrafish models. While low doses of curcumin promoted angiogenesis, high doses exhibited inhibitory effects, indicating a dose-dependent dual modulation of vascular development [100]. Curcumin's anti-angiogenic profile also underpins its antitumour activity (see 3.6.4).

4.1.8 Prevention of Restenosis Following Vascular Interventions

Vascular restenosis remains one of the major complications following interventional procedures such as angioplasty and stent placement. Curcumin has demonstrated significant potential in preventing post-procedural restenosis by targeting multiple pathological mechanisms, including vascular smooth muscle cell (VSMC) proliferation, endothelial dysfunction, oxidative stress, inflammation, and vascular calcification. In combination with advanced drug delivery technologies, curcumin's therapeutic value in vascular repair and remodeling continues to expand. Chenxing Fu et al. developed a self-assembling peptide hydrogel (Cur-NO-Gel) integrating curcumin and a nitric oxide (NO) donor to prevent restenosis after angioplasty. This stent-free hydrogel enabled sustained co-release of NO and curcumin, exerting synergistic anti-restenotic

effects. In vitro, Cur-NO-Gel mitigated oxidative stress-induced endothelial damage and inhibited VSMC activation and adventitial fibroblast proliferation. In a vascular injury model, perivascular application of the hydrogel suppressed neointimal hyperplasia, enhanced re-endothelialization, and prevented vascular constrictive remodeling, significantly reducing restenosis risk. This study provides a novel therapeutic strategy for non-stent-based vascular intervention using curcumin-based delivery systems [101]. Zhang et al. demonstrated that curcumin effectively prevents restenosis after carotid endarterectomy (CEA) by inhibiting VSMC proliferation, neointimal formation, inflammation, and oxidative stress. Both in vitro and in vivo findings revealed that curcumin suppressed the phosphorylation of proteins within the Raf/MEK/ERK signaling cascade, thereby exerting its anti-restenotic effects and offering a potential therapeutic avenue for CEA postoperative management [102]. Li et al. further summarized curcumin's vasoprotective actions in hypertension and vascular remodeling. These include inhibition of VSMC proliferation and migration via suppression of the FAK/PI3K/AKT, MAPK, and PDGFR/ERK1/2 pathways; improvement of endothelial function by enhancing NO bioavailability and eNOS expression; and downregulation of the renin-angiotensin system via suppression of AT1R and modulation of ACE activity. Additionally, curcumin attenuates oxidative stress and inflammation by activating Nrf2/HO-1 and inhibiting NF-κB. Its metabolites and nanoformulations enhance bioavailability and efficacy, underscoring curcumin's promise in managing hypertensive vascular remodeling [103]. Yang et al. highlighted that curcumin, owing to its anti-inflammatory, antioxidant, and anti-proliferative properties, can effectively reduce restenosis after percutaneous coronary intervention (PCI). Nanoformulated curcumin significantly improves bioavailability, allowing better inhibition of abnormal VSMC proliferation and migration, enhanced endothelial function, and reduced oxidative stress. Clinical studies also indicated that curcumin nanomicelles lowered inflammatory markers and improved lipid and antioxidant profiles post-PCI, supporting its potential in preventing stent restenosis and thrombosis [104]. Chen et al. discovered that curcumin alleviates vascular calcification via the exosomal miR-92b-3p/KLF4 axis. In both in vitro and in vivo calcification models, curcumin-enriched exosomes upregulated miR-92b-3p, which suppressed KLF4 and reduced expression of the osteogenic factor RUNX2. These findings confirm curcumin's anti-calcification effects and suggest a role in inhibiting vascular ossification [105]. To target VSMC proliferation, Selvendiran et al. investigated HO-3867, a synthetic curcuminoid, which effectively inhibited VSMC proliferation and arterial restenosis by upregulating PTEN. In both human aortic VSMCs and rat balloon injury models, HO-3867 induced G1 arrest and apoptosis, increased PTEN and caspase-3 activation, and suppressed ERK1/2, MMP-2/9, and NF-κB signaling, ultimately reducing neointimal formation [106]. Lastly, Wang et al. demonstrated that curcumin promotes thrombus resolution in a mouse model of deep venous thrombosis by enhancing therapeutic angiogenesis. Curcumin downregulated miR-499, leading to PTEN upregulation and activation of the PTEN/VEGF/Ang-1 signaling pathway. In HUVECs, miR-499 overexpression reversed these effects, confirming curcumin's role in facilitating thrombus clearance through vascular remodeling [107].

4.1.9 Effects in Other Cardiovascular Disorders

Curcumin exerts diverse protective effects across various cardiovascular conditions beyond atherosclerosis, myocardial infarction, and heart failure. Through its anti-inflammatory, antioxidant, anti-apoptotic, and metabolic regulatory actions, curcumin has shown therapeutic potential in diabetic cardiovascular complications, aneurysms, peripheral artery disease (PAD), coronary heart disease, and coagulation disorders. Advances in delivery systems and mechanistic insights further support its role as a multifunctional agent for cardiovascular prevention and treatment.

Prevention and management of diabetic cardiovascular complications. Curcumin exhibits promising efficacy in alleviating diabetes-associated vascular dysfunction and myocardial injury through multifaceted mechanisms, including anti-inflammatory, antioxidant, autophagy-modulating, metabolic regulatory, and anti-atherogenic activities. In a randomized, double-blind, placebo-controlled trial, Yaikwawong et al. demonstrated that curcumin supplementation significantly reduced atherogenic risk in obese patients with type 2 diabetes. After a 12-month intervention, patients receiving curcumin showed notable improvements in pulse wave velocity and cardiometabolic parameters, accompanied by marked reductions in low-density lipoprotein cholesterol (LDL-C), small dense LDL-C, and inflammatory biomarkers such as high-sensitivity hs-CRP, interleukin (IL)-1β, IL-6, and TNF-α (all $P < 0.001$) [108]. These findings underscore the vascular-protective and anti-inflammatory potential of curcumin in the diabetic population. Further mechanistic insights were highlighted by Zhang and Kitts, who reported that curcumin exerts substantial protective effects against cardiovascular complications in type 2 diabetes by targeting multiple molecular pathways. Specifically, curcumin enhances insulin sensitivity via activation of the IRS-Akt signaling cascade, stimulates glucagon-like peptide-1 (GLP-1) secretion through GPR40/120, and suppresses lipid biosynthesis by downregulating sterol regulatory element-binding proteins (SREBP-1/2), thereby mitigating key metabolic abnormalities associated with vascular injury. Additionally, curcumin attenuates vascular inflammation by inhibiting NF-κB activation and reducing the expression of proinflammatory mediators such as CRP and TNF-α. Its anti-atherogenic properties are further attributed to the suppression of foam cell formation through modulation of scavenger receptor-A and ABCA1, as well as the upregulation of forkhead box O3a (FOXO3a), which improves lipid transport and redox balance. In experimental models of myocardial infarction, curcumin significantly reduced infarct size, inflammatory infiltration, and cardiac fibrosis, effects mediated by activation of the JAK2/STAT3 pathway, inhibition of TLR2/NF-κB signaling, and restoration of SIRT1 expression. Furthermore, curcumin demonstrated cardioprotective effects by reducing cardiomyocyte apoptosis and preventing pathological cardiac hypertrophy through inhibition of p300 histone acetyltransferase activity. Collectively, these findings support the therapeutic potential of curcumin as an adjunctive strategy for the prevention and treatment of diabetic cardiovascular complications [109].

Prevention and treatment of aneurysms. Curcumin has demonstrated potential in preventing the formation and progression of arterial aneurysms by inhibiting angiogenesis, preserving elastin fiber integrity, and modulating inflammatory and apoptotic signaling in vascular tissues. Guo et al. reported that curcumin effectively suppresses the development of abdominal aortic aneurysms (AAA) by epigenetically regulating macrophage polarization through inhibition of the histone acetyltransferase EP300 [110]. Bioinformatics

analysis and molecular docking identified EP300 as a key target of curcumin in AAA pathogenesis. Immunohistochemical and immunofluorescent staining confirmed EP300 localization in macrophage-rich regions of AAA tissues, and RT-PCR revealed significantly elevated EP300 expression in human aneurysm samples. In vitro, EP300 knockout in LPS/IFN-γ-induced RAW264.7 macrophages promoted anti-inflammatory M2 polarization while suppressing M1 polarization, indicating that curcumin alleviates vascular inflammation by modulating macrophage phenotype via EP300 inhibition . Xiong et al. further demonstrated that curcumin nicotinate (CurTn), a structurally modified derivative of curcumin with enhanced solubility and stability, exerts protective effects against AAA by suppressing pyroptosis and inflammation in vascular smooth muscle cells (VSMCs). In an Angiotensin II-induced in vitro model, CurTn downregulated pyroptosis-related proteins and inflammatory cytokines. Mechanistic studies revealed that CurTn acts through the lncRNA PVT1/miR-26a/KLF4 axis, wherein CurTn downregulates PVT1 expression, thereby increasing miR-26a levels and suppressing the transcription factor KLF4. This regulatory cascade inhibits the PI3K/AKT signaling pathway, ultimately reducing pyroptotic cell death in VSMCs, and highlights CurTn's therapeutic potential through epigenetic modulation of vascular inflammation [111]. In a study by Li et al., curcumin was shown to attenuate the progression of thoracic aortic aneurysm (TAA) in both human tissue samples and a rat $CaCl_2$-induced model. Curcumin treatment significantly reduced aneurysm diameter, restored elastic fiber structure, and inhibited neovascularization. These effects were associated with downregulation of VEGF, reduced infiltration of $CD3^+$ T lymphocytes and $CD68^+$ macrophages, and suppressed expression of vascular adhesion molecules (VCAM-1, ICAM-1), monocyte chemoattractant protein-1 (MCP-1), and TNF-α. These findings suggest that curcumin mitigates TAA progression by targeting VEGF-mediated angiogenesis and inflammatory responses in the aortic wall [112]. Bo et al. explored the anti-apoptotic effects of curcumin in a rat model of cerebral aneurysm induced by perivascular $CaCl_2$ application. Curcumin administration (25 and 50 mg/kg) significantly preserved mitochondrial structure and restored vascular smooth muscle cell morphology. Mechanistically, curcumin inhibited apoptosis by reducing the expression of p53, caspase-3, and the bax/bcl-2 ratio. Fluorescence and confocal microscopy confirmed diminished apoptosis in aneurysmal VSMCs following curcumin treatment. These findings indicate that curcumin confers protection against cerebral aneurysm progression by maintaining VSMC integrity and inhibiting apoptosis [113].

Prevention and treatment of peripheral artery disease (PAD). Curcumin has shown promising therapeutic potential in the management of PAD, primarily through its anti-inflammatory, antioxidant, antiglycation, and endothelial-protective effects. As summarized by Froldi and Ragazzi, curcumin enhances vascular health in PAD by targeting key molecular pathways associated with vascular dysfunction. In preclinical models of hindlimb ischemia, curcumin administration promoted perfusion recovery, increased capillary density, inhibited muscle fiber degeneration, and reduced macrophage infiltration. These protective effects are mediated, in part, through suppression of NF-κB and hypoxia-inducible factor-1α (HIF-1α), as well as the upregulation of endothelial nitric oxide synthase (eNOS) and microRNA-93, both of which contribute to neovascularization. Moreover, curcumin attenuates glycation-induced vascular injury by inhibiting the formation of advanced glycation end products (AGEs), scavenging reactive carbonyl species such as

methylglyoxal, and modulating AGE-related receptor expression. Specifically, curcumin downregulates the receptor for AGEs while enhancing the expression of AGE receptor-1, thereby mitigating hyperglycemia-induced vascular damage. Although clinical evidence remains limited, preliminary findings from small randomized controlled trials suggest that curcumin supplementation may improve endothelial function in patients with PAD. Advances in curcumin delivery systems further highlight its potential for enhanced therapeutic efficacy in vascular diseases [114]. In a murine hindlimb ischemia model, Ismaeel et al. demonstrated that curcumin exerts significant protective effects on ischemic skeletal muscle. Intraperitoneal administration of curcumin (100 mg/kg) prior to femoral artery ligation markedly reduced muscle fibrosis, preserved muscle fiber morphology, and improved functional performance, as measured by treadmill endurance. Additionally, oral administration of curcumin (1000 mg/kg/day) for two weeks promoted perfusion recovery and capillary density even under diabetic conditions, underscoring its potential efficacy in both normoglycemic and diabetic PAD models [115].

Prevention and treatment of coronary artery disease (CAD). Curcumin has demonstrated therapeutic potential in the prevention and management of CAD, particularly in patients with metabolic comorbidities or undergoing surgical interventions. In a randomized, double-blind, placebo-controlled clinical trial, Dastani et al. investigated the effects of nano-curcumin supplementation (80 mg/day for 90 days) in patients with type 2 diabetes mellitus and mild-to-moderate CAD. The results revealed significant reductions in high-sensitivity hs-CRP and lipoprotein(a) levels, two key biomarkers associated with systemic inflammation and atherosclerotic risk. Notably, the degree of systemic inflammation was significantly improved post-intervention, suggesting that nano-curcumin may exert cardiovascular protective effects through anti-inflammatory and lipid-lowering mechanisms, potentially reducing the risk of adverse cardiovascular events [116]. Tehrani et al. conducted another randomized, double-blind, placebo-controlled trial to evaluate the impact of curcumin-piperine co-supplementation in patients undergoing coronary artery bypass grafting (CABG). Administration of curcumin (up to 1500 mg/day) combined with piperine over a 5-day postoperative period significantly reduced serum CRP levels ($P = 0.028$) and enhanced total antioxidant capacity ($P = 0.033$). Although levels of CK-MB showed a decreasing trend ($P = 0.077$), other cardiac biomarkers remained unchanged. These findings suggest that curcumin-piperine co-supplementation may offer postoperative benefits by attenuating inflammation and oxidative stress in CABG patients [117]. In patients with coronary slow flow phenomenon (CSFP), a microvascular form of CAD, Rezaei et al. evaluated the clinical efficacy of nano-curcumin (80 mg/day for 12 weeks) using the Seattle Angina Questionnaire (SAQ). The study demonstrated significant improvements across all SAQ domains, including physical limitation, angina stability and frequency, treatment satisfaction, and quality of life. These results indicate that nano-curcumin may help alleviate anginal symptoms and enhance overall cardiovascular health and patient-reported outcomes in individuals with CSFP [118].

Anticoagulant and antiplatelet effects of curcumin. Curcumin has been increasingly recognized for its anticoagulant and antiplatelet properties, which may contribute to its cardiovascular protective effects but also raise concerns regarding bleeding risk, particularly when used concurrently with anticoagulant or antiplatelet

therapies. In human studies, curcumin has been shown to inhibit the activity of coagulation factor Xa, resulting in a prolongation of prothrombin time and activated partial thromboplastin time [119]. In ex vivo human blood samples, curcumin treatment significantly reduced thromboxane B_2 production, indicating its potential to inhibit platelet aggregation [120]. Emerging nanomedicine research has further explored curcumin's role in thrombolytic therapy. Xu et al. developed a platelet membrane-coated curcumin nanoplatform (P-Cur-PFP@PC) for targeted anti-thrombotic and thrombolytic applications during pregnancy. This system incorporates curcumin and perfluoropentane (PFP) within a PLGA core and employs low-intensity focused ultrasound to trigger PFP phase transition and microbubble formation, thereby enhancing thrombolysis and ultrasound imaging. The platelet membrane coating confers biomimetic targeting to thrombi, while curcumin provides both anti-thrombotic and endothelial reparative effects. This approach minimizes systemic drug exposure and fetal risk, offering a novel strategy for safe and effective thrombolytic therapy in pregnancy [121]. However, clinical observations also highlight the potential risks of curcumin-related coagulopathy. Gronich et al. reported a case of spontaneous intramuscular hematoma and anemia in a 74-year-old male taking concurrent clopidogrel, apixaban, and high-dose curcumin (1 g/day). Laboratory tests showed mild thrombocytopenia and borderline elevated coagulation parameters, and imaging confirmed a large intramuscular hematoma. Mechanistically, curcumin may inhibit platelet function, delay clot formation by suppressing factor Xa and thrombin generation, and increase clopidogrel exposure via modulation of P-glycoprotein and cytochrome P450 enzymes such as CYP3A4. These findings underscore the importance of cautious evaluation of curcumin supplementation in patients receiving polypharmacy or drugs with narrow therapeutic windows, particularly anticoagulants and antiplatelet agents. Further clinical pharmacokinetic and pharmacodynamic studies are warranted to clarify the interaction profiles and safety implications of curcumin in anticoagulant regimens [122].

Collectively, accumulating evidence from in vitro, in vivo, and clinical studies underscores the multifactorial cardioprotective potential of curcumin. By targeting key pathological processes—such as endothelial dysfunction, oxidative stress, chronic inflammation, lipid dysregulation, and thrombotic events—curcumin acts on multiple levels of the cardiovascular system. Its regulatory actions involve a range of signaling pathways, including NF-κB, PI3K/Akt, Nrf2/HO-1, TLR4, and SIRT1, among others, which collectively contribute to the attenuation of vascular injury, myocardial remodeling, and atherogenesis. These pleiotropic properties render curcumin a compelling candidate for integrative cardiovascular therapy. For details on the protective and therapeutic effects of curcumin on the cardiovascular system, please see **Table 1**.

Table 1 Curcumin in Cardiovascular Health: From Protective Mechanisms to Clinical Therapy.

Protective and Therapeutic Effects	Type of Research Subject	Pharmacological Effects	Ref.
Anti-atherosclerotic Effects	Rat	Encapsulation of curcumin with gelatin and maltodextrin reduces LDL, triglycerides, atherosclerosis index, and increases HDL, improving atherosclerosis prevention.	[39]
	Rabbit	Intravenous curcumin improves lipid profiles and reduces atherosclerotic lesions in cholesterol-fed rabbits, with higher doses showing stronger effects.	[40]
	Mouse	Curcumin inhibits cholesterol accumulation in VSMCs by regulating the SREBP-1/caveolin-1 pathway, reducing atherosclerotic lesions.	[41]
	THP-1	Curcumin inhibits foam cell formation and inflammation by suppressing the TLR4/NF-κB/miR33a pathway, enhancing cholesterol efflux.	[42]
	Human	Nano-curcumin significantly reduces hs-CRP and lipoprotein(a) levels, improving inflammation and lipid metabolism in type 2 diabetes with coronary heart disease.	[43]
	HUVECs	Curcumin protects against oxidative stress in HUVECs by inhibiting the Notch1 pathway, improving cell vitality and reducing apoptosis.	[44]
	Rat	Curcumin alleviates hypertension and oxidative stress in rats exposed to Pb and Cd by enhancing eNOS expression and reducing ROS.	[45]
	EA.hy926	Curcumin and resveratrol synergistically protect against oxidative stress by activating the Nrf2-HO-1 pathway, enhancing cell viability.	[46]
	EA.hy926, Rat	Curcumin and baicalein synergistically protect diabetic vascular function by activating Nrf2 and MAPK/JNK pathways, improving endothelial health.	[47]
	Mouse	Curcumin inhibits VSMC proliferation and migration in atherosclerosis by blocking the chemerin/CMKLR1/LCN2 axis, delaying disease progression.	[48]
	RVSMCs	Hexahydrocurcumin protects cardiovascular health by inhibiting Ang II-induced VSMC proliferation, migration, inflammation, and ROS production via NOX and PPAR-γ.	[49]
	Mouse	Curcumin alleviates Cd-induced atherosclerosis by restoring gut microbiota balance, inhibiting TMAO synthesis, and reducing macrophage polarization.	[50]
	Mouse, Rabbit, Human, RAW 264.7, THP-1, VSMCs, A7r5, HUVECs	Curcumin modulates macrophage M1/M2 polarization, reducing pro-inflammatory cytokines and enhancing anti-inflammatory factors, aiding atherosclerosis prevention.	[51]
	RAW264. 7	Curcumin inhibits M1 macrophage polarization and pro-inflammatory factor expression by activating STAT6, alleviating	[52]

		atherosclerosis inflammation.	
	Mouse, HUVECs, MMFs	Curcumin prevents atherosclerosis by inhibiting HCMV activity in endothelial cells and modulating the HMGB1-TLRs-NF-κB pathway.	[53]
Prevention and Treatment of Myocardial Infarction	Rat	Curcumin nanoparticles offer superior cardioprotection compared to conventional curcumin, reducing myocardial damage, oxidative stress, and inflammation.	[54]
	Mouse	Curcumin attenuates myocardial infarction-induced inflammation and ventricular remodeling by reprogramming macrophages from M1 to M2 via AMPK activation.	[55]
	Mouse	Heart-targeted extracellular vesicles co-delivering curcumin and miR-144-3p enhance cardiac targeting and therapeutic efficacy in myocardial infarction models.	[56]
	Human	Curcumin plus piperine supplementation in AMI patients significantly reduces HbA1C, LDL, ALT, and ALP, while increasing HDL, without affecting cardiac function.	[57]
	Mouse	ExoCTP, a smart exosome system, enhances curcumin therapy in myocardial infarction by improving cardiac retention, reducing oxidative stress, and showing no toxicity.	[58]
	Mouse	Curcumin protects diabetic mice from myocardial infarction by activating CB2 receptors, improving hemodynamics, reducing inflammation, limiting damage.	[59]
Prevention and Treatment of Cardiac Hypertrophy and Heart Failure	Rat	Curcumin prevents hypertension-induced left ventricular hypertrophy by inhibiting p300 histone acetyltransferase, reducing wall thickness, fibrosis, and GATA4 acetylation.	[60]
	Rat, Human	ASD-Cur, an enhanced bioavailability curcumin formulation, provides comparable cardioprotection to Theracurmin® at a lower dose, improving cardiac function and reducing myocardial hypertrophy and fibrosis.	[61]
	Human	High-absorption curcumin reduces plasma BNP levels in early-stage hypertensive heart disease, potentially preventing cardiac stress without affecting diastolic function.	[62]
	Human	Nanocurcumin showed limited short-term efficacy in acute HFrEF management, with no significant changes in inflammation or renal function markers.	[63]
	Mouse	JM-2, a curcumin analog, improves cardiac function in diabetic cardiomyopathy by reducing inflammation, fibrosis, and macrophage infiltration through NF-κB inhibition.	[64]
	Rat	Curcumin attenuates cardiac hypertrophy and improves function in TAC rats by enhancing NCX and eNOS expression, with vascular effects via NCX regulation.	[65]
	Rabbit	Curcumin improves cardiac function in CHF by upregulating DKK-3 expression and inhibiting p38, JNK, and ASK1 signaling pathways.	[66]
Prevention and Treatment of Ischemia–Reperfusion (I/R) Injury	Human, Rat, Mouse, IPEC-J2, HEK 293	Curcumin protects organs from ischemia/reperfusion injury via antioxidant, anti-inflammatory, anti-apoptotic actions, modulating Nrf2 and SIRT1 pathways.	[67]
	Rat	Curcumin pre-treatment (60 mg/kg) protects against renal I/R injury by reducing serum Cr, BUN, oxidative stress, inflammation, and apoptosis in a dose-dependent manner.	[68]

	Rat, PC12	Curcumin alleviates spinal cord I/R injury by reducing oxidative stress, inhibiting M1 microglia, and suppressing neuroinflammation via the Nrf2/NF-κB axis.	[69]
	Olfactory mucosa-derived mesenchymal stem cells	Curcumin-pretreated olfactory mucosa-derived MSCs alleviate cerebral I/R injury by reducing neuronal PANoptosis and modulating microglial polarization via miR-423-5p-mediated NOD2/NF-κB/MAPK inhibition.	[70]
	PC12, Rat	Curcumin mitigates cerebral I/R injury by preserving blood-brain barrier integrity and reducing Ca^{2+} overload via the PKC-θ pathway.	[71]
	Mouse	Curcumin alleviates hepatic I/R injury by inhibiting neutrophil extracellular traps via MEK/ERK suppression, with enhanced effects when combined with DNase-1.	[72]
	Human, Rat, Mouse, Rabbit, PC12	Curcumin reduces infarct size and improves cardiac function in myocardial I/R injury through antioxidative, anti-inflammatory, anti-apoptotic, and anti-fibrotic mechanisms, with clinical data suggesting benefits in reducing myocardial infarction and MACE, especially at higher doses and longer durations.	[73]
	Rat, Mouse, PC12	Curcumin pretreatment protects against myocardial ischemia/reperfusion injury by inhibiting ferroptosis, autophagy, and apoptosis through HES1 upregulation, reducing oxidative stress, preserving mitochondrial function, and maintaining homeostasis.	[74]
	H9c2, Rat	Curcumin attenuates myocardial I/R injury by inhibiting autophagy-dependent ferroptosis via Sirt1/AKT/FoxO3a, preserving cardiomyocyte viability and function.	[75]
	Rat	Curcumin attenuates I/R injury in liver, pancreas, and heart by reducing oxidative stress, ferroptosis, restoring GPx4, and showing greater efficacy than LoxBlock-1.	[76]
Prevention and Treatment of Stroke	Mouse, Rat	Curcumin reduces stroke damage by enhancing bioavailability, inhibiting inflammation, boosting antioxidant activity, preventing neuronal apoptosis, and preserving BBB.	[77]
	Human	Curcumin-piperine supplementation lowers hs-CRP, cholesterol, CIMT, blood pressure, and weight, improving inflammatory and metabolic profiles in ischemic stroke patients.	[78]
	Rat	Triblock copolymer nanomicelles loaded with curcumin enhance brain bioavailability, reducing inflammation and lipid peroxidation in cerebral ischemia.	[79]
	Mouse, Rat, Rabbit, Monkey, PC12, SH-SY5Y, BMECs, HT-22, N2a, MBMECs	Curcumin protects against cerebral I/R injury through antioxidation, anti-inflammation, anti-apoptosis, BBB preservation, autophagy regulation, mitochondrial protection, and neurogenesis, though its clinical use is limited by low bioavailability.	[80]
	Rat	PAMAM dendrimer-encapsulated curcumin enhanced functional recovery, reduced GFAP expression, and modulated astrocyte reactivity in ischemic stroke models.	[81]

	Mouse, Rat, Rabbit, Monkey, PC12, SH-SY5Y, BMECs, HT-22, N2a, MBMECs, HUVECs	Curcumin exerts neuroprotection in ischemic stroke by modulating autophagy via PI3K/Akt/mTOR, Beclin-1, and AMPK pathways, reducing oxidative stress, inflammation, and apoptosis.	[82]
	Mouse	Curcumin alleviates early brain injury after SAH by activating Nrf2/HO-1, inhibiting ferroptosis, microglial NF-κB activation, and neuroinflammation.	[83]
	Mouse	Curcumin-loaded nanoparticles enhance brain delivery, inhibit ferroptosis via lysosomal, ER, and mitochondrial targeting, and ameliorate ICH-induced neurological deficits.	[84]
	Mouse	Intranasal curcumin nanoparticles reprogram microglia, suppress neuroinflammation, preserve BBB integrity, and enhance neurological recovery after ICH.	[85]
	Mouse	Curcumin attenuates ICH-induced neuronal apoptosis and neuroinflammation by inhibiting JAK1/STAT1 signaling and suppressing M1 microglial polarization.	[86]
	Mouse	Curcumin alleviates ICH-induced brain injury by modulating TLR4/NF-κB signaling, suppressing inflammation, and promoting M2 microglial polarization.	[87]
Lipid-Lowering Effect	Human	Curcumin (500 mg/day, 90 days) significantly lowered fasting glucose, triglycerides, and total cholesterol in Brazilian women with high waist circumference.	[88]
	Human	Nano-micelle curcumin supplementation (80 mg/day for 12 weeks) significantly reduced serum triglyceride levels in patients with metabolic syndrome.	[89]
	Rat, Mouse, Human, NTera-2, BRL-3A, M. alpina 1S-4, 3T3-L1	Curcumin regulates fatty acid metabolism by modulating FAS activity, β-oxidation, and desaturase systems, reducing FFAs and improving metabolic disorders.	[90]
	Human	Curcumin supplementation significantly improves lipid profiles by reducing TC, TG, LDL-C and increasing HDL-C, supporting its potential as a lipid-lowering adjunct.	[91]
	Human	Curcumin/turmeric supplementation significantly lowers TC, TG, LDL-C and raises HDL-C, as confirmed by a meta-analysis of 64 RCTs.	[92]
Anti-angiogenic Effect	HAECs	Curcumin and its metabolites (DMC, BisDMC) inhibit angiogenesis in HAECs by suppressing VEGF-induced VEGFR2 phosphorylation and ERK/Akt signaling.	[93]
	Human Pterygium Fibroblast	Curcumin dose-dependently inhibits VEGF expression in human pterygium fibroblasts, suggesting potential as adjunctive anti-angiogenic therapy.	[94]
	HUVECs.	Curcumin inhibits corneal neovascularization by upregulating miR-1275 and miR-1246, which suppress VEGFB and NKAP, reducing HUVEC proliferation.	[95]

	Rat, Mouse, Ovarian endometriotic stromal cells, HCT-116	Curcumin inhibits VEGF, HIF-1α, VEGFR2, and PDGF-βR, reducing angiogenesis and inflammation in endometriosis, suggesting its therapeutic potential.	[96]
	Rabbit	Curcumin-loaded porous gelatin scaffolds inhibit angiogenesis and osteogenesis, preserving BMSC-mediated cartilage formation in rabbit models.	[97]
	Rat	Curcumin–chitosan-catechol nanoparticles inhibit subchondral angiogenesis and cartilage degeneration via ROS-mediated NF-κB/PI3K-Akt signaling in OA models.	[98]
	Rat	Curcumin suppresses VEGF-induced angiogenesis by modulating VEGF, NF-κB, and angiogenic factors, underscoring its potential to treat diabetic complications.	[99]
	CAM model, Zebrafish model	Curcumin exhibits biphasic regulation of angiogenesis, promoting it at low concentrations and inhibiting it at high concentrations, in CAM and zebrafish models.	[100]
Prevention of Post-interventional Vascular Restenosis	HAECs, Rat, HVSMCs, HBVAFs	Curcumin-NO-loaded hydrogels reduce oxidative stress, inhibit vascular smooth muscle and fibroblast activation, and prevent restenosis post-angioplasty	[101]
	Rabbit VSMCs, Rabbit	Curcumin inhibits VSMC proliferation and neointimal hyperplasia, reducing oxidative stress and inflammation via Raf/MEK/ERK suppression after carotid endarterectomy.	[102]
	Rat, Mouse, Human, VSMCs, A7R5	Curcumin protects against hypertension and vascular remodeling by inhibiting VSMC proliferation, enhancing NO availability, and modulating oxidative stress.	[103]
	Rat, Mouse, Human, Rabbit	Curcumin nanocarriers reduce restenosis post-PCI by inhibiting VSMC proliferation, improving endothelial function, and reducing oxidative stress.	[104]
	VSMCs, Rat	Curcumin alleviates vascular calcification by regulating miR-92b-3p/KLF4 axis, reducing RUNX2 expression in VSMCs and aortic tissue.	[105]
	Human aortic VSMCs, Rat.	HO-3867 inhibits VSMC proliferation and restenosis by upregulating PTEN, inducing G1 arrest, apoptosis, and suppressing ERK1/2 and NF-κB.	[106]
	Mouse, HUVECs	Curcumin promotes venous thrombus resolution by downregulating miR-499, activating PTEN/VEGF/Ang-1 pathways, and enhancing angiogenesis.	[107]
Prevention and Treatment of Diabetic Cardiovascular Complications	Human	Curcumin reduces atherogenic risk, LDL-C, and inflammatory markers in obese type 2 diabetes patients, improving vascular health.	[108]
	INS-1, MIN6, HUVECs, J774.A1, THP-1, NRCMs, Rat, Mouse, Human	Curcumin improves insulin sensitivity, reduces inflammation, protects against foam cell formation, and prevents cardiac hypertrophy in diabetes.	[109]
Prevention and treatment of	RAW264.7, Human	Curcumin inhibits AAA progression by targeting EP300 to modulate macrophage polarization, reducing inflammation and promoting M2 anti-inflammatory phenotype.	[110]

aneurysms	Mouse, Human, RAW264.7, VSMCs	Curcumin nicotinate suppresses pyroptosis and inflammation in AAA by modulating PVT1/miR-26a/KLF4 axis and inhibiting PI3K/AKT signaling.	[111]
	Human, Rat	Curcumin reduces TAA progression by inhibiting VEGF-driven angiogenesis, inflammation, and inflammatory cell infiltration in aortic tissues.	[112]
	Rat	Curcumin reduces cerebral aneurysm progression by inhibiting apoptosis in VSMCs through downregulation of p53, caspase-3, and bax/bcl-2.	[113]
Prevention and treatment of peripheral artery disease	HUVECs, Rat, Mouse	Curcumin protects against PAD by reducing inflammation, oxidative stress, enhancing angiogenesis, and regulating AGE/RAGE pathways to improve endothelial function.	[114]
	Mouse	Curcumin reduces fibrosis, enhances muscle fiber density, and improves perfusion and capillary density in PAD models, including diabetic conditions.	[115]
Prevention and treatment of coronary heart disease	Human	Nanocurcumin (80 mg/day for 90 days) reduces hs-CRP and Lipo(a), improving inflammation and lipid profiles in diabetic CAD patients.	[116]
	Human	Curcumin-piperine supplementation reduces CRP, increases TAC, and offers anti-inflammatory and antioxidant benefits in CABG patients post-surgery.	[117]
	Human	Nanocurcumin (80 mg/day for 12 weeks) significantly improves angina, quality of life, and cardiovascular risk factors in CSFP patients.	[118]
Anticoagulant activity	Rat, Mouse, Human	Curcumin inhibits coagulation factor Xa, prolonging prothrombin time (PT) and activated partial thromboplastin time (aPTT) in humans.	[119]
	Rat, Mouse, Monkey, Human	Curcumin significantly reduces thromboxane B2 formation in blood samples, suggesting its potential to prevent platelet aggregation.	[120]
	Mouse, HUVECs	Platelet-coated curcumin nanomaterial promotes thrombolysis and vascular repair via ultrasound-triggered PFP transition, offering a safe thrombolytic strategy in pregnancy.	[121]
	Human	High-dose curcumin supplementation may enhance clopidogrel's effects, increase bleeding risk, and interact with coagulation and drug metabolism.	[122]

4.2 Protective and Therapeutic Effects of Curcumin on Nervous System

Neurodegenerative diseases represent a class of chronic, progressive disorders with high prevalence and mortality, primarily affecting the structure and function of the central nervous system. Among them, Alzheimer's disease and Parkinson's disease are the most common and widely studied. These disorders are characterized by the gradual loss of neuronal integrity and function, ultimately leading to cognitive decline, motor dysfunction, and significant impairments in quality of life [123].

4.2.1 Anti-Alzheimer's Disease Effects

Alzheimer's disease (AD) is the most prevalent form of dementia in the elderly, characterized by progressive cognitive decline, memory impairment, language deficits, and alterations in personality and behavior. The pathological hallmarks of AD include hippocampal atrophy, dysfunction of the cholinergic neurotransmitter system, extracellular accumulation of β-amyloid (Aβ) plaques, and hyperphosphorylation of tau protein, all of which contribute to neuronal degeneration and synaptic loss [124].

Curcumin exerts neuroprotective effects in Alzheimer's disease through multiple mechanisms, including promoting neurogenesis, inhibiting Aβ and tau pathology, regulating key signaling pathways, modulating insulin signaling, and improving cognitive function.

Promotion of neural stem cell regeneration. Sabouni et al. reviewed the beneficial effects of curcumin and its nanoformulations on neurodegenerative disorders, highlighting their ability to enhance stem cell-mediated regeneration by reducing inflammation, oxidative stress, and apoptosis, while improving curcumin's bioavailability and brain distribution [125]. Chen et al. demonstrated that curcumin activates the SDF-1/CXCR4 axis in neural stem cells, promoting proliferation, migration, and neurosphere formation via ERK, JNK, MAPK, NF-κB, and Akt signaling. These effects were suppressed by the CXCR4 antagonist AMD3100, confirming the pathway's central role [126]. Similarly, Lee et al. found that low-dose curcumin (0.4 mg/kg) enhanced hippocampal neurogenesis and memory retention in young mice, partly through BDNF and phosphorylated CREB upregulation, while higher doses were ineffective [127]. In an AD mouse model, Lou et al. showed that curcumin (100 mg/kg) enhanced hippocampal neurogenesis via Wnt/β-catenin and BDNF pathways, effects that were reversed by pathway inhibition, emphasizing its therapeutic potential in cognitive enhancement [128].

Inhibition of Aβ deposition and tau phosphorylation. Sivanantharajah and Mudher emphasized the need to focus on tau pathology in AD therapy and highlighted curcumin's promise in modulating tau aggregation and phosphorylation [129]. Li et al. reported that curcumin inhibits Aβ-induced tau hyperphosphorylation through the PTEN/Akt/GSK-3β pathway and reduces CDK5 expression, preventing tau aggregation and nuclear transport deficits. Moreover, curcumin interferes with β-amyloid fibril formation, reduces Aβ deposition, restores dendritic architecture, and alleviates neuroinflammation in vivo [130].

Modulation of key signaling pathways. Pan et al. outlined curcumin's ability to attenuate Aβ aggregation and tau pathology through PI3K/Akt/GSK3β signaling, while also exerting antioxidant and anti-inflammatory effects. Despite its limited bioavailability, advanced delivery strategies such as liposomal and

nano-formulations have improved its therapeutic potential [131]. In a mouse model of AD, Shao et al. found that curcumin (150 mg/kg/day) reduced Aβ deposition, neuronal apoptosis, and inflammation while activating AMPK signaling and increasing antioxidant enzyme levels [132]. Ege further summarized curcumin's modulation of Wnt/β-catenin, Notch, PI3K/Akt/mTOR, and ROS/JNK pathways, and reviewed nanocarrier strategies (e.g., liposomes, PLGA, micelles) coupled with targeting ligands (e.g., transferrin, lactoferrin, Tet-1 peptide, chitosan) to enhance brain-specific delivery [133].

Regulation of insulin-like growth factor signaling. Das et al. reported that curcumin restores impaired insulin signaling in AD rats by upregulating IR-β, IGF-1, IRS-1/2, Akt, and glucose transporters GLUT3/GLUT4, leading to improved brain insulin sensitivity and glucose metabolism [134]. Uprety et al. evaluated curcumin in aging rhesus monkeys and found that daily supplementation (500 mg for 18 months) improved cognitive performance and enhanced microglial surveillance morphology in frontal white matter, although inflammatory markers were not significantly altered [135]. Chang et al. showed that curcumin reversed dendritic spine loss and hyperexcitability of prefrontal cortex neurons, improving working memory in middle-aged monkeys, suggesting its utility in age-related cognitive decline [136]. Liu et al. demonstrated that curcumin restores neuronal metabolic function by activating the Thrb/SIRT3 axis, increasing NAD^+/NADH ratio, ATP levels, and cognitive function in Aβ42-treated models [137]. Finally, a meta-analysis by Tsai et al. (n = 389) concluded that curcumin significantly improves working memory (Hedges' g = 0.396, p = 0.015), though effects on other cognitive domains were limited. Notably, gastrointestinal adverse events were more common in curcumin users (OR = 3.019, p = 0.029), warranting further safety evaluation [138].

4.2.2 Anti-Parkinson's Disease (PD) Effects

Parkinson's disease (PD) is a common neurodegenerative disorder of the central nervous system, clinically characterized by resting tremor, muscle rigidity, postural and gait disturbances, and bradykinesia. The core pathological hallmark of PD is the progressive degeneration and loss of dopaminergic neurons in the substantia nigra of the midbrain [139].

Emerging evidence indicates that curcumin, a natural polyphenolic compound derived from *Curcuma longa*, exerts multifaceted neuroprotective effects in Parkinson's disease. These effects are mediated through its potent antioxidant and anti-inflammatory properties, modulation of neurotoxic metabolic pathways, improvement of dopaminergic neuron function, regulation of the gut-brain axis, and interaction with key molecular signaling networks.

Antioxidant and Anti-inflammatory Effects. Curcumin protects dopaminergic neurons against oxidative and inflammatory insults. Nebrisi reviewed the neuroprotective actions of curcumin in PD, highlighting its broad pharmacological activities including antioxidation, anti-inflammation, free radical scavenging, mitochondrial protection, and iron chelation. Although levodopa remains the mainstay of symptomatic PD treatment, its long-term use is often associated with motor complications. Curcumin, as a natural polyphenol derived from turmeric, has been proposed as a complementary therapeutic candidate. Notably, it may activate

α7 nicotinic acetylcholine receptors and modulate the cholinergic anti-inflammatory pathway to exert immunomodulatory and neuroprotective effects [140].

Inhibition of Toxic Metabolites. Rajeswari and Sabesan demonstrated that curcumin and its metabolite tetrahydrocurcumin (ThC) mitigate neurotoxicity in MPTP-induced PD models by inhibiting monoamine oxidase-B (MAO-B) activity and restoring dopamine (DA) and DOPAC levels. High-performance liquid chromatography and fluorescence-based assays revealed that intraperitoneal administration of curcumin (80 mg/kg) or ThC (60 mg/kg) significantly reversed MPTP-induced DA depletion and MAO-B activation, underscoring the role of MAO-B inhibition in their neuroprotective mechanism [141].

Enhancement of Neuronal Function. El-Shamarka et al. investigated the combined neuroprotective effects of curcumin, levodopa, and rasagiline in rotenone-induced PD mice. Their findings showed that curcumin significantly alleviated oxidative stress, reduced DNA fragmentation, and improved behavioral outcomes, with combination therapy exhibiting synergistic effects. Histological analyses confirmed the attenuation of neurodegeneration in the substantia nigra, cortex, and hippocampus [142]. Liu et al. further evaluated dose- and time-dependent effects of curcumin in 6-OHDA-induced PD rats, identifying 160 mg/kg/day for two weeks as the optimal regimen for improving motor performance and preserving dopaminergic neurons in the substantia nigra pars compacta [143].

Neuroprotection in the Cerebellum. Fikry et al. explored the cerebellar protective role of curcumin in rotenone-induced PD rats, a less-studied but relevant aspect of PD pathology. Curcumin treatment reversed Purkinje cell degeneration, reduced gliosis, normalized oxidative stress markers, and improved motor coordination [144]. These findings support its therapeutic potential in cerebellum-associated PD symptoms.

Regulation of Gut Microbiota and Metabolites. Cui et al. revealed that curcumin exerts neuroprotection in PD partly via remodeling the gut microbiota–metabolite axis. In MPTP-induced mice, curcumin not only improved motor function and reduced α-synuclein aggregation but also reshaped microbial composition by increasing beneficial taxa such as Lactobacillaceae and Lachnospiraceae. Metabolomic profiling indicated elevations in tyrosine, methionine, creatine, and creatinine, correlating with microbial changes and brain dopamine metabolism [145].

Suppression of Gut Inflammation via the Gut–Brain Axis. Zhong et al. demonstrated that curcumin ameliorates MPTP-induced PD by attenuating gut inflammation and restoring gastrointestinal function. Curcumin reduced pyroptosis-related markers (AIM2, caspase-1) and inflammatory cytokines, while activating SIRT1/NRF2 signaling in intestinal tissue. These findings underscore the therapeutic promise of targeting gut-derived inflammation in PD management [146].

Modulation of Signaling Pathways. Jin et al. summarized evidence that curcumin activates the BDNF/PI3K/Akt axis, enhancing neuronal survival and suppressing apoptosis in PD models. This neurotrophic signaling plays a pivotal role in dopaminergic neuron regeneration and anti-apoptotic defense [147]. Rathore et al. provided further mechanistic insight, showing that curcumin activates the p62–Keap1–Nrf2 pathway to promote autophagy and reduce α-synuclein aggregation in rotenone-induced

PD. Curcumin restored LC3-II expression, suppressed apoptotic markers (Bax, caspase-3), and enhanced Nrf2-mediated antioxidative responses [148].

Anti-inflammatory Signaling Regulation. Esmaealzadeh et al. highlighted curcumin's ability to inhibit NF-κB activation, thereby reducing the expression of proinflammatory cytokines. Given NF-κB's central role in neuroinflammation across neurodegenerative diseases, including PD, curcumin's modulation of this pathway represents a key mechanism for mitigating neuronal damage [149].

Membrane Stabilization and Protection. Darbinyan et al. reported that curcumin restores the activity of NADPH-dependent superoxide-generating complexes (NLP-Nox) in rotenone-induced PD rats. Curcumin administration (200 mg/kg, i.p. for 63 days) significantly recovered the content and redox capacity of these membrane-associated isoforms, highlighting a novel mechanism by which curcumin stabilizes membrane structures and mitigates oxidative injury [150].

Regulation of Unfolded Protein Response (UPR). Mukherjee et al. discussed curcumin's role in modulating the UPR, a critical pathway in maintaining protein homeostasis. Dysregulation of UPR contributes to ER stress, inflammation, and misfolded protein accumulation in PD and other neurodegenerative conditions. Curcumin was shown to alleviate UPR imbalance, thereby reducing neuronal stress and delaying disease progression [151].

4.2.3 Antiepileptic Effects

Epilepsy is a chronic neurological disorder characterized by sudden, excessive, and abnormal neuronal discharges in the brain, often accompanied by cognitive impairments such as memory decline [152]. Curcumin has demonstrated anticonvulsant and antiepileptic potential, primarily through its multifaceted neuroprotective mechanisms.

Growing evidence supports the antiepileptic potential of curcumin, which exerts protective effects through a range of mechanisms, including anti-inflammatory, antioxidant, and neuroregulatory pathways. These actions collectively contribute to the suppression of seizure onset, reduction in neuronal hyperexcitability, and attenuation of epileptogenesis.

Antioxidant and anti-inflammatory effects. Curcumin mitigates neuronal injury caused by seizures through its antioxidant and anti-inflammatory properties [153].

Neurotransmitter modulation. It helps restore the balance of excitatory and inhibitory neurotransmission, thereby reducing neuronal hyperexcitability [154].

Suppression of proinflammatory mediators. Curcumin downregulates inflammatory cytokines such as TNF-α, IL-6, and NF-κB, contributing to reduced neuroinflammation [155].

Choo and Shaikh conducted a systematic review on *Curcuma longa* and its active compounds in seizure management, emphasizing the antiepileptic effects of curcumin, turmeric oil, and its sesquiterpenes. Proposed mechanisms include corticosterone modulation, enhancement of GABAergic neurotransmission, regulation of sodium channels, reduction of oxidative DNA damage and lipid peroxidation, and upregulation of BDNF [156]. The review also evaluated effective doses in animal studies and extrapolated equivalent human dosages, underscoring the therapeutic promise of *Curcuma longa*–derived agents in epilepsy. Drion et al.

evaluated the anti-epileptogenic and neuroprotective effects of intraventricular curcumin in a rapid kindling model of temporal lobe epilepsy in rats. Curcumin administration for five consecutive days significantly delayed seizure progression, as evidenced by an increased number of stimuli required to reach Racine stage IV seizures [157]. Similarly, Fang et al. reported that curcumin, alone or in combination with oxcarbazepine, alleviated kainic acid-induced epilepsy in juvenile rats by inhibiting the TLR4/MyD88/NF-κB pathway, extending seizure latency, reducing status epilepticus incidence, and protecting hippocampal neurons. Curcumin also reduced astrogliosis and downregulated the expression of TLR4-related proinflammatory genes and proteins, suggesting a synergistic potential in combination therapy. In a pilocarpine-induced epilepsy model, curcumin was shown to prolong latency to seizure onset and reduce seizure frequency. These effects were associated with downregulation of spinal cord markers such as p-CREB, p-ERK, and c-Fos [158]. Moezi Leila et al. demonstrated that bovine serum albumin (BSA)-based nano-curcumin (50 and 100 mg/kg) significantly increased seizure threshold and latency in a PTZ-induced epilepsy model in mice. Notably, its efficacy surpassed that of native curcumin, although it did not modulate hippocampal JNK phosphorylation, suggesting a JNK-independent mechanism [159]. Mina Erfani et al. conducted a double-blind, randomized crossover trial to evaluate the efficacy of nanomicelle-formulated curcumin in children with intractable epilepsy. A daily dose of 4 mg/kg for 4 weeks significantly reduced the mean seizure frequency from 68.76 to 39.85 ($P = 0.01$), supporting its clinical utility in reducing refractory seizure burden [160]. These findings indicate that curcumin may serve as an effective adjunct to conventional antiepileptic drugs, potentially reducing required dosages, minimizing side effects, and improving therapeutic outcomes.

4.2.4 Antidepressant Effects

Depression is a common psychiatric disorder characterized by persistent low mood, anhedonia, and cognitive dysfunction, often accompanied by disturbances in appetite, sleep, and behavior [161]. Extensive research has demonstrated that curcumin not only regulates neurotransmitter systems and neuroinflammatory signaling but also mitigates oxidative stress, enhances neuroplasticity, stabilizes hypothalamic-pituitary-adrenal (HPA) axis function, and provides neuroprotective and immunomodulatory benefits. These pleiotropic effects support its potential as an adjunctive or standalone therapy for depression, particularly in inflammation-related or treatment-resistant subtypes. Lopresti et al. underscored curcumin's ability to modulate monoaminergic transmission, counteract inflammation and oxidative damage, and correct HPA axis dysregulation, highlighting its clinical relevance in major depressive disorder management [162].

Regulation of neurotransmitters. Curcumin has been shown to elevate levels of serotonin (5-HT), norepinephrine (NA), and dopamine (DA) in the hippocampus and frontal cortex, while decreasing their turnover, thereby improving mood-related neurochemical balance [163].

Modulation of genes, signaling pathways, miRNAs, and transcription factors. Nguyen and Kim employed toxicogenomics and network pharmacology to identify that curcumin targets key genes such as BDNF, IL6, GSK3B, NR3C1, and PTGS2, and modulates pathways related to neuroinflammation, glutamatergic transmission, apoptosis, protein phosphorylation, and folate metabolism. Moreover, curcumin was predicted to interact with 74 depression-associated miRNAs (notably hsa-miR-146a-5p) and transcription

factors such as PLSCR1, ATF3, and GTF2B, demonstrating favorable gastrointestinal absorption and central nervous system permeability, supporting its pharmacological potential in depression therapy [164].

Activation of neuroprotective signaling. Guo et al. showed through pharmacological and animal experiments that curcumin alleviates lipopolysaccharide (LPS)-induced depressive-like behavior by activating the PI3K-Akt pathway. The antidepressant effect was associated with reduced neuroinflammation and improved neuronal integrity in the prefrontal cortex. Administration of the PI3K-Akt inhibitor LY294002 abolished curcumin's effect, confirming the critical involvement of this signaling axis [165].

Multifactorial regulation. Ramaholimihaso et al. summarized that curcumin exerts antidepressant effects by regulating monoamine neurotransmitters (5-HT, DA, NE), inhibiting glutamate excitotoxicity, suppressing inflammatory mediators (e.g., TNF-α, IL-1β, IL-6), and modulating the NLRP3 inflammasome. It also improves HPA axis function, enhances insulin sensitivity, activates ERK/BDNF signaling to promote neuroplasticity, and repairs intestinal barrier dysfunction. These effects collectively position curcumin as a promising adjunctive agent for depression, particularly in patients with inflammation-associated subtypes [166].

Interaction with serotonin receptors. Wang et al. demonstrated that curcumin's antidepressant-like effects in a forced swimming test are mediated by serotonergic mechanisms involving 5-HT_{1A}, 5-HT_{1B}, and 5-HT_{2C} receptors. Blockade or depletion of these receptors inhibited curcumin's efficacy, while co-administration of specific agonists enhanced its behavioral effects, suggesting that curcumin may exert part of its action via modulation of serotonin receptor subtypes [167].

4.2.5 Anti-Aging Effects of Curcumin on the Nervous System

Recent studies have increasingly demonstrated that curcumin possesses anti-neuroaging properties by targeting key molecular pathways involved in neuronal survival, oxidative defense, and cellular homeostasis. Through the regulation of oxidative stress responses, inflammatory signaling, autophagy, and neuroprotective cascades, curcumin contributes to the maintenance of neural function and delays age-associated neurodegeneration. The following evidence highlights its mechanisms of action in mitigating neural aging.

PI3K/Akt/GSK-3β signaling pathway. Beltagy et al. demonstrated that nanocurcumin, either alone or in combination with donepezil, significantly attenuated Alzheimer's-like pathology in rats. This neuroprotective effect was mediated through activation of the PI3K/Akt/GSK-3β signaling pathway, leading to improvements in memory and neuronal function, and reductions in oxidative stress, neuroinflammation, Tau hyperphosphorylation, and BACE-1 expression [168].

Nrf2/HO-1 signaling pathway. Elsayed et al. found that curcumin markedly ameliorated streptozotocin-induced diabetic spinal cord neuropathy in rats [169]. The protective effects were attributed to inhibition of neuronal apoptosis and glial activation via upregulation of the Nrf2/HO-1 axis and suppression of NF-κB signaling.

TLR4/NF-κB signaling pathway and related targets. Nguyen et al. reported that curcumin alleviated 1,2-diacetylbenzene-induced neuroinflammation and cognitive impairment in microglial cells by suppressing the TREM-1/DAP12/NLRP3/caspase-1/IL-1β and TLR4/NF-κB pathways [170]. This was accompanied by

reductions in ROS, AGE accumulation, Tau hyperphosphorylation, and GSK-3β activity, as well as activation of the Nrf2 pathway. In silico analysis identified associated genes, transcription factors, and miRNAs underlying curcumin's neuroprotective effects.

Multi-pathway regulation. Joshi et al. reviewed the broad-spectrum neuroprotective actions of curcumin and its analogues across central nervous system disorders. These include modulation of diverse molecular targets such as NF-κB, Nrf2-ARE, SOCS/JAK/STAT, PI3K/Akt, MAPK (ERK1/2, JNK, p38), iNOS/NO, MMPs, and apoptosis-associated pathways, collectively contributing to reductions in oxidative stress, neuroinflammation, and mitochondrial dysfunction [171].

Autophagy modulation. Forouzanfar et al. highlighted the role of curcumin in regulating autophagy, a critical cellular process for maintaining neuronal homeostasis. By enhancing autophagic flux, curcumin exerts protective effects in various neurodegenerative conditions, including Alzheimer's disease, Parkinson's disease, ischemic stroke, traumatic brain injury, and Alexander disease [172].

4.2.6 Other Neurological Disorders

Curcumin has demonstrated neuroprotective potential in a variety of neurological disorders beyond Alzheimer's and Parkinson's disease. Through its anti-inflammatory, antioxidant, and neuro-modulatory properties, curcumin exerts therapeutic effects in neuropathic pain, metal-induced neurotoxicity, and diabetic neuropathy, among others.

Neuropathic Pain. Uddin et al. summarized that curcumin exhibits analgesic and anti-inflammatory effects via multi-target mechanisms, including inhibition of pro-inflammatory mediators, oxidative stress, COX-2, JAK2/STAT3, JNK/MAPK, and ERK/CREB pathways. Moreover, it modulates TRP channels, CaMKIIα, mGlu2, and monoaminergic and opioid systems, underscoring its potential as a broad-spectrum agent for pain and inflammation management [173]. Zhang et al. demonstrated that curcumin alleviates oxaliplatin-induced peripheral neuropathy by suppressing oxidative stress-mediated NF-κB activation, downregulating TNF-α, IL-1β, and IL-6, and enhancing antioxidant enzymes such as SOD, GSH-Px, and CAT, thereby improving nerve conduction and preserving neuronal integrity [174]. Similarly, Limcharoen et al. found that curcumin diethyl diglutarate, a curcumin prodrug, exhibited enhanced anti-allodynic, anti-hyperalgesic, and anti-inflammatory effects in a chronic constriction injury (CCI) model, notably reducing TNF-α, IL-6, COX-2, iNOS, and phosphorylated MAPKs, thus improving both bioavailability and therapeutic efficacy [175]. Huang et al. further reported that curcumin ameliorates CCI-induced neuropathic pain by promoting M2 microglial polarization, suppressing astrocyte activation, reducing proinflammatory cytokines, and enhancing anti-inflammatory signaling in the cuneate nucleus [176].

Expanding on this, Hasriadi et al. reviewed that curcumin attenuates chronic pain primarily by inhibiting microglial and astrocytic activation within the spinal cord. It reduces pro-inflammatory mediators (TNF-α, IL-1β, IL-6, COX-2, iNOS, PGE2) and enhances anti-inflammatory cytokines (IL-10, IL-4, PPAR-α), acting through suppression of MAPK (ERK, JNK, p38), NF-κB, and JAK/STAT pathways. Curcumin also downregulates upstream receptors such as TLR4, TNFR1, and CX3CR1, modulates epigenetic regulators

(e.g., p300/CBP), and inhibits inflammasomes (e.g., NLRP3, caspase-1), thereby reducing pain transmission [177].

Diabetic Neuropathy. In the context of diabetic neuropathic pain, Park et al. demonstrated that curcumin improved sensory responses and reduced pJNK activation in both neurons and astrocytes of the dorsal root ganglion in diabetic rats, indicating its therapeutic effect via JNK pathway modulation [178]. Aydın and Nazıroğlu showed that curcumin alleviates diabetic neuropathy in mice by inhibiting the TRPM7 channel, leading to reduced calcium influx, oxidative stress (mitSOX, ROS), and apoptosis (caspase-3/8/9) in dorsal root ganglion neurons, highlighting TRPM7 downregulation as a key mechanism of neuroprotection [179].

Heavy Metal-Induced Neurotoxicity. Curcumin has also been investigated for its protective role against heavy metal neurotoxicity. Smirnova et al. reviewed that curcumin mitigates metal-induced toxicity primarily through antioxidant and metal-chelating activities. By scavenging ROS, suppressing lipid peroxidation, and forming stable chelates with toxic metals such as Al^{3+}, Cd^{2+}, Hg^{2+}, and Fe^{3+}, curcumin attenuates oxidative damage, inflammation, and apoptosis in the brain and peripheral organs. It also activates Nrf2/ARE signaling and downregulates inflammatory mediators such as NF-κB and TNF-α [180]. In a copper sulfate-induced neurotoxicity model, Sarawi et al. found that both native curcumin (CUR) and nano-curcumin (N-CUR) reduced MDA, NF-κB p65, TNF-α, and IL-6 levels, restored antioxidant defenses (GSH, SOD, CAT), inhibited apoptotic markers (BAX, caspase-3, p53), and upregulated BCL-2 and DNA integrity. Notably, N-CUR displayed superior neuroprotective efficacy, likely due to enhanced bioavailability [181].

Arsenic neurotoxicity. Bahrami et al. highlighted that arsenic exposure induces significant neurotoxicity through mechanisms involving oxidative stress, inflammation, mitochondrial dysfunction, and neuronal apoptosis. Curcumin, a natural polyphenolic compound with potent antioxidant properties, has been shown in multiple in vitro and in vivo studies to effectively mitigate arsenic-induced neurotoxic damage. It exerts its protective effects primarily by scavenging excessive ROS, enhancing the activity of endogenous antioxidant enzymes such as SOD and GSH-Px, and thereby reducing lipid peroxidation and oxidative DNA damage, ultimately preserving neuronal viability. In addition, curcumin suppresses the activation of pro-inflammatory signaling pathways including NF-κB, JNK, and p38 MAPK, leading to decreased expression of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6, and alleviating neuroinflammation. Curcumin also modulates apoptotic pathways by regulating the Bcl-2/Bax ratio, inhibiting cytochrome c release, and suppressing caspase-3 activation, thus preventing neuronal apoptosis. Behavioral studies further demonstrate that curcumin reverses arsenic-induced anxiety- and depression-like behaviors, potentially by modulating acetylcholinesterase activity, neurotransmitter balance, and the overactivation of the HPA axis. Moreover, curcumin contributes to the maintenance of mitochondrial membrane potential and promotes ATP production, supporting the recovery of impaired neuronal energy metabolism. Collectively, these findings suggest that curcumin confers neuroprotection against arsenic toxicity through a multi-targeted and multi-mechanistic approach [182]. Details on the protective and therapeutic effects of curcumin on the nervous system are provided in **Table 2**.

Table 2 Neuroprotective Potential of Curcumin: Mechanistic Insights and Therapeutic Applications.

Protective and Therapeutic Effects	Type of Research Subject	Pharmacological Effects	Ref.
Anti-Alzheimer's Effects	Rat, Mouse, Human, iPSCs, ESCs, MSCs	Curcumin and its nanoformulations enhance neural stem cell regeneration by reducing inflammation, oxidative stress, and apoptosis in neurodegenerative diseases.	[125]
	Rat	Curcumin promotes NSC proliferation and migration via SDF-1/CXCR4 axis activation, enhancing neurogenesis through ERK, JNK, and Akt pathways.	[126]
	Mouse	Low-dose curcumin enhances hippocampal neurogenesis, memory retention, and cognitive function by increasing BDNF and phosphorylated CREB levels.	[127]
	Mouse	Curcumin enhances neurogenesis in AD mice via Wnt/β-catenin and BDNF pathways, improving hippocampal function and cognitive abilities.	[128]
	Nematode, Mouse, HUVECs, Human	Curcumin shows promise in treating AD by targeting tau pathology, with potential for improved treatment through optimized delivery systems.	[129]
	Mouse, Human, SH-SY5Y, Neurons from APPswe/PS1 transgenic mice	Curcumin prevents tau hyperphosphorylation and amyloid deposition in AD by modulating PTEN/Akt/GSK-3β, CDK5, and β-amyloid fibril formation.	[130]
	Mouse, Drosophila, Rat, SH-SY5Y, PC12, N2a/APP, HT22	The PI3K/Akt pathway modulates GSK3 to prevent tau hyperphosphorylation and Aβ deposition, offering potential AD treatment strategies.	[131]
	Mouse	Curcumin improves cognitive function in AD by reducing Aβ deposition, inflammation, oxidative stress, and activating AMPK signaling.	[132]
	Rat, Mouse, Human, SH-SY5Y, PC12, HT22, BV2	Curcumin targets multiple AD pathways (Wnt/β-catenin, PI3K/Akt) but faces brain delivery challenges, improved by nanoparticle-based strategies.	[133]
	Rat	Curcumin improves insulin signaling and glucose metabolism in AD rats by upregulating insulin proteins and glucose transporters.	[134]
	Monkey	Curcumin improves cognitive function and microglial morphology in aging monkeys, potentially enhancing white matter health and delaying cognitive aging.	[135]
	Monkey	Curcumin improves working memory and partially reverses neuron hyperexcitability in middle-aged monkeys, suggesting potential for delaying memory decline.	[136]
	Mouse	Curcumin alleviates Aβ-induced metabolic dysfunction and improves cognition in AD mice via the Thrb/SIRT3 axis, enhancing cell vitality.	[137]
	Human	Curcumin improves working memory and processing speed, with selective cognitive benefits, but has higher gastrointestinal adverse events.	[138]
Anti-Parkinsonian effect	Mouse, Human, SH-SY5Y	Curcumin offers neuroprotection in Parkinson's by reducing inflammation, oxidative stress, and activating α7-nicotinic acetylcholine receptors for immune modulation.	[140]
	Mouse	Curcumin and its metabolite, tetrahydrocurcumin, protect against MPTP neurotoxicity by inhibiting MAO-B, reversing dopamine and DOPAC reduction.	[141]
	Mouse	Curcumin enhances the neuroprotective effects of L-dopa and rasagiline in rotenone-induced PD by improving oxidative stress and neurodegeneration.	[142]
	Mouse	Curcumin (160 mg/kg/day for 2 weeks) significantly improves motor function and protects	[143]

		dopaminergic neurons in 6-OHDA-induced PD.	
	Rat	Curcumin protects the cerebellum in rotenone-induced PD by reducing oxidative stress and improving Purkinje cell morphology and motor function.	[144]
	Mouse	Curcumin improves PD symptoms by modulating gut microbiota and metabolites, enhancing key metabolites and regulating microbial abundances in MPTP mice.	[145]
	Mouse	Curcumin protects against PD by inhibiting intestinal inflammation via the gut-brain axis, enhancing gut barrier and SIRT1/NRF2 signaling.	[146]
	Rat, Mouse, Human, BV2	Curcumin promotes neuronal survival and delays PD progression by activating the BDNF/PI3k/Akt signaling pathway, offering neuroprotective potential.	[147]
	Mouse	Curcumin activates the p62–Keap1–Nrf2 pathway, promoting autophagy and antioxidation, reducing α-syn aggregation and neuronal apoptosis in PD.	[148]
	Rat, Mouse, Human, BV2	Curcumin reduces neuroinflammation by inhibiting NF-κB activation and translocation, lowering inflammatory cytokine levels in neurodegenerative diseases.	[149]
	Rat	Curcumin stabilizes membranes and restores NADPH complex function, reducing oxidative damage in rotenone-induced Parkinson's disease models.	[150]
	Rat, Mouse, HT22, SH-SY5Y, MC65, GSCs	Curcumin modulates the unfolded protein response (UPR), alleviating ER stress and oxidative damage to protect against neurodegenerative diseases.	[151]
Antiepileptic effect	Rat, Mouse, Xenopus laevis, Human, SH-SY5Y, NSC-34	Curcumin modulates oxidative stress, apoptosis, inflammation, and epigenetic changes in epilepsy, with nanocarriers improving its brain bioavailability.	[153]
	Rat, Mouse	Curcumin exhibits antiepileptic effects by reducing seizures, alleviating memory impairment, and modulating monoamine levels in the brain.	[154]
	Rat	Curcumin, especially combined with exercise, modulates TNFα, IL-6, IL-10, and NFκB expression, reducing neuroinflammation in epilepsy.	[155]
	Rat, Mouse, Zebrafish, HEK293	Curcumin and turmerones exert antiepileptic effects by modulating GABA signaling, sodium channels, oxidative stress, corticosterone, and BDNF levels.	[156]
	Rat	Intracerebral curcumin injection delays seizure progression and exerts short-term anti-epileptogenic effects in a rapid kindling TLE model.	[157]
	Rat	Curcumin reduces neuroinflammation via TLR4/MyD88/NF-κB inhibition, enhancing anticonvulsant effects and protecting hippocampal neurons in epilepsy models.	[158]
	Mouse	Nanocurcumin (50–100 mg/kg) enhances seizure threshold and latency in PTZ-induced epilepsy, with increased efficacy over natural curcumin.	[159]
	Human	Nanomicelle curcumin (4 mg/kg) significantly reduces seizure frequency in children with refractory epilepsy, showing promising therapeutic potential.	[160]
Antidepressant effect	Rat, Mouse, Rabbit, Human, BMDCs	Curcumin exerts antidepressant effects by modulating inflammation, neurotransmitters, oxidative stress, HPA axis, neurogenesis, mitochondrial function, and gut-brain axis.	[162]
	Rat, Mouse, Human	Curcumin improves depressive symptoms by increasing 5-HT, NA, and DA levels in the hippocampus and prefrontal cortex, reducing their metabolism.	[163]
	Genes, transcription factors, and miRNAs associated with depression and curcumin, obtained from CTD, GeneMANIA, STRING, Metascape, CHEA3, and MIENTURNET databases	Curcumin exerts antidepressant effects by regulating key genes (e.g., BDNF, IL6), signaling pathways, miRNAs (e.g., hsa-miR-146a-5p), and transcription factors like PLSCR1 and ATF3.	[164]

	Mouse; Genes, transcription factors, and miRNAs associated with depression and curcumin, obtained from CTD, GeneMANIA, STRING, Metascape, CHEA3, and MIENTURNET databases	Curcumin alleviates LPS-induced depression-like behavior by regulating PI3K-Akt signaling, inhibiting neuroinflammation, and protecting prefrontal cortical neurons.	[165]
	Rat, Mouse, Pig, Human	Curcumin exerts antidepressant effects by modulating neurotransmitters, inflammation, HPA axis, ERK/BDNF pathway, oxidative stress, and gut barrier integrity.	[166]
	Mouse	Curcumin alleviates depression and anxiety in chronic pain by modulating 5-HT_{1A}, 5-HT_{1B}, and 5-HT_{2C} receptors in the serotonergic system.	[167]
Anti-neuroaging	Rat	Nanocurcumin improves memory and neuronal function via PI3K/AKT/GSK-3β pathway activation, while reducing oxidative stress, inflammation, Tau, and BACE-1.	[168]
	Rat	Curcumin alleviates diabetic spinal cord neuropathy by inhibiting apoptosis and glial activation via Nrf2/HO-1 upregulation and NF-κB inhibition.	[169]
	Microglial cells; Genes, transcription factors, and miRNAs associated with depression and curcumin, obtained from CTD, GeneMANIA, STRING, Metascape, CHEA3, and MIENTURNET databases	Curcumin alleviates neuroinflammation and cognitive impairment by inhibiting TLR4/NF-κB and TREM-1/NLRP3 pathways and activating Nrf2 signaling.	[170]
	Rat, Mouse, Human, BV2, N9, C6, U373MG, PC12, SH-SY5Y, NSC34, MSCs, HEK293, HUVECs, BMECs	Curcumin protects the central nervous system by modulating NF-κB, Nrf2-ARE, JAK/STAT, PI3K/Akt, MAPK, iNOS/NO, and apoptosis pathways.	[171]
	Rat, Mouse, HT-22, SH-SY5Y	Curcumin exerts neuroprotection by regulating autophagy, contributing to therapy for Alzheimer's, Parkinson's, stroke, brain injury, and Alexander disease.	[172]
Therapeutic effect on neuropathic pain	Rat, Mouse, HK-2, SH-SY5Y, PBMCs	Curcumin alleviates pain and inflammation via multi-target mechanisms, modulating inflammatory pathways, oxidative stress, TRP channels, and neurotransmitter systems.	[173]
	Rat	Curcumin alleviates oxaliplatin-induced neuropathic pain by inhibiting oxidative stress/NF-κB signaling and enhancing antioxidant defenses and neuronal function.	[174]
	Mouse	Curcumin diethyl diglutarate improves bioavailability and alleviates CCI-induced pain by suppressing inflammation, cytokines, COX-2, iNOS, and MAPK pathways.	[175]
	Rat	Curcumin relieves neuropathic pain by promoting microglial M2 polarization, inhibiting astrocyte activation, and modulating inflammatory responses in the cuneate nucleus.	[176]
	Rat, Mouse, Human, BV-2, N9, U-373 MG, C6, Caco-2, THP-1	Curcumin alleviates chronic pain by inhibiting spinal glial activation, suppressing pro-inflammatory pathways, and modulating cytokines, receptors, and inflammasomes.	[177]
	Rat	Curcumin alleviates diabetic neuropathic pain by improving sensory function and inhibiting neuronal and astrocytic pJNK activation in the dorsal root ganglion.	[178]
	Mouse	Curcumin relieves diabetic neuropathic pain by inhibiting TRPM7-mediated calcium influx, reducing oxidative stress and apoptosis in dorsal root ganglion neurons.	[179]
	Rat, Mouse, Human, HepG2, HK-2, PC12, SH-SY5Y, RAW264.7, THP-1, Caco-2	Curcumin protects against metal-induced toxicity by antioxidant, metal-chelation, Nrf2 activation, and inhibition of oxidative stress, inflammation, and apoptosis.	[180]
	Rat	Curcumin and nano-curcumin alleviate copper-induced neurotoxicity by reducing oxidative stress, inflammation, apoptosis, and activating the AKT/GSK-3β pathway.	[181]
	Mouse	Curcumin mitigates arsenic-induced neurotoxicity by scavenging ROS, inhibiting NF-κB/p38 MAPK, regulating Bcl-2/caspase-3, and restoring mitochondria.	[182]

4.3 Protective and Therapeutic Effects of Curcumin on the Respiratory System

Curcumin has demonstrated broad protective and therapeutic effects in respiratory diseases, particularly in chronic obstructive pulmonary disease (COPD), asthma, and other airway-related conditions. These effects are primarily attributed to its anti-inflammatory and antioxidant activities, modulation of gene expression, regulation of key signaling pathways, and maintenance of vascular endothelial integrity. By targeting multiple pathological mechanisms, curcumin offers promising potential for mitigating disease progression and improving pulmonary function in various respiratory disorders.

4.3.1 Therapeutic Effects on Chronic Obstructive Pulmonary Disease (COPD)

COPD is a prevalent chronic inflammatory airway disorder, especially among the elderly. Characterized by persistent airflow limitation, COPD typically encompasses chronic bronchitis and/or emphysema, and in advanced stages may progress to cor pulmonale and respiratory failure [183].

Curcumin exerts protective effects in COPD through a variety of mechanisms targeting inflammation, oxidative stress, mitochondrial dysfunction, and epigenetic regulation. Extensive preclinical and clinical research has highlighted its ability to modulate key molecular pathways—such as NF-κB, Nrf2/HO-1, PI3K/AKT, and SIRT1—as well as its potential to reverse corticosteroid resistance, enhance mitochondrial homeostasis, and regulate extracellular matrix remodeling. Curcumin has been shown to mitigate the progression of COPD through a range of molecular mechanisms. Safari et al. systematically reviewed preclinical studies and concluded that curcumin exerts its therapeutic effects by attenuating airway inflammation, oxidative stress, and ferroptosis, regulating autophagy and endoplasmic reticulum (ER) stress, enhancing mitochondrial function, and modulating key inflammatory pathways such as NF-κB, p66Shc, and PPARγ. Its antioxidant capacity is largely attributed to activation of the Nrf2/HO-1 pathway. These findings underscore curcumin's potential as an adjunct or alternative treatment for COPD, though clinical validation remains necessary [184].

Antioxidant and anti-inflammatory effects. Liu et al. reported that curcumin alleviates PM2.5-induced airway inflammation and oxidative stress via the PTEN/PI3K/AKT signaling pathway [185]. PM2.5 exposure in mice and BEAS-2B cells activated pro-inflammatory cascades and suppressed PTEN, leading to PI3K/AKT and NF-κB activation. Curcumin restored PTEN, suppressed downstream signaling, and reactivated FoxO1, demonstrating protective efficacy against oxidative injury. In a cigarette smoke condensate-induced mouse model, Kim et al. showed that turmeric extract reduced macrophage infiltration, emphysematous damage, and epithelial apoptosis through modulation of ERK/p53 and Bax/Bcl-2/Caspase-3 pathways [186]. In clinical settings, Zare'i et al. found that 80 mg/day nano-curcumin improved FEV1, FVC, and IL-6 levels in patients with severe COPD, indicating anti-inflammatory and functional respiratory benefits [187]. Additionally, Patel et al. demonstrated that liposomal curcumin significantly suppressed cigarette smoke extract-induced IL-8 and IL-24 expression in bronchial epithelial cells, reinforcing its therapeutic potential [188].

Immunomodulation and oxidative regulation. Memarzia et al. highlighted that both turmeric extract and curcumin reduce oxidative and inflammatory markers, including WBCs, eosinophils, phospholipase A2, MDA, and NO, while enhancing antioxidant enzyme activity and modulating Th1/Th2 cytokines [189]. Jo et al. further validated these effects in a randomized controlled trial, showing that curcumin improved antioxidant capacity and reduced pollutant-induced pneumonitis via Keap1 conjugation and Nrf2 activation [190].

Regulation of ECM remodeling and mitochondrial function. Cheng et al. demonstrated that curcumin attenuates pulmonary fibrosis through the miR-29a-3p/DNMT3A axis, regulating extracellular matrix protein expression and mitochondrial function [191]. Kumari et al. reported that intranasal curcumin restored mitochondrial homeostasis, reduced epithelial–mesenchymal transition (EMT) markers, and activated autophagy in silica-induced fibrosis, offering mechanistic insights relevant to COPD pathogenesis [192].

Modulation of gene expression and immune signaling. Mardi et al. found that nanocurcumin suppressed Th17 cell responses and cytokine expression (IL-17, IL-21, IL-23, GM-CSF) in COPD patients, supporting its role in modulating Th17-mediated inflammation [193]. Gan et al. observed that curcumin restored HDAC2 expression and altered histone acetylation/methylation at inflammatory chemokine promoters, enhancing steroid sensitivity via epigenetic mechanisms [194].

Nrf2 activation and ER stress suppression. Kim et al. confirmed that curcumin activates Nrf2/HO-1 and inhibits ERK in UPM-exposed nasal fibroblasts, reducing ROS and restoring antioxidant defenses [195]. Similarly, Tang and Ling showed that curcumin alleviates COPD in rats by enhancing SIRT1-mediated autophagy and reducing ER stress and apoptosis; these effects were reversed by a SIRT1 inhibitor [196].

Inhibition of AP-1 and improved glucocorticoid response. Yen et al. demonstrated that nanoparticle curcumin significantly suppressed ICAM-1 expression by inhibiting MAPK phosphorylation and AP-1 activation in TNF-α-stimulated lung epithelial cells, with superior bioavailability and efficacy compared to conventional formulations [197]. Finally, Chen et al. reported that curcumin-loaded mPEG-PLGA nanoparticles improved corticosteroid sensitivity in cigarette smoke-exposed rat tracheal epithelial cells by enhancing HDAC2 expression and boosting budesonide's anti-inflammatory effect[198].

4.3.2 Preventive and Therapeutic Effects of Curcumin in Asthma

Asthma is a chronic, non-specific inflammatory disease of the airways characterized by the involvement of multiple cells and cellular components, leading to heightened airway hyperresponsiveness and typically accompanied by reversible airflow obstruction [199].

Curcumin alleviates asthma symptoms through multiple mechanisms involving anti-inflammatory, antioxidant, and immunomodulatory actions. Memarzia et al. comprehensively reviewed both experimental and clinical studies on *Curcuma longa* and its major active constituent, curcumin, in respiratory and allergic diseases. They emphasized curcumin's bronchodilatory effects via tracheal smooth muscle relaxation, as well as its ability to attenuate airway inflammation and oxidative damage. These therapeutic effects, largely

attributable to curcumin, support its potential use as an adjunctive treatment for obstructive and allergic airway disorders such as COPD and asthma [200].

Suppression of Inflammatory Mediators. Islam et al. provided the first in vivo evidence that intranasal curcumin ameliorates allergic airway inflammation and fibrosis by inhibiting histone deacetylase 1 (HDAC1) activity, specifically reducing histone H3 acetylation at lysine 9 (H3acK9) and downstream NF-κB signaling. In an ovalbumin-induced asthma mouse model, curcumin significantly attenuated airway inflammatory cell infiltration, oxidative stress markers, serum IgE levels, and the expression of matrix metalloproteinases (MMP-2 and MMP-9), showing comparable effects to sodium butyrate, a known HDAC inhibitor. These findings reveal a novel epigenetic mechanism by which curcumin may exert therapeutic effects in asthma and potentially in COPD, where airway remodeling and HDAC dysregulation are central pathogenic features [201]. Ma et al. demonstrated that curcumin nanoparticles (CUR-NPs) potently inhibit the proliferation, migration, and inflammatory infiltration of airway smooth muscle cells (ASMCs) by targeting the TGF-β1/p-STAT3/CTGF signaling pathway. Compared to free curcumin, CUR-NPs showed enhanced cellular uptake and stability, leading to a greater suppression of TGF-β1-induced ASMC activation both in vitro and in a murine asthma model. Intravenous administration of CUR-NPs significantly reduced lung expression of pro-fibrotic markers and inflammatory mediators, indicating their potential in preventing airway remodeling in chronic airway diseases such as COPD [202]. Sheng et al. reported that curcumin alleviates airway inflammation in rats by promoting regulatory T cell (Treg) differentiation via activation of the STAT5/Foxp3 pathway. In an ovalbumin-induced asthma model, curcumin reduced inflammatory pathology while increasing anti-inflammatory cytokines TGF-β and IL-10 in bronchoalveolar lavage fluid. At the molecular level, curcumin upregulated phosphorylated STAT5 and Foxp3 expression, enhancing Treg differentiation. These effects were blocked by a STAT5 inhibitor, confirming the pathway's involvement. The results provide evidence for curcumin's immunomodulatory role in asthma, with implications for COPD therapy where immune imbalance and Treg dysfunction are also critical [203]. Quan et al. conducted a randomized, double-blind, placebo-controlled phase 2 clinical trial evaluating high-dose oral curcumin (1500 mg twice daily for 12 weeks) in patients with moderate to severe asthma. Curcumin administration improved asthma control, likely through inhibition of NF-κB and activation of the Nrf2/HO-1 pathway, which led to decreased levels of pro-inflammatory cytokines (TNF-α, IL-6) and increased IL-10. Piperine was co-administered to enhance curcumin's bioavailability [204].

Immunomodulation and Signaling Pathway Regulation. Kim et al. demonstrated that turmeric extract (CLE) alleviates airway inflammation in both asthmatic mice and A549 airway epithelial cells by suppressing oxidative stress-induced activation of the MAPK/MMP signaling cascade. CLE treatment reduced eosinophilic infiltration, serum IgE, and pro-inflammatory cytokine levels, while inhibiting MAPK phosphorylation and the expression and activity of MMP-2 and MMP-9, supporting its therapeutic potential in asthma management [205]. Jaiswal et al. found that intranasal curcumin, alone or combined with dexamethasone, significantly attenuated airway inflammation in a lipopolysaccharide (LPS)-induced asthma

exacerbation model by inhibiting NLRP3 inflammasome activation. This effect was associated with reduced expression of TLR-4, NF-κB, NLRP3, caspase-1, IL-1β, IL-5, IL-17, and MMP-9, suggesting a role for curcumin in modulating pyroptosis-associated signaling pathways [206]. Chehardoli et al. reported that curcumin exerts strong immunomodulatory effects against sulfur mustard analog (CEES)-induced inflammation in pulmonary epithelial cells by downregulating inflammasome-related genes. CEES exposure significantly upregulated NLRP1, caspase-1, and IL-1β in a dose- and time-dependent manner, while high-dose curcumin (160 μmol/L) effectively suppressed these pro-inflammatory responses, demonstrating its therapeutic potential via inhibition of inflammasome activation [207]. Chauhan et al. demonstrated that intranasal curcumin alleviates chronic asthma symptoms in ovalbumin-exposed mice by reducing oxidative stress and regulating inflammatory signaling pathways. Curcumin administration lowered ROS and nitrite levels, suppressed MAPK phosphorylation (JNK, ERK1/2, p38), and inhibited COX-2 and NF-κB activity, confirming that its anti-asthmatic effects are mediated through MAPK/NF-κB inhibition [208].

Modulation of Notch1-GATA3 Signaling and Treg Induction. Chong et al. revealed that curcumin suppresses acute allergic airway inflammation by targeting the Notch1-GATA3 signaling axis. In an ovalbumin-induced asthma model, curcumin reduced airway inflammatory infiltration and significantly downregulated Notch1 and GATA3 expression, key regulators of Th2 differentiation. These findings underscore curcumin's ability to rebalance immune responses and attenuate allergic airway inflammation via modulation of the Notch1-GATA3 pathway [209].

Inhibition of Smooth Muscle Thickening and Airway Remodeling. Jia et al. found that curcumol, a sesquiterpenoid from Curcuma species, reduces lung inflammation and airway remodeling in chronic asthma by inhibiting aberrant Wnt/β-catenin signaling. Treatment with curcumol led to reduced airway hyperresponsiveness, collagen deposition, eosinophilic infiltration, and Th2 cytokine levels (IL-4, IL-5, IL-13). It also suppressed the expression of Wnt5a, β-catenin, VEGFA, TGF-β1, fibronectin, and MMP-9, demonstrating its potential as a novel therapeutic candidate for chronic asthma [210].

4.3.3 Therapeutic Effects on Acute Lung Injury (ALI)

Acute lung injury (ALI) is a severe clinical condition characterized by non-cardiogenic pulmonary edema, increased alveolar-capillary permeability, diffuse inflammation, and profound hypoxemia, often triggered by infection, trauma, or other major stressors. Curcumin has demonstrated significant therapeutic potential in the management of ALI by modulating key inflammatory and pyroptotic pathways, enhancing bioavailability through novel delivery systems, and attenuating cytokine storms in preclinical models. Wang et al. demonstrated that curcumin effectively protects against ALI by suppressing inflammation and pyroptosis. In both in vivo and in vitro models, curcumin upregulated SIRT1 expression, which in turn inhibited NF-κB signaling and NLRP3 inflammasome activation, resulting in decreased levels of proinflammatory cytokines, pyroptotic markers, and histopathological lung damage. The reversal of these protective effects by SIRT1 inhibition further confirmed that curcumin's anti-inflammatory and anti-pyroptotic actions are primarily mediated through SIRT1-dependent suppression of NLRP3-driven

pyroptosis [211]. Suresh et al. reported that cyclodextrin-complexed curcumin (CDC), a water-soluble formulation, significantly alleviated lung injury and inflammation in both bacterial and viral models of ALI and ARDS. CDC reduced mortality rates, inhibited NF-κB activation, and downregulated ACE2 and STAT3 expression following Klebsiella pneumoniae infection, suggesting that curcumin may also interfere with viral entry pathways and cytokine cascades relevant to COVID-19 and other ARDS etiologies[212]. To further enhance therapeutic efficacy, Su et al. developed a cross-linked polyphosphazene nanodrug (PHCH) for inflammation-targeted and responsive curcumin delivery. This system improved curcumin's solubility and facilitated its accumulation at inflamed lung sites, where it was selectively released in acidic microenvironments. PHCH exerted anti-inflammatory effects by downregulating TNF-α, IL-1β, and IL-8, suppressing NLRP3 inflammasome activation and NF-κB signaling, and scavenging ROS, thereby effectively mitigating cytokine storms and lung inflammation in ALI models[213]. Details on curcumin's protective and therapeutic roles in the respiratory system are presented in **Table 3**.

Table 3 Curcumin's Roles in Respiratory Diseases: Protective Actions and Therapeutic Implications.

Protective and Therapeutic Effects	Type of Research Subject	Pharmacological Effects	Ref.
Prevention and treatment of COPD	Rat, Mouse, Human, BEAS-2B	Curcumin alleviates COPD by reducing inflammation, oxidative stress, ferroptosis, and modulating NF-κB, Nrf2, autophagy, and mitochondrial function.	[184]
	Mouse, BEAS-2B	Curcumin protects against PM2.5-induced COPD by restoring PTEN expression, inhibiting PI3K/AKT/NF-κB signaling, and reducing inflammation and oxidative stress.	[185]
	Mouse, NCI-H292	Turmeric extract alleviates COPD by reducing inflammation, inhibiting apoptosis via ERK/p53 and Bax/Bcl-2/Caspase 3 pathways, and protecting lung tissue.	[186]
	Human	Nano-curcumin improves lung function, reduces IL-6 levels, and enhances clinical parameters in patients with severe COPD after 3 months.	[187]
	Human bronchial epithelial cells	Liposomal curcumin significantly reduces CSE-induced IL-8 and IL-24 expression in bronchial cells, highlighting its potential for COPD therapy.	[188]
	Rat, Mouse, Human, BEAS-2B, NCI-H292, RAW264.7, PBMC, BV-2	Curcuma longa and curcumin exert anti-inflammatory, antioxidant, and immunomodulatory effects by modulating cytokines, oxidative stress markers, and immune balance.	[189]
	Mouse, Human	Curcumin protects against air pollution-induced pneumonitis by enhancing antioxidant defenses, activating Nrf2, reducing inflammation, and inhibiting alveolar epithelial apoptosis.	[190]
	Mouse	Curcumin attenuates pulmonary fibrosis by regulating the miR-29a-3p/DNMT3A axis, remodeling extracellular matrix and impairing mitochondrial dysfunction.	[191]
	Mouse	Intranasal curcumin alleviates silica-induced pulmonary fibrosis by inhibiting EMT, restoring mitochondrial homeostasis, and activating Nrf2-mediated antioxidant defenses.	[192]
	Human	Nanocurcumin attenuates COPD by suppressing Th17 cell responses, reducing RORγt and Th17 cytokines, highlighting its immunomodulatory therapeutic potential.	[193]
	Rat	Curcumin restores HDAC2 expression and modifies histone acetylation/methylation to suppress inflammatory chemokine genes, improving corticosteroid sensitivity in COPD.	[194]

	Human	Curcumin activates Nrf2/HO-1 and inhibits ERK phosphorylation, reducing ROS and enhancing antioxidant defense in UPM-exposed nasal fibroblasts.	[195]
	Rat	Curcumin alleviates COPD by enhancing SIRT1-mediated autophagy, reducing ER stress and apoptosis, indicating a protective mechanism via SIRT1 signaling.	[196]
	Mouse, A549, U937, HPMECs	Curcumin nanoparticles inhibit AP-1 activation by suppressing ROS, $p47^{phox}$, and MAPK phosphorylation, thereby reducing TNF-α-induced ICAM-1 expression in airway inflammation.	[197]
	Rat tracheal epithelial cells	Curcumin-loaded mPEG-PLGA nanoparticles restore HDAC2 expression, thereby reversing corticosteroid resistance and enhancing anti-inflammatory responses in COPD.	[198]
Prevention and treatment of asthma	Rat, Mouse, Human, Zebrafish, Guinea pig, A549, BEAS-2B, 16HBE, U937, HBSMCs, MRC-5, RAW 264.7, THP-1, $CD4^+$ Th1/Th2/Treg/Th17, RBL-2H3	Curcumin alleviates asthma via bronchodilation, antioxidant, anti-inflammatory, and immunomodulatory mechanisms targeting airway smooth muscle and immune responses.	[200]
	Mouse	Curcumin inhibits HDAC1 activity, reduces H3acK9 acetylation, suppresses NF-κB signaling, and alleviates airway inflammation, oxidative stress, and fibrosis.	[201]
	Mouse, ASMCs	Curcumin nanoparticles inhibit TGF-β1/p-STAT3/CTGF signaling, suppress ASMC proliferation, inflammation, and fibrosis, preventing airway remodeling in asthma	[202]
	Rat	Curcumin promotes Treg cell differentiation via STAT5/Foxp3 signaling, enhances anti-inflammatory cytokines, and reduces airway inflammation in asthma.	[203]
	Human	Curcumin improves asthma control by inhibiting NF-κB, activating Nrf2/HO-1 pathways, reducing pro-inflammatory cytokines, and increasing IL-10.	[204]
	Mouse, A549	Turmeric extract suppresses oxidative stress-induced MAPK/MMP signaling, reduces airway inflammation, eosinophilic infiltration, and proinflammatory cytokines in asthma.	[205]
	Mouse	Curcumin inhibits TLR-4/NF-κB/NLRP3 inflammasome signaling, reducing pyroptosis, inflammatory cytokines, and airway inflammation in asthma exacerbation.	[206]
	A549	Curcumin downregulates NLRP1, Caspase-1, and IL-1β expression, suppressing inflammasome activation and mitigating CEES-induced pulmonary inflammation.	[207]
	Mouse	Curcumin alleviates chronic asthma by reducing oxidative stress and inhibiting MAPK phosphorylation, COX-2 expression, and NF-κB activation.	[208]
	Mouse	Curcumin inhibits Notch1-GATA3 signaling, promotes Treg differentiation, restores immune balance, and alleviates allergic airway inflammation in asthma.	[209]
	Mouse	Curcumol inhibits Wnt/β-catenin signaling, reduces airway smooth muscle thickening, collagen deposition, and Th2 cytokines, alleviating airway remodeling in asthma.	[210]
Therapeutic effect on acute lung injury	Mouse, RAW264.7	Curcumin upregulates SIRT1, inhibits NF-κB and NLRP3 inflammasome activation, reducing inflammation, pyroptosis, and lung injury in ALI models.	[211]
	Rat, Mouse, Human, Guinea pig, RAW 264.7, Calu-3, Vero E6, A549, H460	Cyclodextrin-complexed curcumin suppresses NF-κB, ACE2, and STAT3 expression, mitigating inflammation, lung injury, and mortality in ALI/ARDS models.	[212]
	Mouse, RAW264.7	Inflammation-responsive PHCH nanodrug delivers curcumin to lung lesions, inhibiting NLRP3/NF-κB signaling, reducing cytokines, ROS, and lung inflammation in ALI.	[213]

4.4 Protective and Therapeutic Effects on the Digestive System

Curcumin exhibits a wide range of protective effects in digestive system diseases, including the prevention and treatment of liver injury, inflammatory bowel disease (IBD), and other gastrointestinal disorders. Its mechanisms of action involve anti-inflammatory and antioxidant activities, regulation of gene expression and signaling pathways, and promotion of cellular repair processes.

4.4.1 Hepatoprotective Effects

Liver injury refers to hepatocellular damage induced by various factors such as viral infections, toxins, drugs, and alcohol, typically characterized by abnormal liver function, hepatocyte necrosis, and structural alterations of liver tissue. Chronic liver injury may progress to fibrosis, cirrhosis, and even hepatocellular carcinoma [214].

Curcumin exerts multifaceted hepatoprotective effects through a variety of mechanisms, including the attenuation of oxidative stress, suppression of inflammation and pyroptosis, inhibition of viral replication, and modulation of key fibrogenic signaling pathways. These protective actions have been demonstrated across diverse models of hepatic injury, highlighting curcumin's therapeutic potential in conditions ranging from toxin- and radiation-induced damage to non-alcoholic fatty liver disease and viral hepatitis.

Antioxidant and Anti-inflammatory Effects. Hatipoglu and Keskin demonstrated that curcumin significantly alleviates aflatoxin B1 (AFB1)-induced hepatic injury in rats by mitigating oxidative stress and inflammation. In the AFB1-exposed group, increased MDA and pro-inflammatory cytokines (TNF-α, IL-1β, IL-6), along with decreased GSH and SOD, indicated oxidative and inflammatory damage. Co-administration of curcumin (300 mg/kg/day) restored antioxidant enzyme levels, reduced cytokine expression, and improved liver function parameters, supporting its potential as a protective agent against mycotoxin-induced liver injury [215]. Wang et al. further confirmed that curcumin protects against AFB1-induced liver injury in mice by modulating the NLRP3 inflammasome and Nrf2 signaling pathways. Curcumin administration (100 or 200 mg/kg) downregulated NLRP3, caspase-1, GSDMD, and inflammatory cytokines (IL-1β, IL-18), while upregulating Nrf2 and its downstream antioxidant enzymes (SOD, CAT, HO-1, NQO1) and detoxification genes (e.g., GST, GSH-related genes) [216]. Similarly, Li et al. demonstrated that curcumin alleviates radiation-induced liver damage in rats by inhibiting the NF-κB pathway. Curcumin treatment significantly reduced liver enzymes (ALT, AST, ALP, LDH), oxidative stress markers (MDA), and inflammation, while enhancing SOD and GSH levels and improving histopathology [217]. A meta-analysis by Li et al. of 52 preclinical studies involving 792 animals showed that curcumin attenuates the progression from non-alcoholic fatty liver disease (NAFLD) to fibrosis and hepatocellular carcinoma (HCC). These effects were mediated by anti-inflammatory (↓ IL-1β, IL-6, TNF-α), antioxidant (↑ Keap1/Nrf2), anti-apoptotic (Bax/Bcl-2/Caspase-3), and anti-fibrotic (↓ TGF-β/Smad3) mechanisms, with effective doses ranging from 100–400 mg/kg over 4–10 weeks [218]. Tong et al. further showed that curcumin ameliorates non-alcoholic steatohepatitis (NASH) by inhibiting M1 macrophage polarization and decreasing TNF-α and IL-1β levels, thereby reducing hepatic inflammation and hepatocellular injury [219].

Antiviral Effects. Ardebili et al. reviewed 43 in vitro studies and concluded that curcumin exhibits broad-spectrum antiviral activity against 24 human pathogenic viruses by inhibiting viral entry, replication, and modulating host immune responses [220]. Ferreira et al. highlighted curcumin's antiviral potential against RNA viruses, including arboviruses, HIV, and SARS-CoV-2. Curcumin blocked viral replication machinery and entry processes and showed improved efficacy and solubility when combined with nanocarriers, supporting its promise in antiviral therapy [221].

Anti-fibrotic Pathways. Cui et al. demonstrated that curcumin alleviates AFB1-induced liver pyroptosis and fibrosis in ducks by inhibiting JAK2/STAT3 signaling and downstream NLRP3 activation, reducing liver inflammation and fibrogenesis [222]. Shu et al. found that curcumin suppresses autophagy in activated hepatic stellate cells (aHSCs) via PI3K/Akt/mTOR pathway activation, leading to apoptosis and reduced fibrotic activity [223]. Geng et al. showed that curcumin modulates the gut–liver axis by reducing collagen deposition, restoring intestinal barrier function, improving gut microbial diversity, and normalizing metabolic profiles in CCl_4-induced fibrosis models [224].

4.4.2 Therapeutic Effects on Inflammatory Bowel Disease (IBD)

Inflammatory bowel disease (IBD), encompassing Crohn's disease (CD) and ulcerative colitis (UC), is a chronic and relapsing inflammatory condition affecting the gastrointestinal tract. Its pathophysiological features include oxidative and nitrosative stress, leukocyte infiltration, upregulation of Th1/Th17-associated cytokines (e.g., IL-12, IFN-γ, TNF-α, IL-1, IL-17), and downregulation of Th2 cytokines (e.g., IL-4, IL-5, IL-10) [225].

Curcumin has demonstrated therapeutic potential in IBD through a range of mechanisms, including anti-inflammatory, antioxidant, and immunomodulatory actions, as well as regulation of cytokine expression and maintenance of intestinal barrier function. Yuan et al. comprehensively reviewed the therapeutic potential and underlying mechanisms of curcumin in the management of IBD. They highlighted that curcumin exerts anti-inflammatory, antioxidant, and immunomodulatory effects through modulation of key signaling pathways such as NF-κB, MAPK, JAK/STAT, and PPAR-γ. Evidence from both in vitro and in vivo studies demonstrates that curcumin suppresses pro-inflammatory cytokines (e.g., TNF-α, IL-1β, IL-6), enhances IL-10 production, regulates T cell subsets, and maintains intestinal barrier integrity. Clinical trials further confirmed curcumin's efficacy in inducing and maintaining remission in UC patients when used as an adjunct to standard therapy, with a favorable safety profile. The authors also emphasized the need for advanced formulations to improve bioavailability and advocated for large-scale, multicenter clinical trials to validate curcumin's therapeutic role in IBD [226].

Reduction of pro-inflammatory mediators. Karthikeyan et al. reviewed curcumin and its nanoformulations in IBD, emphasizing its ability to modulate inflammatory pathways including NF-κB, JAK/STAT, MAPKs, TNF-γ, IL-6, PPARγ, and TRPV1. They concluded that curcumin exhibits robust anti-inflammatory activity in both UC and CD models and reduces clinical relapse in quiescent IBD. Given the limitations of conventional therapies, curcumin is highlighted as a safe, plant-based alternative, and the use

of nano-delivery systems may further enhance its therapeutic efficacy [227]. Song et al. reported that curcumin attenuates DSS-induced colitis in mice by regulating memory Th7 cells and inhibiting the IL-7/IL-7R signaling pathway. Treatment reduced colonic inflammation, restored colon length, and rebalanced cytokines by lowering IL-7 and IL-21 while increasing IL-2, IL-4, and IL-10. Curcumin also suppressed IL-7/IL-7R expression at both mRNA and protein levels, suggesting its therapeutic effect is mediated via modulation of Th7 cell activity and cytokine signaling [228]. Zhang et al. further showed that topical curcumin gel markedly alleviated psoriatic inflammation in mice by inhibiting NLRP3 inflammasome activation and IL-22/IL-18-driven inflammatory responses, suppressing IL-22-induced STAT3 phosphorylation by up to 95.6% [229].

Immunomodulatory activity. Zheng et al. demonstrated that curcumin mitigates DSS-induced ulcerative colitis by rebalancing memory Th and Tfh subsets. The treatment reduced mTh1/mTfh1, mTh7/mTfh7, and mTh17/mTfh17 subsets while increasing mTh10/mTfh10 populations. These immunological effects were associated with the downregulation of JAK1/STAT3/SOCS and NF-κB p65 in colonic tissue, indicating a novel immunoregulatory mechanism of curcumin in UC therapy [230]. Wei et al. also found that curcumin restores Treg/Th17 balance in DSS-induced colitis, increasing colonic IL-10 and decreasing IL-6, IL-17, and IL-23 levels. Flow cytometry confirmed curcumin's effect on Treg/Th17 ratios, and the data suggest that its benefit is primarily mediated through modulation of the IL-23/Th17 axis rather than the HIF-1α pathway [231].

Regulation of gene expression. Yu et al. reported that curcumin-loaded chitosan microspheres (CCM) ameliorate UC by downregulating TNF-α, NF-κB, and TLR4 while upregulating miR-224-3p, SDF-1, CXCR4, and IFN-γ, suggesting therapeutic action via the miR-224-3p/TLR4 axis and inflammatory signaling modulation [232]. Kang et al. further demonstrated that curcumin alleviates DSS-induced colitis by regulating macrophage polarization toward the M2 phenotype, reducing proinflammatory cytokines, enhancing anti-inflammatory cytokines, and inhibiting TLR2/TLR4/MyD88/NF-κB and MAPK/AP-1 pathways [233].

4.4.3 Other Digestive Disorders

Prevention and Treatment of Gallstones. Hong et al. reported that curcumin supplementation significantly reduced bile cholesterol supersaturation in hamsters fed a high-fat diet. The protective effect was attributed to curcumin’s ability to modulate gut microbiota composition by enhancing populations of bile acid-producing and short-chain fatty acid (SCFA)-producing bacteria. Additionally, curcumin downregulated intestinal Niemann–Pick C1-like 1 (NPC1L1) expression, thereby promoting hepatic bile acid synthesis and inhibiting intestinal cholesterol absorption. These mechanisms collectively improved cholesterol homeostasis and reduced the risk of gallstone formation [234].

Modulation of Gut Microbiota. Guo et al. demonstrated that curcumin alleviates dextran sulfate sodium (DSS)-induced colitis in mice by restoring intestinal barrier integrity through the upregulation of tight junction proteins. Curcumin also inhibited epithelial apoptosis via the caspase-3 pathway, reduced inflammatory

responses by suppressing the MAPK/NF-κB/STAT3 signaling axis, and modulated gut microbiota composition by increasing beneficial bacterial genera, including Akkermansia and Roseburia [235].

Promotion of Gastrointestinal Motility. Lin et al. found that curcumin ameliorates gastric emptying dysfunction induced by L-arginine and atropine in mice. This effect was mediated through the regulation of interstitial cells of Cajal (ICC), involving modulation of nitric oxide production, acetylcholine signaling, and expression of ICC-associated markers such as c-kit, anoctamin 1, and connexin 43. These findings suggest that curcumin plays a role in restoring normal gastrointestinal motility [236].

In summary, curcumin exhibits a broad spectrum of protective effects across various digestive system disorders through its multifaceted mechanisms. With further clinical validation and optimized delivery strategies, curcumin holds promising potential as a therapeutic agent in the prevention and treatment of gastrointestinal diseases. **Table 4** provides a summary of the protective and therapeutic effects of curcumin on the digestive system.

Table 4 Digestive System and Curcumin: Protection Mechanisms and Clinical Potential.

Protective and Therapeutic Effects	Type of Research Subject	Pharmacological Effects	Ref.
Hepatoprotective and therapeutic effects on Liver Injury	Rat	Curcumin alleviates AFB1-induced liver injury by restoring antioxidant enzymes, reducing MDA and pro-inflammatory cytokines, and mitigating oxidative stress and inflammation.	[215]
	Mouse	Curcumin protects against AFB1-induced liver injury by inhibiting NLRP3-mediated pyroptosis and activating Nrf2-driven antioxidant and detoxification pathways.	[216]
	Rat	Curcumin alleviates radiation-induced liver injury by inhibiting NF-κB signaling, reducing inflammation, oxidative stress, and apoptosis, and enhancing antioxidant defenses.	[217]
	Rat, Mouse, Human, HepG2, H22, Hep3B, HCCLM3, Hepa1-6	Curcumin attenuates NAFLD progression to fibrosis and HCC via anti-inflammatory, antioxidant, anti-apoptotic, anti-fibrotic actions involving Nrf2 and TGF-β/Smad3 pathway.	[218]
	Mouse, RAW 264.7	Curcumin ameliorates NASH by inhibiting macrophage M1 polarization, reducing TNF-α and IL-1β production, and alleviating hepatic inflammation and injury.	[219]
	Mouse, MDCK, Vero, HEK-293T, BHK-21, HeLa	Curcumin exhibits broad-spectrum antiviral effects by inhibiting viral entry, replication, and modulating host immune responses, showing potential as an antiviral agent.	[220]
	Rat, Mouse, Human, HeLa, Vero, A549, Huh-7, HEK-293T	Curcumin and its analogs inhibit RNA virus entry and replication-related enzymes, nanoformulations enhance antiviral efficacy and bioavailability.	[221]
	Duck	Curcumin mitigates AFB1-induced liver pyroptosis and fibrosis by inhibiting JAK2/STAT3 signaling and downstream NLRP3 inflammasome activation in ducks	[222]
	LX-2	Curcumin activates PI3K/Akt/mTOR signaling to suppress autophagy, inducing apoptosis of hepatic stellate cells and reducing liver fibrosis.	[223]
	Rat	Curcumin alleviates liver fibrosis by modulating the gut–liver axis, restoring microbiota balance, intestinal barrier integrity, and metabolic homeostasis.	[224]
Therapeutic effect on Inflammatory Bowel Disease	Mouse, Rat, Human, IEC-6, HT-29, Caco-2, YAMC, T84, RAW264.7, BMDCs, MDCK, Vero, HEK-293T, BHK-21, HeLa	Curcumin treats IBD by targeting NF-κB, MAPK, JAK/STAT, and PPAR-γ pathways, suppressing inflammation, regulating T cells, and preserving intestinal barrier integrity.	[226]

	Mouse, Rat, HT-29, Caco-2, RAW 264.7	Curcumin and its nanoformulations modulate NF-κB, JAK/STAT, MAPKs, PPARγ, and TRPV1 pathways, exerting anti-inflammatory effects and reducing IBD relapse.	[227]
	Mouse	Curcumin alleviates colitis by inhibiting IL-7/IL-7R signaling, regulating memory Th7 cells, and restoring cytokine balance in UC models.	[228]
	Mouse	Topical curcumin alleviates psoriatic inflammation by inhibiting NLRP3 inflammasome activation and suppressing IL-22/STAT3 signaling.	[229]
	Mouse	Curcumin restores immune balance by modulating memory Th/Tfh subsets and inhibiting JAK1/STAT3/SOCS and NF-κB signaling, alleviating UC inflammation.	[230]
	Mouse	Curcumin ameliorates colitis by restoring Treg/Th17 balance and modulating the IL-23/Th17 axis, reducing pro-inflammatory cytokines and enhancing IL-10.	[231]
	Mouse	Curcumin chitosan microspheres ameliorate colitis by modulating the miR-224-3p/TLR4 axis and inhibiting TNF-α, NF-κB, and inflammatory signaling.	[232]
	Mouse	Curcumin alleviates colitis by modulating M1/M2 macrophage polarization and inhibiting TLR2/TLR4/MyD88/NF-κB and MAPK/AP-1 signaling pathways.	[233]
Prevention and treatment of Cholelithiasis	Hamster	Curcumin improves cholesterol homeostasis and lowers gallstone risk by modulating gut microbiota, enhancing bile acid synthesis, and downregulating NPC1L1 expression.	[234]
Regulatory effect on gut microbiota	Mouse	Curcumin alleviates colitis by restoring tight junctions, inhibiting caspase-3-mediated apoptosis, suppressing MAPK/NF-κB/STAT3 signaling, and modulating gut microbiota.	[235]
Promotes GI motility	Mouse	Curcumin alleviates gastric emptying dysfunction by regulating nitric oxide, acetylcholine signaling, and ICC markers (c-kit, anoctamin 1, connexin 43).	[236]

4.5 Protective and Therapeutic Effects on the Endocrine System

4.5.1 Therapeutic Effects on Type 2 Diabetes (T2DM)

Type 2 diabetes mellitus (T2DM) is a prevalent chronic metabolic disorder characterized by progressively increasing incidence and mortality in recent years. The pathogenesis of T2DM is primarily associated with insulin resistance and pancreatic β-cell dysfunction. Moreover, it is often accompanied by various complications, including diabetic nephropathy, cognitive impairment, and diabetic cardiomyopathy.

Curcumin exerts antidiabetic effects through multiple mechanisms, including improving insulin sensitivity, enhancing pancreatic β-cell function, and reducing oxidative stress, thereby offering a comprehensive therapeutic strategy for managing T2DM.

Inhibition of Inflammatory Responses. Curcumin enhances insulin sensitivity and alleviates insulin resistance by downregulating key pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) and suppressing inflammatory pathways such as NF-κB, JNK, and MAPK. Zamanian et al. demonstrated that curcumin ameliorates diabetes and its complications primarily through inhibition of the NF-κB pathway, leading to reduced oxidative stress and inflammation, improved pancreatic β-cell function, enhanced insulin sensitivity, and mitigation of diabetes-related organ damage, including nephropathy, cardiomyopathy, pulmonary injury, and gastroparesis [237]. Zou et al. found that curcumin enhances insulin sensitivity and energy expenditure in high-fat diet-induced obese mice via activation of the FNDC5/irisin pathway and downstream p38

MAPK/ERK signaling, resulting in reduced adiposity, increased thermogenesis, elevated irisin levels, and improved metabolic function in both brown and white adipose tissue [238]. Sarmiento-Ortega et al. showed that curcumin attenuates hepatic insulin resistance induced by sub-chronic cadmium exposure by restoring redox balance and suppressing inflammation through modulation of NF-κB and Nrf2 signaling, as well as inhibition of MAPKs (JNK and p38) and enhancement of the IRS1-Akt insulin signaling cascade [239]. In a comprehensive review, Hussain et al. highlighted curcumin's anti-inflammatory, antioxidant, and enzyme-inhibitory activities, noting that it improves insulin sensitivity via ERK/JNK and PI3K-AKT-GSK3β signaling and alleviates diabetic complications—including retinopathy, nephropathy, cardiomyopathy, and encephalopathy—by modulating multiple molecular pathways [240].

Promotion of Pancreatic β-cell Regeneration and Function. Ni et al. reported that curcumin protects pancreatic β-cells by upregulating Nrf2, HO-1, and GLUT2, thereby enhancing oxidative stress defense, promoting glucose transport, increasing intracellular cAMP levels, stimulating β-cell regeneration, and improving insulin secretion. These effects support curcumin's therapeutic potential in preserving islet function and delaying diabetes progression [241].

Antioxidant Effects. Curcumin exerts potent antioxidant activity, effectively scavenging peroxides and reducing oxidative damage to insulin signaling pathways, thus further improving insulin resistance. Salgıntaş et al. showed that curcumin (50 mg/kg/day) significantly decreased MDA levels and partially restored antioxidant enzymes—SOD, GSH, and CAT—in streptozotocin-induced diabetic rats, while also lowering blood glucose levels [242]. Similarly, Duan et al. demonstrated that curcumin (200 mg/kg) enhances antioxidative and cytoprotective responses by reducing MDA, increasing GPX and SOD activity, and protecting pancreatic β-cells from apoptosis, leading to improved insulin secretion and islet function [243].

Attenuating Oxidative Stress Under Hyperglycemic Conditions. Evidence suggests that curcumin reduces the production of oxygen free radicals under high-glucose conditions, prevents protein glycation and lipid peroxidation, and enhances glucose utilization by red blood cells. Mokgalaboni et al. conducted a systematic review of randomized controlled trials and found that curcumin supplementation significantly improved markers of oxidative stress and inflammation (MDA, TNF-α, hs-CRP, MCP-1) while lowering blood glucose, triglycerides, and liver enzymes (ALT, AST) in individuals with metabolic disorders such as obesity, T2DM, and NAFLD [244]. These findings underscore curcumin's therapeutic promise, though further research is needed to optimize its bioavailability and dosage.

4.5.2 Protective and Therapeutic Effects of Curcumin on Diabetic Complications

In addition to its hypoglycemic properties, curcumin has shown promising protective effects against a range of diabetic complications, including nephropathy and cataract, through mechanisms involving antioxidant, anti-inflammatory, and antifibrotic pathways.

Renal Protection in Diabetic Nephropathy. AlTamimi et al. demonstrated that curcumin (100 mg/kg, orally for 12 weeks) confers significant nephroprotective effects in streptozotocin-induced diabetic rats. These benefits were evidenced by improvements in renal function markers and histopathological changes, as well as

by the inhibition of the PKCβII/p66Shc oxidative stress pathway. Curcumin treatment also reduced inflammatory cytokines and fibrotic markers (TGF-β1, collagen I/III), enhanced antioxidant defenses via Nrf2 and MnSOD upregulation, and activated FOXO-3a, collectively supporting its therapeutic potential in mitigating diabetic nephropathy [245]. Zhao et al. conducted a systematic review and meta-analysis of five randomized, double-blind, placebo-controlled clinical trials involving 290 participants. Their analysis revealed that curcumin supplementation significantly improved key clinical parameters in diabetic kidney disease (DKD), including reductions in serum creatinine, total cholesterol, systolic blood pressure, and fasting blood glucose, although no significant changes were observed in proteinuria or lipid subfractions. These findings support curcumin's potential utility in DKD management and underscore the need for further high-quality trials [246]. Similarly, Zhu et al. comprehensively reviewed preclinical and clinical evidence supporting curcumin's multifaceted pharmacological actions in diabetic nephropathy. These include anti-inflammatory, antioxidant, anti-apoptotic, anti-fibrotic, and autophagy-regulatory effects, positioning curcumin as a promising adjunctive therapeutic option for the prevention and treatment of diabetic kidney complications [247].

Therapeutic Potential in Diabetic Cataract. Liu et al. developed a curcumin-loaded cerium oxide nanoparticle (CeO_2 NP) delivery system encapsulated in PLGA nanoclusters (CCNPs) for the treatment of diabetic cataract. Their findings demonstrated that this formulation significantly attenuated oxidative stress and glycation-induced damage in human lens epithelial cells (HLE-B3) without inducing notable in vivo toxicity. These results suggest that curcumin-loaded CCNPs represent a promising non-invasive strategy for the management of diabetic cataract, offering both antioxidant and anti-glycation benefits [248].

4.5.3 Therapeutic Effects of Curcumin on Metabolic Syndrome (MetS)

Metabolic syndrome (MetS) is a pathological condition characterized by disturbances in the metabolism of proteins, lipids, and carbohydrates, commonly manifesting as central obesity, insulin resistance, dyslipidemia, and hypertension. Although the exact etiology of MetS remains unclear, increasing evidence suggests a strong association with pro-inflammatory cytokines, which are actively involved in the onset and progression of the syndrome [249]. Vafaeipour et al. reviewed in vitro, in vivo, and clinical studies on turmeric (*Curcuma longa*) and its bioactive constituent curcumin, concluding that curcumin confers therapeutic benefits in MetS through diverse mechanisms, including enhancing insulin secretion, reducing lipogenesis, promoting fatty acid uptake, and increasing nitric oxide production. These actions collectively contribute to its antidiabetic, antihyperlipidemic, anti-obesity, and antihypertensive effects. Nevertheless, further clinical trials are warranted to confirm its efficacy and safety as a complementary therapy for MetS [250].

Modulation of Oxidative Stress and Inflammation. Curcumin has shown the ability to restore normal levels of glucose and lipid metabolism markers, oxidative stress parameters, and inflammatory biomarkers in MetS, indicating its potential as a therapeutic agent through attenuation of oxidative stress and inflammatory cascades. Qiu et al. performed a systematic review and meta-analysis of 13 randomized controlled trials

comprising 785 participants, revealing that curcumin supplementation significantly reduced waist circumference, fasting blood glucose, diastolic blood pressure, TNF-α, CRP, and MDA, while increasing HDL-C levels [251].

Regulation of Target Genes, Signaling Pathways, and RNAs. Nguyen and Kim employed in-silico analyses to elucidate the molecular mechanisms by which curcumin ameliorates MetS. They identified several key targets, including INS, NOS3, IL6, ADIPOQ, and especially PPARG, and implicated crucial pathways related to insulin resistance, lipid metabolism, and IL-18 signaling. Furthermore, they highlighted curcumin's modulation of specific microRNAs, such as hsa-miR-155-5p, miR-130b-3p, and miR-22-3p. Despite curcumin's low systemic bioavailability, its favorable drug-likeness and high gastrointestinal absorption underscore the need for formulation optimization to enhance its pharmacological utility in MetS [252].

Given its multi-targeted actions, curcumin holds substantial promise for the prevention and treatment of endocrine disorders. Through mechanisms such as improving insulin sensitivity, enhancing pancreatic β-cell regeneration, exerting anti-inflammatory and antioxidant effects, regulating lipid metabolism, and inhibiting pathological cell proliferation, curcumin exerts protective effects across the endocrine system. These actions involve several critical signaling pathways, including NF-κB, JNK, MAPK, and Nrf2/HO-1. Thus, with further clinical validation and formulation advancements, curcumin may emerge as a valuable therapeutic agent for T2DM, MetS, and their associated complications. A detailed overview of curcumin's effects on the endocrine system is provided in **Table 5**.

Table 5 Curcumin and Endocrine Disorders: Mechanistic Protection and Therapeutic Prospects.

Protective and Therapeutic Effects	Type of Research Subject	Pharmacological Effects	Ref.
Therapeutic effect on type 2 diabetes	Rat, Mouse, Human, 3T3-L1, pancreatic β-cells, BMSCs, ICCs	Curcumin ameliorates diabetes by inhibiting NF-κB signaling, reducing inflammation and oxidative stress, improving β-cell function, and enhancing insulin sensitivity.	[237]
	Mouse	Curcumin improves insulin sensitivity and energy metabolism by activating the FNDC5/irisin pathway and p38 MAPK/ERK signaling in obese mice.	[238]
	Rat	Curcumin ameliorates cadmium-induced hepatic insulin resistance by modulating NF-κB, Nrf2, MAPKs, and enhancing IRS1-Akt insulin signaling.	[239]
	Rat, Mouse, Human, 3T3-L1, HepG2, BMSCs, L6, RAW 264.7	Curcumin improves insulin sensitivity via ERK/JNK and PI3K-AKT-GSK3β modulation, inhibits NF-κB, and alleviates diabetic complications through multi-pathway regulation	[240]
	Rat, Mouse, Human, L6, 3T3-L1, HepG2, HL-7702	Curcumin protects pancreatic β-cells by upregulating Nrf2, HO-1, and GLUT2, enhancing cAMP levels, promoting regeneration, and improving insulin secretion.	[241]
	Rat	Curcumin reduces oxidative stress by lowering MDA levels and restoring SOD, GSH, and CAT activities, improving hyperglycemia in diabetic rats.	[242]
	Rat	Curcumin reduces MDA levels, restores GPX and SOD activity, protects β-cells from apoptosis, and improves insulin secretion and islet function in diabetes.	[243]
	Human	Curcumin improves oxidative stress, inflammation, blood glucose, lipids, and liver enzymes in metabolic diseases, supporting its therapeutic potential.	[244]

	Rat	Curcumin mitigates diabetic nephropathy by inhibiting the PKCβII/p66Shc axis, reducing inflammation and fibrosis, and enhancing Nrf2/MnSOD/FOXO-3a antioxidant defenses.	[245]
	Human	Curcumin improves diabetic kidney disease by reducing serum creatinine, total cholesterol, systolic blood pressure, and fasting glucose, supporting its therapeutic potential.	[246]
	Rat, Mouse, Human, MES-13, H9C2, NRK-52E, HBZY-1, HKC, HEK-293	Curcumin exerts anti-inflammatory, antioxidant, anti-apoptotic, anti-fibrotic, and autophagy-regulating effects, offering multi-target protection against diabetic nephropathy.	[247]
	Rat, HLE-B3	Curcumin-loaded cerium oxide nanoparticles attenuate oxidative stress and glycation damage in lens epithelial cells, offering a promising therapy for diabetic cataract.	[248]
Therapeutic effect on Metabolic Syndrome	Rat, Mouse, Human	Curcumin improves metabolic syndrome by enhancing insulin secretion, reducing lipogenesis, increasing fatty acid uptake, and promoting nitric oxide production.	[250]
	Human	Curcumin improves metabolic syndrome parameters by reducing waist circumference, blood sugar, blood pressure, inflammation, oxidative stress, and increasing HDL-C levels.	[251]
	Genes, transcription factors, and miRNAs related to metabolic syndrome and curcumin, analyzed by CTD, MIENTURNET, Metascape, GeneMANIA, and Cytoscape.	Curcumin targets genes like PPARG and pathways related to insulin resistance, lipid metabolism, and IL-18 signaling, modulating microRNAs in metabolic syndrome.	[252]

4.6 Antitumor Activity

Cancer remains a leading cause of mortality worldwide and poses a significant challenge in medical research. Curcumin, a natural polyphenolic compound extracted from the rhizome of *Curcuma longa*, has garnered considerable attention due to its diverse pharmacological properties, including anti-inflammatory, antioxidant, anticoagulant, lipid-lowering, anti-atherosclerotic and antimutagenic effects. Since the pioneering work of Kuttan et al. in 1985, which first reported the antitumor potential of turmeric and curcumin [253], extensive in vitro and in vivo studies have demonstrated that curcumin exerts potent inhibitory effects against a variety of tumor types.

4.6.1 Induction of Apoptosis in Tumor Cells

Curcumin has been shown to induce tumor cell apoptosis through both intrinsic and extrinsic pathways, engaging multiple molecular mechanisms. These include mitochondrial dysfunction, modulation of the p53 signaling axis, activation of caspase cascades, and generation of ROS. Bai et al. demonstrated that curcumin induces mitochondrial-mediated apoptosis in human hepatoma cells (HepG2 and SK-Hep-1) by downregulating BCLAF1 and inhibiting the PI3K/AKT/GSK-3β signaling pathway. This led to reduced cell proliferation, G_0/G_1 phase cell cycle arrest, loss of mitochondrial membrane potential, and increased apoptotic activity. These effects were further validated in vivo using a xenograft mouse model, suggesting that curcumin exerts potent antitumor effects in hepatocellular carcinoma through BCLAF1-mediated oncogenic signaling suppression [254]. Li et al. reported that curcumin selectively induces apoptosis and S phase cell cycle arrest in colon cancer cells by modulating the Rb/E2F/p53 pathway. This was associated with upregulation of pro-apoptotic Bax, and downregulation of cell cycle–related proteins, phosphorylated Rb, and E2F transcription factors. These effects were dose-dependent, non-toxic to normal colon epithelial cells, and

confirmed in vivo in a mouse xenograft model, highlighting curcumin's therapeutic potential in colorectal cancer [255]. In another study, Sritharan and Sivalingam found that curcumin induces ROS-mediated apoptosis in both mutant p53 (HT-29) and wild-type p53 (HCT-116) colon adenocarcinoma cell lines. Rapid ROS generation and mitochondrial membrane potential dissipation were observed following treatment, and the antioxidant N-acetylcysteine attenuated these effects, particularly in HT-29 cells. These findings suggest that curcumin induces both p53-dependent and -independent apoptotic mechanisms via oxidative stress in colorectal cancer cells [256]. Yavuz Türel et al. further demonstrated that curcumin triggers apoptosis in human colon carcinoma SW480 cells via a caspase-dependent mechanism. Curcumin significantly reduced cell proliferation and increased apoptosis in a time-dependent manner, as confirmed by BrdU, TUNEL, and caspase-3 staining. Gene expression analysis revealed significant upregulation of FADD, CASP8, and CASP3 at 72 hours, supporting the activation of the extrinsic apoptotic pathway and underscoring curcumin's potential as an anticancer agent in colorectal cancer therapy [257]. Additionally, Wu et al. showed that curcumin overcomes chemoresistance in human lung cancer A549 sublines resistant to docetaxel and vincristine by inducing apoptosis through ROS-mediated activation of the p38 MAPK pathway [258]. ROS generation was essential for curcumin's pro-apoptotic effect, as it was abolished by NAC, and p38 MAPK knockdown significantly reduced apoptosis. These findings identify p38 MAPK as a key downstream effector in curcumin-induced apoptosis in chemoresistant lung cancer cells.

4.6.2 Induction of Autophagy in Tumor Cells

In addition to promoting apoptosis, curcumin has also been shown to induce autophagy in tumor cells, which plays a dual role in cancer progression and therapy. Zhang et al. revealed that curcumin induces autophagic cell death in human thyroid cancer cells by promoting the conversion of LC3-I to LC3-II, increasing beclin-1 expression, and facilitating p62 degradation, accompanied by the formation of acidic vesicular organelles [259]. Mechanistically, curcumin activates the MAPK pathway while inhibiting the AKT/mTOR axis, selectively reducing thyroid cancer cell viability without affecting normal epithelial cells. These findings suggest that curcumin-induced autophagy may serve as a promising therapeutic strategy for thyroid cancer treatment.

4.6.3 Inhibition of Tumor Cell Proliferation and Metastasis

Curcumin inhibits tumor cell proliferation and metastasis by modulating multiple molecular targets and signaling pathways. Its anti-cancer activity involves the regulation of non-coding RNAs, suppression of oncogenic gene expression, induction of cell cycle arrest, and reprogramming of the tumor microenvironment. Through the inhibition of key signaling cascades such as PI3K/Akt, NF-κB, MAPK, and Wnt/β-catenin, curcumin effectively disrupts processes essential for cancer progression, including angiogenesis, EMT, migration, and invasion. These findings collectively highlight the potential of curcumin as a multi-targeted therapeutic agent for limiting tumor growth and metastatic spread. Wang et al. reviewed the multifaceted anti-tumor mechanisms of curcumin, highlighting its regulation of non-coding RNAs (ncRNAs) and major molecular signaling cascades, including PI3K/Akt, JAK/STAT, MAPK, Wnt/β-catenin, p53, and NF-κB.

These pathways are implicated in cancer cell proliferation, angiogenesis, EMT, invasion, and metastasis [260]. Curcumin was shown to downregulate oncogenic microRNAs and upregulate tumor-suppressive microRNAs, underscoring its potential as a targeted therapeutic agent in cancer treatment. In acute myeloid leukemia (AML), Zhou et al. demonstrated that curcumin exerts strong anti-leukemic activity by inducing cell cycle arrest and apoptosis via inhibition of the AKT signaling pathway. Curcumin markedly downregulated phosphorylated AKT and its downstream targets, including PRAS40, 4E-BP1, P70S6K, RAF-1, and p27. These effects were further enhanced by the AKT inhibitor afuresertib, both in vitro and in AML xenograft models, supporting the therapeutic potential of curcumin as an AKT-targeting agent [261]. Shahbaz et al. emphasized curcumin's crucial role in regulating oncogene and tumor suppressor gene expression. Curcumin downregulated a variety of oncogenes such as Bcl-2, cyclin D1, COX-2, and c-Myc, while upregulating tumor suppressors including Bax, p21, and p53. Moreover, curcumin suppressed the activity of transcription factors NF-κB and AP-1, thereby indirectly modulating the transcription of inflammatory and apoptosis-related genes, contributing to its anti-inflammatory, pro-apoptotic, and anticancer effects [262]. Davoodvandi et al. summarized the antimetastatic effects of curcumin in oral and gastrointestinal cancers, demonstrating that curcumin targets multiple genes and proteins involved in tumor invasion, angiogenesis, EMT, and immune evasion. Specifically, curcumin downregulated metastasis-promoting factors such as MMPs, VEGF, CXCR4, and the transcription factors Snail, Twist, and Slug, while upregulating tumor suppressors like E-cadherin and p53. It also modulated several key signaling pathways—NF-κB, ERK, PI3K/Akt, Wnt/β-catenin, and Hedgehog—thereby inhibiting tumor cell migration and invasion, and disrupting the metastatic cascade [263]. Furthermore, Jiang et al. demonstrated that curcumin reprograms tumor-associated macrophages (TAMs) from a protumorigenic M2 phenotype to an antitumor M1 phenotype by inhibiting the MAO-A/STAT6 signaling pathway. This phenotypic switch contributed to the suppression of cancer cell migration and invasion, highlighting curcumin's immunomodulatory potential in the tumor microenvironment [264].

4.6.4 Anti-angiogenic Activity

Angiogenesis is a fundamental process for tumor growth, progression, and metastasis, providing nutrients and oxygen to proliferating cancer cells. Curcumin has demonstrated strong anti-angiogenic effects in various tumor models by targeting key signaling pathways and pro-angiogenic mediators. These effects are primarily mediated through the suppression of VEGF/VEGFR-2 signaling, modulation of PI3K/Akt and NF-κB pathways, and enhancement of tumor suppressor genes, making curcumin and its derivatives promising candidates for anti-angiogenic cancer therapies. Fidha Latheef investigated the anti-angiogenic effects of supercritically extracted 95% curcumin in both the chick embryo chorioallantoic membrane (CAM) assay and MDA-MB-231 breast cancer cell line. The results showed significant inhibition of neovascularization, especially at a concentration of 25 μg/mL. Moreover, qRT-PCR revealed that curcumin suppressed the expression of VEGF and upregulated the pro-apoptotic gene BAX, further supporting its anti-cancer potential [265]. Liu developed an NGR-modified polymeric micelle loaded with curcumin (Cur-NGR-PM) that targets tumor neovasculature. The micelle promoted curcumin uptake via NGR-mediated

endocytosis, induced tumor cell apoptosis, and significantly inhibited tumor angiogenesis and growth in vivo, confirming its potent anti-angiogenic activity [266]. Nayak et al. explored the combination of curcumin and quinacrine (QC) in breast cancer stem cell (CSC)-enriched models, including SP cells, primary tumor cells, CAM, and PDX models. Under hypoxic conditions, ABCG2 promoted VEGF-A release and angiogenesis via the PI3K-Akt-eNOS pathway. Curcumin and QC synergistically downregulated ABCG2, thereby inhibiting VEGF-A–mediated angiogenesis. Functional assays confirmed that ABCG2 overexpression enhanced, while its knockdown reduced, angiogenesis. This study was the first to identify ABCG2 as a key regulator of tumor angiogenesis and demonstrated the efficacy of Cur + QC in targeting this pathway [267]. Aziz et al. demonstrated that the curcumin analog DK1 exerts both anti-metastatic and anti-angiogenic effects in human osteosarcoma cells (U-2 OS and MG-63) by modulating the PI3K/Akt and NF-κB pathways. DK1 treatment enhanced the expression of tumor suppressor genes such as PTEN and FOXO, while downregulating pro-angiogenic and pro-metastatic mediators, including MMP3, VEGF, and uPA [268]. Similarly, Zhang et al. reported that the combination of curcumin and omacetaxine synergistically inhibited lymphoma cell proliferation, migration, invasion, and angiogenesis. This effect was mediated through the suppression of VEGF/VEGFR2/Akt signaling and a reduction in VEGFA levels in both cells and exosomes, indicating a potential therapeutic strategy targeting the VEGF/Akt axis in lymphoma [269].

In addition to blocking angiogenic signaling, curcumin also inhibits endothelial cell proliferation and migration. Giménez-Bastida et al. found that physiologically relevant concentrations of curcumin and its analogs—demethoxycurcumin (DMC) and bisdemethoxycurcumin (BisDMC)—effectively suppressed VEGF165-induced angiogenesis in human aortic endothelial cells by inhibiting VEGFR2 phosphorylation and downstream ERK/Akt signaling. Notably, DMC and BisDMC exhibited stronger anti-tubulogenic activity than curcumin itself [270]. Moreover, Chou et al. showed that curcumin and DMC downregulate endoglin and phosphorylated Smad1 signaling in human umbilical vein endothelial cells (HUVECs), thereby inhibiting angiogenic behaviors. These findings suggest that curcumin and its derivatives may enhance anti-VEGF therapy and potentially overcome resistance to agents such as semaxanib [271].

4.6.5 Enhancement of Chemosensitivity and Radiosensitivity

Curcumin has been shown to enhance the antitumor efficacy of both chemotherapy and radiotherapy by increasing drug sensitivity, reducing resistance, and exerting synergistic effects with conventional treatments. It achieves these benefits through modulation of key signaling pathways, inhibition of drug efflux transporters, suppression of inflammation, and promotion of apoptosis, while also providing protection to normal tissues. Hussain et al. reviewed that co-administration of curcumin with cisplatin enhances the chemotherapeutic response while mitigating cisplatin-induced toxicity and drug resistance, suggesting a dual role in efficacy enhancement and toxicity reduction [272]. Liu et al. demonstrated that a MnO_2-shelled nanoformulation co-delivering doxorubicin and curcumin significantly improved chemo-immunotherapeutic efficacy against colorectal cancer by inhibiting both primary and metastatic tumors and activating adaptive antitumor immune responses [273]. Similarly, Zheng et al. reported that low-dose curcumin sensitizes

colorectal cancer cells to 5-fluorouracil by downregulating L1 expression and inhibiting pERK signaling, resulting in enhanced tumor growth suppression and apoptosis in vitro and in vivo [274]. In breast cancer models, Lin et al. found that the co-delivery of paclitaxel and curcumin via PEG–PLGA nanoparticles reversed multidrug resistance by downregulating P-glycoprotein and inhibiting NF-κB activity, ultimately leading to improved therapeutic outcomes [275]. In the context of radiotherapy, Raeisi et al. systematically reviewed 24 preclinical studies and concluded that nano-curcumin formulations potentiate the effects of radiation by inhibiting NF-κB signaling, promoting ROS accumulation, and activating pro-apoptotic genes in cancer cells. Notably, curcumin also protected normal tissues from radiation-induced damage through its antioxidant, anti-inflammatory, and DNA-protective properties [276]. These findings collectively highlight curcumin's potential as an effective radiosensitizer and chemosensitizer in cancer therapy.

4.6.6 Combination Therapy with Targeted Agents

In addition to enhancing the efficacy of conventional chemotherapy and radiotherapy, curcumin has demonstrated synergistic potential when used in combination with targeted therapies. By modulating key oncogenic pathways and reversing drug resistance, curcumin enhances the sensitivity of tumor cells to molecularly targeted agents, thereby improving therapeutic outcomes. Chiu et al. showed that curcumin suppresses proliferation and induces apoptosis in vemurafenib-resistant melanoma cells (A375.S2/VR) by downregulating the EGFR/AKT/ERK signaling pathway and activating intrinsic caspase-dependent apoptosis. Notably, curcumin exhibited enhanced antitumor effects when combined with the EGFR inhibitor gefitinib [277]. Similarly, Miyazaki et al. reported that curcumin reverses lenvatinib resistance in hepatocellular carcinoma by suppressing the EGFR/PI3K/AKT signaling pathway, and that co-treatment exerted synergistic anti-tumor activity in resistant HCC cell lines and tumor spheroids [278]. These findings suggest that curcumin may serve as an effective adjuvant to targeted therapies by sensitizing tumor cells and overcoming resistance mechanisms.

4.6.7 Combination Therapy with Photodynamic and Sonodynamic Treatments

Photodynamic therapy (PDT) and sonodynamic therapy (SDT) are emerging non-invasive cancer treatment strategies that utilize light or ultrasound to activate sensitizers, leading to the generation of ROS and subsequent tumor cell death. Curcumin, with its intrinsic photosensitizing and sonosensitizing properties, has demonstrated significant potential in enhancing the efficacy of both modalities. In PDT, curcumin acts as a natural photosensitizer capable of producing high levels of ROS upon laser irradiation, thereby disrupting tumor cell membranes and organelles and inducing apoptosis. Ailioaie et al. highlighted that nanoformulated curcumin enhances tumor-specific targeting in PDT, promotes ROS-mediated apoptotic signaling, and helps overcome chemoresistance and radioresistance, underscoring its value in integrative oncologic therapy [279]. In SDT, curcumin combined with low-intensity ultrasound (LIUS) has shown synergistic anticancer effects. Shi et al. demonstrated that curcumin and LIUS co-treatment effectively suppressed glioma cell proliferation and induced apoptosis by downregulating the AKT signaling pathway, suggesting a promising therapeutic approach for glioma [280]. Additionally, Sowa-Kasprzak et al. reported that a novel curcumin–oleanolic acid

hybrid compound significantly enhanced cytotoxicity under ultrasound exposure in oral squamous carcinoma cells, supporting its potential role as an effective sonosensitizer in SDT [281].

4.6.8 Antioxidant and Immunomodulatory Activities

Oxidative stress and immune dysregulation play critical roles in tumor initiation and progression. Curcumin exhibits dual functions in redox modulation, acting both as an antioxidant to protect normal tissues and as a pro-oxidant to selectively induce cancer cell death. Chen et al. reported that liposomal curcumin shows superior stability and free radical scavenging activity compared to its free form, thereby enhancing its antioxidant capacity and tumor-suppressive effect. In addition, curcumin–metal complexes have demonstrated the ability to chelate metal ions and scavenge ROS more efficiently, possibly through proton- or electron-donating mechanisms, further strengthening their anticancer potential. In vivo studies confirmed that curcumin enhances endogenous antioxidant defenses, thereby delaying tumor progression. Moreover, curcumin and its derivatives can elevate intracellular ROS levels in cancer cells, disrupt mitochondrial membrane potential, induce cell cycle arrest and apoptosis, suggesting a context-dependent "antioxidant–pro-oxidant" dual mechanism in tumor suppression [282]. Hu further highlighted that curcumin activates the Nrf2–antioxidant response element (ARE) pathway to reduce ROS generation in normal tissues, while simultaneously exerting cytotoxic effects in tumor cells by promoting oxidative stress. This is achieved through its interactions with intracellular enzymes such as carbonyl reductase, glutathione S-transferase P1, and NADPH-related systems, ultimately leading to mitochondrial dysfunction, ROS accumulation, and apoptosis. Although curcumin suffers from poor stability and pharmacokinetics in vivo, strategies such as combination therapy, structural derivatives, and nanocarrier systems have significantly improved its antitumor efficacy. These findings underscore the potential of curcumin in redox modulation and oxidative stress-mediated cancer cell elimination [283]. In terms of immunomodulation, Focaccetti et al. demonstrated that curcumin, in combination with resveratrol at physiologically relevant concentrations, not only retains its anticancer activity but also enhances immune responses. The combination increased T cell activation without affecting peripheral blood mononuclear cell (PBMC) viability. Although resveratrol antagonized curcumin-induced IFN-γ expression in T cells, the co-treatment elevated IL-10 secretion in regulatory T cells (Tregs), boosted NK cell activity, modulated activating and inhibitory receptors, and upregulated CD68 expression in monocytes and macrophages. These findings support the potential of curcumin as an immunomodulatory agent that enhances antitumor immunity through coordinated regulation of immune cell function and cytokine profiles [284].

4.6.9 Inhibition of Gene Mutation and DNA Damage

DNA damage and gene mutation are fundamental events in cancer initiation and progression. Curcumin has been shown to exert protective effects against genomic instability by inhibiting carcinogen activation, reducing oxidative DNA lesions, and modulating epigenetic regulatory mechanisms [324]. As a natural antioxidant, curcumin effectively scavenges ROS and reactive nitrogen species (RNS), thereby limiting oxidative stress–induced DNA strand breaks and base modifications [323]. It also downregulates the

bioactivation of chemical carcinogens and prevents the formation of DNA adducts, contributing to its antimutagenic and chemopreventive properties [327].

In addition to its antioxidant function, curcumin acts as an epigenetic modulator. Fabianowska-Majewska et al. reported that curcumin regulates DNA methylation by reversing aberrant hypermethylation of tumor suppressor gene promoters and inhibiting the hypomethylation of oncogene promoters in breast cancer cells. These epigenetic modifications restore normal gene expression patterns, thereby contributing to curcumin's antitumor and chemopreventive effects. The ability of curcumin to target both genetic and epigenetic instability highlights its potential in cancer prevention and as an adjunct in therapies aimed at maintaining genome integrity [285].

Owing to its broad-spectrum anticancer activity and low toxicity, curcumin has been recognized by the U.S. National Cancer Institute as a third-generation cancer chemopreventive agent and has entered clinical trial evaluation. Extensive preclinical and clinical studies suggest that curcumin holds great promise in cancer prevention and treatment, particularly in enhancing the sensitivity of tumors to chemotherapy and radiotherapy while reducing drug-associated toxicities. Curcumin exerts its anticancer effects through multiple mechanisms, including the induction of apoptosis, inhibition of proliferation, metastasis, and angiogenesis, modulation of oxidative stress and immune responses, and enhancement of therapeutic responsiveness. These effects are mediated through the regulation of key molecular targets and signaling pathways such as NF-κB, AKT/mTOR, Wnt/β-catenin, p53, and the Bcl-2 protein family. With continued advancements in formulation technology and clinical validation, curcumin is expected to emerge as a safe and effective therapeutic candidate for the prevention and management of various cancers. For details on the antitumor effect of curcumin, please see **Table 6**.

Table 6 Antitumor Effect of Curcumin.

Therapeutic Effect	Type of Research Subject	Cancer Types	Mechanism of Action	Ref.
Induction of apoptosis in tumor cells	HepG2, SK-Hep-1	Hepatocellular Carcinoma	Curcumin induces mitochondrial apoptosis in hepatoma cells by downregulating BCLAF1 and inhibiting PI3K/AKT/GSK-3β signaling, suppressing proliferation and promoting cell death.	[254]
	MC38, HCT116, MCEC, A549, B16, 4T1	Colon Cancer	Curcumin induces apoptosis and S-phase arrest via Rb/E2F/p53, selectively inhibiting colon tumors without affecting normal cells.	[255]
	HT-29, HCT-116	Colon Cancer	Curcumin triggers ROS-mediated apoptosis via p53 pathways, disrupting mitochondrial potential in colon cancer.	[256]
	SW480	Colon Cancer	Curcumin induces caspase apoptosis in colon cancer cells by upregulating FADD, CASP8, and CASP3, activating the extrinsic pathway.	[257]
	A549	Lung cancer	Curcumin overcomes chemoresistance by inducing ROS-mediated p38 MAPK activation, causing apoptosis in resistant A549 cells.	[258]
Induction of autophagy in tumor cells	BCPAP	Thyroid Cancer	Curcumin induces autophagic cell death in thyroid cancer cells by activating MAPK signaling and inhibiting the AKT/mTOR pathway, selectively suppressing tumor viability.	[259]

Inhibition of tumor cell proliferation and metastasis	Rat, Mouse, Human, RAW264.7, HEK-293T, Vero, BHK-21, HeLa, MDCK, Caco-2, HT-29	Multiple types of Cancers	Curcumin inhibits tumor progression by regulating ncRNAs and key pathways (PI3K/Akt, JAK/STAT, MAPK, Wnt/β-catenin, p53, NF-κB), modulating proliferation, EMT, and metastasis.	[260]
	HL-60, ML-2, MOLM-13, OCI-AML3, OCI-AML5, U937	Acute Myeloid Leukemia	Curcumin exerts anti-AML effects by inactivating AKT signaling, inducing cell cycle arrest and apoptosis, and synergizing with AKT inhibitor afuresertib.	[261]
	Rat, Mouse, Human, CAM, H1650, H1975, A549, MCF-7, PC-3, LNCaP, HCT-116, HCT-15, HT-29, NCI-H460, HeLa, K562, RS4, REH, SUP-B15, TC1889, OSCC, PANC-1, MIA PaCa-2, HSC-4, Ca9-22, SAS, MTEC1	Multiple types of Cancers	Curcumin downregulates oncogenes (Bcl-2, cyclin D1, COX-2, c-Myc) and upregulates tumor suppressors (Bax, p21, p53), inhibiting NF-κB/AP-1 to modulate gene expression.	[262]
	Mouse, Beagle dogs, Human, HCT-116, CT26, SW480/SW620, SCC-25, CAL27, HSC-4/Ca9-22, MDA-MB-231, Tca8113	Multiple types of Cancers	Curcumin inhibits metastasis by downregulating MMPs, VEGF, CXCR4, EMT transcription factors, and modulating NF-κB, ERK, PI3K/Akt, Wnt/β-catenin, and Hedgehog pathways.	[263]
	Raw264.7, CAL27	Oral carcinoma	Curcumin reprograms TAMs from M2 to M1 phenotype by inhibiting MAO-A/STAT6 signaling, reducing cancer cell migration and invasion.	[264]
Anti-angiogenic effect	U-2 OS, MG-63	Osteosarcoma	Curcumin analog DK1 inhibits metastasis and angiogenesis in osteosarcoma by modulating PI3K/Akt and NF-κB pathways, upregulating PTEN/FOXO, and downregulating MMP3, VEGF, and uPA.	[265]
	CAM model, MDA-MB-231	Breast Cancer	Curcumin inhibits angiogenesis via VEGF downregulation and promotes apoptosis through BAX upregulation.	[266]
	HepG2, EA.hy926 cells, H22 , Mouse	Hepatocellular Carcinoma	Curcumin-loaded NGR-modified micelles enhance tumor uptake, induce apoptosis, and effectively inhibit tumor angiogenesis and growth.	[267]
	Breast cancer stem cell, SP, CAM model, Patient-derived xenograft models	Breast Cancer	Curcumin and quinacrine inhibit angiogenesis by downregulating ABCG2 and suppressing VEGF-A-mediated vascularization.	[268]
	U937, Raji	Lymphoma	Curcumin combined with HHT synergistically inhibits lymphoma progression by downregulating VEGF/VEGFR2/Akt signaling and reducing VEGFA in cells and exosomes.	[269]
	HAECs	Multiple types of Cancers	Curcumin and its analogs inhibit VEGF165-induced angiogenesis by reducing VEGFR2 phosphorylation and downstream ERK/Akt signaling in endothelial cells, with DMC and BisDMC showing stronger effects.	[270]
	HUVECs	Multiple types of Cancers	Curcumin and demethoxycurcumin inhibit HUVEC angiogenesis by downregulating endoglin and p-Smad1 signaling, potentially enhancing anti-VEGF therapy and overcoming resistance.	[271]
Enhancement of chemo- and radiosensitivity	Mouse, A549, HeLa, MG63	Multiple types of Cancers	Curcumin co-delivery with cisplatin enhances chemotherapy efficacy while reducing cisplatin-induced toxicity and drug resistance.	[272]
	Mouse	Colorectal Cancer	MnO_2-shelled nanoformulation with curcumin and doxorubicin boosts chemo-immunotherapy by inhibiting tumors and activating immunity.	[273]
	Mouse, SW620	Colorectal Cancer	Low-dose curcumin enhances 5-FU chemosensitivity by downregulating L1 and inhibiting pERK, promoting apoptosis and limiting proliferation.	[274]
	Mouse, 4T1, MDA-MB-231	Breast Cancer	Paclitaxel–curcumin co-delivery via PEG-PLGA	[275]

			nanoparticles reverses breast cancer resistance by downregulating P-gp and inhibiting NF-κB.	
	Rat, Mouse, Human, 4T1, MCF-7, A549, H1299, HCT116, SW480/SW620, SK-OV-3, OVCAR-3, SH-SY5Y	Multiple types of Cancers	Nano-curcumin enhances radiotherapy by sensitizing cancer cells via NF-κB inhibition and ROS accumulation, while protecting normal tissues through antioxidant and anti-inflammatory effects.	[276]
Combination with targeted therapies	A375.S2/VR	Melanoma	Curcumin induces apoptosis in vemurafenib-resistant melanoma by inhibiting EGFR/AKT/ERK signaling and activating caspase-dependent pathways, with enhanced effects when combined with gefitinib.	[277]
	HCC	Hepatocellular Carcinoma	Curcumin reverses Lenvatinib resistance in hepatocellular carcinoma via EGFR/PI3K-AKT downregulation, showing synergistic anti-tumor effects.	[278]
Combination with photodynamic and sonodynamic therapies	Mouse, CAM, MCF-7, MDA-MB-231, A431, HaCaT, Caco-2, HepG2, A549, SNB-19, Me180, MKN45, CT26, 4T1	Multiple types of Cancers	Nanoformulated curcumin acts as a photosensitizer in PDT by enhancing tumor targeting, inducing ROS-mediated apoptosis, and overcoming chemo- and radiotherapy resistance.	[279]
	U87, U251	Glioma	Curcumin plus low-intensity ultrasound inhibits glioma proliferation and induces apoptosis via AKT downregulation, offering a synergistic strategy.	[280]
	SCC-25, FaDu	Oral Carcinoma	Curcumin–oleanolic acid hybrid enhances cytotoxicity under low-intensity ultrasound, serving as a sonosensitizer in sonodynamic therapy.	[281]
Antioxidant and immunomodulatory effects	Rat, Mouse, Human, MCF-7, A549, MDA-MB-231, PC-3, HCT-116, SKOV3, HepG2, K562, RAW264.7, J774A.1, U937, L929, EA.hy926	Multiple types of Cancers	Liposome-encapsulated and metal-complexed curcumin enhance antioxidant activity, modulate redox homeostasis, and induce apoptosis via dual antioxidant–pro-oxidant antitumor mechanisms.	[282]
	Rat, Mouse, Human, A549, MCF-7, 3T3, HCT116, HT-29, MDA-MB-231, HepG2, FaDu, MCF-7/TH, SW620/AD300, H146, A549/ADR, H1299, H460, HCT116R, SCC-25, Beas-2B, RAW264.7	Multiple types of Cancers	Curcumin induces oxidative stress–mediated tumor cell death by activating Nrf2 and disrupting mitochondrial function via binding to intracellular reductases and NADPH; strategies like drug combinations, structural derivatives, and nanocarriers enhance its in vivo antitumor efficacy despite poor pharmacokinetics.	[283]
	SCC-15, A253, MCF-7, MDA-MB-468, MM-B1, MM-F1, H-Meso-1, PC-3, DU 145, HCT 116, PBMCs	Multiple types of Cancers	Curcumin–resveratrol combination modulates antitumor immunity by enhancing T and NK cell activity, increasing IL-10, and upregulating CD68 in monocytes/macrophages without impairing PBMC viability.	[284]
Inhibition of gene mutation and DNA damage	Mouse, MCF-7, MDA-MB-231, MCF-10A, MCF-12F	Breast Cancer	Curcumin acts as an epigenetic modulator by correcting aberrant DNA methylation of tumor suppressor and oncogene promoters, exerting anti-cancer and chemopreventive effects in breast cancer.	[285]

4.7 Other Therapeutic Potentials of Curcumin

4.7.1 Anti-inflammatory Effects in Specific Diseases

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease characterized by persistent synovial inflammation, pain, and progressive joint destruction. Curcumin has emerged as a potential anti-rheumatic agent by modulating multiple signaling pathways. Early studies have demonstrated that curcumin suppresses the activation of MAPK, AP-1, and NF-κB pathways in chondrocytes, thereby reducing the expression of inflammatory cytokines and matrix metalloproteinases (MMPs), which are

critically involved in cartilage degradation [286]. Furthermore, curcumin protects chondrocytes from damage by inhibiting IL-1β-induced expression of type II collagen and β1-integrin, as well as suppressing caspase-3 activation [287].

Osteoarthritis (OA), a degenerative joint disorder marked by cartilage degradation and chronic inflammation, also responds to curcumin treatment. Curcumin exerts anti-inflammatory and chondroprotective effects by downregulating NF-κB and AP-1 transcriptional activity, leading to reduced production of pro-inflammatory cytokines such as TNF-α and IL-1β. In addition, curcumin promotes autophagy and inhibits apoptosis in chondrocytes, further alleviating OA-related symptoms [288].

Periodontitis is a chronic inflammatory disease affecting the supporting structures of the teeth, primarily driven by local microbial factors. Curcumin has been shown to significantly reduce the levels of IL-6, IL-1β, IFN-γ, and TNF-α in experimental models of periodontitis, while also modulating collagen fiber integrity and preventing alveolar bone loss [289]. Ridho et al. reported that curcumin exerts its anti-inflammatory effects by inhibiting key pro-inflammatory mediators—including IL-1, IL-6, TNF-α, MMPs, PGE2, and COX-2—through the suppression of NF-κB and STAT1 signaling, while simultaneously enhancing the expression of anti-inflammatory cytokines IL-4 and IL-10. These findings underscore curcumin's therapeutic potential in both preclinical and clinical settings for periodontitis management [290].

4.7.2 Antimicrobial Activities

Antibacterial effects. Curcumin has demonstrated broad-spectrum antibacterial activity, including efficacy against multidrug-resistant pathogens. Hussain et al. reported that curcumin effectively inhibits Staphylococcus aureus and Escherichia coli, and shows promising synergistic effects when combined with conventional antibiotics against Helicobacter pylori and Mycobacterium tuberculosis [291]. Moreover, curcumin’s integration into nanocarrier delivery systems has significantly enhanced its bioavailability and antimicrobial efficacy, suggesting its potential application in infection control and as an antibacterial coating for orthopedic implants.

Antifungal effects. Curcumin has shown potent antifungal activity in vitro against 23 fungal strains, including Candida spp., Cryptococcus neoformans, Spathiphyllum shenkii, Paracoccidioides brasiliensis, and Aspergillus spp. [292]. Notably, curcumin exhibits therapeutic potential against dermatophytic infections and fungal skin diseases such as psoriasis and cutaneous mycoses, particularly through its fungicidal activity against Trichophyton mentagrophytes and Trichophyton rubrum. In addition, curcumin has demonstrated significant inhibitory effects against a wide range of pathogenic fungi including Trichophyton rubrum, Microsporum canis, Epidermophyton floccosum, Candida albicans, Rhizoctonia solani, Phytophthora infestans, and Blumeria graminis, supporting its use in the treatment of inflammatory skin disorders [293].

Antiviral effects. Curcumin has attracted increasing interest for its antiviral properties, particularly in the context of human immunodeficiency virus (HIV) and coronavirus infections. Butnariu et al. reviewed the pharmacological potential of curcumin in HIV treatment, highlighting its ability to interfere with multiple stages of viral infection. These include inhibition of gp120 binding to host cells, suppression of integrase,

protease, and topoisomerase II activities, and modulation of the immune response, thereby exerting both antiviral and protective effects against HIV-related complications [294]. In the context of the COVID-19 pandemic, curcumin has been proposed as a potential therapeutic candidate. Thimmulappa et al. reported that curcumin exerts antiviral activity against enveloped viruses such as SARS-CoV-2 through diverse mechanisms, including disruption of viral membrane proteins, envelope destabilization, inhibition of viral proteases, and activation of host antiviral defenses. Moreover, curcumin attenuates COVID-19-associated complications such as pneumonia and acute respiratory distress syndrome (ARDS) by downregulating NF-κB, inflammasome signaling, IL-6 transduction, and HMGB1 pathways, supporting its role as a safe and immunomodulatory prophylactic agent [295]. Ardebili et al. conducted a comprehensive review of 43 studies on the antiviral effects of curcumin against 24 viruses. Their findings confirmed curcumin's broad-spectrum antiviral efficacy, mediated by interference with viral envelope integrity, inhibition of viral entry and replication, and modulation of host signaling pathways including NF-κB and PI3K/AKT [296].

4.7.3 Antifibrotic Effects

In recent years, curcumin has gained increasing attention for its promising antifibrotic activity across various organ systems, including the liver, lungs, kidneys, and heart. Its antifibrotic properties are primarily attributed to its ability to regulate multiple molecular pathways involved in fibrosis progression. Yu et al. conducted a comprehensive review of curcumin's antifibrotic mechanisms, highlighting its regulatory effects on oxidative stress–related signaling pathways in hepatic, renal, pulmonary, and cardiac fibrosis. Curcumin exerts its protective actions by modulating key molecular targets such as ROS, NRF2, PPARs, and TGF-β1, which collectively contribute to the inhibition of abnormal ECM deposition and attenuation of fibrosis-related organ dysfunction [297].

4.7.4 Anti-aging Effects

In recent years, the potential of curcumin in delaying aging and preventing age-related decline has gained increasing attention. Its anti-aging properties are attributed to its strong antioxidant capacity, anti-inflammatory effects, regulation of cellular signaling pathways, and protection of cognitive and cardiovascular function.

Antioxidant activity and free radical scavenging. Oxidative stress is a key contributor to the aging process, with excessive ROS causing lipid peroxidation, DNA damage, and protein dysfunction, thereby accelerating cellular and tissue aging. Curcumin has demonstrated potent antioxidant activity by reducing ROS generation, scavenging free radicals, and restoring the activity of endogenous antioxidant enzymes such as SOD, GSH-Px, and CAT. He et al. reviewed the anti-aging effects of curcumin, highlighting its capacity to reduce oxidative damage, regulate apoptosis, and improve brain health. They emphasized that curcumin exerts these effects by modulating signaling pathways such as AMPK, AKT/mTOR, NF-κB, and PI3K/MAPK, ultimately delaying cellular senescence and disease progression [298].

Anti-inflammatory effects. Chronic low-grade inflammation is a hallmark of aging and contributes to the development of age-associated disorders such as cardiovascular disease, neurodegeneration, and metabolic

syndrome. Curcumin reduces systemic inflammation by inhibiting the activation of pro-inflammatory transcription factors, including NF-κB and AP-1, and by suppressing the expression of cytokines such as TNF-α, IL-1β, and IL-6 [299]. Through its anti-inflammatory effects, curcumin helps mitigate tissue deterioration and functional decline associated with aging.

Regulation of signaling pathways and genomic stability. Aging is closely associated with alterations in cell signaling and loss of genomic integrity. Curcumin modulates key aging-related pathways, including mTOR, AMPK, and SIRT1. By downregulating mTOR and activating AMPK and SIRT1, curcumin enhances mitochondrial function, improves energy metabolism, facilitates DNA repair, and maintains genome stability. Additionally, curcumin has been shown to regulate telomerase activity, which may indirectly influence cellular longevity [300].

Neuroprotection and cognitive preservation. Aging is often accompanied by neurodegeneration and cognitive impairment. Curcumin confers neuroprotective effects through its antioxidant and anti-inflammatory properties, stabilization of neuronal membranes, and modulation of neuroplasticity-associated signaling. In models of Alzheimer's disease and Parkinson's disease, curcumin has been shown to attenuate neuronal damage and apoptosis, thereby preserving cognitive function and offering preventive potential for age-related neurodegenerative disorders [301].

Improvement of metabolic and cardiovascular function. Age-related metabolic dysfunction and cardiovascular decline are common features of aging. Curcumin improves lipid metabolism, reduces hyperlipidemia, and enhances insulin sensitivity, thereby lowering the risk of atherosclerosis and metabolic syndrome. Its vascular-protective effects include the preservation of endothelial integrity, maintenance of vascular elasticity, and reduction of vascular inflammation, which collectively help delay cardiovascular aging [302, 303].

Curcumin exerts its anti-aging effects through multiple mechanisms, including enhancement of antioxidant defenses, suppression of chronic inflammation, maintenance of genomic stability, and protection of the nervous and cardiovascular systems. While current evidence from cellular and animal studies supports its therapeutic potential, large-scale and long-term clinical trials are still needed to confirm its efficacy, safety, and optimal dosage in human aging. Further investigations will be crucial to establish curcumin as a viable intervention for promoting healthy aging and improving the quality of life in the elderly.

4.7.5 Anti-obesity Effects

Curcumin has emerged as a promising adjunct for obesity prevention and management by simultaneously targeting multiple pathophysiological nodes that drive excess adiposity. A systematic review by Kasprzak-Drozd et al. collated evidence from cell-based studies, animal models, and preliminary clinical trials, concluding that curcumin safely reduces body-fat accretion and mitigates weight gain through a constellation of inter-related mechanisms [304]. At the metabolic level, curcumin activates AMPK and PPARα, thereby accelerating fatty-acid β-oxidation and limiting hepatic and adipocytic lipid storage. Concomitantly, it suppresses de-novo adipogenesis by down-regulating the master transcriptional regulators

PPARγ, C/EBPα, and SREBP-1c while reinforcing Wnt/β-catenin signalling that preserves pre-adipocytes in an undifferentiated state. Curcumin further impairs the vascularisation and survival of expanding adipose depots by inhibiting angiogenic signalling and promoting adipocyte apoptosis, actions that collectively constrain tissue hypertrophy. Beyond direct lipid regulation, curcumin reshapes the gut microbial ecosystem—most notably enriching Akkermansia spp.—to strengthen epithelial barrier integrity, diminish metabolic endotoxaemia, and attenuate NF-κB–driven systemic inflammation. Its antioxidant capacity neutralises reactive oxygen species, curtailing oxidative stress that otherwise potentiates insulin resistance. Finally, curcumin enhances whole-body energy expenditure by inducing browning of white adipose tissue: it up-regulates uncoupling protein-1 (UCP1) and engages the TGR5–cAMP–PKA axis to amplify thermogenesis. These convergent actions provide a mechanistic rationale for curcumin's anti-obesity efficacy and underscore the need for rigorously powered clinical trials to refine dosage, evaluate long-term benefits, and determine its place in comprehensive obesity-care algorithms.

4.7.6 Renal Protective Effects

Acute and chronic kidney injury have become major global health and economic concerns. Curcumin has shown promising potential in preserving renal function and mitigating kidney damage, particularly in models of diabetic nephropathy, oxidative stress-induced injury, and chemical toxicity.

Diabetic nephropathy and inflammatory response. Chronic inflammation plays a central role in the progression of diabetic kidney disease. Curcumin has been shown to suppress the NF-κB signaling pathway, leading to reduced expression of pro-inflammatory cytokines such as TNF-α and MCP-1, thereby attenuating renal inflammation associated with diabetes. Additionally, curcumin downregulates COX-2 expression, suggesting a protective role in renal tissue remodeling and anti-fibrotic effects [305].

Protection against nephrotoxicity induced by Heavy metal, chemical toxicant, and ischemia-reperfusion-induced nephrotoxicity. Al Fayi et al. demonstrated that curcumin, especially in combination with thymoquinone, confers significant protection against cisplatin-induced nephrotoxicity primarily by activating the Nrf2/ARE signaling pathway. This activation promotes the nuclear translocation of Nrf2 and enhances the transcription of antioxidant and phase II detoxifying enzymes, including HO-1, SOD, CAT, GPx, and GR. Curcumin also disrupts the Keap1-Nrf2 complex, thereby facilitating sustained Nrf2 activation. Concurrently, it suppresses the NF-κB signaling cascade, leading to reduced expression of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β. In addition, curcumin downregulates renal injury markers like KIM-1 and MRP-1 and modulates apoptosis by inhibiting pro-apoptotic proteins such as Bax and caspase-3 while upregulating the anti-apoptotic protein Bcl-2. Through these combined antioxidative, anti-inflammatory, and anti-apoptotic mechanisms, curcumin exerts a comprehensive nephroprotective effect against heavy metal and chemical toxicant-induced renal injury [306]. Curcumin has been reported to attenuate cyclosporine A (CsA)-induced nephrotoxicity via its potent antioxidant properties and hemodynamic regulatory effects. In experimental models, curcumin improved antioxidant enzyme activity and alleviated histopathological alterations in the kidney following CsA exposure. Furthermore, a

randomized controlled trial in renal transplant patients demonstrated that curcumin supplementation improved early post-transplant renal function, reduced acute cellular rejection, and mitigated neurotoxicity—possibly through the induction of HO-1 [307]. Curcumin also exhibits significant renoprotective effects in models of renal I/R injury, adriamycin-induced nephropathy, and oxidative stress–induced renal damage. These effects are mediated through free radical scavenging, reduction of lipid peroxidation, and inhibition of oxidative damage to renal cells. Curcumin efficiently neutralizes various reactive species—including superoxide anion, hydroxyl radical, and peroxynitrite—and has been shown to significantly suppress lipid peroxidation in multiple animal models, thereby preserving renal structural and functional integrity [308].

In summary, curcumin protects renal function by inhibiting inflammatory mediators, reducing ROS generation, enhancing antioxidant defense systems, and modulating cytokine expression. Its efficacy has been demonstrated across a range of renal injury models, including diabetic nephropathy, heavy metal and chemical toxicant exposure, immunosuppressant and chemotherapy-induced nephrotoxicity, and I/R injury. These findings provide a strong foundation for the further development of curcumin-based therapeutic agents targeting kidney protection.

4.7.7 Wound Healing Promotion

Tissue repair and wound healing are complex physiological processes involving sequential phases of inflammation, granulation tissue formation, and tissue remodeling. Amrita Kumari et al. conducted a comprehensive review of the wound-healing mechanisms of curcumin and its nanoformulations, highlighting its therapeutic efficacy across multiple biological pathways. Curcumin promotes wound healing by suppressing pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 through inhibition of the NF-κB signaling pathway. It enhances antioxidant defenses by activating the Nrf2/Keap1 pathway and upregulating endogenous antioxidants, including GSH and CAT. In the proliferative phase, curcumin facilitates fibroblast proliferation, collagen synthesis (types I and III), and extracellular matrix remodeling through modulation of the TGF-β/Smad and FGF signaling pathways. Furthermore, it stimulates angiogenesis via upregulation of VEGF and accelerates re-epithelialization by promoting keratinocyte migration and proliferation. Notably, nanoformulations of curcumin—such as liposomes, solid lipid nanoparticles, and polymeric micelles—address its pharmacokinetic limitations by improving solubility, enhancing bioavailability and tissue retention, and enabling controlled drug release. These advancements significantly improve the therapeutic efficacy of curcumin in both acute and chronic wound models, including diabetic foot ulcers [309].

4.7.8 Ophthalmological Applications

In the field of ophthalmology, curcumin has shown considerable therapeutic potential in suppressing proliferative disorders, preventing cataract formation, inhibiting neovascularization, and modulating the proliferation of lens epithelial cells and retinal pigment epithelial cells. Adriana Ribeiro et al. elucidated the multifaceted mechanisms underlying curcumin's therapeutic efficacy in ocular diseases. Curcumin modulates several key molecular pathways, including inflammatory (NF-κB, TLR4, NLRP3), antioxidant (Nrf2/Keap1),

angiogenic (VEGF), and apoptotic (Bcl-2/Bax, caspase-3) signaling cascades. These mechanisms allow curcumin to suppress cytokine storms, reduce oxidative damage, inhibit pathological angiogenesis, and protect retinal and corneal cells from apoptosis. In addition, curcumin's immunomodulatory and antibacterial properties help maintain epithelial barrier integrity and regulate the ocular immune microenvironment. Despite its poor aqueous solubility and limited ocular bioavailability, recent advances in ocular delivery systems—such as nanoparticles, cyclodextrin inclusion complexes, proniosomal gels, and in situ forming gels—have significantly improved curcumin's solubility, corneal penetration, and ocular tissue retention. These delivery strategies support its application in both anterior and posterior segment conditions, including diabetic retinopathy, age-related macular degeneration, glaucoma, dry eye disease, and infectious keratitis [310]. Given its wide availability, low cost, and favorable safety profile, curcumin holds great promise as a natural therapeutic agent for the prevention and treatment of proliferative ocular diseases. Its antifibrotic, antiproliferative, and pro-apoptotic properties make it a particularly attractive candidate for ophthalmic applications, potentially expanding its clinical utility across a range of vision-threatening disorders.

4.7.9 Protective Effects on the Skeletal Muscular System

Emerging evidence has also highlighted curcumin's role in preserving skeletal muscle integrity and promoting muscle regeneration. Vargas-Mendoza et al. systematically summarized the multifaceted protective mechanisms of curcumin (*Curcuma longa Linn*) on skeletal muscle health, demonstrating its ability to prevent muscle atrophy and promote regeneration through modulation of key molecular pathways. Curcumin inhibits muscle protein degradation by suppressing the ubiquitin–proteasome system, primarily through downregulation of E3 ubiquitin ligases such as atrogin-1/MAFbx and MuRF-1 via inhibition of NF-κB, FoxO, and p38 MAPK signaling. Concurrently, it promotes protein synthesis and hypertrophy by activating the PI3K/Akt/mTOR pathway, and supports muscle regeneration by enhancing satellite cell proliferation and myogenic differentiation through upregulation of MyoD, myogenin, and related transcriptional regulators. Moreover, curcumin mitigates oxidative stress and inflammation by boosting endogenous antioxidant systems via Nrf2 activation and reducing pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6. In various disease and injury models—including sepsis, cancer cachexia, diabetes, COPD, chronic kidney disease, and immobilization-induced muscle atrophy—curcumin has been shown to restore mitochondrial function, regulate apoptosis-related proteins (e.g., Bcl-2, caspase-3), and activate PGC-1α/SIRT3 signaling. Although its natural bioavailability is limited, the development of advanced nanoformulations has markedly improved systemic absorption and therapeutic outcomes for muscle preservation and recovery [311].

Taken together, a single phytochemical—curcumin—modulates a constellation of molecular switches (e.g., ↓ NF-κB, ↑ SIRT1, ↑ eNOS) that converge on system-specific benefits ranging from plaque regression and improved FEV_1 to tumor shrinkage and immune homeostasis. **Figure 4** provides an at-a-glance synthesis of these cross-organ mechanisms, the functional intermediates they govern, and the clinical end-points already documented in pre-clinical or human studies.

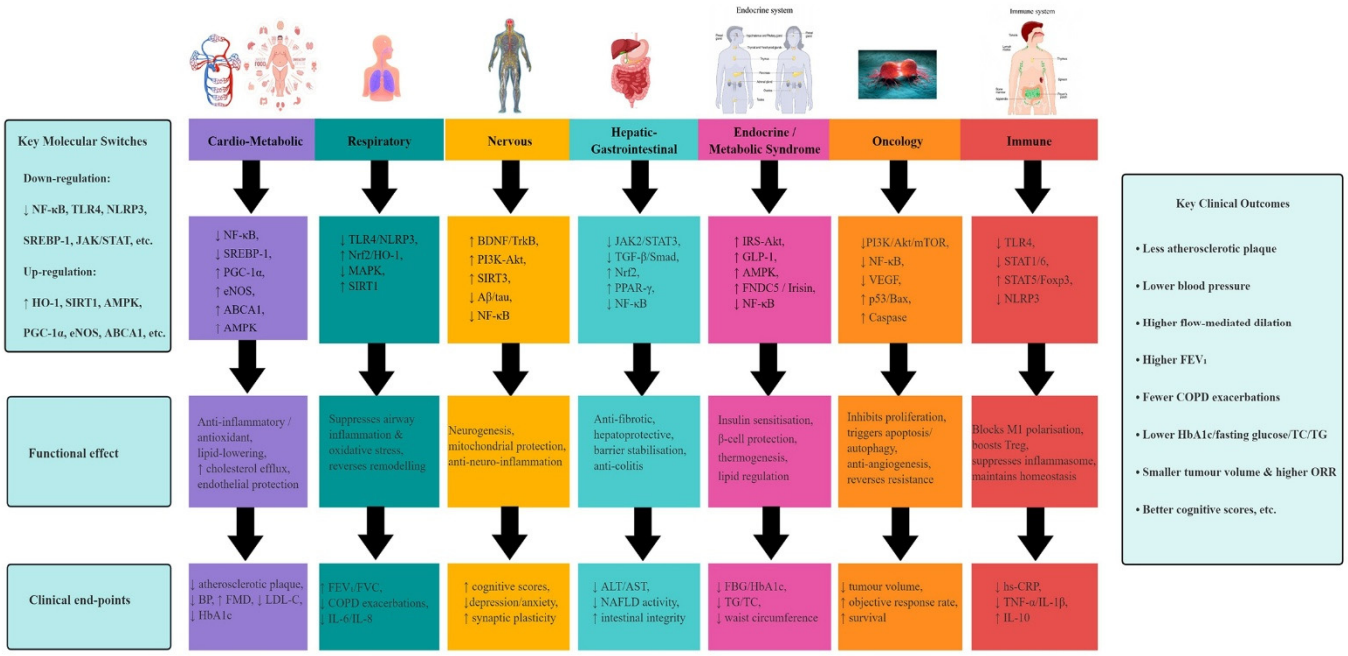

Fig. 4. Multisystem protective mechanisms of curcumin.

5. Assessing Toxicity and Safety

With the advancement of the food industry, food colorants have attracted growing attention from consumers as essential additives for enhancing the visual appeal of products. However, increasing concern has also emerged regarding the potential adverse effects of food additives on human health. Curcumin, a naturally occurring pigment and bioactive component, has received substantial attention due to its anti-tumor and antioxidant properties. Nonetheless, it also exhibits potential pro-oxidant activity [282] and remains under scrutiny for its possible carcinogenicity under specific conditions [312]. The Food and Agriculture Organization (FAO)/World Health Organization (WHO) Joint Expert Committee on Food Additives and the European Food Safety Authority (EFSA) have set the acceptable daily intake (ADI) for curcumin at 0–3 mg/kg body weight [313]. Despite numerous studies evaluating its safety and efficacy, the findings on its toxicological effects remain inconclusive. The precise mechanisms of curcumin's toxicity are still not fully elucidated, and its absorption and metabolism in vivo remain incompletely understood.

Animal toxicology studies suggest that curcumin, when used within conventional dosage ranges, does not exhibit subchronic toxicity, genotoxicity, or teratogenicity [314]. For example, Dadhaniya et al. conducted acute and subchronic toxicity evaluations of a solid lipid curcumin particle formulation, reporting that the oral LD_{50} values exceeded 2000 mg/kg in both rats and mice, with no observable adverse effects. In a 90-day subchronic study, Wistar rats received oral doses up to 720 mg/kg/day without showing any clinical symptoms, alterations in physiological or hematological parameters, or organ toxicity, establishing a no-observed-adverse-effect level (NOAEL) of 720 mg/kg/day [315]. Phipps et al. evaluated a novel, highly bioavailable turmeric extract in 28- and 90-day repeated-dose oral toxicity studies in rats and found no evidence of genotoxicity or treatment-related toxicity. The NOAEL was determined to be 3000 mg/kg/day [316]. Dandekar et al. assessed the toxicological safety of pH-sensitive curcumin nanoparticles,

demonstrating no acute toxicity at doses up to 2000 mg/kg. Subacute studies further confirmed safety at both therapeutic (100 mg/kg) and double doses, while genotoxicity tests revealed no cytotoxic effects—even at triple the therapeutic dose—supporting its high safety margin [317]. Similarly, Phipps et al. investigated the genotoxic profile of solid lipid curcumin granules and reported no mutagenic activity against Salmonella typhimurium strains. In vivo micronucleus assays in mice, even at doses up to 2000 mg/kg, showed no chromosomal damage, confirming the genotoxic safety of the formulation [318]. Dziwenka et al. evaluated a novel curcumin complex and reported no adverse effects in rats following acute oral administration of doses up to 5000 mg/kg. A 4-week repeated-dose toxicity study at 1000 mg/kg/day demonstrated good tolerability, while a comprehensive genotoxicity battery—including bacterial reverse mutation, in vitro chromosomal aberration, and in vivo micronucleus assays—revealed no mutagenic potential [319]. Jantawong et al. examined the acute and chronic toxicity of curcumin-loaded nanocomposites (CNCs) in mice and hamsters. The oral LD_{50} values were 8.9 g/kg in mice and 16.8 g/kg in hamsters (equivalent to approximately 2.5 and 4.7 g/kg of curcumin, respectively). At standard doses (0.27 g/kg/day in mice and 0.54 g/kg/day in hamsters), no toxicity was observed. Although high-dose groups exhibited changes in biochemical and histopathological markers, most of these abnormalities resolved within 28 days post-treatment. The NOAELs were determined to be 0.27 g/kg/day and 0.54 g/kg/day in mice and hamsters, respectively, suggesting high safety and potential for clinical development [320].

Conversely, the U.S. National Toxicology Program (NTP) conducted a comprehensive evaluation of turmeric oleoresin containing 79%–85% curcumin to assess its toxicity and carcinogenic potential. In a 13-week dietary study, high doses (50,000 ppm) resulted in gastrointestinal mucosal hyperplasia in rats and increased liver weights in mice, although no significant clinical toxicity was observed. In a two-year feeding study, there was no evidence of carcinogenicity in male rats. However, equivocal evidence was reported in female rats and in both male and female mice, including increased incidences of hepatocellular adenomas, intestinal tumors, and thyroid follicular cell hyperplasia. Additionally, mild chromosomal damage was detected in some in vitro genotoxicity assays [321].

Clinical studies have demonstrated that oral administration of curcumin at doses up to 8–12 g/day for up to three months is generally well tolerated in humans. Most reported adverse effects are mild and transient, including gastrointestinal discomfort (e.g., abdominal pain, nausea, diarrhea), skin rash, headache, and yellow-colored stool—classified as Grade 1 (mild) under WHO toxicity criteria [322]. Curcumin has been widely recognized for its diverse pharmacological activities, including antioxidant, anti-inflammatory, cardiovascular- and neuroprotective, anti-tumor, anticoagulant, metabolic regulatory effects, and other related benefits. These multifaceted therapeutic properties have led to its application in various disease models and functional food development. However, growing evidence has also highlighted the need to evaluate its safety profile, particularly in the context of high-dose or long-term use, due to potential concerns regarding toxicity. However, despite these broad therapeutic potentials, some studies have raised concerns about its potential toxicity, particularly in the context of high-dose or long-term use. Reported effects

include cytotoxicity [323], genotoxicity and anti-genotoxicity [324], as well as phototoxicity and dermal toxicity [325].

Notably, curcumin exhibits dose-dependent dual biological effects. At low concentrations, it displays protective antioxidant and anti-tumor properties, whereas at high doses it may induce oxidative stress, DNA damage, and cytotoxic or genotoxic responses [326, 327]. This bidirectional behavior highlights the critical role of dose in determining curcumin's safety or toxicity. Furthermore, structural modifications of the curcumin molecule—such as the introduction of different substituent groups—may influence its toxicological profile, providing a foundation for future structure–activity relationship (SAR) research and novel drug development.

In summary, curcumin is a naturally derived compound with broad availability, low cost, and generally favorable safety, and has been widely applied in multidisciplinary clinical research. When used at appropriate doses and durations, it appears to be safe and may serve as a natural "anti-aging food" or health-promoting supplement. However, the potential risks associated with high-dose, long-term use or condition-specific toxicity warrant continued investigation and careful evaluation. For details on the safety and toxicity observations of curcumin in medical use, please see **Table 7**.

Table 7 Safety and Toxicity Observations of Curcumin in Medical Use.

Study Subjects	Dosage	Dosing Regimen / S9 Condition	Key Observational Findings	Ref.
Rat, Mouse	2000 mg/kg/day	Single oral gavage; observation for 15 days	No mortality or clinical toxicity; LD_{50} > 2000 mg/kg/day; no gross pathological changes.	[315]
Rat	180, 360, 720 mg/kg/day	Daily oral gavage for 90 days; recovery groups observed for 28 additional days	No treatment-related effects on behavior, body weight, feed intake, hematology, serum biochemistry, organ weights, or histopathology. NOAEL: 720 mg/kg/day.	
Rat	500, 1500, 3000 mg/kg/day	Oral gavage, once daily for 91 (males) or 92 (females) consecutive days	No item-related deaths, toxicity, or histopathology; slight liver weight increase (high dose) without biochemical or microscopic hepatotoxicity. NOAEL: 3000 mg/kg/day.	[316]
Rat	500, 1500, 3000 mg/kg/day	Oral gavage, once daily for 28 days	No treatment-related effects on clinical signs, body or organ weights. Yellowish coat/feces at high dose due to formulation color; toxicologically insignificant.	
Rat	Cur-NP 2000 mg/kg	Single oral gavage	No mortality or toxicity; gross pathology normal.	[317]
	Cur-NP 100 & 200 mg/kg	Oral gavage once daily for 28 days	No behavioral/clinical toxicity; hematology, biochemistry, organ weight, histopathology normal.	
Mouse	Cur-NP 100, 200, 300 mg/kg;	Oral gavage once daily for 2 days (Micronucleus assay)	No increase in micronucleated cells or PCE/NCE ratio change; genotoxicity negative.	
Rat	Cur-NP 100, 200, 300 mg/kg;	Oral gavage once daily for 2 days (Chromosome Aberration assay)	No significant chromosome aberrations vs. control; genotoxicity negative.	
	Cur-NP 100, 200, 300 mg/kg;	Oral gavage once daily for 2 days (Comet assay)	No comet formation or DNA damage; genotoxicity negative.	

Salmonella typhimurium strains, Mouse	500, 1000, or 2000 mg/kg/day	For bacteria: standard Ames assay conditions with and without S9 metabolic activation; for mice: oral gavage twice in 24 h	No mutagenicity was observed in the bacterial reverse mutation assay, nor were micronucleated erythrocytes or chromosomal aberrations increased in mice, indicating the lipidated curcumin formulation is non-genotoxic.	[318]
Rat	1000, 2000, 5000 mg/kg (single dose); 100, 300, 1000 mg/kg/day (28-day)	Oral gavage, single dose and daily for 4 weeks	No mortality or toxicity in single-dose study; NOAEL 1000 mg/kg/day in 28-day study with no toxicologically significant histopathology or clinical changes.	[319]
Mouse	500, 1000, 2000 mg/kg/day	Oral gavage, 2 doses, 23.5–24 h apart	No increase in micronucleus formation; no dose-response; CuminUP60® considered non-mutagenic.	
Salmonella typhimurium	51.2–2000 μg/plate	In vitro Ames test, with/without S9 metabolic activation	No mutagenicity observed; revertant colonies comparable to vehicle control.	
Chinese hamster lung fibroblasts	0.512–20 μg/mL	In vitro chromosomal aberration assay (3 h ± S9; 24 h − S9)	No chromosomal aberrations observed across all conditions; non-mutagenic.	
Mouse	0.1, 1.1, 11 g/kg (equiv. to 0.03, 0.3, 3 g/kg curcumin)	Single oral dose, observed for 14 days	LD50: 8.9 g/kg; high dose increased spleen weight and altered biochemical parameters (e.g., BUN, TP, globulin); liver inflammation noted at 11 g/kg.	[320]
Hamster	0.2, 2.1, 21.4 g/kg (equiv. to 0.06, 0.6, 6 g/kg curcumin)	Single oral dose, observed for 14 days	LD_{50}: 16.8 g/kg; high dose increased liver, heart, stomach weights; no major serum changes; mild liver inflammation at 21.4 g/kg.	
Mouse	0.09, 0.27, 0.8 g/kg/day (equiv. to 0.025, 0.075, 0.225 g/kg curcumin)	Daily oral gavage for 6 months, plus 28-day recovery	NOAEL: 0.27 g/kg/day; high dose induced elevated liver enzymes (ALT, AST), organ-weight changes (stomach, intestine, pancreas), and reversible liver inflammation.	
Hamster	0.18, 0.54, 1.61 g/kg/day (equiv. to 0.05, 0.15, 0.45 g/kg curcumin)	Daily oral gavage for 6 months, plus 28-day recovery	NOAEL: 0.54 g/kg/day; high dose raised AST, altered glucose, cholesterol, organ weights (stomach, heart); mild liver inflammation and ER stress reversed post-treatment.	
Rat	0, 1,000, 5,000, 10,000, 25,000, 50,000 ppm(≈50–2,600 mg/kg/day in males, 60–2,800 mg/kg/day in females)	Dietary, daily for 13 weeks	↑ Liver weight in both sexes at ≥5,000 ppm; hyperplasia in cecum/colon at 50,000 ppm; no significant hematological changes; NOAEL ~10,000 ppm.	[321]
Mouse	0, 1,000, 5,000, 10,000, 25,000, 50,000 ppm(≈150–7,700 mg/kg/day in males, 200–9,300 mg/kg/day in females)	Dietary, daily for 13 weeks	↑ Liver weight at ≥5,000 ppm in males, ≥10,000 ppm in both sexes; no significant hematological or histopathological effects; NOAEL ~5,000 ppm.	
Rat	2,000, 10,000, 50,000 ppm (≈80–2,000 mg/kg/day in males, 90–2,400 mg/kg/day in females)	Dietary, daily for 104/103 weeks	↑ Liver weight and GI tract lesions at 50,000 ppm; ↓ RBC/Hb/HCT, ↑ platelets; clitoral gland adenomas ↑ in all exposed groups; NOAEL ~10,000 ppm.	
Mouse	2,000, 10,000, 50,000 ppm (≈220–6,000 mg/kg/day in males, 320–8,400 mg/kg/day in females)	Dietary, daily for 103 weeks	↑ Liver weight at ≥10,000 ppm; hepatocellular adenomas ↑ at 10,000 ppm; thyroid hyperplasia (females, 50,000 ppm); NOAEL ~2,000 ppm.	
Rat	Up to 5,000 mg/kg turmeric extract	Single oral dose	No signs of toxicity or mortality; LD_{50} > 5,000 mg/kg.	[322]
Rat	0.05%, 0.5%, 1.0% turmeric oleoresin in diet (~45, 450, 900 mg/kg/day)	Daily oral administration for 90 days	No toxicologically relevant changes; NOAEL = 900 mg/kg/day; no liver/kidney pathology.	
Mouse	0.5, 1.0, 2.0 g/kg turmeric oleoresin	Single oral dose	No genotoxicity; no increase in micronucleus frequency.	

Rat	Up to 2,200 mg/kg/day	Oral administration during gestation	No teratogenicity; slight maternal toxicity at 2,200 mg/kg/day.
Salmonella strains	Up to 5,000 μg/plate turmeric oleoresin	With/without S9 metabolic activation	No mutagenic activity observed across bacterial strains.
Rat, Mouse	0.05%–1% turmeric oleoresin in diet	Oral administration for 2 years	No increase in tumor incidence; no carcinogenic effects.
Human	500–2,000 mg/day	Daily for 1–2 months	Well tolerated; no serious adverse effects; occasional mild GI symptoms.
Human	8–12 g/day	Daily for up to 3 months	No serious toxicity reported; occasional nausea, diarrhea, or abdominal discomfort.

6. Discussion

6.1 Modern delivery systems — quantitative gains, cost and safety

Native curcumin suffers from very low oral bioavailability—absolute F rarely exceeds 1%–2% because of its poor aqueous solubility, rapid intestinal conjugation and extensive first-pass metabolism [8, 29]. During the past decade five main formulation strategies have been developed to overcome this bottleneck: piperine-assisted absorption enhancers, phospholipid phytosomes, polymeric or surfactant micelles, lipid-based nanoparticles (including solid-lipid nanoparticles, nano-emulsions and self-nano-emulsifying drug-delivery systems) and amorphous solid dispersions typified by Theracurmin®. Head-to-head pharmacokinetic studies show that all of these platforms increase the area-under-the-curve (AUC) by at least an order of magnitude, with some nano-micellar preparations pushing gains beyond 180-fold [16, 34, 35, 38, 62].

Among the fast-to-market options, piperine co-administration and phytosomal complexation generally raise systemic exposure 20–30-fold. Costs remain low because both can be produced with capsule-grade excipients and conventional mixing or simple solvent-evaporation steps. Their clinical maturity is high—more than a dozen randomised controlled trials (RCTs) have already documented metabolic, anti-inflammatory and musculoskeletal benefits—but piperine's broad inhibition of CYP3A4 and P-gp obliges prescribers to watch for drug–drug interactions, especially with anticoagulants or immunosuppressants [25, 36]. Phytosomes share a similar efficacy record without those interaction concerns, and gastrointestinal events are usually limited to mild dyspepsia in fewer than five per cent of participants [16].

High-performance nano-vehicles—polymeric micelles, nano-emulsions, solid-lipid nanoparticles and SNEDDS—routinely break the 100-fold AUC barrier, making extra-intestinal targets such as brain and myocardium pharmacologically accessible [34, 38]. The trade-off is economic and logistical: manufacture requires high-pressure homogenisation, specialised surfactants or nano-milling, and quality control for particle size and polydispersity. Raw-material costs are typically three- to five-times higher than for piperine blends, and lipid-rich systems may demand cold-chain storage. Human data remain sparse—only a handful of phase-1 PK trials and early phase-2 efficacy studies are available—yet reported adverse events have been limited to transient bloating or nausea [34, 37].

Amorphous solid dispersions such as Theracurmin® occupy a pragmatic middle ground. Wet-milling or spray-drying with food-grade carriers yields particles < 200 nm that are physically stable at room

temperature and boost AUC by roughly 30- to 50-fold [62]. More than fifteen RCTs across cardiovascular, metabolic and neurological indications confirm favourable tolerability, with gastrointestinal complaints occurring at frequencies comparable to placebo and no signals for hepatotoxicity, QT prolongation or haemostatic impairment [62, 314-316]. Because production relies on standard spray-dry equipment, scale-up costs are lower than for most nano-emulsions, and no cold-chain is needed.

Pooled across > 40 clinical trials, formulated—or "nano-"curcumin—remains well tolerated: mild gastrointestinal symptoms are the most frequent adverse events (≤ 7% versus ≈ 3% with placebo), while serious toxicity has not been documented [16, 315, 316, 320]. Intravenous liposomal curcumin has reached 300 mg m^{-2} without dose-limiting toxicity, although two oncology studies noted transient bilirubin rises. Taken together, these data show that curcumin bioavailability can now be engineered upwards by one to two orders of magnitude; the choice of platform should therefore be guided by the intended therapeutic target, acceptable manufacturing cost and the interaction profile of co-medications.

6.2 Translational prospects, knowledge gaps and future research

Curcumin has travelled an unusual path from culinary colourant to experimental "food-as-medicine" ingredient. Six decades of work now show that this diarylheptanoid couples potent redox modulation with wide-ranging effects on inflammatory, metabolic and immune signalling [8]. Within the remit of Food Science these insights translate into two practical opportunities. First, at culinary intakes that remain below the established acceptable daily intake (0–3 mg kg^{-1} bw day^{-1}) [7] curcumin can be positioned as a functional pigment capable of contributing measurable antioxidant capacity to staple foods [5]. Second, when it is embedded in engineered food matrices—solid-lipid nanoparticles, micelles, protein–polysaccharide complexes or co-crystals with piperine—its bioavailability increases by one to two orders of magnitude [15], opening realistic prospects for targeted benefits such as intestinal anti-inflammatory action, lipid lowering and glycaemic control [88]. Thus the long-standing "poor absorption" bottleneck has become a tractable food-technology problem.

Pharmacokinetic data from rodents and humans converge on the conclusion that native curcumin is largely restricted to the intestinal lumen and mucosa, where it is rapidly conjugated [29]. This exposure profile explains why high-dose powders affect colonic end-points yet rarely influence extra-intestinal tissues [31]. Formulated preparations that raise the area under the plasma curve by 10- to 200-fold clearly blur that boundary, but inter-individual variation remains wide and the modifying effect of meal composition is poorly mapped [37]. Capturing the dynamic gut–liver–systemic gradient will require real-time flux methodologies that combine food-omics, imaging and microbiome read-outs [15].

Toxicologically, curcumin occupies a wide safety margin. Sub-chronic (6-month) and long-term feeding studies of 103–104 weeks—up to 2 years—in rats and mice broaden the evidence base, yielding NOAELs of roughly 200–900 mg kg^{-1} day^{-1} and showing only reversible hepatomegaly or mild intestinal hyperplasia at ≥ 1 g kg^{-1} day^{-1} [321]. In humans, doses as high as 12 g day^{-1} have produced nothing more than mild gastrointestinal discomfort [27]. In the same two-year NTP bioassay, however, a marginal increase in

hepatocellular adenomas appeared only in the 10 000 ppm group, not at lower doses [321], implying that extremely prolonged, high-level exposure could trigger tumour-promoting signals.

Nevertheless, two further caveats warrant attention. First, life-long very-high feed concentrations caused equivocal rises in hepatocellular and intestinal tumours in rodents [320], hinting at a hormetic pro-oxidant switch under chronic overload [325]. Second, case reports of bleeding in patients receiving anticoagulants point to a plausible interaction via platelet inhibition and CYP/P-gp modulation [124]. These findings do not undermine the culinary use of curcumin, but they do argue for formulation-specific safety monitoring in susceptible populations. It should also be emphasised that the longest follow-up in human supplementation trials so far is only four months; data on ≥ 12-month continuous high-dose exposure are still missing, and the possibility of cumulative hepatotoxicity or perturbations in bilirubin metabolism therefore warrants prospective surveillance.

The rich catalogue of cardiovascular, neuroprotective and renoprotective effects described in preclinical studies will only be clinically relevant if tissue concentrations can be raised beyond the gut [302]. Delivery science provides proof-of-concept—nano-curcumin co-delivered with paclitaxel [274], or MnO_2-shelled immunonanoparticles [272]—but the influence of realistic food vehicles on absorption, lymphatic transport and enterohepatic cycling remains to be clarified [34]. Embedding advanced carriers into edible matrices therefore represents a promising bridge between pharmacology and food innovation [328].

Methodologically, curcumin research would benefit from greater standardisation. Dose units vary (mg versus mol kg^{-1}), purity is inconsistently reported, and many cell studies employ micromolar concentrations far above biorelevant exposure [12]. Adopting minimum-information standards that include full chromatographic fingerprints, conjugate profiling and validated reference materials would greatly improve cross-study comparability [15].

Looking ahead, three research avenues seem particularly fertile. Matrix-directed delivery could exploit slowly digested lipids or fermentable fibres to steer curcumin into lymph and microbiota pathways [34]. Multi-compound synergy, already hinted at with resveratrol and baicalein [45, 46], calls for systematic nutrient–nutrient mapping. Finally, precision-nutrition trials that stratify by genotype, microbiome and disease phenotype will reveal who benefits most and at what dose [28]. Addressing these challenges will not only cement curcumin's role in evidence-based food science but will also provide a template for translating other low-bioavailability phytochemicals from spice rack to clinic.

7. Conclusions

Curcumin exemplifies how a culinary pigment can mature into a data-driven nutraceutical. Decades of research now align around four inter-locking pillars of action: (i) redox modulation, (ii) anti-inflammatory signalling, (iii) metabolic re-balancing and (iv) immune regulation. Collectively, these pathways confer cardiometabolic, neuro- and hepato-gastro-protective, respiratory, endocrine and anti-infective benefits, among others, that recur across pre-clinical models and early-phase trials.

Pharmacokinetics remain the principal hurdle. Native curcumin is water-insoluble and rapidly conjugated, yet modern carriers—solid-lipid nanoparticles, micelles, protein–polysaccharide hybrids and bio-enhancer co-crystals—can raise systemic exposure by ~10–100-fold without safety signals so far observed beyond the current ADI of 0–3 mg kg^{-1} bw day^{-1}. Larger, formulation-specific trials are warranted to define dose–response relationships and identify responder sub-groups stratified by microbiome, genotype or comorbidity.

Future work should pair rigorous pharmacokinetic profiling with foodomics and advanced imaging (e.g., MALDI-MSI, PET tracers) to map curcumin's gut–liver–systemic journey in real time. Standardised reporting of purity, conjugate speciation and absolute exposure will improve reproducibility and enable meta-analyses robust enough for regulators. High-throughput synergy screening and food-matrix-directed delivery could then embed curcumin in the next generation of functional foods that are both sensorially attractive and clinically validated.

In brief, curcumin has progressed well beyond the spice rack; it now serves as a prototype for translating culinary phytonutrients into safe, scalable interventions for chronic-disease prevention and management.

Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Availability of data and materials

No new data were generated or analyzed in support of this review. Information and data cited in this article are derived from previously published sources, which are listed in the references.

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