Review

Nano-Delivery Systems for Curcumin

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Review

Nano-Delivery Systems for Curcumin

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Abstract. Curcumin, a polyphenol with a rich history spanning two centuries, has emerged as a promising therapeutic agent targeting multiple signaling pathways and exhibiting cellular-level activities that contribute to its diverse health benefits. Extensive preclinical and clinical studies have demonstrated its ability to enhance the therapeutic potential of various bioactive compounds. While its reported therapeutic advantages are manifold, predominantly attributed to its antioxidant and anti-inflammatory properties, its efficacy is hindered by poor bioavailability stemming from inadequate absorption, rapid metabolism, and elimination. To address this challenge, nano-delivery systems have emerged as a promising approach, offering enhanced solubility, biocompatibility, and therapeutic effects for curcumin. We have analyzed the knowledge on curcumin nano-encapsulation and its synergistic effects with other compounds, extracted from electronic databases. We discuss the pharmacokinetic profile of curcumin, current advancements in nano-encapsulation techniques, and the combined effects of curcumin with other agents across various disorders. By unifying existing knowledge, this analysis intends to provide insights into the potential of nano-encapsulation technologies to overcome constraints associated with curcumin treatments, emphasizing the importance of combinatorial approaches in improving therapeutic efficacy. Finally, this compilation of study data aims to inform and inspire future research into encapsulating drugs with poor pharmacokinetic characteristics and investigating innovative drug combinations to improve bioavailability and therapeutic outcomes.

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Turmeric, a traditional spice derived from the rhizomes of Curcuma longa, has garnered significant attention in scientific research owing to its rich phytochemical composition and diverse therapeutic potential. Over millennia, turmeric has been utilized across various cultures for its purported health benefits, supported by an extensive body of research spanning multiple organ systems in humans [1-4]. The bioactive compounds within turmeric, particularly curcumin, have been extensively studied for their antimicrobial, antioxidant, and anti-inflammatory properties, which underpin their therapeutic efficacy [5]. Moreover, computational docking and in-vitro experiments conducted previously in our laboratory revealed that curcumin exhibits a strong binding affinity towards the active sites of steroid metabolizing cytochrome P450 proteins. Specifically, our findings demonstrated inhibition of androgen metabolizing CYP17A1 and estrogen metabolizing CYP19A1 enzymes by curcuminoids, suggesting a promising avenue for the development of novel compounds with enhanced efficacy and safety profiles for targeting both prostate and breast cancers and other hyperandrogenic disorders [6]. The exponential growth in scientific publications related to curcumin shows its overall significance in biomedical research, with over 2500 publications as of 2023, highlighting its clinical potential (Figure 1).

Curcumin, the principal curcuminoid found in turmeric, has captivated researchers since its isolation over two centuries ago, originating from India. Structurally, curcumin exists as a yellowish diarylheptanoid crystalline powder, soluble in certain organic solvents but exhibiting limited solubility in others [7]. Curcuminoids, including curcumin, demethoxycurcumin, and bisdemethoxycurcumin, constitute the primary derivatives isolated from turmeric, each contributing

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to its therapeutic profile [2,4,8-10]. Despite the promising bioactivities of curcumin and other phytochemicals, their translation into effective therapeutic agents faces challenges stemming from inherent limitations, including poor solubility, structural instability, and low bioavailability [11-15]. These constraints hinder their clinical utility, necessitating innovative strategies to enhance their pharmacokinetic and pharmacodynamic properties. Nanoformulation technologies have emerged as a promising approach to address these challenges, offering avenues to improve the solubility, stability, and targeted delivery of curcumin.

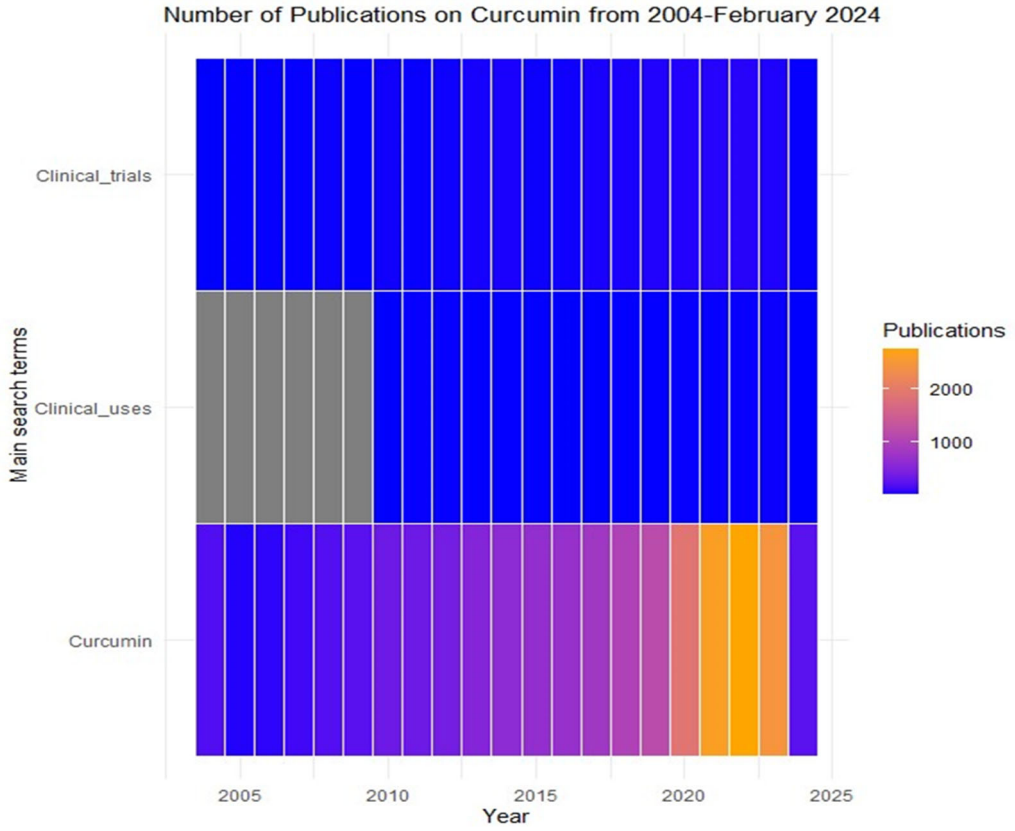

Figure 1. Number of publications related to Curcumin per year. The data were obtained from PubMed using the following keywords: Curcumin, curcuminoids, nanoparticle, clinical uses, clinical trials.

Nanoformulations encompass a diverse array of carriers, including polymeric complexes, biofriendly inorganic substances, and lipids, each offering unique advantages for drug delivery [16]. Notably, nanocarriers such as dendrimers, nanocrystals, polymersomes, and liposomes have gained prominence in biomedical research and pharmaceutical applications due to their ability to traverse biological barriers and exert therapeutic effects within the body [17-22]. Polymer-based nanoparticles and lipid-based nanocarriers have dominated the landscape of nanoformulations, comprising nearly 99% of reported data, indicative of their widespread adoption and research interest (Figure 2). Polymer-based nanoparticles and lipid-based nanocarriers represent versatile platforms for drug delivery, offering distinct advantages in terms of biocompatibility, tenable properties, and targeted delivery. Polymer-based nanoparticles, such as poly (lactic-co-glycolic acid) (PLGA) and polyethylene glycol (PEG) derivatives, offer a customizable framework for encapsulating curcumin, thereby improving its solubility and stability while facilitating controlled release kinetics [23]. These nanoparticles can be tailored to modulate drug release profiles, enhance cellular uptake, and achieve prolonged circulation times in vivo, thus optimizing the therapeutic efficacy of curcumin [5,24].

Similarly, lipid-based nanocarriers, including liposomes, solid lipid nanoparticles (SLNs), and nanoemulsions, exhibit inherent biocompatibility and the ability to encapsulate lipophilic compounds like curcumin within their hydrophobic cores [25]. Liposomes, composed of phospholipid bilayers, can encapsulate curcumin within aqueous compartments or lipid bilayers,

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enabling targeted delivery to specific tissues or cells while minimizing off-target effects [25]. SLNs offer advantages in terms of stability and sustained release, making them suitable candidates for encapsulating curcumin and overcoming its inherent limitations [26]. Nanoemulsions, comprising oil-in-water or water-in-oil formulations, provide a stable platform for delivering hydrophobic compounds like curcumin, enhancing its bioavailability and therapeutic efficacy [27,28].

The dominance of polymer-based nanoparticles and lipid-based nanocarriers in nanoformulation research shows their versatility and effectiveness in addressing the challenges associated with curcumin delivery. By harnessing the unique properties of these nanocarriers, researchers can overcome barriers to curcumin's clinical translation, unlocking its full therapeutic potential for various applications, including antimicrobial, antioxidant, anti-inflammatory, neuroprotective, and anticancer interventions [29,30]. Furthermore, advancements in nanotechnology offer opportunities to innovate novel delivery systems, such as hybrid nanoparticles and stimuli-responsive carriers, further enhancing the bioavailability and efficacy of curcumin-based therapeutics [31,32].

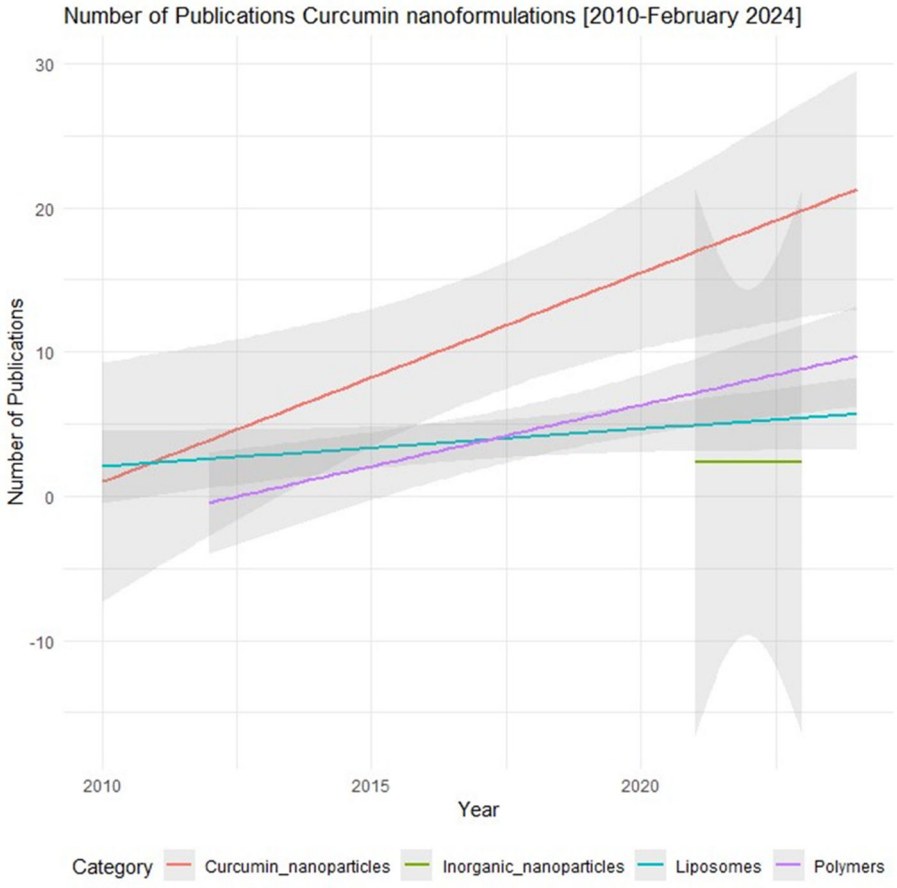

Figure 2. Number of publications related to Curcumin nano-formulation from 2010-February2024. The data were obtained from PubMed using the following keywords: Curcumin plus nanoparticle, Inorganic nanoparticles, polymers/polymersomes, lipid-based nanoparticle/liposomes.

The following sections review recent biomedical applications of curcumin nanoformulations (CNF) as a targeted drug delivery system to improve its bioavailability and efficacy. This review particularly focuses on CNF strategies to resolve the inherent limitations of curcumin and its derivatives. In this comprehensive review, we delve into the intricate landscape of curcumin pharmacokinetics, nanoformulations, and synergistic combinations, shedding light on recent advancements and promising approaches. We begin by elucidating the pharmacokinetic profile of curcumin, unravelling the complexities of its absorption, distribution, metabolism, and excretion (ADME) in vivo. Drawing insights from preclinical and clinical studies, we examine the factors influencing curcumin's bioavailability and propose strategies to overcome these barriers.

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Furthermore, we explore the burgeoning field of nanoformulations tailored to encapsulate curcumin, offering enhanced solubility, stability, and targeted delivery. From lipid-based nanoparticles to polymeric micelles and solid lipid nanoparticles, we dissect the diverse array of nanoformulation approaches employed to harness the therapeutic potential of curcumin. Through a critical analysis of preclinical and clinical data, we evaluate the efficacy and safety of these nanoformulations, delineating key parameters governing their design and optimization.

Moreover, we investigate the synergy between curcumin and other bioactive compounds, elucidating how combinatorial approaches can potentiate the therapeutic effects of curcumin while mitigating potential adverse effects. From phytochemicals and nutraceuticals to conventional drugs and natural products, we scrutinize the multifaceted interactions underlying synergistic combinations with curcumin, offering mechanistic insights and therapeutic implications. Additionally, we discuss the role of nanotechnology in enhancing the delivery of these synergistic combinations, highlighting the potential for targeted and sustained release formulations.

In summary, this review provides a comprehensive overview of the pharmacokinetics, nanoformulations, and synergistic combinations with curcumin, highlighting their potential to revolutionize therapeutic interventions across a spectrum of diseases. By elucidating the underlying mechanisms and translational challenges, we aim to inspire future research endeavours and therapeutic innovations, ultimately advancing the clinical utility of curcumin-based therapies. Moreover, we address the regulatory considerations and translational hurdles in bringing curcumin nanoformulations and synergistic combinations from bench to bedside, emphasizing the importance of interdisciplinary collaborations and translational research efforts in realizing the full therapeutic potential of curcumin.

Pharmacokinetic Profile of Curcumin

Curcumin demonstrates rapid solubility in organic solvents such as acetone, ethanol, dimethyl sulfoxide (DMSO), and dimethylformamide. However, curcumin's stability varies depending on diluent pH. While it remains stable under acidic pH conditions, it degrades into ferulic acid and feruloylmethane in neutral and basic pH environments [33]. Its stability is compromised in buffer solutions at neutral pH, although it remains stable in the presence of ascorbic acid, N-acetylcysteine, and glutathione. The gastrointestinal absorption of curcumin is notably poor, as evidenced by minimal absorption observed in humans' subjects and animal models and following oral administration. However, studies have shown improved absorption rates, more than 20% absorption observed with an oral dose of 100-1500 mg [15,34,35]. When taken orally, curcumin goes through quick changes in the small intestine, liver, and kidneys, transforming into curcumin glucuronide, curcumin sulphate, and methylated curcumins [15,34,36,37]. These altered forms are then rapidly eliminated from the body through urine and feces. The scheme of curcumin conjugation and reduction in the humans are depicted in Figure 3. In the bloodstream, curcumin mainly exists as these modified compounds, which are not as biologically active, resembling the behavior of other polyphenols [15,33,34,37].

Additionally, intestinal microorganisms play a role in extensively reducing curcumin to dihydrocurcumin, tetrahydrocurcumin, and hexahydrocurcumin [15,33,34,36,37]. The maximum recommended oral dose for humans is 8 g/day for up to 3 months, with no reported toxic or hazardous effects at this dosage level [38]. Recent advancements in curcumin research have shed light on its potential therapeutic applications beyond its traditional uses. From neuroprotective effects to modulation of gut microbiota and metabolic pathways, curcumin's versatility continues to be explored in various disease contexts. Moreover, novel delivery systems such as nanoformulations aim to improve its bioavailability and therapeutic efficacy, paving the way for its translation into clinical practice.

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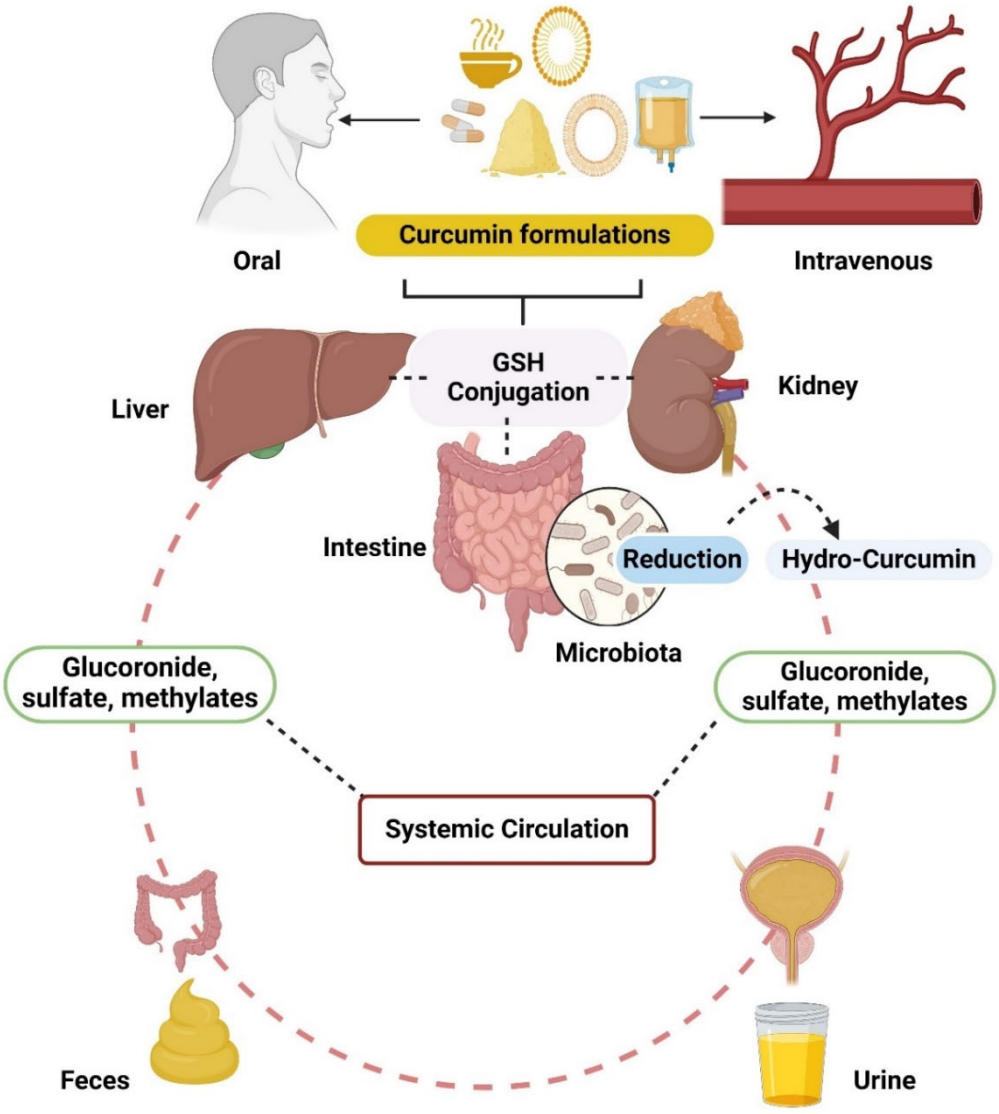

Figure 3. Oral or Intravenous administration of different formulations curcumin results mainly in conjugated or reduced curcumin detected in systemic circulation (plasma), and intravenous administration results mainly in only reduced curcumin metabolites (hydrocurcumins).

Numerous studies have elucidated the enhanced pharmacokinetic profile of curcumin when administered in nanoformulations or as colloidal dispersion [39-46].

Current Curcumin Nanoformulations and Their Pharmacological Profile

Nanoformulations of curcumin have garnered significant interest in recent years as a promising strategy to address its inherent challenges of poor solubility and bioavailability. Among these nanoformulations, lipid-based nanoparticles, solid lipid nanoparticles, nanoemulsions, polymeric nanoparticles, dendrimers, and nanocrystals have emerged as frontrunners due to their unique properties and biocompatibility (Figure 4).

For instance, a phase I open-label study evaluated the safety and efficacy of liposomal curcumin in patients with metastatic tumors. This investigation identified 300 mg/m^2 of liposomal curcumin as the tolerated dose and observed promising tumor marker responses in select patients. The curcumin liposomes sustained curcumin plasma concentrations, highlighting its potential as a delivery system for targeted cancer therapy [47]. In another double-blinded, placebo-controlled trial, Campbell et al, [47] administered curcumin formulated with fenugreek soluble fiber to obese men for 12 weeks. The

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enhanced bioavailable curcumin, resulted in favorable changes in cardiovascular biomarkers such as homocysteine and high-density lipoprotein concentrations, hinting potential cardiovascular health benefits. The combination of curcumin with fenugreek soluble fiber enhanced curcumin's bioavailability, leading to improved metabolic parameters and lipid profile [48].

Furthermore, a randomized, double-blind, placebo-controlled trial investigated the effects of nano-curcumin supplementation on metabolic status in diabetes patients undergoing haemodialysis. They observed that nano-curcumin demonstrated significant improvements in glucose metabolism, lipid profile, and inflammatory markers compared to placebo. The nanomicelle formulation of curcumin enhanced its solubility and bioavailability, leading to better therapeutic outcomes in diabetic patients on haemodialysis [49]. Curcumin nanomiscelle is also reported to promote bone strengthening in postmenopausal women [50] and prevent oral mucositis in patients undergoing head and neck chemotherapy [51].

Pharmacokinetic studies of a standardized novel solid lipid curcumin particle, commercially available as Longvida®, showcased increased bioavailability compared with a generic curcumin extract, suggesting the potential for sustained release in both in-vitro and in-vivo studies [52-54]. Moreover, clinical studies have demonstrated the safety of Longvida® and evaluated the cognitive and mood-enhancing effects a highly in healthy older adults. Participants supplemented with Longvida® showed improvements in working memory and mood parameters compared to placebo. The solid-lipid curcumin preparation (SLCP) used in the study demonstrated superior cognitive benefits and neuroprotective effects, highlighting its potential in age-related cognitive decline [55].

Ahmadi et al, [56] conducted a 12-month, double-blind, randomized, placebo-controlled trial evaluating nanocurcumin as an adjunctive treatment for amyotrophic lateral sclerosis (ALS). Nanocurcumin supplementation showed promising results, improving survival rates, and demonstrating a favorable safety profile in ALS patients. The nanocurcumin formulation exhibited potent anti-inflammatory and antioxidant properties, providing neuroprotective effects, and enhancing patient outcomes in ALS.

Additionally, nanocurcumin has shown strong antiviral effects, particularly in mitigating inflammatory responses and reducing mortality rates in COVID-19 patients. Studies investigating the immunomodulatory effects of nanocurcumin in COVID-19 patients reported reductions in inflammatory cytokine levels, suggesting its potential as an adjunctive therapy in COVID-19 management. The nanocurcumin formulation mitigated cytokine storm and inflammatory responses, offering a promising adjunctive therapy for COVID-19 patients [57-62].

Collectively, these studies show the potential of nanoformulations of curcumin in overcoming the challenges associated with its poor bioavailability and unlocking its full therapeutic potential. From cancer treatment to cardiovascular health, metabolic disorders, neurodegenerative diseases, and viral infections like COVID-19, nano-curcumin holds promise as a versatile and effective therapeutic agent. Further research and clinical trials are warranted to elucidate its mechanisms of action, optimize dosage regimens, and validate its efficacy across diverse medical conditions. With continued advancements in nanotechnology, nano-curcumin stands poised to revolutionize modern medicine and improve healthcare outcomes worldwide.

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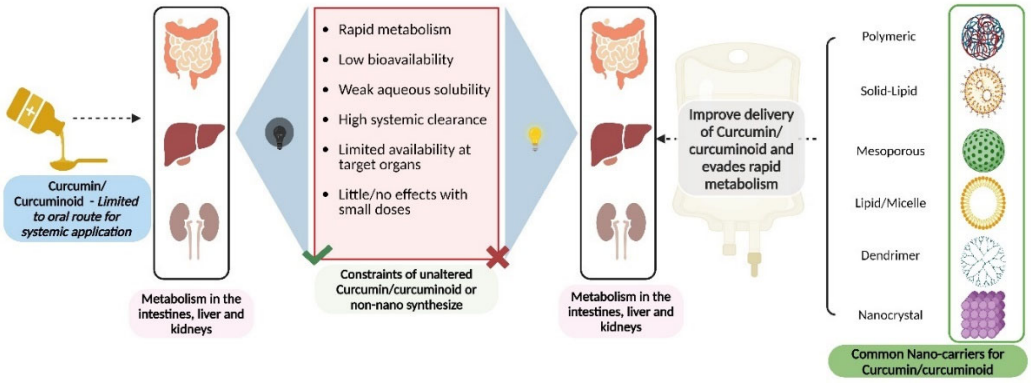

Figure 4. Schematic Representation of the Limitations of curcumin bioavailability and Nano-Carrier-Mediated Improvements in Delivery. Raw curcumin/curcuminoids faces numerous challenges hindering its therapeutic efficacy, including rapid metabolism, low bioavailability, weak aqueous solubility, high clearance, limited availability to target organs, and minimal effects at small doses. Nano-carriers, such as polymeric, solid-lipid, mesoporous, liposomes, dendrimer nanoparticles, and nanocrystals, encapsulated curcumin/curcuminoids, shield it from rapid metabolism and enhancing its stability in circulation. The utilization of nano-carriers represents a promising strategy to enhance the delivery of curcumin, circumventing its inherent limitations and maximizing its therapeutic potential in various disease treatments.

Other Novel Formulations of Curcumin

In addition to nanoformulations, other investigations have elucidated a range of innovative curcumin formulations tailored to enhance its bioavailability and therapeutic efficacy in addressing diverse health conditions.

Galactomannan Biopolymer Formulation: Matthewman et al. [15] discussed the use of natural fiber, specifically galactomannan biopolymer from Trigonella foenum graecum (fenugreek), to enhance the pharmacokinetics and efficacy of curcuminoids. This patented formulation, known as Curcumin-galactomannoside (CGM), combines 35-40% curcuminoids with 60% fenugreek galactomannan dietary fiber [63]. Pre-clinical and clinical studies with CGM have demonstrated superior efficacy compared to standard unformulated curcumin, attributed to improved bioavailability and tissue distribution [64-66]. Mechanistic evidence suggests CGM interacts with various cellular targets, regulating genes involved in cancer pathogenesis [15,64,65].

Phytosomal Curcumin: Phytosomes are plants metabolites with complex chemistry. Phytosomes contains amphipathic molecules that makes them resistant to degradation and highly absorbed in the gut improving their bioavailability [67-69]. Curserin® is a commercially available phytosomal curcumin containing phosphatidylserine, phosphatidylcholine, and piperine. Cicero et al. [70] investigated the effects Curserin® on subjects with overweight and impaired fasting glucose. After 8 weeks of treatment, significant improvements were observed in various metabolic parameters, including fasting plasma insulin, lipid profile, liver function tests, and serum cortisol levels, compared to baseline and placebo.

Colloidal Submicron-Particles and amorphous Formulation (Theracurmin® and CurcuRouge™): Theracurmin®, a commercial bioavailable curcumin, and has garnered attention for its enhanced bioavailability and therapeutic potential. Theracurmin® is water-dispersible, with significantly improved absorption and tissue penetration capabilities, represents a novel approach to alleviating challenges associated with curcumin therapeutics. Reports that compared the absorption efficiency of Theracurmin® with other curcumin drug delivery system (DDS) preparations, showed that Theracurmin® exhibited significantly higher absorption efficiency, with more than 2-5-fold higher plasma curcumin concentration and 2-6 fold higher area under the concentration-time curve compared to the other DDS [42,43,71,72]. Recent study by Sunagawa et al.[39] compared the bioavailability of an amorphous formulation (curcuRouge™) with Theracurmin®. Both animal and

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human studies showed that curcuRouge™ exhibited superior bioavailability, achieving 3.7-fold higher plasma concentration in rats and 3.4-fold higher bioavailability in human volunteers compared to Theracurmin®. But curcuRouge™ has not been investigated for its efficacy in various disorders. Specifically, Theracurmin® shown promise in treating various conditions such as muscle damage, inflammation, and alcohol intoxication. Studies have indicated its efficacy in managing knee osteoarthritis, with patients experiencing reduced knee pain and decreased reliance on anti-inflammatory medications when administered Theracurmin® [45]. Moreover, Theracurmin® has demonstrated an inhibitory effect on alcohol intoxication in human subjects. This effect is evidenced by a reduction in blood acetaldehyde concentration following alcohol consumption [42]. The multifaceted therapeutic potential of Theracurmin®, includes its effects in musculoskeletal disorders [44] and improving symptoms of neurodegenerative disorders [73].

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Combinations of Curcumin with Other Therapeutic Agents

Combination therapy, integrating multiple druggable agents, has emerged as a fundamental strategy in disease therapeutics. By combining drugs targeting similar or different pathways, it enhances pharmacodynamic outcomes, potentially reducing drug resistance. Curcumin, an FDA-approved nutraceutical, offers extensive health benefits but faces limitations in mainstream healthcare due to costly modifications. Hence, approaches combining FDA-approved drugs with nutraceuticals are gaining traction across various diseases [74-76]. Different scientific reports have shed lights on the pharmacokinetic and pharmacodynamic profile of curcumin combinatory therapy (Table 1).

During the 1990s, preclinical studies revealed compelling findings regarding the administration of curcumin alongside piperine. In murine models, this combination led to a remarkable 154% increase in serum concentration. Even more impressively, human trials demonstrated a staggering 2000% surge in serum concentration, with no reported adverse effects [77].

In a separate clinical study, patients administered a capsule containing 500 mg of curcumin combined with 5 mg of piperine experienced enhanced vitality. Moreover, the study meticulously evaluated various biochemical and clinical parameters, including complete blood count, liver enzymes, blood glucose levels, lipid parameters, kidney function, and C-reactive protein levels, demonstrating the safety and potential efficacy of this combination [78].

Furthermore, another research group investigated the impact of curcumin-piperine combination therapy on patients recovering from ischemic stroke. The results were promising, with a significant increase in total antioxidant capacity ($p < 0.001$). Moreover, the combination therapy led to reductions in serum levels of high-sensitivity C-reactive protein ($p = 0.026$), total cholesterol ($p = 0.009$), triglycerides ($p = 0.001$), carotid intima-media thickness ($p = 0.002$), weight ($P = 0.001$), waist circumference ($p = 0.024$), as well as systolic and diastolic blood pressure ($p < 0.001$) [79].

Other studies highlight the pharmacokinetic and pharmacodynamic profiles of curcumin combinatory therapy. For instance, curcumin's phototherapeutic effect has been explored in combination with photodynamic therapy (PDT), demonstrating broad-spectrum efficacy against oral microorganisms [80,81]. Additionally, curcumin, combined with various agents, promising outcomes across different disease contexts.

Oral Health: Curcumin, combined with blue light and other compounds, effectively disinfects the oral cavity, offering potential applications in dental care [82-84]. Moreover, its anti-inflammatory properties can aid in gum disease management. Clinical trials demonstrate the efficacy of curcumin in combination with blue light and other compounds in disinfecting the oral cavity, with potential applications in dental care [82-84]. Curcumin combined with other agents efficacy in oral submucous fibrosis treatment, reducing symptoms and improving treatment outcomes [85,86]. Its anti-inflammatory and antioxidant properties contribute to oral health improvement.

Neurological Disorders: Additionally, curcumin exhibits neuroprotective effects and may have potential in managing neurodegenerative disorders. Combination therapy involving curcumin-coated poly lactide-co-glycolide (PLGA) nanoparticles enhances drug transport to the brain, showing efficacy in treating malignant gliomas [24].

Gastrointestinal Disorders: Curcumin combined with standard medications significantly reduces chronic inflammation in patients with gastritis caused by H. pylori, while boosting antioxidant defenses [87]. Furthermore, curcumin promise in managing inflammatory bowel diseases. In patients with mild-to-moderate irritable bowel syndrome (IBS) symptoms, a capsule containing curcumin and fennel essential oil effectively alleviates symptoms and improves quality of life [88].

Metabolic Syndromes: The anti-inflammatory and antioxidant properties exhibited when combined with bioactive agents as chlorogenic acid, coconut yogurt, ferrous sulphate, and boswellic acid can mitigate metabolic dysfunctions [89-92]. Curcumin supplementation alongside omega-3 polyunsaturated fatty acids demonstrates promising effects on triglyceride levels, insulin sensitivity, and metabolic syndrome components [93,94].

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Cancer Treatment: Curcumin's anti-cancer properties offer potential adjuvant therapy in various cancer types. Combinations of curcumin with chemotherapy agents or other bioactive compounds enhance cancer treatment efficacy, promoting apoptosis, inhibiting tumor growth, and improving treatment outcomes [24,95-97]. A large number of potential applications of curcumin based compounds in cancer therapy have been pursued and currently under consideration world wide.

Osteoarthritis Management: Curcumin-based combinations exhibit down-regulatory effects on mediators implicated in osteoarthritis pathogenesis, offering potential therapeutic benefits [98,99]. Moreover, its anti-inflammatory effects can alleviate joint pain and improve mobility [100].

Chronic Kidney Disease: Combination therapy with resveratrol and curcumin induces beneficial effects on muscle, bone mass, and fat reduction in patients with chronic kidney disease undergoing haemodialysis [101]. This combination therapy addresses multiple complications associated with chronic kidney disease.

Inflammations associated different pathologies: Combination therapy involving curcumin and chlorogenic acid exhibits acute anti-inflammatory properties in postmenopausal women [91]. This combination may have potential applications in managing inflammatory conditions prevalent in postmenopausal women.

A randomized trial investigated the efficacy and tolerability of a combination therapy comprising curcuminoid complex and diclofenac versus diclofenac alone in patients with knee osteoarthritis. The results demonstrated that both treatment groups exhibited improvements in pain relief and quality of life. However, patients receiving the combination therapy displayed significantly superior enhancement in various outcome measures, particularly in pain and quality of life scores ($p < 0.001$) compared to the diclofenac monotherapy group. Furthermore, the combination therapy was well-tolerated, with fewer adverse effects reported [102].

In another study, the efficacy of a combination therapy involving curcumin and omega-3 fatty acids was investigated in individuals suffering from episodic migraine. The findings revealed that supplementation with this combination resulted in a significant reduction in serum vascular cell adhesion molecule (VCAM) levels, indicating a modulation of inflammatory processes associated with migraine pathology. Additionally, participants reported improvements in migraine symptoms and overall well-being [103].

Table 1. Summary of the drug combinations with curcumin for treating various diseases.

Form of Curcumin	Combinatory Agent (s)	Clinical Use	Outcome	Type of Study	Reference
Nano-Curcumin	Docetaxel	Glioma	Easy passage through the BBB and reduce the toxic effects of high dose docetaxel	Preclinical	[24]
Curcumin	Omeprazole, amoxicillin, and metronidazole	Gastritis–associated *Helicobacter pylori* infection.	Eradication of Helicobacter pylori infection	Clinical	[87]
Curcumin	Long-chain omega-3 polyunsaturated fatty acids	Type II Diabetes	Reduces blood lipids, increase insulin sensitivity but has no effect on blood glucose	Clinical	[93,94]

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Curcumin	Chlorogenic acid and coconut yogurt	Inflammation	Anti-inflammatory effects	Clinical	[91]
Curcumin	Fennel essential oil	Irritable bowel syndrome	Safe and effective	Clinical	[88]
Curcumin	Docetaxel	Metastatic castration-resistant prostate cancer	No therapeutic benefit	Clinical	[97]
Curcumin	Aloe Vera gel	Oral Submucous Fibrosis	Anti-inflammatory	Clinical	[85]
Curcumin	Piperine	COVID-19, ischemic stroke	Increase bioavailability and Energy booster	Preclinical and Clinical	[77-79]
Curcumin	Alendronate	Osteoporosis	Anti-inflammatory	Clinical	[99]
Curcumin	Dexamethasone and hyaluronidase	Oral Submucous Fibrosis	Anti-inflammatory	Clinical	[86]
Curcumin and curcuminoids, entrapped in a patented delivery system (LipiSperse®)	Ferrous sulphate	Inflammation	Anti-inflammatory effects	Clinical	[90,92]
Curcumin and curcuminoid	Blue light, Sodium dodecyl sulphate	Oral disinfectant	Reduction of salivary microorganisms	Clinical	[82-84]
Curcumin	Resveratrol	Malnutrition	Increase in Bone and Muscle mass, reduction in fat	Clinical	[101]
Curcumin and desmethoxycurcumin and bisdemethoxycurcumin	folinic acid-5-fluorouracil-oxaliplatin chemotherapy	Metastatic Colorectal Cancer	Improves the quality of life of Metastatic Colorectal Cancer patients	Clinical	[95,96]
Curcuminoids and Turmeric oil	Diclofenac	Knee osteoarthritis	Tolerable and analgesic	Clinical	[102]
Curcuminoids extract	Hydrolysed collagen, and green tea extract	Osteoarthritis	Modulates key catabolic, inflammatory, and angiogenesis factors associated with osteoarthritis progression.	Clinical	[98]
Nanocurcumin	Omega-3 fatty acids	Episodic migraine	Reduce serum VCAM level	Clinical	[103]
Turmeric Phytosome®	*Boswellia serrata* (BSE) gum resin	Oxidative stress and inflammation	Anti-inflammatory	Clinical	[89]

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(equivalent to 10 mg of curcumin)			and antioxidant effects		
Turmeric volatile oil	Boswellic acid extract from Indian frankincense root	Osteoarthritis	Analgesic	Clinical	[100]

Conclusions

In conclusion, the synthesis of evidence presented in this review highlights the remarkable potential of nano-encapsulation strategies to address the challenges associated with curcumin therapeutics. By enhancing solubility, bioavailability, and therapeutic efficacy, nano-delivery systems offer a promising avenue for overcoming the limitations of conventional curcumin formulations. Moreover, the synergistic effects observed through the combination of curcumin with other bioactive compounds shows the value of combinatorial approaches in augmenting therapeutic outcomes across various disorders. While significant progress has been made in elucidating the pharmacokinetic profile and therapeutic applications of curcumin, further research is warranted to optimize nano-encapsulation techniques and explore novel drug combinations. Future studies should focus on refining nano-delivery systems to maximize drug loading capacity, improve targeted delivery, and minimize potential toxicity. Additionally, investigating the mechanisms underlying the synergistic interactions between curcumin and other compounds can provide valuable insights into designing tailored therapeutic interventions. Overall, this review shows the importance of continued exploration and innovation in curcumin therapeutics, with nano-encapsulation and combinatorial approaches holding great promise for advancing the field and ultimately improving health outcomes for individuals worldwide.

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