

Curcumin and Its Derivatives: Therapeutic Perspective

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Abstract: The plant *Curcuma longa* yields a polyphenol called curcumin (diferuloylmethane), which is utilized extensively in Southeast Asia, China, and India for both culinary and therapeutic uses. In an effort to clarify its pharmacological characteristics, scientists from a variety of fields have been interested in this traditional medicine since the latter half of the previous century. Curcumin's potential to treat neurological illnesses like Alzheimer's disease (AD), Parkinson's disease (PD), and cancer is of great interest. All of these illnesses have an inflammatory foundation, characterized by elevated levels of reactive oxygen species (ROS) within cells and oxidative damage to proteins, lipids, and nucleic acids. Through the control of transcription factors, cytokines, and enzymes linked to nuclear factor kappa beta (NFκB) activity, curcumin's therapeutic advantages for several neurodegenerative illnesses appear to be multifactorial. In this study, the chemistry, stability, and biological activity of curcumin—including its anti-inflammatory, anti-cancer, anti-microbial, and antioxidant qualities—as well as its historical usage in medicine are discussed. The review goes on to address curcumin's pharmacology and offers new insights into both its therapeutic potential and limitations.

Keywords: curcumin; therapeutic; inflammatory; arthritis; anticancer

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1. Introduction

Curcumin is obtained from the plant *Curcuma longa*. It is a bright yellow colored compound present in turmeric. It is a diarylheptanoid belonging to the class of curcuminoids, natural phenols that provide turmeric its yellow color [1-3]. Curcumin is in the tautomer existing in the enolic form in organic solvents and the keto form in water. It belongs to the family Zingiberaceae [4,5]. It has been used as an herbal supplement, a cosmetic ingredient, a food flavoring, and a food coloring agent since ancient period. Curcumin has hepatoprotective, neuroprotective, antidiabetic, anti-inflammatory, etc properties [6-10]. Curcumin is poorly soluble in the digestive system, so to overcome this, a number of formulations have been

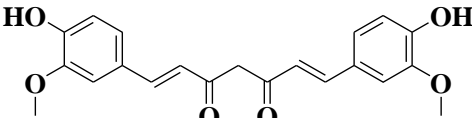
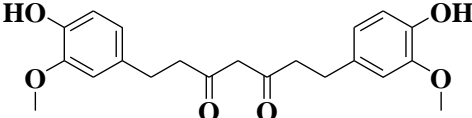
developed. Curcumin is also called diferuloylmethane. It is the main natural polyphenol found in the rhizomes of *Curcuma longa* [11]. Curcumin has been shown to target multiple signaling molecules and demonstrate activity at the cellular level, supporting its multiple health benefits [12-15]. Clinical trials in humans show that when curcumin is administered orally, its systemic bioavailability is relatively low, and that mostly metabolites of curcumin, instead of curcumin itself, are detected in plasma or serum following oral consumption [16,17]. In the intestine and liver, curcumin is conjugated to obtain curcumin glucuronide and curcumin sulfate or reduced to tetra-hydro curcumin, hexa-hydro curcumin, and octa-hydro curcumin [18]. An early clinical trial conducted in Taiwan indicated that serum curcumin concentrations peaked at 0.41 to 1.75 micromoles/liter (μM) one hour after oral doses of 4 to 8 g of curcumin [19]. Another clinical trial conducted in the UK found that plasma concentrations of curcumin, curcumin sulfate, and curcumin glucuronide ranged from 0.01 μM at 1 hour after a 3.6 g oral dose of curcumin [20]. Evidence also shows that orally administered curcumin accumulates in gastrointestinal tissues. For example, when colorectal cancer patients administer 3.6g/day of curcumin orally for seven days before the surgery, curcumin was detected in both malignant and normal colorectal tissue [21]. But the exception is that curcumin was not detected in the liver tissue of patients who have liver metastases of colorectal cancer after the administration of the same oral dose of curcumin, showing that oral curcumin administration may not effectively deliver curcumin to tissues outside the gastrointestinal tract [22]. The safety, efficacy, and effectiveness of several curcumin formulations are currently being explored in preclinical settings to enhance curcumin's absorption, bioavailability, and tissue-targeted delivery [23]. Examples of approaches include conjugation to peptide carriers (e.g., poly (lactic-co-glycolic acid) [PLGA]), complexation with essential oils, co-administration with piperine, and encapsulation into nanoparticles, liposomes, phytosomes, polymeric micelles, and cyclodextrins [24].

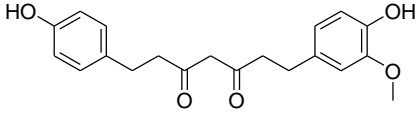
2. Historical Background

The name curcumin was given in 1815 by Vogel & Pierre Joseph Pelletier, who reported the 1st time isolation of a yellow-colored matter from the rhizomes of turmeric. Later on, this substance was found to be a mixture of resin & turmeric oil. In 1842, Vogel Jr. obtained a pure preparation of curcumin but did not report its formula [25]. In the decades that followed, several chemists reported possible structures of curcumin [26-28]. However, before 1910, Milobedzka and Lampe had not identified the chemical structure of curcumin as diferuloylmethane, or 1,6-heptadiene-3,5-dione-1,7-bis (4-hydroxy-3-methoxyphenyl)-(1E,6E) [29]. Subsequently, Srinivasan separated and quantified the components of curcumin by chromatography [30]. The primary source of curcumin, turmeric, has been used for thousands of years in Asian countries as a culinary spice and medical treatment for human diseases, but its biological properties were not discovered until the middle of the 20th century. Schraufstatter and colleagues discovered in a 1949 Nature study that curcumin is a physiologically active substance with antibacterial characteristics. The authors found that curcumin was active against strains of *Staphylococcus aureus*, *Salmonella paratyphi*, *Trichophyton gypsum*, and *Mycobacterium tuberculosis* [31]. Despite such results, over the following 20 years, only 5 studies on curcumin were published. In the 1970s, curcumin became the subject of scientific investigation, and three independent groups reported diverse activities, including cholesterol-lowering [32], anti-diabetic [33], anti-inflammatory [34], and antioxidant [35] activities. Later, in the 1980s, Kuttan and colleagues demonstrated the anti-cancer activity of curcumin in both *in vitro* and *in vivo* models [36]. In 1995, our group was the first to

demonstrate that curcumin exhibits anti-inflammatory activity by suppressing the pro-inflammatory transcription factor nuclear factor (NF)- κ B; we also delineated the molecular mechanism of the inhibition [37]. Curcumin has the ability to directly or indirectly affect a variety of signaling pathways. This polyphenol has been proven to be active in animal models of numerous human disorders. Curcumin has been shown in human clinical trials to be both safe and effective, and the US Food and Drug Administration has approved it as a "safe compound". Curcumin has been shown to be therapeutically effective against many human diseases, but its poor bioavailability is a major problem [38], likely due to poor absorption, rapid metabolism, and rapid systemic elimination. After that, scientists and researchers tried to improve curcumin's bioavailability by improving its features. Many adjuvants were used to increase the bioavailability of this polyphenol. For example, in humans receiving a 2 g dose of curcumin alone, serum levels were either undetectable or very low, but concomitant administration of piperine increased curcumin bioavailability by 2000% [39]. Furthermore, the effect of piperine in enhancing curcumin's bioavailability is much greater in humans than in rats [40]. Other promising approaches to increase curcumin bioavailability include nanoparticles [41], liposomes [42], micelles [43], phospholipid complexes [44], and structural analogs [45,46]. Curcumin has emerged as a new, safe medicine with significant potential in numerous countries, and it is now used as a supplement. Curcumin, which is found in turmeric, has various applications, such as curries in India, tea in Japan, cosmetics in Thailand, drinks in China, antiseptics in Malaysia, anti-inflammatory agents in Pakistan, and use as a preservative and coloring in mustard sauce, cheese, butter, and chips in the United States. Curcumin is offered in a variety of formats, including capsules, pills, and ointments. Considering all these facts, in this review we have compiled data highlighting the importance of curcumin in controlling oxidative stress in various neurological and inflammatory disorders, as shown in Table 1.

Table 1. Curcumin and its analogues have diverse biological activities.

Compound(s)	Biological activity	Reference(s)	
 <p style="text-align: center;">Curcumin</p>	cyclooxygenase inhibitory activity	Selvam <i>et al.</i> , 2005 [47]	
	Pancreatic cancer	Dhillon <i>et al.</i> , 2008 [48]	
	Antioxidant	Weber <i>et al.</i> , 2005 [49]	
	Prostate cancer	Banerjee <i>et al.</i> , 2016 [50]	
	Cardioprotective	Hernández <i>et al.</i> , 2016 [51]	
	Antidiabetic	Chuengsamarn <i>et al.</i> , 2012 [52]	
	Antibacterial	Betts <i>et al.</i> , 2016 [53] Subhan <i>et al.</i> , 2016 [54] Haukvik <i>et al.</i> , 2011 [55]	
	Antifungal	Neelofar <i>et al.</i> , 2011 [56] Kim <i>et al.</i> , 2003 [57]	
	Antiviral	Zandi <i>et al.</i> , 2010 [58]	
	Antidepressant	Ali <i>et al.</i> , 2016 [59]	
	Arthritis	Daily <i>et al.</i> , 2016 [60]	
	 <p style="text-align: center;">Tetrahydrocurcumin</p>	Oxidative stress and cardiovascular dysfunction	Kukongviriyapan <i>et al.</i> , 2016 [61]
		Antioxidant	Sugiyama <i>et al.</i> , 1996 [62]
Anti-inflammatory		Murakami <i>et al.</i> , 2008 [63]	
Oxidative stress-induced renal injury		Okada <i>et al.</i> , 2001 [64]	
Osteoarthritis		Park <i>et al.</i> , 2016 [65]	

Compound(s)	Biological activity	Reference(s)
 Demethoxycurcumin	Diabetes	Murugan <i>et al.</i> , 2006 [66]
	Anticancer	Pettinari <i>et al.</i> , 2014 [67]
	Autoimmune arthritis	Gullaiya <i>et al.</i> , 2013 [68]
	Antioxidant	Jayaprakasha <i>et al.</i> , 2006 [69]
	Alzheimer's disease	Fiala <i>et al.</i> , 2007 [70]

3. Chemistry

Curcumin has several functional groups, which were first identified in 1910 [47]. The phenolic aromatic ring systems are linked by a pair of α , β unsaturated carbonyl groups. The diketone readily deprotonates to form enolates, which form stable enols; the β -unsaturated carbonyl group is an excellent Michael acceptor and adds nucleophilically. Structures of keto and enol forms are shown in Figure 1.

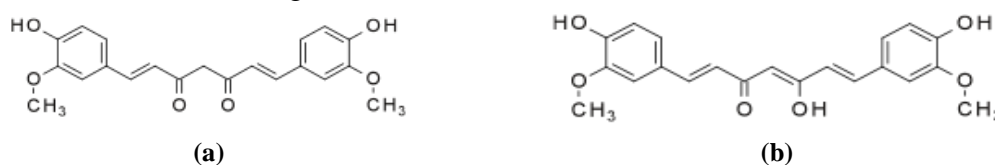


Figure 1. (a) Keto form; (b) Enol form.

3.1. Biosynthesis.

Biosynthetic pathway is presented in Figure 2.

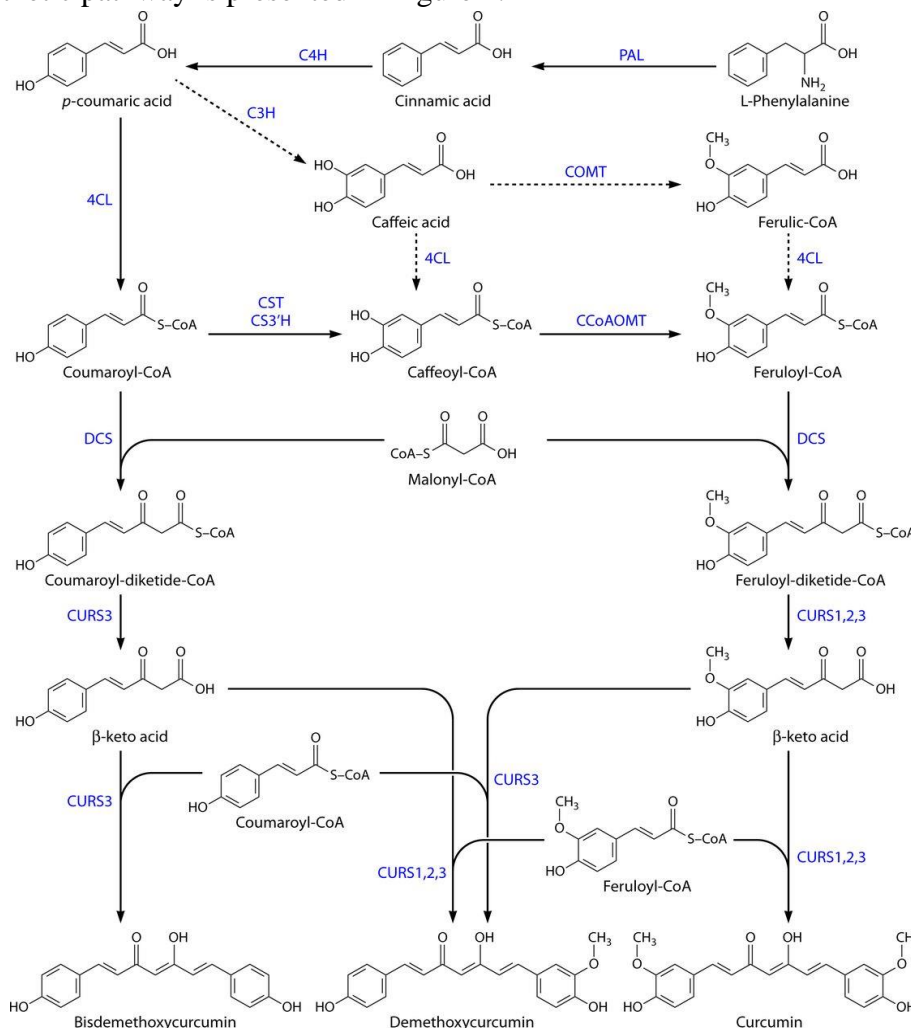


Figure 2. Biosynthetic pathway of curcumin.

3.1.1. Steps.: Steps for biosynthesis shown in Figure 3.

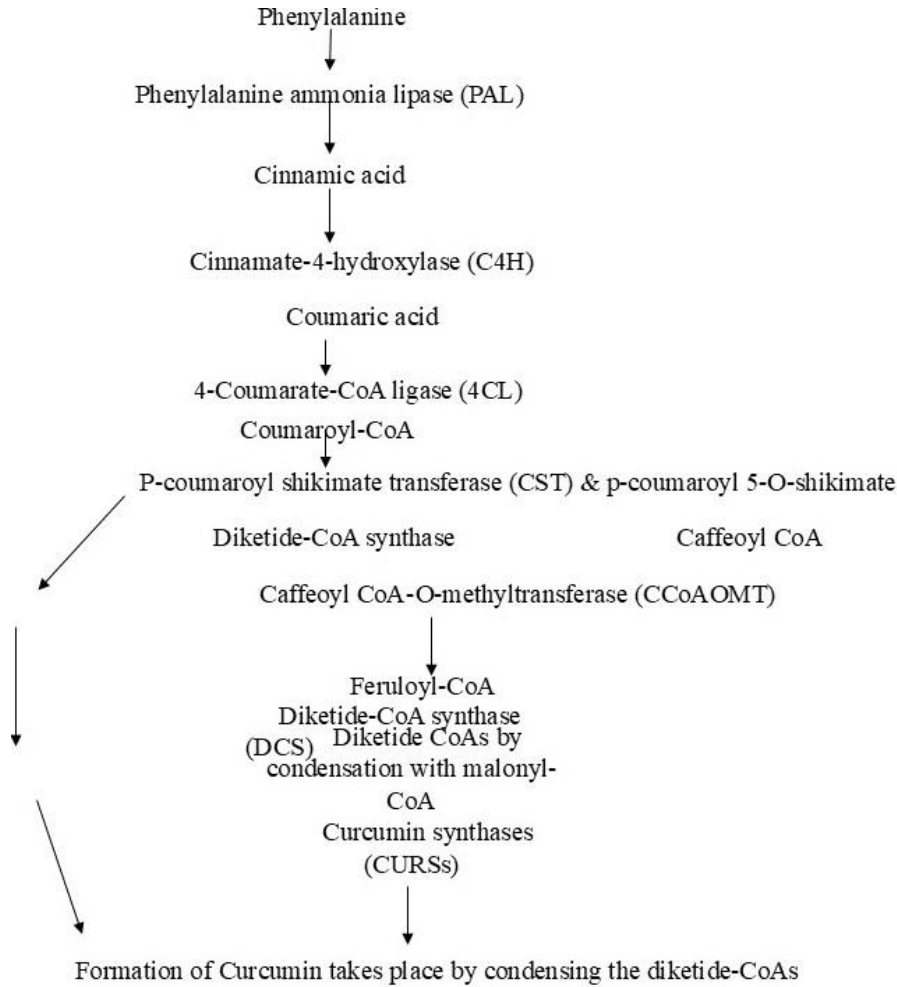


Figure 3: Steps involve in the biosynthesis of Curcumin

4. Different Pharmacological Activities of Curcumin

4.1. Cancer.

Cancer is a group of diseases in which abnormal cell growth takes place and can spread to other parts of the body. But in benign tumors, it does not spread. [71]. Signs and symptoms are lump, abnormal bleeding, prolonged cough, unexplained weight loss, and a change in bowel movements [72]. Over 100 types of cancers affect humans. Tobacco use has been found to be the main cause of cancer; other factors include certain infections, exposure to ionizing radiation, and environmental pollutants [73]. Curcumin acts as an anticancer agent by inhibiting the proliferation of cancer cells. It can also inhibit carcinogen bioactivation by suppressing specific cytochrome P450 isoforms. It also induces the activity or expression of the phase 2 carcinogen detoxifying enzyme. Some facts and figures are presented in Table 1.

Table 1. Statistics of death due to cancer.

S.N.	Cause	Death percentage	Reference
1.	Tobacco	22%	[42]
2.	Obesity	10%	[42]
3.	Poor diet	10%	[45]
4.	Less physical exercise	10%	[46]

Ali H. El-Far *et al.* examined the effects of thymoquinone (TQ), curcumin (Cur), and caffeine (Caff) on apoptosis in senescent colon cancer HCT116 and breast cancer MCF7 cells treated with doxorubicin. The results indicate that p53, P-p53, and some of the proteins are upregulated, and that bromodeoxyuridine incorporation is reduced. Additionally, there is an increase in the aggregation of senescence-associated β -galactosidase (SA- β -gal) and cell cycle arrest. When Curcumin (15 μ M), Caffeine (10 mM), and Thymoquinone (65 μ M; $P < .001$) were added to Doxorubicin-treated MCF7 (breast cancer, Michigan Cancer Foundation 7) and HCT116 cells, the number of annexin-V–positive cells increased by two to six times. When comparing proliferative and senescent cells of either MCF7 or HCT116 (human colon cancer), Caff at 12.5 mM and TQ at 23 μ M significantly increased the number of cells that underwent apoptosis when treated with doxorubicin, in contrast to proliferative cells. Data suggests that TQ, caffeine, and curcumin may have caused apoptosis in both proliferative and senescent HCT116 and MCF7 cells. To acknowledge this outcome, Clinical trials and in vivo studies are crucial [74].

Manuela Curcio *et al.* showed that doxorubicin may be delivered in vitro to treat adrenocortical carcinoma using the redox-responsive activity of nanoparticles. Human serum albumin was conjugated to curcumin and lipoic acid. Redox-responsive doxorubicin release was observed from loaded nanoparticles, thereby considerably increasing the drug's cytotoxicity against H295R adrenocortical carcinoma cells. The nanoparticle systems were prepared by the modified desolvation method. Dynamic light scattering, differential scanning calorimetry, and Fourier transmission infrared spectroscopy are used to characterize nanoparticles. Up to 10 times greater when exposed to spherical, 70 nm-diameter glutathione nanoparticles (10 mM) was the result. Thus, based on all of these, it was determined that the presence of both lipoic acid and curcumin moieties, which increase glutathione responsiveness and drug cytotoxicity, is associated with the delivery vehicle's efficiency [75].

Tin Tin San *et al.* examined the effects of curcumin on two carcinoma cell lines, HuCCT1 and TFK-1, by culturing them on poly(2-hydroxyethyl methacrylate). The AI-CCA cells showed responses to curcumin therapy in combination with anticancer medications, as assessed by a cell viability assay. Gene expression in AI-cells was evaluated using quantitative real-time PCR. Curcumin by itself significantly decreased AI-cell colony growth and survival. Additionally, on AI-HuCCT1 and AI-TFK-1 cells, the curcumin combination significantly increases the therapeutic efficacy. A gene expression study revealed that AI-CCA cells showed a significant increase in ANGPTL4, and that lowering ANGPTL4 tended to render AI-cells more vulnerable to therapies and cell death. Moreover, injection of curcumin decreased the expression levels of several gene factors, as well as phosphorylated STAT3. Collectively, these results demonstrate curcumin's ability to enhance the effects of chemotherapy on cancer cells, suggesting its potential application in cancer treatment [76].

Elena Gazzano *et al.* found that a chitosan coating was necessary for the safe and efficient loading of curcumin into biocompatible solid lipid nanoparticles (SLNs), thereby enhancing cellular absorption, homogeneous water dispersibility, and stability. The results of the experiments showed that both curcumin-loaded solid nanoparticles and free curcumin were 6–10 times more effective at increasing intracellular retention and doxorubicin's toxicity in the treatment of glycoprotein-expressing triple-negative breast cancer (TNBC). Additionally, the data demonstrated a drop in intracellular reactive oxygen species. Furthermore, curcumin-loaded solid liquid nanoparticles against drug-resistant triple-negative breast cancer effectively restored the sensitivity to doxorubicin without displaying any signs of systemic toxicity. These

results suggest that doxorubicin- and curcumin-loaded SLN-based combined therapy is a safe and effective treatment for P-gp-mediated chemoresistance in TNBC [77].

Ana Saric *et al.* investigated, using Image flow cytometry, the mechanistic aspects of curcumin's destabilization of the ER and the status of the lysosomal compartment. Curcumin induces Endoplasmic Reticulum stress, triggering an unfolded protein response and calcium release, destabilizing the mitochondrial compartment and inducing apoptosis. These events are also associated with secondary lysosomal membrane permeabilization that occurs later, together with the activation of caspase-8, mediated by cathepsins and calpains, which ultimately disrupts mitochondrial homeostasis. These two pathways, of different intensities and momentum, converge to amplify cell death. In conclusion, curcumin-induced autophagy failed to rescue all cells that underwent type II cell death after the initial autophagic process. However, a small number of cells were rescued (successful autophagy) to give rise to a novel proliferation phase [78].

4.2. Depression.

Depression is a disorder in which the sufferer experiences sadness and a loss of interest. It affects the person's ability to feel, think, and behave. It is also known as major depressive disorder or clinical depression. It can lead to a variety of issues, either emotionally or physically. Risk factors for depression might include major life events, trauma, other physical ailments (like cancer), a family history of mood disorders, and even certain drugs, according to the National Institute of Mental Health. However, depression's primary etiology is still a mystery. Depression symptoms vary between adults and children. When it comes to children, it may resemble anxiety or nervous behavior more [79-82].

Curcumin is also responsible for showing antidepressant activity by the MAO enzyme, both A and B. Monoamine oxidase is the enzyme that is involved in the degradation of nor-epinephrine, serotonin, and dopamine, and by inhibiting the activity of the MAO enzyme, the concentration of these neurotransmitters in the synapse increases. The duration of action increases [83-86].

Li Wang *et al.* explored the antidepressant effects of curcumin in olfactory bulbectomy in male albino rats. The test group was subjected to a swim in the uy7a depression test model following a prolonged course of treatment. Curcumin was administered to each of the four experimental animal groups for 45 days. The group observed that curcumin produced behavioral abnormalities, increased locomotion in the open area, decreased immobility time, and significantly reduced olfactory bulbectomy-induced behavioral abnormalities. In the hippocampal regions of male albino rats, curcumin therapy dramatically lowered levels of noradrenaline, serotonin, 3-hydroxyphenylacetic acid, and 5-hydroxyindoleacetic acid. Furthermore, curcumin restores normal levels of dopamine, noradrenaline, and 5-hydroxyindoleacetic acid in the frontal cortex of rats. When these results are taken together, they may indicate that curcumin is a powerful substance that fights depression in albino rats [87].

Xianchan Li *et al.* employed single-cell amperometry to examine whether curcumin and bisdemethoxycurcumin (BDMC), compounds that have been linked to memory and learning impairments, have an impact on monoamine oxidase. According to their findings, curcumin and BDMC require prolonged therapy of 72 hours in this case to significantly affect exocytosis. This conclusion can be drawn from metrics derived from individual exocytosis events: BDMC and curcumin have distinct effects on exocytosis. While BDMC decreases the

quantity released per exocytotic event without altering the event dynamics, curcumin does not alter the amount released per exocytotic event and enhances the event dynamics. This single-cell study of the effects of BDMC and curcumin on exocytosis sheds light on several mechanisms that may lead to distinct biological actions. The analysis found that the curcuminoid has antidepressant properties [88].

James Golder *et al.* examined curcumin's effects on the GABA receptor's benzodiazepine site as well as its anxiolytic and depressive properties. In order to verify this, intraperitoneal injections of vehicle, curcumin, curcumin+umazenil, midazolam, and midazolam+curcumin were given to 55 male laboratory rats. The forced swim test, open field test, and elevated plus maze were used for behavioral testing. The data were analyzed using a 2-tailed multivariate analysis of variance and post hoc least significant difference tests. Curcumin did not alter behavioral despair or have any anxiolytic effects in our mice. Additionally, there was no evidence of a curcumin-benzodiazepine receptor interaction in the neurological system. Flumazenil may potentially cause anxiety or even sedation in rats by the interaction of two chemicals in an unknown manner, by acting at another site or receptor in the central nervous system [89].

Bombi Lee *et al.* investigated how curcumin reversed serotonin malfunctioning to reduce anxiety symptoms in mice following a single extended stress (SPS) exposure. In the rats exposed to SPS, curcumin (30, 40, or 80 mg/kg, i.p., OD) was given for two weeks. Following curcumin administration, there was a noticeable increase in central zone crossings in the open field, a decrease in grooming behavior in the elevated plus maze (EPM) test, and an increase in open-arm visits. When curcumin was administered, the freezing reaction to contextual fear conditioning was significantly reduced. Neurochemical abnormalities were resolved by curcumin, and SPS decreased 5-HT tissue levels in the striatum, amygdala, and hippocampus. Curcumin has been shown to have anxiolytic-like effects on the biochemical and behavioral signs of anxiety. Therefore, curcumin may be a useful agent for treating or preventing psychiatric disorders [90]. Some important enzymes inhibited by curcumin are shown in Table 2.

Table 2. Some important enzymes inhibited by Curcumin

S.N.	Inhibited enzyme	References
1.	Cyclooxygenase-2(COX-2)	[57]
2.	lipoygenase (LOX),	[50]
3.	inducible nitric oxide synthase (iNOS).	[51]

COX is a main enzyme that is responsible for the conversion of arachidonic acid to prostaglandins. Arachidonic acid metabolites derived from LOX pathways play an important role in growth-related signal transduction. Curcumin is shown to inhibit both COX and LOX. Inducible nitric oxide synthase catalyzes the oxidative deamination of L-arginine to produce nitric oxide, a potent pro-inflammatory mediator.

Ga-Young Choi *et al.* investigated the impact of curcumin on cell survival and brain plasticity. Using Western blot analysis, they determined the expression level of the inflammatory mediator COX-2. The stressed group showed a notable increase in COX-2 protein levels in the hippocampus. Compared with the control group, COX-2 levels were reduced by 242.2% and 268.8%, respectively, following treatment with 50 mg/kg and 100 mg/kg curcumin. These findings demonstrate that curcumin reduced COX-2 levels in the hippocampal regions of chronically stressed rats. Curcumin's impact on COX-2 expression was

noteworthy at both levels; however, curcumin at 100mg/kg was so potent that it did not differ significantly from the sham group [91].

Cuiqin Fan *et al.* studied curcumin's molecular mechanisms underlying its ability to protect neurons against inflammation-induced apoptosis and behaviors associated with depression in a rat model of depression. Their findings showed that curcumin (35 mg/kg, i.p., for continuous five weeks) administered chronically prior to stress exposure reduced depressive-like behaviors and the expression of the pro-inflammatory cytokine interleukin-1 β (IL-1 β). Additionally, it reduced neuronal death in the ventromedial prefrontal cortex (vmPFC) of wild-type rats. Curcumin therapy reduced p38 MAPK activation caused by IL-1 β overexpression via intracerebral infusion of AAV. Additionally, curcumin could significantly reduce neuronal apoptosis with long-term administration. Taken together, these results show that curcumin prevents IL-1 β -induced neuronal apoptosis, which is linked to the expression of depression-like behaviors in stressed rats. Furthermore, they provide a new perspective on the mechanisms and therapeutic potential of curcumin in the treatment of inflammation, which is somewhat related to neuronal deterioration in this disorder [92].

4.3. Osteoarthritis.

A breakdown of the underlying bone and joint cartilage causes a disease known as osteoarthritis (OA). Joint stiffness and discomfort are the most prevalent symptoms. Typically, the symptoms worsen gradually over time. These might first only happen after activity, but they might eventually become regular. Additional signs and symptoms of these conditions include reduced range of motion, swollen joints, and, in cases where the back is impacted, arm and leg paralysis or numbness. The knee and hip joints, the joints in the neck and lower back, the two joints at the tips of the fingers, and the joint at the base of the thumbs are the joints that are most frequently affected. One side of the body's joints is frequently more damaged than the other [93-95].

Xiao-dong Yao *et al.* investigated the association between curcumin and differentially expressed genes in synovial tissues from patients with osteoarthritis. Microarray analysis was used to screen for the DEG in osteoarthritis synovial cells. Western blot was used to check the expression levels of fibronectin 1 and collagen III protein. MTT assay was used to examine the effects of different concentrations of curcumin on cell viability. Matrix metalloproteinase-3 expression levels were validated by western blot and quantitative real-time polymerase chain reaction. Clone formation assay, flow cytometry, and the TUNEL method were performed to detect cell proliferation and apoptosis rates. MMP3 was highly expressed in osteoarthritis synovial cells. By inhibiting MMP3 expression, curcumin can reduce cell viability, inhibit cell proliferation, increase cell apoptosis, and eventually alleviate inflammation in osteoarthritis [96].

Yun Zhang *et al.* investigated the protective effect of curcumin on monosodium iodoacetate (MIA)-induced OA. In 4 experimental groups, random arrangements of 48 rats were done. Hematoxylin-eosin staining was used to judge the histological changes of the knee joint. Using ELISA, the expression of synovial fluid cytokine levels was measured, and the paw withdrawal threshold was collected. The expression of synovial fluid inflammatory biomarkers in the OA curcumin group was found to be lower than in other test groups. Compared to the control group, the protein expression of the TLR4 receptor was raised in the OA. The results indicate that curcumin can block the TLR4/NF- κ B signaling pathway and

reduce inflammation, thereby preventing knee wounds in OA rats. Curcumin may be a suitable medication for the treatment of knee OA [97].

Xin Yang *et al.* investigated the role of mitochondrial dysfunction in OA pathology. During total knee arthroplasty, a total of thirty cartilage samples presenting an outer-bridge score ranging between 0 and III were collected. Half of the samples were embedded for observation by transmission electron microscopy. The rest of the samples were digested, and chondrocytes were isolated from normal and OA tissues. The results showed that curcumin partially reverses the effects of arthritis. The present data suggested that mitochondrial function was impaired in OA chondrocytes, resulting in an increased chondrocyte. In addition, treatment with curcumin protected the mitochondrial function and prevented cartilage degeneration. The results suggested that mitochondrial dysfunction may aggravate cartilage degeneration in the pathogenesis of OA [98].

Roberta Ettari *et al.* investigated the potential of curcumin, flavocoxid, and β -caryophyllene in combination for the treatment of osteoarthritis in human articular chondrocytes. The results showed that the synergistic effect of the combined drug in the suppression of arthritis causes factors to be expressed. A synergistic action for the reduction of the inflammatory phenotype in human chondrocytes was observed for the combination of curcuminflavocoxid with a percentage(10-90) and for the combination of curcumin- β caryophyllene from (50-90). IC_{50} doses of curcumin, β -caryophyllene, and flavocoxid alone or in combination were safe and did not affect cell vitality. Moreover, the same IC_{50} doses reduced transcription factor and mRNA expression, and, interestingly, the effects of the combinations were greater than those of the natural products alone [99].

Ahsa Lee *et al.* investigated the effects of curcumin in the form of theracurmin (TC) in the treatment of osteoarthritis. The group divided the 78 Wister rats into 6 groups. The rats were treated with a dose of curcumin of 500, 1300, or 2600 mg/kg for 35 days. The results revealed that TC treatment significantly reduced cartilage damage. The TC-treated groups exhibited a significant reduction in the number of immunoreactive cells in a dose-dependent manner. In the end, it was found that TC administration contributes to the anti-arthritic effect in rats [100].

5. Conclusion

In this review, we reaffirm curcumin's status as a multifaceted therapeutic agent with potential applications across a wide spectrum of health conditions. Curcumin's ability to modulate inflammatory pathways and scavenge free radicals makes it a promising candidate for managing inflammatory and oxidative stress-related disorders. However, challenges such as poor bioavailability necessitate further research into novel delivery systems and formulations to harness their therapeutic benefits fully. Polyphenols have also been shown to be active in animal models of numerous human disorders [101]. Nonetheless, the accumulating evidence supports the integration of curcumin into preventive and therapeutic strategies for various diseases, pending further clinical validation. This review highlighted the available information on curcumin, but it still lacked sufficient clinical relevance.

Author Contributions

Conceptualization, N.M. and P.D.; methodology, P.D.; software, N.M.; validation, T.H., and A.L.; formal analysis, M.G.; investigation, R.C.K.; resources, R.C.K.; data curation, N.M.;

writing—original draft preparation, P.D.; writing-review and editing, N.M.; visualization, M.G.; supervision, T.H.; project administration, A.L.;
All authors must confirm their agreement with the contribution statement before submission.

Institutional Review Board Statement

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Informed Consent Statement

Not applicable.

Data Availability Statement

Data supporting the findings of this study are available upon reasonable request from the corresponding author.

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Conflict of Interest

The authors declare no conflict of interest.

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