ISSN No: -2456-2165 https://doi.org/10.38124/ijisrt/26apr1592

Curcumin in Modern Medicines: Therapeutic Potential and Challenges

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Publication Date: 2026/05/04

Abstract: Curcumin, the primary polyphenolic compound from *Curcuma longa* (turmeric), alongside desmethoxycurcumin and bisdemethoxycurcumin, exhibits potent anti-inflammatory, antioxidant, antibacterial, anticancer, and neuroprotective effects. However, its therapeutic utility is hindered by poor aqueous solubility, chemical instability, rapid metabolism, and low oral bioavailability (<1%). Nanotechnology addresses these limitations through advanced nanocarriers—including liposomes, nano emulsions, polymeric micelles, dendrimers, polymeric nanoparticles, solid lipid nanoparticles, and nanostructured lipid carriers—which enhance solubility, stability, gastrointestinal absorption, and site-specific drug release, often achieving 20-50 fold bioavailability improvements. Gut microbiota profoundly modulates curcumin's pharmacokinetics and efficacy in neurodegenerative diseases, cardiovascular disorders, cancer, and diabetic complications by generating bioactive metabolites. Preclinical and clinical evidence supports curcumin's synergy with conventional therapies, reducing adverse effects, while bioenhancers like piperine and structural analogs further optimize outcomes. This review elucidates curcumin's tautomeric behaviour, metabolic pathways, microbiome interactions, and nanodelivery strategies, emphasizing translational challenges such as scalability and safety. Harnessing nanotechnology and microbiome modulation holds transformative promise for precision medicine applications.

Keywords: *Curcumin; Nanotechnology; Nanocarriers; Bioavailability enhancement; Gut Microbiota; Drug Delivery; Pharmacokinetics; Bioenhancers.*

How to Cite: Sunidhi Sharma; Anjali Bhagria; Sanjiv Duggal (2026) Curcumin in Modern Medicines: Therapeutic Potential and Challenges. *International Journalof Innovative Science and Research Technology*, 11(4), 3090-3101. https://doi.org/10.38124/ijisrt/26apr1592

I. INTRODUCTION

➢ *Curcumin:*

Rhizome of turmeric Curcuma longa has been used as an herbal medicine, coloring agent, spice, and food additive for thousands of years in various countries of the world, especially in Asian countries. It has been used in the treatment of various diseases in many traditional medicine schools, including Islamic traditional medicine, Chinese traditional medicine, and Ayurveda [1]. The main compound found in Curcuma longa is a low molecular weight, lipophilic compound that easily diffuses through the cell membrane. It is identified as a polyphenol compound based on its molecular structure. The compound is used as a food coloring agent because of its vibrant yellow color. The relationship between structure and activity is appropriate because of the simple molecular structure and arrangement of functional groups. The ability of curcumin to interact with different kinds of protein makes it easier to selectively modulate a number of cellular signaling pathways associated with various kinds of chronic illnesses. The main molecules that interact with curcumin include transcription factors, inflammatory mediators, and enzymes such as histone acetyltransferase, reductase, and protein kinase [2]

Table 1 Physical and Chemical Properties of Curcumin [3]:

Physical and Chemical Properties	Curcumin
Molecular formula and molecular weight	$C_{21}H_{20}O_6$
Melting point	183°C (361.4°F)
Color and odor	Yellow and Odorless
Taste and Stability	Slightly bitter and chemically unstable
Class and Isomer	Polyphenolic and Geometric isomer
Solubility in water	Low

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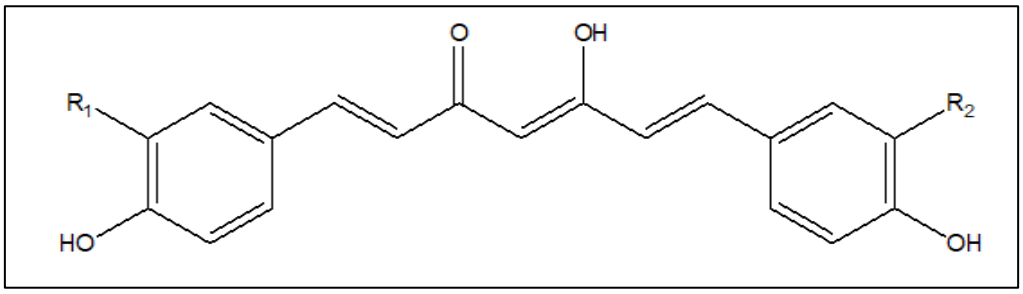

Fig 1 Chemical Structure of Curcumin

Curcumin, commonly referred to as diferuloylmethane, is a polyphenol found in the rhizome of the Curcuma longa plant. It is 1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5 dione.

Turmeric, also known as curcuma longa powder, is a spice that is used to make curry. An orange-yellow crystalline substance called turmeric powder is used as a food colour. Due to its antioxidant, anti-inflammatory, antibacterial, anticancer, and neuroprotective qualities, turmeric powder has been used in Asian countries as a medical preparation to treat a variety of ailments.

II. CURCUMIN SOLUBILITY, KINETICS, BIOAVAILABILITY, AND METABOLISM

➢ *Solubility and Stability*

Due to curcumin's poor solubility in aqueous solutions, chemical instability, and adverse pharmacokinetic characteristics (ADME: absorption, distribution, metabolism, and excretion), its therapeutic potential is constrained. As a result of its lipophilic nature, curcumin is almost completely insoluble in aqueous solution at ambient temperature and neutral pH. In light of this, using organic solvents such as (methanol, ethanol, acetone, or dimethyl sulfoxide). Additionally, curcumin is comparatively fragile. It swiftly breaks down into a number of chemicals, predominantly dicyclopentadiene, at both neutral and alkaline pH. [2]

➢ *Bioavailability*

According to animal research, oral administration of curcumin resulted in low absorption, a quick metabolism, and rapid elimination. When curcumin is consumed orally, conjugates such curcumin glucuronide and curcumin sulfate are quickly formed in the small intestine, liver, and kidneys. The conjugates quickly leave the body through feaces and urine. Even at a level of 12 g/day, curcumin has a limited absorption in humans. Additionally, curcumin has a limited oral bioavailability in humans due to its poor absorption in the small intestine, substantial liver reduction and conjugation into metabolites, and subsequent excretion through the gall bladder. Curcumin has an oral bioavailability of about 1%, according to pharmacokinetic tests done on rats. For instance, following oral administration of 1 g/kg curcumin, a maximum concentration (Cmax) in the serum of just 500 ng/mL was found. In a different investigation, the Cmax value was 60 ng/mL following oral administration of 0.5 g/kg curcumin, but a maximum serum concentration of 360 ng/mL was attained with i.v. injection of 10 mg/kg curcumin. After oral administration of increasing dosages of curcumin ranging from 500 mg to 12 g in humans, a Cmax value of 50 ng/mL was found. Although an oral dose of up to 8 12 g/day might be taken without experiencing any negative side effects, most clinical investigations revealed that curcumin's absorption and bioavailability are relatively low because it is rarely found in the serum of most patients. This results in extremely low curcumin levels in tissue when combined with the high levels of intestinal retention and retro-enteral efflux . The distribution of curcumin throughout the body has been explored in rats, where a significant variation in t issue distribution was noted. However, due to the extremely low quantities of curcumin found in tissues, it is still challenging to assess the significance of these finding. [3]

➢ *Metabolism*

The main metabolic pathway for curcumin involved reduction and conjugation. The primary degradation byproducts of reduction are di-, tetra-, hexa-, and octahydrocurcumin, which is mostly accomplished by alcohol dehydrogenase. Phase two metabolism quickly conjugates curcumin and its reduced metabolites through glucuronidation/sulfonation conjugation. As a result, the body only absorbs a minimal quantity of curcumin, which is why glucuronide and sulfate metabolites are identified in the blood.

➢ *Pharmacokinetics of Curcumin [4]*

- Absorption: Low intestinal absorption due to its lipophilic nature.
- Absorption rate: After oral administration 60-66%
- Metabolism: Undergo first pass metabolism via glucuronidation and sulfonation
- Clearance: Rapidly clear from the body

Curcumin’s therapeutic application is restricted due to its lack of solubility and quick metabolism, which results in low bioavailability. It is susceptible to the blood brain barrier.

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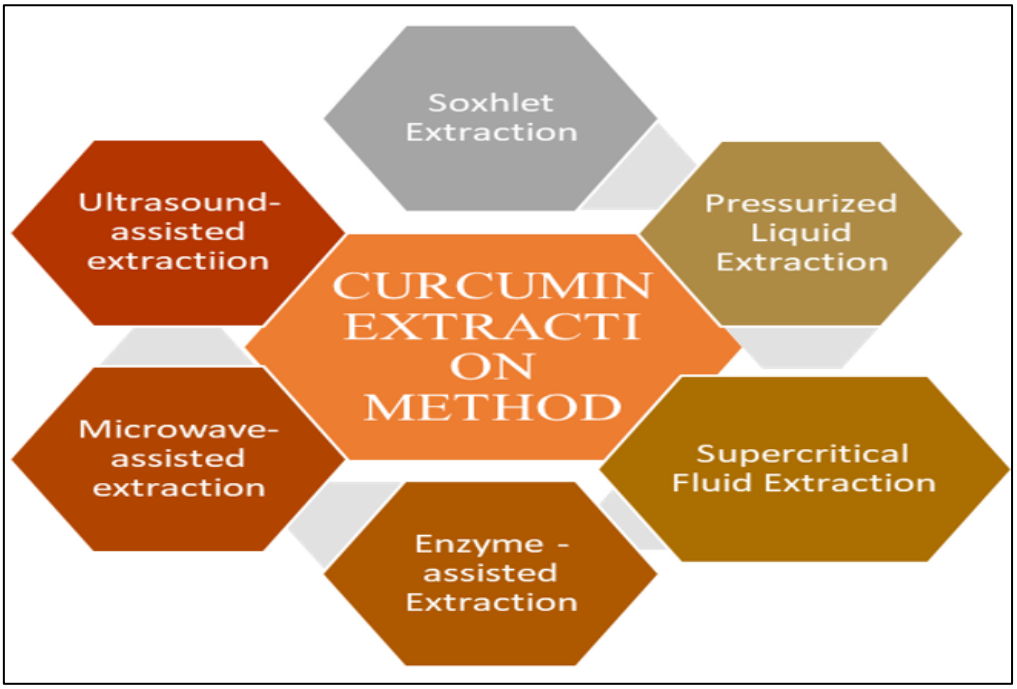

Fig 2 Curcumin Extraction Methods

➢ *Pharmacological Actions and Their Mechanism:*

Table 2 Pharmacological and Mechanism of Action of Curcumin:

Pharmacological actions	Mechansim of Action	Reference
Anti-inflammatory	✓Curcumin controls a variety of transcription factors, cytokines, protein kinases, adhesion molecules, redox status, and enzymes related to inflammation. ✓Its anti-inflammatory role can also be achieved by inhibiting several molecules related to inflammation.	[6]
Anti-Bacterial	✓Curcumin suppressed the homotypic biofilm formation of *Porphyromonas gingivalis* and dose-dependently reduced the biofilm development of *Streptococcus gordonii*. ✓Bacterial growth was almost completely inhibited even at very low concentrations of curcumin.	[7]
Antioxidant	✓Curcumin's antioxidant activity was evaluated through various in vitro assays, such as hydrogen peroxide scavenging and 1,1-diphenyl-2-picryl-hydrazyl (DPPH) free radical scavenging.	[8,9]
Gatrointestinal Activity	Curcuma longa contains two components that exert several positive effects on the gastrointestinal tract: sodium curcuminate, which suppresses intestinal spasm, and p-tolymethylcarbinol, which enhances the secretion of gastrin, bicarbonate, and pancreatic enzymes.	[10]
Cardioprotective Activity	✓Turmeric's antioxidant effects help protect the cardiovascular system by lowering triglyceride and cholesterol levels, decreasing the susceptibility of low-density lipoproteins (LDL) to lipid peroxidation, and inhibiting platelet aggregation. It reduces plasma levels of cholesterol and triglycerides.	[11,12]
Hepatoprotective activity	✓Owing to its antioxidant properties and ability to suppress the production of pro-inflammatory cytokines, turmeric demonstrates hepatoprotective and renoprotective effects similar to those of silymarin.	[12]

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Anti-Cancer	Breast Cancer: ✓BRCA1 mutations occur in about 55–65% of cases, while BRCA2 mutations are found in approximately 45–50% of cases. ✓Curcumin, in combination with 45 mg of dimethyl sulfoxide (DMSO), inhibited the growth of gastrointestinal tumors and reduced the prevalence of BRCA gene mutations.	[13]

➢ *Health Implications:*

Curcumin shows promising therapeutic potential for several neurologic disorders, including Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS), ischemic brain injury, and anxiety. [22].

Table 3 Disease and Their Health Implications:

DISEASE:	HEALTH IMPLICATIONS:
In Alzheimer's Disease	In models of AD, curcumin exhibits neuroprotective properties via reducing metabolic dysfunction and memory loss. It may also lessen the symptoms of AD by modifying metabolic pathways and neural plasticity. Furthermore, curcumin enhances the good gut bacteria, which indirectly affects cognitive processes[23].
In Parkinson's Disease	Curcumin reduces neuroinflammation and motor impairments in Parkinson's disease by modifying the gut microbiota-metabolite axis. Additionally, it improves motor impairments in PD models and has neuroprotective properties [23,24].
In Multiple Sclerosis	The experimental autoimmune encephalomyelitis severity is suppressed by the curcumin derivative CMG, which modifies the composition of the gut microbiota. This inhibition is associated with shifts in the abundance of particular bacterial species in ileal and fecal contents [25].
In Ischemic Brain Injury	Curcumin inhibits the hyperphosphorylation of tau proteins and breaks down their fibers, reducing infract volume, cerebral edema, and blood- brain barrier permeability in ischemic brain damage. It improves neurological results and cognitive impairment. Curcumin treatment changed the composition of the gut microbiome [23,25].

➢ *Natural Compounds as Potential Sources of Drug Discovery[26]:*

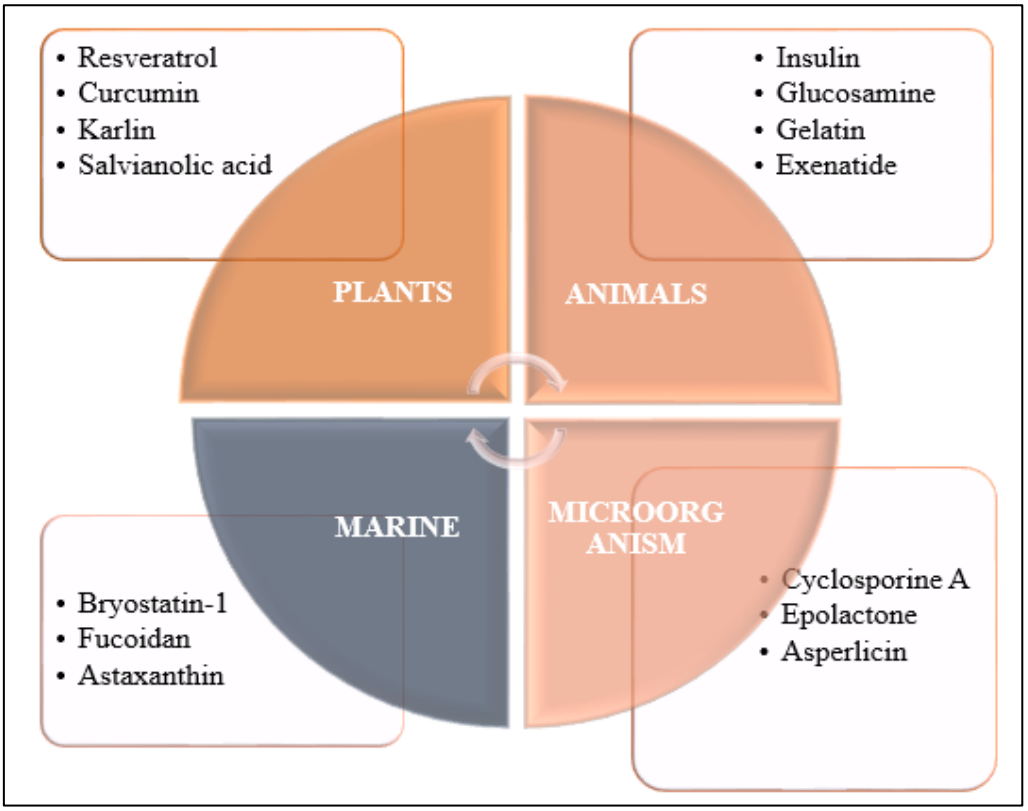

Fig 3 Natural Compounds as Potential Sources of Drug Discovery

ISSN No: -2456-2165 https://doi.org/10.38124/ijisrt/26apr1592

➢ *Nanocarrier Systems for Overcoming Formulation Challenges of Curcumin:*

- Nano-based delivery systems for curcumin have been developed specifically to enhance its solubility, bioavailability, and therapeutic efficacy while minimizing toxicity. [27]. This review systematically presents data on how incorporating curcumin into various nanosystems—such as liposomes, nanoemulsions, polymeric micelles, dendrimers, polymeric nanoparticles, solid lipid nanoparticles, and nanostructured lipid carriers—can enhance its beneficial properties, either alone or combined with other drugs. [28].
- The review also examines newly granted patents and ongoing clinical trials, offering a broad view of the rapidly evolving field of curcumin delivery. Researchers are currently exploring key nanocarrier features such as surface modification, high drug-loading capacity, biodegradability, biocompatibility, and intrinsic targeting specificity and selectivity [29].
- Sometimes, regulatory approval is still waiting and there are ongoing safety concerns, thus the use of nanocarriers for curcumin administration is still in its early stages.

➢ *Role of Nanoparticles in Curcumin Delivery:*

- The development of drug delivery methods based on nanoparticles holds promise for resolving these issues and enhancing curcumin's efficacy in a range of medical applications. Curcumin can be encapsulated in nanoparticles to increase its solubility and prevent gastrointestinal tract breakdown. This increases absorption and, ultimately, bioavailability [28,29].
- Nanoparticles' sustained release profile can extend curcumin's therapeutic effects and reduce dosing frequency, thereby improving patient compliance. Functionalizing nanoparticles with ligands or antibodies enables targeted curcumin delivery, optimizing therapeutic outcomes while minimizing side effects on healthy tissues. [30].
- Nanoparticles enable curcumin to penetrate cells by bypassing cell membrane barriers. Common encapsulation methods include liposomes, nanoemulsions (NEs), and lipid nanoparticles such as solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs). Polymeric micelles (PMs), dendrimers, and polymeric nanoparticles (PNs) made from biocompatible polymers are also used for curcumin delivery, providing protection and sustained release. [31].

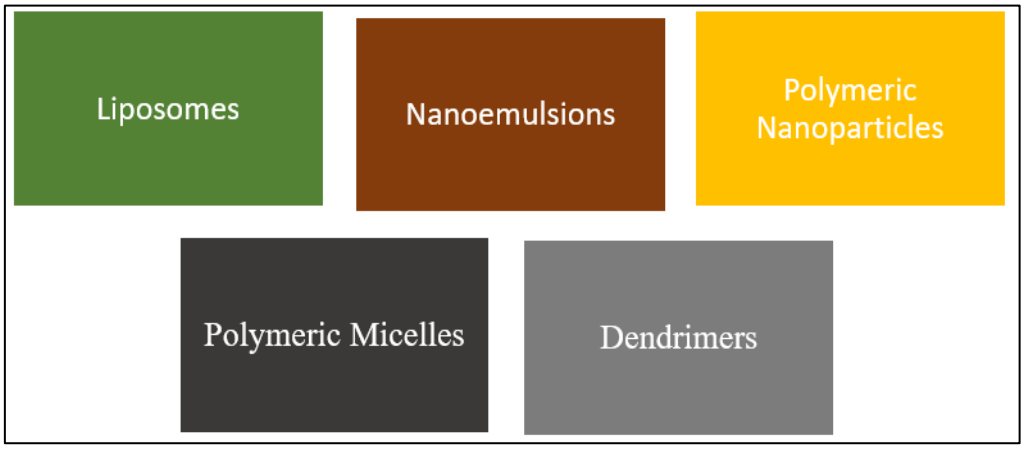

Fig 4 Different Types of Nanoparticles Used for Curcumin Delivery

III. LIPOSOMES

➢ Liposomes, microscopic vesicles composed of lipid bilayers, can encapsulate genes, drugs, or other bioactive substances. They improve drug pharmacokinetics and bioavailability while reducing side effects and enhancing therapeutic efficacy through targeted and controlled release of medicinal molecules. [32].

➢ Advances in liposomal technology have led to the development of liposomal formulations that are multifunctional and stimuli-responsive, hence broadening their uses in personalized medicine and diagnostics [33].

Table 4 Methods, Process, and Key Discoveries for Curcumin-Encapsulated Liposome Preparation

Methods	Procedure	Key discoveries	Refrences
Thin film hydration	Phospholipids and curcumin were initially dissolved together in pure ethanol, followed by ethanol removal via rotary evaporation using the thin-film hydration method. Curcumin-loaded liposomes were then formed by hydrating the resulting film with ultrapure water for 30 minutes.	The diffraction pattern of the thin-film curcumin revealed a crystalline structure. Liposomes stored at 4°C for one month became unstable and exhibited signs of curcumin leakage. The formulation achieved bioaccessibility and transformation levels of 55.4% and 43.4%, respectively, comparable to those of the pH-driven method (54.1%).	[33]

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➢ *Nanoemulsions:*

- Microemulsions (MEs) are thermodynamically stable, transparent, single-phase, homogeneous colloidal dispersions composed of water, oil, surfactant, and co-surfactant..
- Despite having smaller droplet sizes compared to nanoemulsions, both terms remain in common use. Microemulsions provide superior drug solubility, stability, absorption, and targeted delivery for enhanced therapeutic outcomes, positioning them as promising drug delivery vehicles. [34].
- Due to their unique ability to encapsulate both lipophilic and hydrophilic compounds, nanoemulsions (NEs) have emerged as versatile nanocarriers offering diverse options for drug delivery applications. NEs have demonstrated significant potential in enhancing the pharmacokinetics and clinical efficacy of various drugs. [35]

➢ *Curcumin-Loaded Nanoemulsions' Preparation Technique, Biological Activity, and Salient Features:*

Table 5 Curcumin-Loaded Nanoemulsions' Preparation Technique, Biological Activity, and Salient Features:

Methods	Biological actions	Salient features
High pressure homogenization	Anti-arthritic action	Curcumin nanoemulsions (NEs) inhibited the production of inflammatory mediators such as TNF and IL-1 while reducing NF-κB expression. An optimized formulation demonstrated enhanced bioavailability in rats, with AUC and Cmax values over three times higher than those of the nanosuspension. In rheumatoid arthritis models, oral and intravenous nanoformulations yielded comparable therapeutic effects. [36]

➢ *Nano-Structured Lipid Carriers:*

- NLCs, classified as lipid-based nanoparticles for biomedical and pharmaceutical applications, function as drug carriers to enhance the stability, solubility, and efficacy of poorly water-soluble drugs. They consist of a blend of solid and liquid lipids, creating a distinctive nanostructure that improves drug entrapment efficiency and transport. [37].
- By incorporating both liquid and solid lipids, NLCs form a more versatile lipid matrix that minimizes drug expulsion during storage and improves drug-loading capacity. [38].
- The effectiveness of curcumin-loaded NLCs for topical or dermal delivery has been evaluated through various gel formulations. Numerous studies have also assessed the efficacy of curcumin-containing NLCs, used alone or in combination, in treating different types of cancer. [39].

➢ *An Overview of the Curcumin-Loaded NLCs' Composition, Activity, Preparation Techniques, and Main Conclusions:*

Table 6 An Overview of the Curcumin-Loaded NLCs' Composition, Activity, Preparation Techniques, and Main Conclusions:

Methods	Activity	Key Highlights	Refrences
Emulsion evaporation-solidification	Healing and antibacterial properties	Curcumin-loaded NLCs exhibited a potent 2-fold inhibitory effect against Gram-positive, Gram-negative, and fungal species, surpassing the antimicrobial activity of free curcumin. Compared to both curcumin alone and the control, NLCs demonstrated significantly greater ($p < 0.0001$) wound closure during the first week..	[40]

➢ *Polymeric Micelles:*

- Polymeric micelles (PMs) are nanoscale drug delivery systems formed by amphiphilic block copolymers that self-assemble in aqueous media into core-shell nanoparticles, featuring a hydrophilic outer shell and a hydrophobic inner core..
- One key advantage of these particles' unique structure is enhanced solubility of hydrophobic drugs, which improves bioavailability and thereby boosts therapeutic efficacy. [41].
- PMs enable controlled and sustained drug release, minimizing side effects while extending therapeutic effects. Functionalizing biocompatible, biodegradable PMs allows active targeting for precise delivery to specific tissues or cells, improving efficiency. The hydrophilic coating provides stealth properties, enhancing blood circulation and reducing immune clearance, while also promoting tumor accumulation through enhanced permeability and retention. [42].

Table 7 Composition, Experimental Procedures, Observed Activity, and Salient Features of Curcumin-Loaded Polymeric Micelles

Dialysis	Chitosan micelles grafted with siRNA and complexed with curcumin-cholesterol conjugate formed successfully at a 40 N/P ratio. Endocytosis inhibitors confirmed time-dependent and effective uptake of the resulting micelles by the human lung cancer A549 cell line..	Cancer of the colon	Folate-PEG/Hyd-curcumin/C18-g-PSI micelles significantly reduced the viability of SW480 colon cancer cells compared to non-folate variants. These folate-targeted micelles show promise for colon cancer treatment due to their superior inhibition of the Wnt/β-catenin pathway over other micelle formulations..	[42,43]

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- Numerous studies have been carried out on flexible PM-based anticancer delivery systems that combine ligand-based targeting and stimuli-responsive characteristic
- Curcumin shows promise as a breast cancer treatment by targeting multiple intracellular signaling pathways, including enzymes, growth factors, cytokines, and receptors. These mechanisms encompass activation of hepatic stellate cells, the PI3K/Akt pathway, lipid peroxidation products, and suppression of pro-inflammatory cytokines. [44].
- By facilitating controlled and sustained medication release, PMs can reduce side effects and prolong therapeutic effects. Functionalization of biocompatible and biodegradable PMs enables active targeting, enabling targeted medication delivery to target tissues or cells and enhancing delivery efficiency.

➢ *Dendrimers:*

- Dendrimer nanoconstructs, typically composed of polymeric macromolecules such as polyamidoamine (PAMAM), feature a highly branched, star-like structure. Their key physical and chemical properties include excellent water solubility, encapsulation capacity, monodispersity, and numerous surface functional groups available for modification. [45].
- The ability of dendrimers to enhance curcumin's effectiveness was investigated. Their capacity to increase uptake in cancer cells was tested across three different cancer cell types and compared to various curcumin nanoformulations. [46].
- PAMAM dendrimers not only enhance curcumin solubility but also enable surface conjugation of drugs and/or specific ligands. Reports indicate that curcumin-loaded PAMAM dendrimers conjugated with the MUC-1 aptamer demonstrated a high therapeutic index against colorectal cancer adenocarcinoma. [48]
- It was disclosed that curcumin-loaded PAMAM dendrimers surface-modified with a triphenylphosphonium ligand for targeted treatment of hepatocellular carcinoma . The findings showed that by delivering the medication to the mitochondria of cancer cells, ligand-conjugated curcumin-dendrimer caused apoptosis and cell cycle stoppage at the G2/M phase.

Table 8 Curcumin-Based Nanoformulations Created for a Variety of Illnesses and Ailments are Currently Under Clinical Trials:

Clinical Trials	Inditcations/Conditions	Nanocarrier	Phase	References
Evaluate the clinical improvement in individuals with amyotrophic lateral sclerosis who receive liposome-encapsulated resveratrol and curcumin (G04CB02).	Lateral sclerosis caused by amyotrophic	Liposomes	Phase 2	[50,51]

IV. THERAPEUTIC POTENTIAL OF CURCUMIN IN DIABETIC RETINOPATHY

➢ *Diabetic Retinopathy:*

- Diabetic retinopathy (DR), a retinal microangiopathy triggered by diabetes mellitus, ranks as the leading cause of blindness among working-age adults globally. Its incidence is rising in younger diabetic populations, necessitating lifelong management. Pathogenic mechanisms involve hyperglycemia, hyperlipidemia, oxidative stress, and inflammation, while standard treatments include anti-VEGF therapies, retinal photocoagulation, and vitrectomy. [52].
- Diabetes mellitus, a global condition with complex progression and diverse complications, has gained increased focus recently. The International Diabetes Federation projects 700 million adults aged 20-79 with diabetes by 2045, three-quarters of working age.
- Factors like BMI, fat distribution, metabolic syndrome, and sex differences influence its development. Complications split into microvascular (kidney, retina, nerves) and macrovascular (CVD). Hyperglycemia drives diabetic retinopathy (DR), once viewed as purely microvascular but now linked to retinal neurodegeneration. [53].
- Curcumin, the main active compound in turmeric, serves not only as a spice but also offers diverse therapeutic effects. It acts as an anticancer agent against breast, prostate, ovarian, and stomach cancers, while its anti-inflammatory properties help treat hepatic inflammation, acute vascular inflammation, and chronic obstructive pulmonary disease (COPD).
- This review aimed to explore curcumin's therapeutic potential for diabetes mellitus and diabetic retinopathy (DR), along with elucidating the underlying mechanisms. [54].

➢ *Curcumin's Bioavailability and Strategies for Enhancing it:*

- The weak permeability of the gastrointestinal mucosa, curcumin's low solubility, and its quick elimination in vivo could all contribute to its low bioavailability. Despite curcumin's ability to treat diabetes and related conditions, clinical trial data have shown that even when a high dosage of curcumin (12,000 mg/day) is administered to the body, the serum's curcumin level stays low[55].
- Further research shows that dendritic nanoparticles enhance both curcumin's bioavailability and in vivo solubility. Studies demonstrate that curcumin-loaded solid lipid nanoparticles achieve high stability with sustained in vitro release over 12 hours, while curcumin lipid nanocarriers increased tissue and plasma curcumin levels in asthmatic rat models.
- Curcumin's structural analogs, such as EF24, offer superior therapeutic efficacy—particularly against leukemia—compared to curcumin itself. These strategies, by boosting bioavailability, amplify curcumin's overall medicinal potential [56].
- The administration of piperine within one hour of the administration of curcumin has also been shown to

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improve its bioavailability, raise the serum levels of curcumin in rats and humans, and have no negative effects[57].

➢ *Curcumin's Therapeutic Impact on Diabetes:*

- Diabetes represents a metabolic disorder whose prevalence has surged dramatically in recent decades. As a chronic condition damaging multiple organs, its prevention and management have grown increasingly vital. Studies indicate curcumin protects cultured cells or diabetic patients in vitro [58].
- Curcumin intervention during the prediabetic phase has been shown to significantly reduce progression to type 2 diabetes after 9 months. Additionally, curcumin treatment enhances overall β-cell function. In high-fat diet and streptozotocin-induced diabetic rats, Al-Saud's research demonstrated curcumin's hypoglycemic effects, along with reduced tissue insulin resistance and improved diabetic symptoms. [59].
- In vitro studies demonstrate curcumin's protective effects on cells exposed to high glucose conditions. A study on INS-1 cells under high glucose—with or without curcumin—examined insulin levels, NADPH oxidase subunit expression, islet cell morphology, ROS production, superoxide dismutase and catalase activities, INS-1 cell proliferation, and apoptotic factor expression. [60].
- The study revealed that curcumin elevated insulin levels, suppressed apoptotic markers and NADPH oxidase subunits, and effectively mitigated high glucose-induced oxidative stress and proliferation damage in INS-1 cells. It also protected islet cells from apoptosis and high glucose/palmitate-induced oxidative stress via NADPH pathway modulation.
- These results indicate curcumin safeguards islet cells through anti-inflammatory and anti-apoptotic mechanisms, potentially offering therapeutic benefits in diabetes by directly lowering blood glucose. [61].

➢ *Curcumin's Protective Effects on Diabetic Retinopathy:*

- Curcumin's antioxidant properties: Oxidative stress drives diabetic microvascular complications. Under diabetic metabolic dysregulation, mitochondria and microvascular endothelial cells produce excess superoxide. High glucose depletes NADPH—essential for glutathione (GSH) synthesis, a key ROS scavenger—leading to heightened ROS accumulation. This triggers endothelial cell and pericyte apoptosis, worsened by oxidative damage and local inflammation. [62].
- The intraretinal fluid leakage is the result of a disruption in the barrier function of the tight junctions of retinal capillary epithelial cells. In the diabetic rat retina, Kowluru and Kanwar showed that the amount of oxidation-modified DNA in the cells was rising.

➢ *Effects of Curcumin on Antioxidant Stress:*

- Curcumin boosts antioxidant capacity by upregulating T-AOC and SOD expression while elevating Nrf2, DNMT, and GSH levels. It also reduces oxidative stress by downregulating MDA and suppressing LOX, XOD, PKC, and catalase activities. (Nrf2: nuclear factor E2-related factor 2; DNMT: DNA methyltransferase; GSH: glutathione; T-AOC: total antioxidant capacity; SOD: superoxide dismutase; LOX: lipoxygenase; XOD: xanthine oxidase; MDA: malondialdehyde; PKC: protein kinase C). [63].

➢ *Curcumin's Anti-Inflammatory Properties:*

- Inflammation has a key role in the development and course of DR. According to some researchers, the pathophysiology of DR is comparable to that of chronic inflammation, and pro-inflammatory cytokines are more prevalent in the retina and vitreous of diabetic individuals and animals[64].
- Retinal Müller cell activation significantly influences early inflammation and late-stage retinal damage in DR. ICAM-1 and VCAM-1 levels elevate during DR's initial pathogenic phase, while NPDR tissues show increased inflammatory cytokines like IL-1β, IL-6, IL-8, TNF-α, and MCP-1.
- High glucose exposure in retinal pigment epithelial cells (RPECs) raises IL-1β and IL-6. IL-1 activation triggers ROS and NF-κB release, boosting pro-inflammatory mediators in a self-reinforcing feedback loop. Inflammation and oxidative stress synergistically drive DR onset and progression. [65].
- Vascular endothelial cells may be harmed by TNF-α, which can result in cell hypoxia and necrosis. Furthermore, insulin resistance and chronic inflammation are tightly associated with TNF-α, an inflammatory cytokine.

V. CONCLUSION

Curcumin, the principal bioactive compound of *Curcuma longa*, has emerged as a multifunctional therapeutic agent with anti-inflammatory, antioxidant, anticancer, neuroprotective, and cardioprotective properties. Despite its remarkable pharmacological profile, its clinical translation remains limited due to poor aqueous solubility, chemical instability, rapid metabolism, and extremely low oral bioavailability. Advances in nanotechnology—including liposomes, nanoemulsions, polymeric micelles, dendrimers, solid lipid nanoparticles, and nanostructured lipid carriers—have significantly enhanced curcumin’s solubility, stability, absorption, and targeted delivery, often achieving manifold improvements in bioavailability. Furthermore, modulation of gut microbiota and the use of bioenhancers such as piperine have shown synergistic potential in optimizing therapeutic outcomes.

Preclinical and clinical studies highlight curcumin’s promise in managing chronic diseases such as neurodegenerative disorders, cardiovascular complications,

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cancer, diabetes, and diabetic retinopathy. However, challenges remain in terms of large-scale production, regulatory approval, long-term safety, and consistent therapeutic efficacy. Future research should focus on integrating nanocarrier systems with precision medicine approaches, microbiome modulation, and structural analog development to overcome translational barriers. With continued innovation, curcumin holds the potential to evolve from a traditional herbal remedy into a cornerstone of modern pharmacotherapy.

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