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A comprehensive review on Nanocurcumin: Advances in bioavailability and therapeutic applications

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Abstract

Curcumin, the active compound in turmeric, exhibits broad therapeutic potential but is limited by poor bioavailability. Nanocurcumin—curcumin formulated into nanoscale carriers—addresses these challenges by enhancing solubility, stability, targeted delivery, and circulation time. This review explores various nanocarrier systems including liposomes, micelles, nanoemulsions, nanogels, and polymeric nanoparticles, highlighting their role in improving curcumin's pharmacokinetics and therapeutic impact. Nanocurcumin has demonstrated superior efficacy in preclinical models of cancer, neurodegenerative diseases, diabetes, and inflammatory conditions, often at lower doses than native curcumin. Despite encouraging results, clinical adoption remains limited due to regulatory, manufacturing, and safety evaluation hurdles. The review emphasizes the need for standardized formulations, in-depth toxicological assessments, and large-scale clinical trials to validate nanocurcumin's translational value. With further refinement, nanocurcumin holds promise as a powerful agent in personalized and precision medicine.

Keywords: Curcumin, nano-curcumin, limitations, bioavailability, therapeutic application, safety and toxicity

1. Introduction

Humans historically relied on herbs used as medicine for healing and well-being, fostering a longstanding belief in the vital role of plants for sustenance and benefits ^[1]. The bond between people and plants is firmly established in our culture and spiritual values, influencing traditional medicine and society as a whole ^[2]. Curcumin from turmeric offers diverse health benefits, but limited therapeutic use, attributed to poor solubility and low bioavailability, hinders its effectiveness ^[3]. Nanotechnology aims to leverage nanoscience advantages. Nanotherapeutics focuses on nanoparticles for controlled drug delivery in healing different diseases. Nanodrugs are stable, have high carrying capacity, and can address conventional medication drawbacks. Nanometric carriers encapsulate diverse drugs for targeted administration ^[4, 5]. The purpose of this review is to offer a comprehensive analysis of curcumin and nanocurcumin, highlighting the advantages, limitations, and potential applications of nanocurcumin in various disease.

2. Curcumin

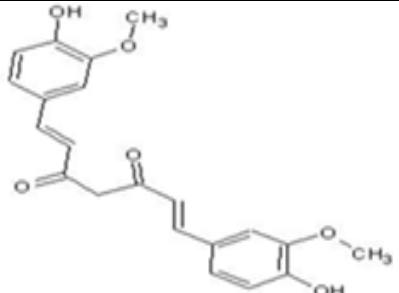
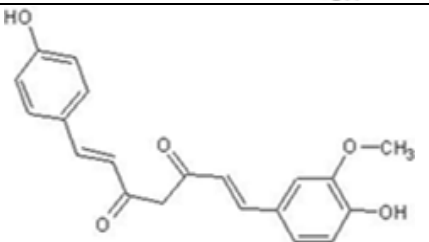
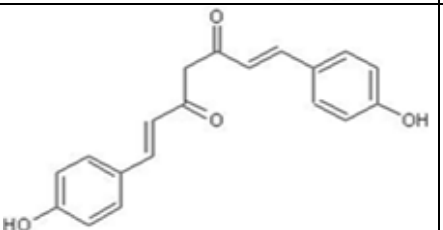
Curcumin, a bioactive molecule produced from the rhizome of *Curcuma longa* (turmeric), has received substantial interest for its varied range of biological as well as pharmacological results ^[6]. Turmeric, a spice belonging to the ginger family (Zingiberaceae), includes the primary curcuminoid known as curcumin. Desmethoxycurcumin and bis-desmethoxycurcumin are the other two curcuminoids ^[7]. It began in India mostly in Ayurveda and is now extensively cultivated in regions such as China, Sri Lanka, West and East Africa, and other tropical areas. In China, the biomolecule is referred as Jianghuang or Huangjiang ^[8]. Traditional Chinese Medicine (TCM) and Indian system of medicine employs it for the treatment, prevention, and oversight of a range of health issues. Because of its chemical structure, it belongs to the category of polyphenols ^[9]. Curcumin, often known as Natural Yellow 3, is an environmentally friendly dye that has been assigned the E number E100 for use in food coloring ^[10]. Its bioactive substances have a range of medicinal effects. These span actions range from antioxidant and anti-inflammatory characteristics, to possible anticancer and neuroprotective benefits ^[11].

2.1 Chemical Properties

1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione is generally known to be curcumin with the chemical formula C₂₁H₂₀O₆, exhibiting a crystalline yellow-orange, a molecular weight of 368.39 g/mol, and a melting point of 183 °C. Curcumin is a diferuloylmethane exhibits keto-enol tautomerism, indicating that while its more stable enol form is

dominant in solid states and alkaline environments. Its primary keto form is present in neutral and acidic conditions [3]. Additionally, demethoxycurcumin or 1-(4-hydroxy-3-methoxyphenyl)-7-(4-hydroxyphenyl)-1,6-heptadiene-3,5-dione and bisdemethoxycurcumin, 1,7-bis(4-hydroxyphenyl)-1,6-heptadiene-3,5-dione. Turmeric has three different types of curcuminoid [12].

Table 1: Chemical formula and structure

Sl. No.	Compound	Chemical formula	Chemical structure	References
1	Curcumin	C ₂₁ H ₂₀ O ₆		3
2	Demethoxycurcumin	C ₂₀ H ₁₈ O ₅		12
3	Bisdemethoxycurcumin	C ₁₉ H ₁₆ O ₄		12

2.2 Pharmacological Properties

2.2.1 Anti-inflammatory

Curcumin has been recognized for a long time as a powerful immunomodulator and anti-inflammatory agent, and recent studies continue to back this assertion. Psoriasis, arthritis, atherosclerosis, and inflammatory bowel disease (IBD) are all linked to inflammation, a complex condition [13]. Curcumin inhibits inflammation by targeting NLRP3 and cytokines, aiding in managing psoriasis, IBD, and arthritis by promoting gut health and modulating immune cells. Curcumin aids cardiovascular health by reducing vascular inflammation and foam cell formation, showing promise as a natural anti-inflammatory with broad applications [14]. Studies confirmed curcumin's anti-inflammatory effects on rats, mice, and cats. It matched phenylbutazone in one test but was half as effective in chronic inflammation models [15].

2.2.2 Anticancer

Curcumin plays a crucial role in regulating multiple cancer-associated signaling pathways, including NF-κB, STAT3, PI3K/Akt, and Wnt/β-catenin. This modulation results in enhanced apoptosis, reduced cellular proliferation, suppressed angiogenesis, and diminished metastatic potential [16]. Additionally, curcumin is potential in the therapy of breast cancer by preventing the WNT/β-catenin pathway and alleviating chronic inflammation and oxidative stress via PPARγ activation. Curcumin also regulates circadian genes, and its efficacy can be enhanced through nanoparticle and

liposome application despite its low bioavailability [17]. In lung cancer, curcumin disrupts JAK2/STAT3 signaling and regulates microRNAs involved in apoptosis and cell cycle control, further impeding cancer development [18]. Curcumin has also demonstrated promising effects in colorectal cancer by downregulating COX-2 expression, inducing mitochondrial-mediated apoptosis, and targeting microRNA pathways associated with tumor growth [19]. This study examines curcumin's potential as a treatment for cutaneous T-cell lymphoma (CTCL), a rare skin-related non-Hodgkin's lymphoma with few therapies and poor prognosis. Derived from turmeric, curcumin impacts inflammation, cell survival, and apoptosis, possibly through STAT-3 and NF-KB signaling [20].

2.2.3 Nervous system disorder

Curcumin shows therapeutic potential in neurological disorders like multiple sclerosis, Parkinson's, and Alzheimer's, due to its antioxidant and anti-inflammatory effects. It helps protect neurons, reduces tau protein hyperphosphorylation in Alzheimer's, and preserves dopaminergic neurons in Parkinson's by modulating key pathways. Its ability to cross the blood-brain barrier makes it a promising treatment for neurodegenerative conditions [21]. Epilepsy treatment often involves conventional drugs with side effects. This study investigates utilizing Curcumin from *Curcuma longa* to treat epilepsy. Curcumin reduces seizures and benefits brain health, showing promise as a protective therapy. Further research is

needed to confirm its effectiveness in epilepsy management [22].

2.2.4 Antidepressant

The present investigation study investigates the antidepressant potential of curcumin, which is a key constituent of *Curcuma longa*, and its interaction with the monoaminergic system. It explores curcumin's capacity to modulate dopamine and serotonin levels, suppress MAO enzymes, and augment the antidepressant effects of some drugs. It also considers the action of piperine, a bioavailability booster, in augmenting the pharmacological actions of curcumin. The conclusion is that curcumin, especially when used in conjunction with piperine, may be beneficial natural therapy for treating depression by acting on neurotransmitter levels and enzymatic activities [23].

2.2.5 Diabetes

Diabetes mellitus is an increasing global health challenge, marked by high blood sugar due to insulin resistance or deficiency, which can lead to complications in essential organs. Herbal remedies like *Curcuma longa* (turmeric) have long been used for treating various conditions. Curcumin, its key polyphenol, shows promise in diabetes management because of its anti-inflammatory, antioxidant, and blood sugar-lowering properties. It improves insulin sensitivity, lowers glucose levels, and helps prevent complications like nephropathy, neuropathy, and retinopathy. Although curcumin has low bioavailability, advanced delivery methods enhance absorption [24]. This research investigates curcumin extract as a possible preventive measure against type 2 diabetes (T2DM) in individuals with prediabetes. The trial involved 240 people monitored for nine months, revealing that those taking curcumin had no T2DM development, unlike 16.4% on placebo. Curcumin improved beta-cell function, reducing insulin resistance and enhancing anti-inflammatory cytokines. It suggests curcumin could lower T2DM risk from prediabetes and improve metabolic markers underscores the importance of safe, affordable, and accessible [25].

2.3 Limitations and Consideration

Curcumin demonstrates strong therapeutic efficacy but suffers from poor bioavailability due to low absorption, rapid metabolism, and limited tissue distribution. Despite its intrinsic activity, studies over the past three decades reveal that curcumin undergoes quick metabolism and elimination, reducing its effectiveness. Factors such as low serum concentration, short half-life, and minimal tissue penetration further hinder its therapeutic potential [3]. These factors collectively impede the effective delivery and sustained presence of curcumin in the body, thereby constraining its therapeutic applications in various health conditions. Despite its well-documented anti-inflammatory, antioxidant, and anti-cancer properties, the bioavailability challenges associated with curcumin have spurred ongoing research efforts aimed at enhancing its absorption and retention within the body for improved therapeutic outcomes. Research is underway on nano formulations and modifications to enhance effectiveness and overcome issues related to low bioavailability [26, 27].

3. Nano-curcumin

Nanocurcumin, a nanoparticle version of curcumin, has higher solubility, absorption, and cellular uptake efficiency. It facilitates targeted distribution to afflicted areas, improves therapeutic effectiveness, and needs lower doses than its natural form [28]. To address limitation issue of curcumin scientists have been focusing increasingly on curcumin nanoformulations (nanocurcumin) to enhance its delivery, bioavailability, and therapeutic efficacy in order to address these limitations. Incorporating curcumin into nanocarriers through various methods is suitable and advantageous to enhance its biological activity, thereby increasing its bioavailability and solubility, extending its circulation time, and improving its retention in the body, as well as overcoming physiological barriers [29]. Thus far, the outcomes of this type of medication delivery technology have been very encouraging. The nano form significantly improved the systemic availability of curcumin due to its superior water dispersion compared to free curcumin [30]. Consequently, nanoencapsulation of curcumin may facilitate enhanced retention and circulation of the medication within the body. This shifts the perception of curcumin from merely a nutritious spice to a therapeutic medicine by reducing the dosage while still maintaining the necessary compound level [31].

3.1 Types of Nanocurcumin Formulation

- **Polymeric Nanoparticles:** Biodegradable polymer-based nanoparticles, such as those made from PLGA, help improve curcumin's ability to circulate in the bloodstream for extended periods while also increasing its absorption by cells [32].
- **Liposomes:** Liposomes, spherical carriers with layers of phospholipids enclosing an aqueous compartment, enhance drug stability, solubility, and targeting. They encapsulate water-soluble and fat-soluble drugs, aiding absorption and controlled release for therapeutic benefits [33].
- **Solid nanoparticles:** These lipid-based delivery systems enhance curcumin's water solubility and absorption in the body while ensuring a controlled and sustained release of the drug, optimizing its therapeutic efficacy [34].
- **Micelle:** A micelle is created by surfactant molecules in water, forming a spherical nanocarrier used to enhance drug delivery for poorly soluble compounds like curcumin in biological systems [35].
- **Nanogels:** A nanogel, formed via polymer cross-linking, is a tiny hydrogel particle (10-100 nm) ideal for storing and releasing drugs efficiently. This technology delivers drugs directly to cells, enhancing stability and efficacy while minimizing immune response activation [36].
- **Nano emulsions:** Nanoemulsions are tiny oil-in-water systems with oil droplets smaller than 100 nm, enclosed in a surfactant layer to enhance drug delivery by improving solubility, absorption, and stability in aqueous environments [37].

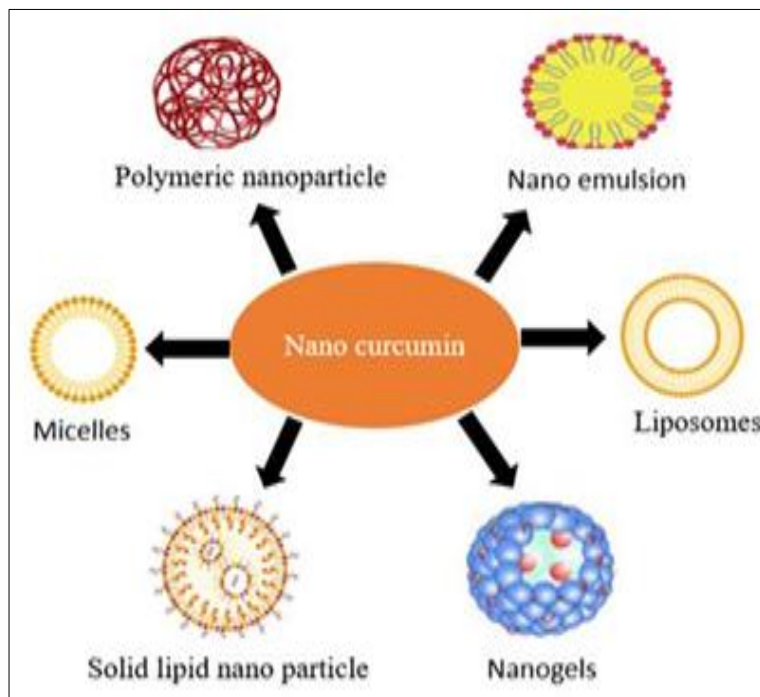


Fig 1: Different nanocurcumin formulation

3.2 Bioavailability enhancement of nano-curcumin over natural curcumin

3.2.1 Improving Bioavailability and Therapeutic Effectiveness via Nanoformulation

Concerns persist about drug properties and bioavailability improvement. Strategies focus on optimizing molecular structure and developing micro or nanoscale formulations [38]. Chitosan and PLGA are biodegradable polymers used for drug delivery, offering a protective framework for curcumin that boosts stability and enables sustained release, addressing issues like rapid metabolism, low bioavailability, and water solubility limitations [39]. PLGA and chitosan carriers boost curcumin's effectiveness against cancer, inflammation, and for neuroprotection. They reduce frequent dosing needs, enhance drug retention in target tissues via controlled, extended release [40]. Liposomes, composed of phospholipid bilayers, improve curcumin's solubility and stability, safeguarding it from breakdown, aiding transport through membranes, and enhancing therapeutic effectiveness [41]. Curcumin in solid lipid nanoparticles improves drug retention, controlled release, and absorption. SLNs protect it from pH changes and enzymatic breakdown, preserving pharmacological effects longer [42]. Nanostructured lipid carriers (NLCs), an advanced form of solid lipid nanoparticles (SLNs), incorporate liquid and solid lipids to boost drug loading capacity and delay drug release. These carriers enhance the stability, solubility, and absorption of curcumin, making them ideal for medicinal use. Studies show that curcumin-loaded NLCs significantly improve retention of drugs in targeted tissues, enhancing medication efficacy [43]. Amphiphilic block copolymers form polymeric micelles, self-assembled nanoscale structures that encapsulate curcumin, enhancing its transport across barriers and bioavailability. The application of different nanoformulations like polymeric nanoparticles and liposomes has greatly improved curcumin's therapeutic effectiveness [44].

3.2.2 Enhanced Dispersibility and Solubility

Nanocurcumin has a unique advantage over bulk curcumin because of its superior water solubility and dispersibility. At

nanoscale, its smaller size, higher crystallinity, and enhanced surface-to-volume ratio enable better interaction with water molecules, preventing clumping that often occurs with bulk curcumin [45]. To improve the solubility of water and overcome the various limitations of curcumin, nanocurcumin was developed. Research indicates that nanocurcumin, which has a diameter of 65-75 nm and is produced through wet-ball milling, dissolves significantly faster than bulk curcumin [46]. Nanoemulsions, which consist of oil-in-water or water-in-oil formulations, offer a stable medium for the delivery of hydrophobic compounds such as curcumin, enhancing its bioavailability and therapeutic effectiveness [47]. Curcumin nanoparticles were created through various methods that do not involve nanocarriers, such as anti-solvent precipitation (Cur-ASP), sonication (Cur-SM), and nano-suspension (Cur-NSM), aimed at enhancing the solubility of curcumin in water [48].

3.2.3 Targeted Drug Delivery

Nanocurcumin formulations enable precise drug targeting for effective therapy of diseases by customizing delivery methods. This approach overcomes curcumin's drawbacks like rapid metabolism, systemic elimination, and poor solubility, preserving surrounding structures and focusing treatment where needed [49]. Integrating a particular molecule combined with nano-curcumin targeted curcumin effectively. Methods like protein carriers, liposomes, and nanofibers were discussed to improve solubility and bioavailability [50]. Poly lactic-co-glycolic acid (PLGA) and derivatives of polyethylene glycol (PEG) are types of polymeric nanoparticles that offer a versatile structure for the encapsulation of curcumin, enhancing its stability and solubility while allowing for controlled release kinetics [51]. The therapeutic effectiveness of curcumin can be enhanced by tailoring these nanoparticles to modify drug release behaviour's, boost cellular uptake, and extend circulation times *in vivo* [52]. Phospholipid bilayers in liposomes encapsulate curcumin for specific tissue targeting, reducing off-target effects [53]. Nanoparticles extending curcumin's benefits and decreasing dosing frequency could enhance

patient adherence. Customizing nanoparticles with ligands enables precise curcumin delivery, optimizing efficacy and minimizing harm to healthy tissues. Various studies have found that nanocurcumin is more therapeutically effective than traditional curcumin because it improved bioavailability and targeted distribution in disease models [54]. The cancer society has not yet recognized curcumin as a treatment, even though it shows significant promise as a safe and effective option for cancer therapy and chemoprevention. The primary reason for this reluctance is the low curcumin's bioavailability when taken orally, which restricts its therapeutic effects to the lower gastrointestinal tract [55].

3.3 Therapeutic applications

3.3.1 Colon Cancer

The mouse model showed nanocurcumin's superiority over standard curcumin in combating inflammation and cancerous growth, especially by increasing VEGF and inflammatory markers like TNF, IL1, and IL6. Nanocurcumin could be a promising treatment for colon cancer [56]. Nanocurcumin shows strong anticancer effects in colorectal cancer by influencing key pathways like NF- κ B, STAT3, and p53. Combining it with standard therapies reduces angiogenesis, promotes cell death, limits tumor growth, and improves response to chemotherapy. Various nanoformulations, including liposomes, micelles, and gold nanoparticles, are used to for the effective transport of curcumin in colorectal cancer treatment [57]. The investigation carried out to assess the impact of nano-curcumin on rat colon cancer. Thirty rats were divided into groups treated with curcumin, nano-curcumin, or control. Azoxymethane was administered every two weeks. Nano-curcumin showed fewer cell alterations and reduced COX-2 and Ki-67 proteins. The study suggests using nanoparticles to enhance curcumin's effectiveness in cancer therapy [58]. Research suggests curcumin affects cancer progression by influencing angiogenesis, inflammation, and metastasis. In colorectal cancer treatment, drugs are administered via the colon, using innovative delivery methods like encapsulation to enhance bioavailability and reduce side effects. Focus on curcumin nano-formulations addresses delivery challenges effectively [59].

3.3.2 Breast cancer

The study analyzes the usefulness of nano-curcumin in reducing breast cancer cell proliferation, primarily targeting the MCF7 cell line. A comparison was made between nano-curcumin, natural curcumin with increased bioavailability, and traditional chemotherapy medications. The study found that nano-curcumin effectively reduces breast cancer cell proliferation, surpassing traditional chemotherapy drugs. Nano-curcumin inhibited cyclinD1 expression crucial for cancer cell growth, unlike conventional chemo. Its potential as a breast cancer treatment requires further investigation for safety and efficacy [60]. Among 528 papers reviewed, 26 showed Cur-NP effectiveness in *in vivo* breast cancer models. Curcumin, delivered in various NP forms, reduced tumor size, enhanced cell mortality, and inhibited growth. Benefits included decreased angiogenesis and cancer stem cells with confirmed safety. Improved outcomes were seen in different cancer model types in contrast to free curcumin [61]. Nanocurcumin preparations coupled with using photodynamic treatment appear promising, as they reduce tumor mass and stop metastasis in *in vitro* studies using MCF-7 and MDA-MB-231 cell lines. Mouse experiments have confirmed the high efficacy of nanocurcumin in slowing tumor progression

when used in conjunction with PTT and PDT, without causing toxic effects [62]. These findings highlight the potential of nanocurcumin-based therapies for breast cancer treatment, underscoring the necessity for additional clinical investigations to validate their application in cancer therapies.

3.3.3 Gastric cancer

Gastric cancer ranks as the fifth most prevalent type of cancer and the third primary cause of cancer-related deaths around the world. The main contributor to stomach cancer is the infection caused by *Helicobacter pylori* additional risk factors include smoking, inadequate nutrition, and obesity [63]. Nanocurcumin outperformed indigenous curcumin by inhibiting gastric cancer cells by 97% at 40 μ M for 72 hours. Its lower IC₅₀ of 18.78 μ M, compared to native curcumin's 24.20 μ M, led to higher cytotoxicity. Nanocurcumin induced cancer cell apoptosis by halting progression to the sub-G0 phase. It exhibited stronger with an MIC of 8 μ g/ml, surpassing native curcumin's 16 μ g/ml [64]. This research proposes using a nano-emulsion delivery system to boost the effectiveness of curcumin and clarithromycin against *Helicobacter pylori* infections. The Curcumin-Clarithromycin Nano-Emulsion (Cur-CLR-NE) showed superior results in inhibiting *H. pylori*, with improved efficacy in eliminating bacteria and higher eradication rates in *in vivo* studies in contrast to free forms of the drugs [65].

3.3.4 Ovarian Cancer

While curcumin has exhibited potential in enhancing the anticancer effects of cisplatin, its therapeutic efficacy is limited by its poor bioavailability. To address this limitation and boost curcumin's effectiveness against ovarian cancer, nanocurcumin was developed. In a study utilizing a rat model of ovarian cancer induced by DMBA, the combined treatment of cisplatin and nanocurcumin significantly reduced both the weight and size of tumors. This combination therapy inhibited the PI3K/Akt and JAK/STAT3 signaling pathways, leading to levels of expression of Ki67 and TGF- β . Additionally, the reduction in tumor growth was associated with decreased JAK expression, less phosphorylation of STAT3, and lower IL-6 levels. These results show that nanocurcumin enhances the therapeutic impact of cisplatin, offering promising prospects for ovarian cancer treatment [66].

3.3.5 Liver Cancer

This study investigated the effects of both free curcumin and its nanoparticulate form on liver cancer induced by chemical agents in mice. The results indicated that nanoparticulate Curcumin possessed a greater effect than natural curcumin on the levels of various liver enzymes, vascular endothelial growth factor, tumor necrosis factor- α , α -fetoprotein, malondialdehyde, and nuclear factor- κ B. Furthermore, nanoparticulate curcumin prevented notable histological changes in the liver tissue and enhanced serum albumin levels along with tissue antioxidant activity. In the end, the study found that nanoparticulate curcumin inhibits the advancement of hepatocellular carcinoma more effectively than curcumin [67]. Curcumin's potent anticancer properties target vital molecular pathways involved in tumor development and progression, encompassing PI3K/Akt, Wnt/ β -catenin, JAK/STAT, p53, MAPKs, and NF- κ B. Yet, limited clinical efficacy stems from bioavailability issues, quick metabolism, and low solubility. Nanotechnology, like micelles and liposomes, enhances curcumin delivery, elevating its effectiveness in treating liver cancer with reduced side effects

[68]. Curcumin nanoparticles (Cur-NPs) showed promising effects on liver cancer cells, with sizes around 141.2 nm. They effectively induced cytotoxicity in liver cancer cells at 6.25 µg/mL after 48 hours without harming normal cells. Notably, Cur-NPs inhibited cancer migration of cells and angiogenesis, demonstrating proapoptotic effects by regulating key proteins like Bax, p53, and Bcl-2. This study affirms the potential of Cur-NPs in treating liver cancer by suppressing cell growth and promoting apoptotic pathways [69].

3.3.6 Diabetes Mellitus

Nanocurcumin provides better bioavailability and effectiveness for diabetes than conventional curcumin. Formulations utilizing nanotechnology enhance its absorption and stability. It helps to lower blood sugar levels, improves lipid profiles, possesses antioxidant and anti-inflammatory properties, assists in managing weight, and could improve methods for managing diabetes treatment [70]. A study at Mashhad University of Medical Sciences examined nano-curcumin's effects on metabolic parameters in type-2 diabetics. 70 participants took either nano-curcumin or a placebo for three months. Nano-curcumin lowered HbA1c, FBG, TG, and BMI significantly ($p < 0.05$). It also reduced eAG, LDL-C, and improved lipid profile. Though TC, HDL-C, and TG showed no significant changes, nano-curcumin offers promise in managing diabetes by lowering glucose levels and improving lipid metabolism [71]. Another research investigated the impacts of curcumin and nano-curcumin on insulin resistance, glucose levels, Apelin concentrations, and lipid profiles in rats with type 2 diabetes. Both substances significantly decreased insulin resistance, blood glucose, Apelin, cholesterol, triglycerides, LDL, and VLDL levels ($p < 0.05$). Nano-curcumin demonstrated greater efficacy in improving the lipid profile and raising HDL levels. Particularly at a dosage of 100 mg/kg, nano-curcumin exhibited potential in diabetes management by enhancing glycemic regulation and reducing insulin resistance [72].

3.3.7 Neurological Disorders

Given that nanocurcumin can enhance the bioavailability and therapeutic effectiveness of curcumin, it has become a promising treatment option for Alzheimer's disease (AD). The polyphenol curcumin, originating from *Curcuma longa*, possesses neuroprotective properties by mitigating inflammation, oxidative stress, and the aggregation of amyloid-beta ($A\beta$) three critical pathogenic factors in AD. However, its therapeutic application is limited because of its quick metabolism and poor solubility. Nanotechnology-based formulations, such as lipid carriers, liposomes, and polymeric nanoparticles, improve curcumin's stability, solubility, and targeted delivery across the blood-brain barrier. Research indicates that nanocurcumin can slow the progression of AD by decreasing tau hyperphosphorylation, inhibiting $A\beta$ aggregation, and modulating neuroinflammatory pathways. Additionally, in experimental models, nanoparticles loaded with nanocurcumin have shown potential in enhancing neurogenesis and cognitive function. This formulation protects neurons, enhances mitochondrial function, reduces amyloid-beta aggregation, diminishes inflammation, offers support, and helps modulate immune responses in different conditions [73,74]. The study highlighted that nano-based drug delivery systems effectively improved the aqueous solubility and bioavailability of curcumin, making it an ideal candidate for treating neurological disorders. Clinical trials demonstrate

safety and effectiveness, while continued research is necessary for optimizing formulations and ensuring long-term safety [75].

3.3.8 Oral Mucositis

Curcumin's anti-inflammatory and anticancer effects, nanomicelle curcumin effectively alleviates the degree of oral mucositis severity in individuals with neck and head cancer undergoing radiation therapy, presenting itself as a potentially and safe treatment option. A clinical study involving 32 participants showed a notable reduction in mucositis for those treated with nanocurcumin compared to the placebo group. These positive outcomes highlight the potential of nanomicelle curcumin in addressing oral mucositis during radiation therapy for head and neck cancer [76]. The study carried out a thorough review and meta-analysis regarding the efficacy of curcumin/turmeric in both preventing and managing oral mucositis (OM) resulting from radiation or chemotherapy in individuals with head and neck cancer (HNC). The results indicated that patients suffering from OM due to cancer treatments experienced improvements when using nanocurcumin (80 mg/day/0.1%) mouthwash, including reduced severity of OM, delayed onset, and alleviated pain [77]. Following PRISMA guidelines, a thorough analysis and meta-analysis, which was registered with PROSPERO, investigated the impact of curcumin-based treatments compared to placebos in cancer patients suffering from oral mucositis (OM). The review included six trials comprising 159 participants, with 40% being female and an average age of 50 years. Curcumin, whether administered as pills, mouthwash, or gel, significantly reduced both the severity and discomfort associated with OM, particularly when applied as a mouthwash during radiation therapy. The overall incidence of OM decreased by 6%, while those using curcumin mouthwash saw a 37% reduction. Further studies are suggested to improve formulations and treatment outcomes [78].

3.3.9 Wound Healing

Utilizing silica nanoparticles that are mesoporous in a nanoformulation enhances curcumin's pharmacokinetic profile and boosts its ability to facilitate wound healing. A study comparing nanocurcumin with standard sulfadiazine treatment in animals demonstrated improved wound contraction and faster reepithelialization, alongside reduced inflammation and enhanced angiogenesis and collagen synthesis. These findings show that curcumin in a nanoformulation could serve as an effective treatment for the healing of wounds [79]. To ensure curcumin formulations serve as effective treatments for wound healing, it is essential to tackle problems related to its low water solubility, inadequate tissue absorption, and brief plasma half-life caused by rapid metabolism. In order to enhance curcumin's bioavailability, innovative curcumin nanoformulations were created [80].

3.3.10 COVID-19

This research on nanocurcumin for mild to moderate COVID-19 cases showed promising results. Sixty participants had a double-blind trial, with one group taking nanocurcumin soft gels twice daily for two weeks. Benefits included faster symptom relief, improved lymphocyte counts, and decreased CRP levels. No side effects were reported. Further research with larger groups is recommended for potential COVID-19 recovery enhancement [81].

3.4 Challenges and future directions

However, nanocurcumin has demonstrated promising results in various disease models, several challenges and unresolved issues remain. Among these difficulties are the necessity for additional high-quality randomized controlled trials, clinical trials, further investigation into the long-term safety and efficacy of nanocurcumin, and a more thorough understanding of its molecular modes of action ^[82]. Future research should therefore incorporate standardized nanoformulations, rigorous pharmacovigilance, and a comprehensive evaluation of immunogenic potential, unintended effects, and interactions with other medications ^[83]. Research is needed to determine the long-term impacts and possible toxicity of ongoing nanocurcumin use, despite preclinical studies generally showing low toxicity levels for the compound ^[84]. Future studies need to emphasize the creation of innovative curcumin formulations, carry out rigorous randomized controlled trials, and clarify how nanocurcumin functions in different disease models ^[85].

3.5 Safety, toxicity and regulation

The safety profile of nanocurcumin has been shown to be excellent in preclinical studies. For example, formulations of curcumin-loaded polymeric NPs (namely using Eudragit S100) showed no toxicity in acute doses up to 2 g/kg body weight in experimental animals. In addition, no abnormal side effects were observed at therapeutic doses in the 28-day sub-chronic toxicity evaluations, indicating that these preparations were biocompatible ^[86]. Another study investigates the efficacy and safety of using nanocurcumin in addition to riluzole as a therapy for amyotrophic lateral sclerosis (ALS). Year-long double-blind research with placebo control study evaluated nanocurcumin, which is known for it has antioxidant and anti-inflammatory properties. With survival as the primary metric, patients were randomly assigned to either nanocurcumin or a placebo. This study explores the potential benefits of curcumin for ALS, specifically for individuals with bulbar symptoms, since it has shown promise in treating neurodegenerative diseases. Its safety was confirmed by the absence of any serious negative effects. Larger-scale research is required to confirm these results ^[87]. Despite the positive safety profiles that indicate nanocurcumin's safety, potential toxicological ramifications must furthermore be taken into account. In addition to their dimensions and surface charge, the particular type and composition of the nanoparticles also influence how they interact with biological systems ^[88]. The intricacy of compositions makes regulatory clearance challenging. Complete characterisation of nanomedicines nanocurcumin, including physicochemical qualities, stability, and repeatability, is also required by regulatory bodies such as the (EMA) and the U.S. (FDA). This is important as it has to do with public health ^[89].

4. Discussion

A novel way to overcome curcumin's drawbacks, especially its high metabolism and low bioavailability, is nanocurcumin. Despite its many pharmacological advantages, such as anti-inflammatory, anti-cancer, neuroprotective, and antidiabetic effects, traditional curcumin has poor absorption and is quickly taken out of the body. Formulations based on nanotechnology greatly improve the stability, solubility, and targeted drug delivery of curcumin, maximizing its therapeutic potential. To increase cellular absorption and prolong circulation time, nanocurcumin makes use of a

variety of nanocarriers, including liposomes, micelles, polymeric nanoparticles, and nanoemulsions. Because nanocurcumin efficiently modulates important pathways like NF- κ B and PI3K/Akt, causing apoptosis and reducing tumor proliferation, this has led to noteworthy advancements in the treatment of cancer. In a similar vein, its capacity to penetrate the blood-brain barrier increases its effectiveness in neurodegenerative diseases like Parkinson's and Alzheimer's. By increasing insulin sensitivity and reducing blood sugar, nanocurcumin helps manage diabetes in addition to oncology and neurology. Its anti-inflammatory qualities also aid in the treatment of oral mucositis, wound healing, and even infectious illnesses like COVID-19. Despite these encouraging uses, more clinical studies are needed to determine dosage recommendations, assess toxicity risks, and guarantee regulatory compliance before they are extensively applicable in medicine.

5. Conclusion

The limitations of natural curcumin, including its rapid metabolism and poor bioavailability, are effectively overcome by nanocurcumin, signifying a noteworthy breakthrough in medication delivery technologies. Various nano-formulation methods have enhanced curcumin's therapeutic potential, particularly in treating infectious diseases, diabetes, cancer, and neurodegenerative disorders. Comparative research illustrates nanocurcumin's superiority in addressing disease pathways, improving absorption, and prolonging drug retention. Despite these promising results, challenges remain, such as the need for further clinical trials to assess long-term safety and efficacy. Future studies ought to concentrate on improving nano-formulations, ensuring scalable production, and expanding its applications in personalized medicine for improved therapeutic outcomes.

6. Conflict of Interest

The authors declare no conflict of interest.

7. Acknowledgement

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8. References

1. Ernst E. The efficacy of herbal medicine-an overview. *Fundamental & Clinical Pharmacology*. 2005;19(4):405-409.
2. Pal SK, Shukla Y. Herbal medicine: current status and the future. *Asian Pacific Journal of Cancer Prevention*. 2003;4(4):281-288.
3. Anand P, Kunnumakkara AB, Newman RA, Aggarwal BB. Bioavailability of curcumin: problems and promises. *Molecular Pharmaceutics*. 2007;4(6):807-818.
4. Gelperina S, Kisich K, Iseman MD, Heifets L. The potential advantages of nanoparticle drug delivery systems in chemotherapy of tuberculosis. *American Journal of Respiratory and Critical Care Medicine*. 2005;172(12):1487-1490.
5. Muqbil I, Masood A, Sarkar FH, Mohammad RM, Azmi AS. Progress in nanotechnology-based approaches to enhance the potential of chemopreventive agents. *Cancers*. 2011;3:428-445.
6. Iweala EJ, Uche ME, Dike ED, Etumnu LR, Dokunmu TM, *et al.* *Curcuma longa* (turmeric): Ethnomedicinal uses, phytochemistry, pharmacological activities and

- toxicity profiles—A review. *Pharmacological Research-Modern Chinese Medicine*. 2023;6:100222.
7. Akram M, Shahab-Uddin AA, Usmanghani KH, Hannan AB, Mohiuddin E, Asif M. *Curcuma longa* and curcumin: a review article. *Romanian Journal of Biology-Plant Biology*. 2010;55(2):65-70.
 8. Tung BT, Nham DT, Hai NT, Thu DK. *Curcuma longa*, the polyphenolic curcumin compound and pharmacological effects on liver. In: *Dietary Interventions in Liver Disease*. 2019; p. 125-134.
 9. Den Hartogh DJ, Gabriel A, Tsiani E. Antidiabetic properties of curcumin II: evidence from *in vivo* studies. *Nutrients*. 2019;12(1):58.
 10. Almeida HH, Barros L, Barreira JC, Calhelha RC, Heleno SA, *et al*. Bioactive evaluation and application of different formulations of the natural colorant curcumin (E100) in a hydrophilic matrix (yogurt). *Food Chemistry*. 2018;261:224-232.
 11. Lestari ML, Indrayanto G. Curcumin. *Profiles of Drug Substances, Excipients and Related Methodology*. 2014;39:113-204.
 12. Hassanizadeh S, Shojaei M, Bagherniya M, Orekhov AN, Sahebkar A. Effect of nano-curcumin on various diseases: a comprehensive review of clinical trials. *Biofactors*. 2023;49(3):512-533.
 13. Salehi B, Stojanović-Radić Z, Matejić J, Sharifi-Rad M, Kumar NV, *et al*. The therapeutic potential of curcumin: a review of clinical trials. *European Journal of Medicinal Chemistry*. 2019;163:527-545.
 14. Jurenka JS. Anti-inflammatory properties of curcumin, a major constituent of *Curcuma longa*: A review of preclinical and clinical research. *Alternative Medicine Review*. 2009;14(2).
 15. Peng Y, Ao M, Dong B, Jiang Y, Yu L, *et al*. Anti-inflammatory effects of curcumin in the inflammatory diseases: status, limitations and countermeasures. *Drug Design, Development and Therapy*. 2021;15:4503-4525.
 16. Srimal RC, Dhawan BN. Pharmacology of diferuloyl methane (curcumin), a non-steroidal anti-inflammatory agent. *Journal of Pharmacy and Pharmacology*. 1973;25(6):447-452.
 17. Vallée A, Lecarpentier Y, Vallée JN. Curcumin: a therapeutic strategy in cancers by inhibiting the canonical WNT/ β -catenin pathway. *Journal of Experimental & Clinical Cancer Research*. 2019;38:1-6.
 18. Wu L, Guo L, Liang Y, Liu X, Jiang L, Wang L. Curcumin suppresses stem-like traits of lung cancer cells via inhibiting the JAK2/STAT3 signaling pathway. *Oncology Reports*. 2015;34(6):3311-3317.
 19. Ismail NI, Othman I, Abas F, Lajis NH, Naidu R. Mechanism of apoptosis induced by curcumin in colorectal cancer. *International Journal of Molecular Sciences*. 2019;20(10):2454.
 20. Zhang C, Li B, Zhang X, Hazarika P, Aggarwal BB, Duvic M. Curcumin selectively induces apoptosis in cutaneous T-cell lymphoma cell lines and patients' PBMCs: potential role for STAT-3 and NF- κ B signaling. *Journal of Investigative Dermatology*. 2010;130(8):2110-2119.
 21. Genchi G, Lauria G, Catalano A, Carocci A, Sinicropi MS. Neuroprotective effects of curcumin in neurodegenerative diseases. *Foods*. 2024;13(11):1774.
 22. Choo BK, Shaikh MF. Mechanism of *Curcuma longa* and its neuroactive components for the management of epileptic seizures: a systematic review. *Current Neuropharmacology*. 2021;19(9):1496-1518.
 23. Kulkarni SK, Bhutani MK, Bishnoi M. Antidepressant activity of curcumin: involvement of serotonin and dopamine system. *Psychopharmacology*. 2008;201(3):435-442.
 24. Silva PA, Arawawala LD, Kumari MW, Galappaththy P. Effect of *Curcuma longa* L. and curcumin on diabetes and its complications: a review. *Journal of Ayurvedic and Herbal Medicine*. 2021;7(2):109-118.
 25. Chuengsamarn S, Rattanamongkolgul S, Luechapudiporn R, Phisalaphong C, Jirawatnotai S. Curcumin extract for prevention of type 2 diabetes. *Diabetes Care*. 2012;35(11):2121-2127.
 26. Ma Z, Wang N, He H, Tang X. Pharmaceutical strategies of improving oral systemic bioavailability of curcumin for clinical application. *Journal of Controlled Release*. 2019;316:359-380.
 27. Jamwal R. Bioavailable curcumin formulations: a review of pharmacokinetic studies in healthy volunteers. *Journal of Integrative Medicine*. 2018;16(6):367-374.
 28. Chen YJ, Inbaraj BS, Pu YS, Chen BH. Development of lycopene micelle and lycopene chylomicron and a comparison of bioavailability. *Nanotechnology*. 2014;25(15):155102.
 29. Muller RH, Keck CM. Challenges and solutions for the delivery of biotech drugs—a review of drug nanocrystal technology and lipid nanoparticles. *Journal of Biotechnology*. 2004;113(1-3):151-170.
 30. Sahu A, Kasoju N, Bora U. Fluorescence study of the curcumin-casein micelle complexation and its application as a drug nanocarrier to cancer cells. *Biomacromolecules*. 2008;9(10):2905-2912.
 31. Das RK, Kasoju N, Bora U. Encapsulation of curcumin in alginate-chitosan-pluronic composite nanoparticles for delivery to cancer cells. *Nanomedicine: Nanotechnology, Biology and Medicine*. 2010;6(1):153-160.
 32. Flora G, Gupta D, Tiwari A. Nanocurcumin: a promising therapeutic advancement over native curcumin. *Critical Reviews in Therapeutic Drug Carrier Systems*. 2013;30(4).
 33. Mishra H, Chauhan V, Kumar K, Teotia D. A comprehensive review on liposomes: a novel drug delivery system. *Journal of Drug Delivery and Therapeutics*. 2018;8(6):400-404.
 34. Faraji AH, Wipf P. Nanoparticles in cellular drug delivery. *Bioorganic & Medicinal Chemistry*. 2009;17:2950-2962. doi:10.1016/j.bmc.2009.02.043
 35. Wang S, Ha Y, Huang X, Chin B, Sim W, Chen R. A new strategy for intestinal drug delivery via pH-responsive and membrane-active nanogels. *ACS Applied Materials & Interfaces*. 2018;10:36622-36627. doi:10.1021/acsami.8b15661
 36. Ye Q, Kwon S, Gu Z, Selomulya C. Stable nanoemulsions for poorly soluble curcumin: from production to digestion response *in vitro*. *Journal of Molecular Liquids*. 2024 Jan 15;394:123720.
 37. Pathak K, Raghuvanshi S. Oral bioavailability: issues and solutions via nanoformulations. *Clinical Pharmacokinetics*. 2015 Apr;54:325-357.
 38. Gupta SC, Patchva S, Aggarwal BB. Therapeutic roles of curcumin: lessons learned from clinical trials. *The AAPS Journal*. 2013 Jan;15:195-218.

39. Astete CE, Sabliov CM. Synthesis and characterization of PLGA nanoparticles. *Journal of Biomaterials Science, Polymer Edition*. 2006 Jan 1;17(3):247-289.
40. Xu H, Gong Z, Zhou S, Yang S, Wang D, Chen X, *et al.* Liposomal curcumin targeting endometrial cancer through the NF- κ B pathway. *Cellular Physiology and Biochemistry*. 2018 Aug 23;48(2):569-582.
41. Ban C, Jo M, Park YH, Kim JH, Han JY, Lee KW, *et al.* Enhancing the oral bioavailability of curcumin using solid lipid nanoparticles. *Food Chemistry*. 2020 Jan 1;302:125328.
42. Sadegh Malvajerd S, Azadi A, Izadi Z, Kurd M, Dara T, Dibaei M, *et al.* Brain delivery of curcumin using solid lipid nanoparticles and nanostructured lipid carriers: preparation, optimization, and pharmacokinetic evaluation. *ACS Chemical Neuroscience*. 2018 Oct 17;10(1):728-739.
43. Li X, Chen T, Xu L, Zhang Z, Li L, Chen H. Preparation of curcumin micelles and the *in vitro* and *in vivo* evaluation for cancer therapy. *Journal of Biomedical Nanotechnology*. 2014 Aug 1;10(8):1458-1468.
44. Rajasekar A. Facile synthesis of curcumin nanocrystals and validation of its antioxidant activity against circulatory toxicity in Wistar rats. *Journal of Nanoscience and Nanotechnology*. 2015 Jun 1;15(6):4119-4125.
45. Kumar V, Kumar R, Jain VK, Nagpal S. Preparation and characterization of nanocurcumin based hybrid virosomes as a drug delivery vehicle with enhanced anticancerous activity and reduced toxicity. *Scientific Reports*. 2021 Jan 11;11(1):368.
46. Shaker DS, Ishak RA, Ghoneim A, Elhuoni MA. Nanoemulsion: a review on mechanisms for the transdermal delivery of hydrophobic and hydrophilic drugs. *Scientia Pharmaceutica*. 2019;87(3):17.
47. Kanwal Q, Ahmed M, Hamza M, Ahmad M, Yousaf N, Javaid A, *et al.* Curcumin nanoparticles: physicochemical fabrication, characterization, antioxidant, enzyme inhibition, molecular docking and simulation studies. *RSC Advances*. 2023;13(32):22268-22280.
48. Bhunchu S, Muangnoi C, Rojsitthisak P. Curcumin diethyl disuccinate encapsulated in chitosan/alginate nanoparticles for improvement of its *in vitro* cytotoxicity against MDA-MB-231 human breast cancer cells. *Die Pharmazie-An International Journal of Pharmaceutical Sciences*. 2016;71(12):691-700.
49. Gayathri K, Bhaskaran M, Selvam C, Thilagavathi R. Nano formulation approaches for curcumin delivery—a review. *Journal of Drug Delivery Science and Technology*. 2023 Apr 1;82:104326.
50. Danhier F, Ansorena E, Silva JM, Coco R, Le Breton A, Préat V. PLGA-based nanoparticles: an overview of biomedical applications. *Journal of Controlled Release*. 2012 Jul 20;161(2):505-522.
51. Shehzad A, Wahid F, Lee YS. Curcumin in cancer chemoprevention: molecular targets, pharmacokinetics, bioavailability, and clinical trials. *Archiv der Pharmazie*. 2010 Sep;343(9):489-499.
52. Müller RH, Radtke M, Wissing SA. Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) in cosmetic and dermatological preparations. *Advanced Drug Delivery Reviews*. 2002 Nov 1;54:S131-S155.
53. Kushwaha P, Yadav A, Samim M, Flora SJ. Combinatorial drug delivery strategy employing nano-curcumin and nano-MiADMSA for the treatment of arsenic intoxication in mouse. *Chemico-Biological Interactions*. 2018 Apr 25;286:78-87.
54. Rashwan AK, Karim N, Xu Y, Hanafy NA, Li B, Mehanni AH, *et al.* An updated and comprehensive review on the potential health effects of curcumin-encapsulated micro/nanoparticles. *Critical Reviews in Food Science and Nutrition*. 2023 Nov 17;63(29):9731-9751.
55. Hanna DH, Saad GR. Nanocurcumin: preparation, characterization and cytotoxic effects towards human laryngeal cancer cells. *RSC Advances*. 2020;10(35):20724-20737.
56. Sharma RA, McLelland HR, Hill KA, Ireson CR, Euden SA, Manson MM, *et al.* Pharmacodynamic and pharmacokinetic study of oral *Curcuma* extract in patients with colorectal cancer. *Clinical Cancer Research*. 2001 Jul 1;7(7):1894-1900.
57. Wong KE, Ngai SC, Chan KG, Lee LH, Goh BH, Chuah LH. Curcumin nanoformulations for colorectal cancer: a review. *Frontiers in Pharmacology*. 2019 Mar 5;10:152.
58. Khaniki M, Azizian S, Alizadeh AM, Hemmati H, Emamipour N, Mohagheghi MA. The antiproliferative and anticancerogenic effects of nano-curcumin in rat colon cancer. *Tehran University Medical Journal*. 2013 Aug 1;71(5).
59. Sardou HS, Nazari SE, Abbaspour M, Akhgari A, Sheikh A, Kesharwani P, *et al.* Nano-curcumin formulations for targeted therapy of colorectal cancer. *Journal of Drug Delivery Science and Technology*. 2023 Oct 1;88:104943.
60. Hosseini S, Chamani J, Hadipanah MR, Ebadpour N, Hojjati AS, Mohammadzadeh MH, *et al.* Nano-curcumin's suppression of breast cancer cells (MCF7) through the inhibition of cyclinD1 expression. *Breast Cancer: Targets and Therapy*. 2019 Mar 13:137-142.
61. Ombredane AS, Silva VR, Andrade LR, Pinheiro WO, Simonelly M, Oliveira JV, *et al.* *in vivo* efficacy and toxicity of curcumin nanoparticles in breast cancer treatment: a systematic review. *Frontiers in Oncology*. 2021 Mar 9;11:612903.
62. Ailioaie LM, Ailioaie C, Litscher G. Latest innovations and nanotechnologies with curcumin as a nature-inspired photosensitizer applied in the photodynamic therapy of cancer. *Pharmaceutics*. 2021 Sep 26;13(10):1562.
63. Chang AH, Parsonnet J. Role of bacteria in oncogenesis. *Clinical Microbiology Reviews*. 2010 Oct;23(4):837-857.
64. Alam J, Dilnawaz F, Sahoo SK, Singh DV, Mukhopadhyay AK, Hussain T, *et al.* Curcumin encapsulated into biocompatible co-polymer PLGA nanoparticle enhanced anti-gastric cancer and anti-*Helicobacter pylori* effect. *Asian Pacific Journal of Cancer Prevention*. 2022 Jan;23(1):61-68.
65. Mosallam FM, Bendary MM, Elshimy R, El-Batal AI. Curcumin clarithromycin nano-form: a promising agent to fight *Helicobacter pylori* infections. *World Journal of Microbiology and Biotechnology*. 2023 Dec;39(12):324.
66. Sandhiutami NM, Arozal W, Louisa M, Rahmat D, Wuyung PE. Curcumin nanoparticle enhances the anticancer effect of cisplatin by inhibiting PI3K/AKT and JAK/STAT3 pathway in rat ovarian carcinoma induced by DMBA. *Frontiers in Pharmacology*. 2021 Jan 18;11:603235.
67. Mohammed ES, El-Beih NM, El-Hussieny EA, El-Ahwany E, Hassan M, Zoheiry M. Effects of free and nanoparticulate curcumin on chemically induced liver

- carcinoma in an animal model. Archives of Medical Science. 2020 Mar 17;17(1):218-225.
68. Al-Hawary SI, Jasim SA, Kadhim M, Saadoon SJ, Ahmad I, Romero Parra RM, *et al.* Curcumin in the treatment of liver cancer: from mechanisms of action to nanoformulations. Phytotherapy Research. 2023 Apr;37(4):1624-1639.
 69. Harakeh S, Saber SH, Al-Raddadi R, Alamri T, Al-Jaouni S, Qari M, *et al.* Novel curcumin nanoformulation induces apoptosis, and reduces migration and angiogenesis in liver cancer cells. Artificial Cells, Nanomedicine, and Biotechnology. 2023 Dec 31;51(1):361-370.
 70. Marton LT, Pescinini-e-Salzedas LM, Camargo ME, Barbalho SM, Haber JF, Sinatora RV, *et al.* The effects of curcumin on diabetes mellitus: a systematic review. Frontiers in Endocrinology. 2021 May 3;12:669448.
 71. Rahimi HR, Mohammadpour AH, Dastani M, Jaafari MR, Abnous K, Mobarhan MG, *et al.* The effect of nano-curcumin on HbA1c, fasting blood glucose, and lipid profile in diabetic subjects: a randomized clinical trial. Avicenna Journal of Phytomedicine. 2016 Sep;6(5):567-577.
 72. Shamsi-Goushki A, Mortazavi Z, Mirshekar MA, Mohammadi M, Moradi-Kor N, Jafari-Maskouni S, *et al.* Comparative effects of curcumin versus nano-curcumin on insulin resistance, serum levels of apelin and lipid profile in type 2 diabetic rats. Diabetes, Metabolic Syndrome and Obesity. 2020 Jul 3;2337-2346.
 73. Barman DK, Sahoo H. Therapeutic role of nanocurcumin in Alzheimer's and Parkinson's disease. In: Curcumin and Neurodegenerative Diseases: From Traditional to Translational Medicines. Singapore: Springer Nature Singapore; 2024. p. 337-352.
 74. Kakkar V, Kumari P, Adlakha S, Kaur IP. Curcumin and its nanoformulations as therapeutic for Alzheimer's disease. Nanobiotechnology in Neurodegenerative Diseases. 2019:343-367.
 75. Yavarpour-Bali H, Ghasemi-Kasman M, Pirzadeh M. Curcumin-loaded nanoparticles: a novel therapeutic strategy in treatment of central nervous system disorders. International Journal of Nanomedicine. 2019 Jun 17:4449-4460.
 76. Delavarian Z, Pakfetrat A, Ghazi A, Jaafari MR, Homaei Shandiz F, Dalirsani Z, *et al.* Oral administration of nanomicelle curcumin in the prevention of radiotherapy-induced mucositis in head and neck cancers. Special Care in Dentistry. 2019 Mar;39(2):166-172.
 77. Dharman S, Maragathavalli G, Shanmugasundaram K, Shanmugam RK. A systematic review and meta-analysis on the efficacy of curcumin/turmeric for the prevention and amelioration of radiotherapy/radiochemotherapy-induced oral mucositis in head and neck cancer patients. Asian Pacific Journal of Cancer Prevention. 2021 Jun;22(6):1671-1677.
 78. Amatto PD, Chaves L, França SD, Carvalho JC, Carmona F, Pereira AM. Efficacy of different pharmaceutical forms of *Curcuma longa* or curcumin in reducing oral mucositis severity and incidence in cancer patients: a systematic review and meta-analysis. Frontiers in Pharmacology. 2025 Apr 2;16:1560729.
 79. Hamam F, Nasr A. Curcumin-loaded mesoporous silica particles as wound-healing agent: an *in vivo* study. Saudi Journal of Medicine & Medical Sciences. 2020 Jan 1;8(1):17-24.
 80. Salehi B, Rodrigues CF, Peron G, Dall'Acqua S, Sharifi-Rad J, Azmi L, *et al.* Curcumin nanoformulations for antimicrobial and wound healing purposes. Phytotherapy Research. 2021 May;35(5):2487-2499.
 81. Ahmadi R, Salari S, Sharifi MD, Reihani H, Rostamiani MB, Behmadi M, *et al.* Oral nano-curcumin formulation efficacy in the management of mild to moderate outpatient COVID-19: A randomized triple-blind placebo-controlled clinical trial. Food Science & Nutrition. 2021 Aug;9(8):4068-4075.
 82. Karthikeyan A, Senthil N, Min T. Nanocurcumin: a promising candidate for therapeutic applications. Frontiers in Pharmacology. 2020 May 1;11:487.
 83. Zeng L, Yang T, Yang K, Yu G, Li J, Xiang W, *et al.* Efficacy and safety of curcumin and *Curcuma longa* extract in the treatment of arthritis: a systematic review and meta-analysis of randomized controlled trials. Frontiers in Immunology. 2022 Jul 22;13:891822.
 84. Yallapu MM, Nagesh PK, Jaggi M, Chauhan SC. Therapeutic applications of curcumin nanoformulations. The AAPS Journal. 2015 Nov;17:1341-1356.
 85. Jacob S, Kather FS, Morsy MA, Boddu SH, Attimarad M, Shah J, *et al.* Advances in nanocarrier systems for overcoming formulation challenges of curcumin: current insights. Nanomaterials. 2024 Apr 12;14(8):672.
 86. Li L, Zhang X, Pi C, Yang H, Zheng X, Zhao L, *et al.* Review of curcumin physicochemical targeting delivery system. International Journal of Nanomedicine. 2020 Dec 7;15:9799-9821.
 87. Ahmadi M, Agah E, Nafissi S, Jaafari MR, Harirchian MH, Sarraf P, *et al.* Safety and efficacy of nanocurcumin as add-on therapy to riluzole in patients with amyotrophic lateral sclerosis: a pilot randomized clinical trial. Neurotherapeutics. 2018 Apr 1;15(2):430-438.
 88. Huang YW, Cambre M, Lee HJ. The toxicity of nanoparticles depends on multiple molecular and physicochemical mechanisms. International Journal of Molecular Sciences. 2017 Dec 13;18(12):2702.
 89. Boroughani M, Moaveni AK, Hatami P, Mansoob Abasi N, Seyedoshohadaei SA, Pooladi A, *et al.* Nanocurcumin in cancer treatment: a comprehensive systematic review. Discover Oncology. 2024 Oct 1;15(1):515.