

Review Article

Therapeutic Applications of Curcumin Nanoformulations

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Abstract. Curcumin (diferuloylmethane) is a bioactive and major phenolic component of turmeric derived from the rhizomes of *curcuma longa linn*. For centuries, curcumin has exhibited excellent therapeutic benefits in various diseases. Owing to its anti-oxidant and anti-inflammatory properties, curcumin plays a significant beneficial and pleiotropic regulatory role in various pathological conditions including cancer, cardiovascular disease, Alzheimer's disease, inflammatory disorders, neurological disorders, and so on. Despite such phenomenal advances in medicinal applications, the clinical implication of native curcumin is hindered due to low solubility, physico-chemical instability, poor bioavailability, rapid metabolism, and poor pharmacokinetics. However, these issues can be overcome by utilizing an efficient delivery system. Active scientific research was initiated in 2005 to improve curcumin's pharmacokinetics, systemic bioavailability, and biological activity by encapsulating or by loading curcumin into nanoform(s) (nanoformulations). A significant number of nanoformulations exist that can be translated toward medicinal use upon successful completion of pre-clinical and human clinical trials. Considering this perspective, current review provides an overview of an efficient curcumin nanoformulation for a targeted therapeutic option for various human diseases. In this review article, we discuss the clinical evidence, current status, and future opportunities of curcumin nanoformulation(s) in the field of medicine. In addition, this review presents a concise summary of the actions required to develop curcumin nanoformulations as pharmaceutical or nutraceutical candidates.

KEY WORDS: cancer; curcumin; drug delivery; nanoparticles; nanotechnology.

INTRODUCTION

Chemotherapy is a major form of treatment modality for various human diseases and disorders in both developing and developed countries. This intervention has been associated with a number of side effects and poor compliance. Therefore, in recent years, a significant effort has been put forward for finding a better treatment modality that uses natural compounds or extracts. Among many naturally occurring polyphenol compounds, curcumin is a highly safe yellow pigment molecule, widely used as a food coloring agent, and can be used to treat various pathological conditions. Curcumin's use for various disease indications is primarily due to its active biological functions, i.e., anti-inflammatory, anti-oxidant, anti-microbial, anti-Alzheimer, anti-tumor, anti-diabetic, and anti-rheumatic activities (1,2). In addition, curcumin has been proven as a hypoglycemic, hepato-, nephron-, cardio-, and neuro-protective molecule (3). More importantly, this molecule also suppresses thrombosis and protects against myocardial infarction. It is, by far, the most prominent polyphenol, widely consumed on a daily

basis along with food (in India, Eastern Asia, and some African countries), which leads to better compliance. Curcumin usage began in ancient days; however, in 1949, the first scientific evidence of its anti-bacterial activity at very low concentrations was reported in the journal "Nature" and extensive research began only after 1994. During the last two decades, collective scientific data (~8000 peer-reviewed articles/reports/reviews/opinions, patents, and clinical trials) (Fig. 1a) has proven that curcumin is indeed a potential therapeutic molecule. In addition, this molecule is considered "generally recognized as safe (GRAS)" by the US Food Drug Administration (USFDA) (<http://www.nutraingredients-usa.com/Suppliers2/Sabinsa-gets-FDA-no-objection-letter-for-GRAS-status-of-its-Curcumin-C3-Complex>, <http://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&cad=rja&uact=8&ved=0CB8QFjAA&url=http%3A%2F%2Fwww.researchgate.net%2Fpublictopics.PublicPostFileLoader.html%3Ffid%3D543-f9169d5a3f25e128b45f3%26key%3D8e986fed-99cb-4b43-8d9b-be2c826c0e7c&ei=XAITVd27LsPOsQSIhoCwBQ&usq=AFQjC-NGX7Z-SnJ2nrcA0rLo3yO88LQ8fg&bvm=bv.89217033,d.cWc>). Moreover, the curcumin molecule exhibits a multitargeting ability in various pathological conditions, which allows translation into a therapeutic or nutraceutical agent.

Like many other lipophilic therapeutic small drug molecules, curcumin also has limitations (Fig. 1b) for its efficient use in clinical scenarios, in order to treat disease conditions. These include the following: (i) low hydrophilicity

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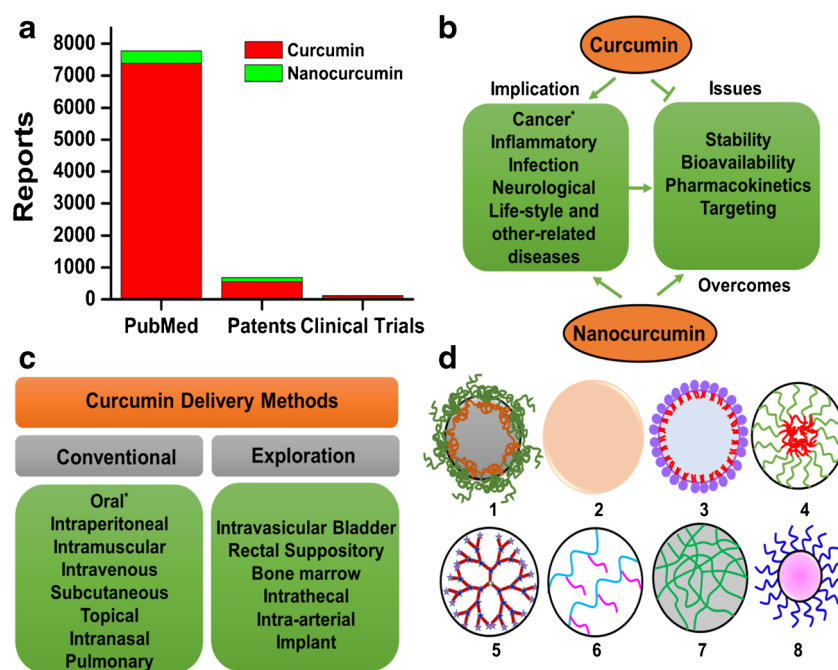


Fig. 1. Schematic transition of “curcumin” into “curcumin nanoformulations”. **a** Graphical representation of literature using PubMed (<http://www.ncbi.nlm.nih.gov/pubmed/>), patents (Google Patents), and clinical trial (<https://clinicaltrials.gov/>) websites (search conducted April 2015). **b** Implication of curcumin and nanocurcumin (curcumin nanoformulations) in various diseases (*asterisk* indicates widely studied implication). **c** Feasible delivery methods of curcumin and curcumin nanoformulations (*asterisk* represents commonly used route to deliver curcumin). **d** Commonly used types of nanocarriers (1–8: polymer nanoparticles, solid nanoparticles, liposome/lipid nanoparticles, micelles, dendrimers, polymer conjugates, nanogels, and metal/metal oxide nanoparticles, respectively) to deliver curcumin efficiently

and intrinsic dissolution rate(s), (ii) low physico-chemical instability, (iii) rapid metabolism, (iv) low bioactive absorption, (v) poor pharmacokinetics and bioavailability, and (vi) low penetration and targeting efficacy (4–6). All these factors significantly affect the efficient use of curcumin as a therapeutic molecule. Thus, different formulations including native, modified, and micro/nanofoms of curcumin formulations, produced as emulsion, cream, solution, pill, gel, band aid, and so on (7–9), have been designed for conventional or explorative administration (Fig. 1c) to achieve optimum outcomes in various pathological conditions. Both invasive and noninvasive routes of administration have been established for effective local, circulatory, affinity, or active targeting applications (9). Personalized and individual methods of administration may need to be adapted to deliver therapeutic dose of curcumin to the disease site. While there are some critical challenges that need to be addressed, curcumin exhibits numerous strengths, such as its traditional use for centuries; superior biological activity; and extensive pre-clinical, animal, clinical, and human trials that promote rapid development of curcumin or curcumin formulations into medicine(s). These positive indications have encouraged nanotechnologists to design or formulate useful nanocurcumin formulations (Fig. 1d) for improved solubility, stability, cellular uptake/internalization efficacy, specificity, tolerability, and therapeutic index (7,10). Primarily, these newer formulations or compositions may enhance sustained release of curcumin at the cellular targets to improve therapeutic benefit (5).

During the last decade, numerous nanoformulation-based approaches have been undertaken to enhance curcumin use in *in vitro*, *in vivo*, and pre-clinical settings that involve the use of adjuvants, stabilizers, conjugates/polymer conjugates, lipid/liposomes, hydro/micro/nanogels, and nanoparticles (NPs) (7,11,12). The specific roles and advantages of each delivery system are presented in Table I. Many of these efforts initially dealt with improved bioavailability, but newer formulations pay attention to efficient targeting of curcumin at the diseased area with the aid of antibody, aptamer, and peptide mediation (10). Efficient curcumin delivery using nanotechnology not only helps to overcome solubility, rapid drug metabolism, degradation, and drug stability issues but also should diffuse or target indent tissues while minimizing unintended toxicity to surrounding normal cells/tissues.

CURCUMIN NANOFORMULATIONS

Table II documents a number of important recent review articles that have dealt with curcumin nanoformulations. All these documents detail the (i) design of curcumin nanoformulations, (ii) types of different nanocarriers used for curcumin delivery, (iii) improved bioavailability and pharmacokinetics, (iv) human serum protein interactions, and (v) implications for anti-cancer activity. However, there is no review document that specifically describes the use of curcumin nanoformulation(s) in various human disease applications. Therefore, the main emphasis of this review article is to outline the latest developments in nanoparticle-

Table I. Commonly Used Systems to Deliver Curcumin and Their Specific Advantages over Conventional Systems and Other Nanocarriers

Type of nanoformulations	Significance and comments	Number of publications
Nanoparticles	Nanoparticles, in particular, biodegradable nanoparticles, have been used for encapsulation of curcumin due to its biocompatibility and biodegradability. In fact, some systems have reached clinical practice.	425
Liposomes	Liposomes are generated from phospholipid bilayers. This is the second most widely used vehicle to solubilize/encapsulate curcumin. Various types of liposomes have been tested for delivery of a number of clinically used drugs and are clinically used in clinics.	139
Cyclodextrins	Cyclodextrins are cyclic oligosaccharides that can solubilize curcumin in a lipophilic cavity, and the hydrophilic outer surface helps in greater dispersion of the formulation.	88
Polymers	Polymers have been exploited to improve solubility and bioavailability of curcumin. Polymeric carriers have been widely studied for efficient delivery of curcumin.	563
Conjugates	Conjugation of curcumin to small molecules and hydrophilic polymers is a known practice to increase aqueous solubility.	69
Micelles	Micelles or polymeric micelles are composed of amphiphilic block copolymers that spontaneously form 20–100 nm micelles in aqueous solution at the above critical micellar concentration. The hydrophobic core of micelles can effectively house curcumin for solubilization and targeted delivery.	138
Dendrimers	Dendrimers are composed of highly branched and star-shaped networks of macromolecules. Typically, dendrimers are formed symmetrically around the core at nanometer-scale dimensions and are three-dimensionally spherical in morphology. These carriers are highly suitable for conjugation and loading of curcumin.	13
Lipid nanoparticles	Lipid nanoparticles are typically spherical in shape with a lipid core matrix that can solubilize curcumin. The lipid core is usually stabilized by surfactant molecules.	90
Nanogels	Nanogels are hydrogel nanoparticles of swollen physical/chemically cross-linked networks composed of hydrophilic or amphiphilic polymer chains. These carriers can be designed to transport various drug molecules including curcumin. These carriers mimic human tissues due to higher hydrophilicity in the system due to swollen nature.	12
Gold nanoparticles	Gold nanoparticles are emerging as a novel platform as photothermal agents, contrast agents, and radiosensitizers. In addition, current literature supports their use in the delivery of curcumin.	11
Magnetic nanoparticles	Magnetic nanoparticles are a class of nanoparticles that can be used for multifunctional purposes including delivery of drugs (curcumin), magnetic resonance imaging, and hyperthermia.	35
Solid dispersions	Solid dispersions are dispersions of curcumin in a suitable inert matrix.	16

mediated delivery of curcumin (7,10,14) for improved therapeutic outcome.

Nanoparticles (whose size is typically 10–200 nm in diameter), in general, can improve the circulation time of the loaded therapeutic molecule and improve its residence at the pathological site by enhance permeation and retention (EPR) effect, which is a very important factor in drug delivery technology (18,19), especially in cancer therapeutics. Pre-clinical to clinical implementation of various therapeutic nanoparticle formulations have been under investigation (20). Abraxane (paclitaxel albumin nanoformulation), Doxil (doxorubicin liposome), Genexol-PM (paclitaxel micelle), CALAA-01 (small interfering RNA (siRNA)-targeted nanoformulation), MCC-465 (doxorubicin immunoliposome), and BIND-014 (prostate-specific membrane antigen, PSMA)-targeted docetaxel nanoformulation) (21) are well-known and approved USFDA formulations for clinical use or are under clinical trials. Therefore, in this review article, we delineate therapeutic applications of curcumin nanoformulations for various disease treatments by exploiting chemical design, composition, modification, and attachment/link with targeted motif (19). The use of combinational loading of drugs with curcumin is discussed with emphasis on synergistic action (22,23). Additionally, translational potential and required steps for clinical evaluation of curcumin nanoformulations are summarized.

Significant progress in the development of delivery systems for curcumin (liposome, polymeric nanoparticles, solid lipid nanoparticles, dendrimer, polymer conjugates, micelles, solid lipids, and nanogels) suggests its role in physico-chemical properties and biological activity of nanoformulations. A proposed view of these aspects has been summarized in our recent review articles (7,10). A large body of evidence suggests that curcumin exhibits poor physico-chemical stability and limited solubility in aqueous medium. It undergoes acidic/alkaline degradation, susceptible oxidation, and photodegradation. Thus, most of the earlier studies of curcumin nanoformulations were aimed at improving the stability characteristic of curcumin (5,17). As a first attempt, a curcuminoid-loaded solid-lipid-based nanoformulation exhibited ≈ 440 nm with 70% loading in a cream-based product stable for 6 months (24). Another investigation showed that poly(*N*-butyl cyanoacrylate) (PBCA) nanoparticles preserve up to 79–89% of the curcuminoids even in the presence of sunlight for about 6 months at storage conditions, demonstrating 3–5% reduction due to photodegradation (25). Furthermore, there was no significant change in particle size and zeta potential of curcumin nanoparticles due to storage and degradation. The crystal solid dispersion formulation of curcumin remained 83% curcumin in its active form upon exposure to UVA/B (750 W/m^2) for 1 h, indicating photochemical stability (26). In addition, this formulation

Table II. Summary of Review Articles on Curcumin Nanoformulations

Details of review article	Description of review article
Bioavailability of curcumin: problems and promises. Anand P, Kunnumakkara AB, Newman RA, Aggarwal BB. <i>Mol Pharm.</i> (2007) 4(6):807–18. (5)	This review article is the first attempt to discuss enhanced bioavailability of curcumin for therapeutic application with human disease.
Advanced drug delivery systems of curcumin for cancer chemoprevention. Bansal SS, Goel M, Aqil F, Vadhanam MV, Gupta RC. <i>Cancer Prev Res.</i> (2011) 4(8):1158–71. (13)	This article describes a broad overview of various delivery systems and discusses future strategies to enable the implementation of such chemopreventive strategies.
Curcumin nanoformulations: a future nanomedicine for cancer. Yallapu MM, Jaggi M, Chauhan SC. <i>Drug Discov Today.</i> (2012) 17(1–2):71–80. (7)	This is the first comprehensive review focused on the design and development of various nanoformulations (nanoparticles, self-assemblies, nanogels, liposomes and complex fabrication) for sustained and efficient curcumin delivery. A few novel multifunctional and composite nanosystem strategies are also discussed due to their simultaneous therapy and imaging characteristics.
Advances in nanotechnology-based delivery systems for curcumin. Sun M, Su X, Ding B, He X, Liu X, Yu A, Lou H, Zhai G. <i>Nanomedicine.</i> (2012) 7(7):1085–100. (14)	This review discusses nanotechnology-based curcumin delivery (liposomes, polymeric nanoparticles, solid lipid nanoparticles, micelles, nanogels, nanosuspensions, nanoemulsions, complexes, and dendrimer/dimer) approaches to enhance oral bioavailability, biological activity, and tissue-targeting ability.
Curcumin nanomedicine: a road to cancer therapeutics. Yallapu MM, Jaggi M, Chauhan SC. <i>Curr Pharm Des.</i> (2013) 19(11):1994–2010. (10)	This study reviews advanced drug delivery of curcumin to leverage therapeutic benefits by improving bioavailability and pharmacokinetics for tumor-specific curcumin.
Plasma proteins interaction with curcumin nanoparticles: implications in cancer therapeutics. Yallapu MM, Ebeling MC, Jaggi M, Chauhan SC. <i>Cur Drug Metab.</i> (2013) 14(4):504–15. (15)	This review examines possible interactions between the surface of curcumin nanoparticles and plasma proteins, the role of nanoparticle–protein complex architecture parameters, and the rational design of clinically useful curcumin nanoformulations.
Nanocurcumin: a promising therapeutic advancement over native curcumin. Flora G, Gupta D, Tiwari A. <i>Crit Rev Ther Drug Carrier Syst.</i> 2013;30(4):331–68. (16)	This review discusses various nanometric formulations of curcumin for its controlled and targeted delivery. It also demonstrates the biological applications, patented technologies, and current status of the ongoing clinical trials related to curcumin nanoformulations.
Curcumin nanoformulations: a review of pharmaceutical properties and preclinical studies and clinical data related to cancer treatment. Naksuriya O, Okonogi S, Schiffelers RM, Hennink WE. <i>Biomaterials.</i> (2014) 35(10):3365–83. (12)	This review summarizes the design and development of curcumin nanoformulations utilizing liposomes, polymeric nanoparticles and micelles, conjugates, peptide carriers, cyclodextrins, solid dispersions, lipid nanoparticles, and emulsions. Up-to-date efficacy of curcumin nanoformulations using cancer cell lines, <i>in vivo</i> models, and human clinical trials is also provided.
Nanotechnology-applied curcumin for different diseases therapy. Ghalandarlaki N, Alizadeh AM, Ashkani-Esfahani S, <i>BioMed Res Inter.</i> (2014) Article ID 394264, 23 pages (11)	New additions of nanotechnology approaches for curcumin delivery using liposomes, micelles, niosomes, cyclodextrins, dendrimers, nanogels, chitosans, gold nanoparticles, silver, and solid lipid nanoparticles are reported.
Recent advances in curcumin nanoformulation for cancer therapy. Lee W-H, Loo C-Y, Young PM, Traini D, Mason RS, Rohanizadeh R. <i>Expert Opin. Drug Deliv.</i> (2014) 11(8):1183–1201 (17)	This review reports (1) key properties of nanoparticles: size, surface modification, and targeting; (2) development of liposomal, micelles, nanogels, cyclodextrin–curcumin complexes, and other formulations; and (3) <i>in vitro</i> and <i>in vivo</i> efficacy of curcumin nanoformulations.
Dose escalation and pharmacokinetic study of nanoparticle curcumin. Kanai M, Imaizumi A, Otsuka Y, Sasaki H, Hashiguchi M, Tsujiko K, et al. <i>Cancer Chemother Pharmacol.</i> (2012) 69(1):65–70 (18)	Theracurmin can safely increase plasma curcumin levels in a dose-dependent manner at least up to 210 mg without saturating the absorption system.

exhibited 16-fold increase in the oral bioavailability of curcumin in the male Sprague–Dawley rats. The inclusion complexes or self-assemblies of curcumin and cyclodextrin or poly(cyclodextrin) exhibiting $\approx 88\%$ remained in active form (27,28). Similarly, a number of nanoformulations have been proven to enhance the physico-chemical stability of curcumin upon incorporating in nanosized particles.

The critical physico-chemical and biological properties depend on the type of preparative method, composition, particle size, particle shape, surface charge, stability, curcumin loading and its release, surface modification and functionalization, bioavailability, and pharmacokinetics of developed curcumin nanoformulations (Fig. 2). Apart from

various reports, our (10) recent review article composed of 30 curcumin nanoformulations dealing with “(1) various principles to encapsulate curcumin molecule in various nanoformulations and to prepare curcumin nanoformulations, their composition, and particle evaluation; (2) curcumin loading, release, and uptake behavior of various curcumin nanoformulations; (3) pharmacokinetics properties and bioavailability of curcumin nanoformulations”; and (4) the potential of curcumin nanoformulation. Therefore, readers are encouraged to read the review article (10) for all typical pharmaceutical (preparation, characterization), biopharmaceutical (bioavailability and PK-PD), and potential aspects of various curcumin nanoformulations and below “Preparative

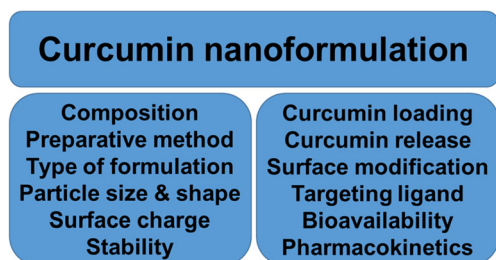


Fig. 2. Critical physico-chemical properties and biological functions to consider in generating a successful curcumin nanoformulation

Method,” “Size, Shape, Surface Charge, and Composition of Nanoparticles,” “Curcumin Loading and Release,” and “Surface Bio-Functionalization” sections.

Preparative Method

Curcumin nanoparticles are usually prepared by (i) dispersing polymer or co-polymers and surfactants (solvent evaporation, spontaneous emulsification/solvent diffusion, nanoprecipitation, salting out/emulsion-diffusion, supercritical fluid technologies, etc.); (ii) polymerization of monomers; (iii) reduction or oxidation of metal salts; (iv) pulverization of bulk formulations; and (iv) chemical modification. Each method produces nanoparticles with distinctly different physico-chemical properties.

Size, Shape, Surface Charge, and Composition of Nanoparticles

Nanoparticles with a 10–200 nm hydrodynamic diameter are highly suitable for medicinal applications. However, for local therapeutic applications, even micro-size particles serve a purpose. The spherical-shaped particle is usually produced by conventional preparative methods. Recent studies also involve the generation of various shapes of nanoparticles. The surface and its charge on nanoparticles offer immediate bio-nanointeractions with cells. A slight positive charge (cationic groups) on the surface of nanoparticles is considered ideal because it increases internalization capacity while higher positive charge contributes to the significant toxicity to the cells. On the other hand, negative charge (anionic groups) promotes a particle’s stability in circulation. Recent review articles describe particle size, shape, surface charge, and its implications in elimination from the body (cutoff by kidney and vascular, blood–brain barrier cutoff), EPR, and active targeting (7,10,17).

Curcumin Loading and Release

Curcumin is a less potent molecule than many clinically used chemotherapy drugs; therefore, its higher loading and encapsulation in nanoparticles may be useful because of its immediate availability to the cells when released from the nanoparticles. As found in literature, curcumin can be loaded up to 25 wt/wt%. Each method of preparation determines its encapsulation efficiency and release phenomenon. Cellular microenvironment plays a major role in degradation of nanoparticles and curcumin release from the

nanoformulations. These properties can be used as external stimuli for targeted delivery of curcumin.

Surface Bio-Functionalization

Functionalizing a specific antibody, ligand, peptide, or aptamer to the surface of nanoparticles that promotes specific interaction with intended cells is highly relevant. Such formulations bind *via* receptor proteins to the specifically overexpressing proteins on cell membrane. This creates an opportunity for targeted delivery of curcumin to diseased site.

Scale-Up Process

Developing a successful scale-up and manufacturing a pharmaceutical-grade curcumin nanoformulation are considerable challenge. It may be suitable for a top–down approach where bulk curcumin nanotized using milling method (a traditional process of producing drug nanocrystals). NanoCrystals[®] technology is already a developed area of technology which can be adopted for developing curcumin nanoformulations as well. However, this technology may not offer a great monodispersity of nanoparticles (often lead to polydispersity). Additionally, particle size of nanotized curcumin nanoparticles is slightly bigger. Considering all these aspects, a bottom–up approach-based nanoparticle generation with curcumin encapsulation is an alternative promising approach. Recently published data demonstrates various steps involved in scaling up of the nanoformulation process that are essential for the development of a poly(lactide-*co*-glycolide)-based curcumin nanoparticle formulation (29). This process involves optimizing and scaling-up using solid-oil/water emulsion technique. This scale-up process was designed for a 5-g batch by changing the feeds of polymer (PLGA), stabilizer (PVA), solvent (ethyl acetate), sonication tip, and sonication time. The ideal parameters that were created produce curcumin nanoparticles with a particle size of 158.5±9.8 nm (polydispersity of 0.141±0.011) and encapsulation efficiency of 90.34±2.3 with a curcumin loading of about 10.32±1.4%. Various companies (NanoLiposomes, USA; Life Enhancement Products, Inc., USA; Bestvite Inc., USA; Konark Herbals & Health Care, India; Advanced Orthomolecular Research, Inc., Canada; International Nutrition, Inc., USA; Lee Silsby Compounding Pharmacy, USA; Nano Tech Miso, Korea, Sabinsa Corporation, USA; etc.) (7) produce curcumin nanoformulations. Sabinsa Corporation is notably highly involved in both research and development aspects of curcumin C3 complexes. Signpath Corporation (<http://signpathpharma.com>) is in the process of developing three pharmaceutical-grade intravenous nanoparticle-sized formulations, namely, liposomal, polymeric, and PLGA nanoformulations. Their products have been examined for proof of efficacies against human tumor xenografts. Additionally, in collaboration with the Nanotechnology Characterization Laboratory, their nanoformulations were evaluated for endotoxin analysis, particle size and zeta potential, *in vitro* cellular cytotoxicity, immunological assays, metabolism, and pharmacokinetic studies before actual implementation (documented as NCL201304A report, <http://www.signpathpharma.com/resources/NCLCharacterizationNanocurcuminPharma.pdf>).

Additional steps to further develop curcumin nanoformulations for efficient use in clinical settings have been suggested in “Expert Opinion” section.

THERAPEUTIC APPLICATIONS OF CURCUMIN NANOFORMULATIONS

From the literature, it is evident that poor solubility, bioavailability, and pharmacokinetics are major barriers to the clinical translational use of curcumin. Various strategies (mentioned in Table I) have been developed to overcome these problems. In numerous *in vitro* and *in vivo* studies, nanoformulations of curcumin exhibited superior therapeutic benefits over the free curcumin (7,10) in a side-by-side setting (“Cancer,” “Cardiovascular Diseases,” “Neurodegenerative, Alzheimer’s, and Brain Diseases,” “Stroke,” “Inflammatory Diseases,” “Diabetes,” “Lung Diseases,” “Anti-Microbial and Wound Healing,” “Ophthalmic,” “Skin Diseases,” “Malaria,” “Cystic Fibrosis,” “Osteoporosis,” and “HIV” sections). Recent clinical trials demonstrate that curcumin nanoformulations exhibit improved bioavailability of curcumin (Table III) and thus provide a strong rationale for future clinical use once additional important mechanistic perspectives are understood. In this section, we precisely discuss the use of various curcumin nanoformulations in a number of diseases. Although, there is no report out there demonstrating clinical benefit of curcumin nanoformulation, but since curcumin nanoformulation(s) have shown superior outcomes in both *in vitro* and *in vivo* studies, we believe that greater effects can be expected from curcumin nanoformulations over free curcumin.

Cancer

Following heart diseases, cancer is still the second leading cause of death in human. The most commonly used treatment modalities include surgery, chemotherapy, radiation therapy, targeted therapy, immunotherapy, hyperthermia, photothermic therapy, and other alternative therapies. Traditionally, chemotherapy is highly recommended for both solid and metastatic tumors. However, chemotherapy-associated side effects are quite deleterious to normal/healthy tissues/organs. Thus, curcumin and its nanoformulations play a significant role in enhancing chemo/radiosensitization and can act as treatment modality to provide a proper dose at the tumor site. This section deals with how curcumin nanoformulations efficiently reduce the growth and metastasis potential of tumor cells or tumor burden. Curcumin nanoformulations significantly internalize in cancer cells through endocytosis or receptor-mediated pathways in the presence of endocytosis inhibitors and release curcumin in active form in order to induce its biological effects (30,31). Dextran-CCM nanoparticles were significantly taken up in HeLa cells while very minimal uptake was found in two normal cell lines. Furthermore, curcumin nanoformulations retain molecular targeting effects, even though curcumin is encapsulated in nanoparticles or nanocarrier. Our previous review article documented a number of curcumin formulations and discussed their *in vitro* and *in vivo* effects against cancer cell proliferation and tumor progression (7). More importantly, Maitra’s group

has engineered a curcumin nanoformulation (NanoCurc™) (32–34). This formulation was developed by a random copolymerization of *N*-isopropylacrylamide with *N*-vinyl-2-pyrrolidone, poly(ethylene glycol)-monoacrylate in the presence of *N,N*-methylenebisacrylamide, ammonium persulfate, ferrous ammonium sulfate, and tetramethylethylenediamine. This formulation produced micellar aggregates of 50 nm amphiphilic polymers which release 40% of curcumin at physiological pH. NanoCurc formulation possesses high systemic bioavailability in plasma and tissues over free curcumin (32–34). Widely tested in animal studies for cancer treatment (35–38), this formulation demonstrated tumor growth inhibition attributed to significant reduction in activation of nuclear factor kappa B (NF- κ B), inhibition in the expression of matrix metalloproteinase-9 (MMP-9) and cyclin D1. The combination of NanoCurc™ and gemcitabine indicated an additive therapeutic effect (37).

A recent study demonstrated that a number of newer approaches exist to deliver curcumin with augmented activity. For instance, layer-by-layer deposition of polyelectrolytes (polystyrene sulfonate/polyallylamine hydrochloride, polyglutamic acid/poly-L-lysine, dextran sulfate/protamine sulfate, and carboxymethyl cellulose/gelatin loaded with curcumin formulations) blocks the hepatocyte growth factor-induced signaling in the breast cancer cell line, MDA-MB-231 (39). Curcumin encapsulation in Eudragit S100 polymer nanoparticles, which dissolves at colonic pH, influences cellular uptake and exhibits a two-fold superior anti-cancer potential in HT-29 human colorectal cell line (40). Novel formulations allow a multitiered approach in which imaging and therapeutic function are included (41–44). Such curcumin nanoformulations are usually built with gold (45,46) and magnetic (47,48) nanoparticles. Additionally, dual layers of magnetic and gold nanoparticle (magnetoplasmonic nanoparticles) not only incorporate high-contrast magnetic resonance imaging properties but also enhance apoptosis in leukemia HL-60 cells (49). Some of these curcumin nanoformulations make an augmented approach possible by combining mild hyperthermia, pH, radiofrequency (RF), and thermosensitivity (50–52). For example, a composite chitosan-g-poly(*N*-vinyl caprolactam) nanoparticle with embedded gold nanoparticles encapsulated with curcumin exhibits controlled release of curcumin and apoptosis to cancer cells. Additionally, this composite formulation confirms its residence in internal tumors for a week, which can offer potential new avenues of RF-assisted cancer treatment (53). Magnetic nanoparticles of curcumin could increase in temperature under an external magnetic field, which can induce hyperthermia potential in cancer therapy.

Targeted delivery of curcumin using nanoparticles is always more advantageous over conventional formulations. We reported that PSMA-targeted curcumin PLGA NPs specifically target PSMA overexpressing prostate cancer cells both in cell line and xenograft tumors (30). Development of a number of targeted curcumin nanoformulations has been presented in Table IV.

Cardiovascular Diseases

Proliferation and migration of vascular smooth muscle cells (VSMCs) are observed during vascular development in response to vascular injury and atherogenesis. Vascular injury

Table III. Clinical Trials Dealing with Curcumin Nanoformulations and the Study Outcome

Type of nanoformulations	Purpose outcome or outcome measures
Study investigating the ability of plant exosomes to deliver curcumin to normal and colon cancer tissue (NCT01294072) Phase I (recruiting); University of Louisville, USA.	To investigate the ability of plant exosomes to deliver curcumin to normal colon tissue and colon tumors and to compare to oral tablets of curcumin alone.
Improved oral bioavailability of curcumin incorporated into micelles (NCT01982734) Phase 0 (recruiting); University of Hohenheim, Germany.	To test the application of phytochemicals and micellar solubilization, alone and together, to enhance the absorption of curcumin into the body. For this, the plasma concentrations of curcumin, demethoxycurcumin, and bisdemethoxycurcumin are evaluated. Also, to evaluate serum aspartate transaminase, alanine, gamma-glutamyl transferase, phosphatase, bilirubin, uric acid, creatinine, total cholesterol, HD/LDL cholesterol, and triglycerols.
Oral bioavailability of curcumin from micronized powder and liquid micelles in healthy young women and men (NCT01925287) Phase 0 (completed); University of Hohenheim, Germany.	This study was aimed to develop novel curcumin formulations with enhanced oral bioavailability and to study the safety of the formulations in humans. A single oral dose of 500 mg curcumin as native powder, micronized powder, or liquid micelles resulted in an area under the plasma concentration–time curve. The micronized curcumin exhibited 14-, 5-, and 9-fold and micellar curcumin 277-, 114-, and 185-fold better bioavailability than native curcumin in women, men, and all subjects, respectively.
Evaluation of liposomal curcumin in healthy volunteers (NCT01403545) Phase I (completed); Medical University of Vienna, Austria.	Safety and tolerability of increasing doses of intravenous liposomal curcumin in healthy subjects by means of adverse events, vital signs, and safety laboratory assessments was evaluated. Liposomal curcumin was tolerated well, but a transient red blood cell echinocyte formation with concomitant increase in mean cellular volume was observed at dosages ≥ 120 mg/m ² .
Micro-Particle Curcumin for the Treatment of Chronic Kidney Disease (NCT02369549) Phase III (recruiting), Lawson Health Research Institute, The Kidney Foundation of Canada, and Canadian Institutes of Health Research, Canada.	This is an investigator-initiated pilot clinical trial to compare the effect of micro-particle curcumin <i>versus</i> placebo over 24 weeks in patients who have chronic kidney disease. This study will monitor and determine the safety and efficacy of curcumin relative to placebo in reducing albuminuria, urinary IL-18, and the loss of eGFR.
Micellar Curcumin and Metabolic Syndrome Biomarkers (NCT01925547) Phase 2 (recruiting); University of Hohenheim and German Federal Ministry of Education and Research, Germany.	To evaluate metabolic profiles upon oral treatment of micellar curcumin, i.e., C-reactive protein, plasma curcumin concentrations, serum alanine transaminase activity, blood glucose, TNF- α , serum uric acid, serum total cholesterol, serum triacylglycerols, cholesterol, serum aspartate transaminase activity, gamma-glutamyl transferase activity, alkaline phosphatase activity, bilirubin, IL-6, body weight, and diastolic/systolic blood pressure, etc.

eGFR estimated glomerular filtration rate, HD/LDL high-density/low-density lipoprotein, IL interleukin, TNF- α tumor necrosis factor alpha

usually happens just after angioplasty, organ transplantation, or stent implantation. Cardiovascular medicine, such as the statins, efficiently blocks migration of VSMCs. Wang *et al.* (62) designed a self-assembled amphiphilic carbomethyl-hexanol chitosan nanomatrix with curcumin, which manipulates the cellular internalization and low-dose sustained and controlled cytotoxic effect on growth and migration of VSMCs. Doxorubicin hydrochloride (DOX) is a first-line chemotherapy, but this therapy is highly associated with severe cardiotoxicity. This side effect can be mitigated by co-administration of the pluronic loaded nanocurcumin formulation by reducing apoptosis and reactive oxygen species (ROS) levels (63). Pramanik *et al.* (64) further confirmed that a nanocurcumin formulation could overcome multidrug resistance in cancer cells and ameliorate doxorubicin-associated cardiomyopathy by reducing DOX-induced intracellular oxidative stress (an indicative of total glutathione levels and glutathione peroxidase activity) in cardiac tissue. Angiogenesis plays a crucial role in atherosclerosis and other cardiovascular diseases and has emerged as a major vague issue (65). The curcumin in poly(ester amine) nanoparticles efficiently inhibited angiogenesis in a

transgenic zebra fish model, representing a novel anti-angiogenesis therapy (66).

Neurodegenerative, Alzheimer's, and Brain Diseases

Many human diseases evolve in the central nervous system (CNS), brain, or the spinal cord. Delivery of curcumin at these sites requires overcoming complexity of the blood–brain barrier (BBB). A promising strategy is to functionalize apolipoprotein E (ApoE)-derived peptides (residues 141–150) to nanoparticles (67).

Alzheimer's disease (AD) progresses with the accumulation of β -amyloid peptide (A β) in senile plaques, which is toxic to species in monomeric and fibrillary form and is a hallmark lesion of AD. Curcumin is a molecule that can target the amyloid pathology, and therefore, delivery of curcumin has received great attention, and its imaging capacity offers diagnostic capabilities. Biodegradable PLGA–curcumin nanoformulations exhibit nontoxicity in human neuroblastoma SK-N-SH cells and protect H₂O₂-induced elevation of ROS. This formulation is able to prevent the induction of the redox-sensitive transcription factor Nrf2

Table IV. Evaluation of Targeted Curcumin Nanoformulations for Cancer Therapeutics

Details of article	Description of results
Transferrin (TF)-mediated solid lipid nanoparticles (54)	TF-tagged curcumin nanoformulations show a 5-fold increased uptake by MCF-7 cancer cells. This formulation induces 44.5% apoptosis compared to curcumin nanoparticles (32.4%) at 10 μ M.
Transferrin-targeted polymeric micelles co-loaded with curcumin and paclitaxel (55)	TF-targeted combination polymer micelles induce significant cytotoxic effect of curcumin and paclitaxel. A constant curcumin nanoformulation (5 and 10 μ M) was able to reduce the paclitaxel-required IC50 concentration from \sim 1.78 and 0.68 μ M to \sim 0.74 and 0.1 μ M.
Anti-PSMA conjugated curcumin loaded PLGA NPs (30)	PSMA-targeted curcumin-loaded nanoparticles target only PSMA-expressing cancer cells both <i>in vitro</i> and <i>in vivo</i> . This formulation also exhibits superior anti-cancer effects against prostate cancer cells compared to native curcumin and its nanoformulation.
Folic acid conjugated cross-linked acrylic polymer hydrogel (56)	This curcumin nanoformulation showed higher cellular uptake in human cervical cancer cell lines than the nonfolate conjugated form.
Multifunctional targeting nano-carrier drug delivery system based on CD44 receptor and tumor microenvironment pH condition (57)	The anti-tumor activity of the targeted nanoformulation was most efficient in suppressing tumor growth in an animal model.
Magnetic core-shell nanocapsules with dual-targeting capabilities and co-delivery of multiple drugs to treat brain gliomas (58)	The combinational effects, i.e., curcumin in nanoformulation, magnetic guidance, and targeting lactoferrin receptor, have been maximal in brain tumor-bearing mice not only achieving high accumulation, but also efficiently suppressing cancer growth, either curcumin alone or in combination with doxorubicin.
Enhancement of cellular uptake and cytotoxicity of curcumin-loaded PLGA nanoparticles by conjugation with anti-P-glycoprotein (59)	Anti-Pgp-conjugated curcumin nanoparticles exhibit superior cellular uptake by KB-V1 cells and thus enhance cytotoxicity.
Folate decorated dual drug loaded nanoparticle: role of curcumin in enhancing therapeutic potential of nutlin-3a (22)	Folate-targeted curcumin nanoformulations are capable of inducing enhanced expression of proapoptotic, down-regulation of anti-apoptotic proteins, and down-regulation of bcl2 and NF- κ B gene/protein.
Surface functionalization of PLGA nanoparticles by noncovalent insertion of a homo-bifunctional spacer (60)	This novel surface-modified targeted nanoformulation internalizes more in annexin A2-positive cells than in negative cells.
Multistage polymeric micelles based on amphiphilic poly(β -amino ester) derivatives (61)	pH-responsive curcumin micelles are proven to have enhanced cancer growth inhibition (65.6%) ability.

TF transferrin, PLGA poly(lactide-co-glycolide) PSMA prostate-specific membrane antigen, MCF-7 Michigan Cancer Foundation-7 breast cancer cell line, NF- κ B nuclear factor kappa B, IC50 half maximal inhibitory concentration, NP nanoparticle

in the presence of H₂O₂, indicative strategy to protect neurons against oxidative damage that is commonly observed in AD (68). Additionally, curcumin formulations containing biotin coupling poly(ethylene glycol)ylated (PEGylated), biodegradable poly(alkyl cyanoacrylate) (69), PEG liposomes with the anti-transferrin (70), lipid conjugate liposome (71), nanoliposomes (72), PEG-poly(lactic acid) block co-polymer (72), and click-chemistry-based nanoliposomes (73) have shown aggregation inhibition of A β and toxicity rescue of A β , indicative of AD treatment and diagnosis. Another important study using NanoCurc™ formulation revealed that decreased levels of H₂O₂, increased level of glutathione, and decreased levels of caspase 3 and caspase 7 activities in athymic mice brain suggest a favorable redox intracellular environment worthy of implementation of this treatment for AD (74). In addition, ApoE3-conjugated and curcumin-loaded PBCA polymer nanoparticles offer a great advantage in the treatment of A β -induced cytotoxicity in AD (75). Curcumin functionalized gold nanoparticles efficiently interact with amyloid protein/peptide and simultaneously inhibit amyloid fibrillation and dissolve amyloid fibrils by acting as artificial molecular chaperones (76).

An adverse effect of aluminum (AlCl₃, neurotoxicant) was completely reversed by an oral administration of lipid

nanoformulation of curcumin in male Lacca mice (77) that resulted in a 97% recovery in membrane lipids and 73% recovery in acetylcholinesterase. Similarly, neurotoxicity induced by acrolein can be reversed by using PLGA-based curcumin nanoformulations. This reversal was achieved by restoring the expression of γ -glutamylcysteine synthetase, ROS, and reactive nitrogen species levels but had no effect on the decrease of glutathione display neuroprotection (78).

A novel approach of superparamagnetic iron oxide conjugated with curcumin demonstrated that amyloid plaques could be visualized in *ex vivo* magnetic resonance imaging (MRI) in Tg2576 mouse brains and no plaque was found in nontransgenic mice (79). Significant accumulation and colocalization of nanoparticles with amyloid plaques were observed in immunohistochemical examination of the mouse brains. Therefore, this formulation has great potential for noninvasive diagnosis of AD using MRI over positron emission tomography (PET) scan imaging. Anti-amyloid antibody-conjugated and curcumin/dexamethasone-loaded gadolinium/magnetic nanoparticles are ideal for early diagnosis, effective targeting, and as therapeutic agent(s) of cerebrovascular amyloid (80).

Mitochondrial dysfunctions cause numerous human disorders, including Huntington's disease. Attenuation of

mitochondrial impairments could provide a potential therapeutic intervention for this disease. *In vitro* screening of a library of charge- and size-varied formulation of PLGA-b-PEG-triphenylphosphonium polymer (PLGA-b-PEG-TPP)-based curcumin nanoformulation confirms significant cytosolic and mitochondrial fractions in cells, indicating mitochondria-targeting chemotherapeutics (81). Another solid-lipid-based curcumin nanoformulation attenuates 3-nitropropionic-acid-induced Huntington's disease in rats by increasing complex II activity, restoring the glutathione and superoxide dismutase (82). Intervention of ameliorated mitochondrial dysfunctions in HD was also due to the reduction in mitochondrial swelling, lipid peroxidation, protein carbonyls, and reactive oxygen species (82).

Stroke

Stroke causes irreversible deterioration of the CNS due to interruption of blood, oxygen, and nutrient supply. Curcumin may limit the risk for stroke by lowering cholesterol, limiting the clogging of arteries, and acting as blood thinning agent. A proof-of-concept study in Balb/c mice confirms that bioavailability is 32–1555 times higher, pharmacodynamics is 3–4 times higher, and brain targeting is 8.135 times higher when curcumin is used in the form of solid lipid nanoparticles (83) for stroke treatment. Such efficient targeting can be verified using a sensitive method employing liquid chromatography coupled with tandem mass spectrometry for the simultaneous determination of curcumin in mouse plasma and brain tissue, using salbutamol as an internal standard (84). Ramalingam *et al.* (85) proposed an oral curcumin nanoformulation from *N*-trimethyl chitosan surface-modified solid lipids for successful brain distribution of curcumin. Poly(*N*-isopropyl acrylamide)-curcumin nanoformulation has shown improved neurobehavioral activity and reduced cytokine levels (tumor necrosis factor alpha (TNF- α) and IL-1 β) in middle cerebral artery occlusion-induced cerebral ischemic rats (86). This formulation is also capable of reducing oxidative stress-associated brain injury after middle cerebral artery occlusion in rats (87). The efficacy of this formulation was assessed by grip strength, locomotor activity, and biochemical studies in the brain. A recent study by Kalani *et al.* (88) demonstrated the role of curcumin encapsulated in exosomes with 200 nm size as an epigenetic agent in cerebral stroke. Another efficient solid lipid nanoparticle of curcumin alleviates behavioral, oxidative, and nitrosative stress; acetylcholinesterase; and mitochondrial enzyme complexes, and physiological parameters in cerebral ischemic reperfusion injury in rats (89) indicate its protective role against cerebral ischemic insult.

Inflammatory Diseases

Inflammation is the body's protective biological response to harmful injury or infection. There are more than dozen inflammatory-related disorders. Monocyte-derived myeloid cells help to fight against inflammation-related infections. Curcumin has been proven to have anti-inflammatory, anti-oxidation, and neuro-protective properties. Nanotized formulation of curcumin successfully inhibits lipopolysaccharide

(LPS)-induced inflammation in rat model (90). At the same time, the employed concentration does not cause adverse effects as measured by blood and brain lactic acid concentrations, kidney function, and neuronal apoptosis. Another PLGA-Eudragit[®] S100-based curcumin nanoformulation significantly reduced TNF- α secretion by LPS-activated macrophages (J774 cells) (91). In *in vivo* studies, this formulation also minimized neutrophil infiltration and TNF- α discharge in a murine dextran sulfate sodium-induced colitis model, indicating that it is a suitable treatment approach for inflammatory bowel disease (IBD). Shukla *et al.* (92) proved that nanoemulsion of curcumin in rats exhibited LPS-induced lung- and liver-associated injury due to minimizing neutrophil migration, reducing TNF- α levels, and oxidative stress. Exosome-mediated curcumin delivery can be efficient to activate myeloid cells *in vivo* (in a lipopolysaccharide (LPS)-induced septic shock mouse model) (93).

A novel nanocarrier transdermal gel curcumin nanoformulation was designed against inflammation and was determined to be nonirritant (skin irritation scored 0.49) and safe for human use (94). This may be developed as a treatment modality for localized inflammation. Curcumin-loaded solid lipid nanoparticles effectively reduced levels of IL-1 β expression and decreased expression of serum proinflammatory cytokines (IL-6, TNF- α , and IL-1 β), anti-inflammatory (cytokine IL-10), and suppressed NF- κ B activation and I κ B α degradation levels, suggesting its role in treating sepsis (95). A synergistic action of the drug combination of celecoxib and curcumin nanoformulation was achieved in an ulcerative colitis model in rats (96). In addition, curcumin-loaded solid nanoparticles have also been tested for hepatoprotection (97). This has been confirmed by examining the following: (i) extent of liver damage and repair, (ii) levels of alanine aminotransferase and aspartate aminotransferase, (iii) oxidative stress markers (malondialdehyde, superoxide dismutase, and reduced glutathione), and (iv) TNF- α , in a carbon tetrachloride-induced hepatic injury rat model.

Rheumatoid arthritis is a chronic inflammatory disease occurring in joints and cartilages. Arora *et al.* (98) established an effective curcumin-loaded solid lipid nanoparticle utility in complete Freund's adjuvant-induced arthritis rat model. The results in arthritic rat model showed a significant increase in (i) blood leukocyte count, (ii) oxidative-nitrosative stress, (iii) TNF- α and C-reactive protein, (iv) cyclic citrullinated peptide antibody levels, and (v) radiological alterations, which support protective effects against arthritis.

Diabetes

Diabetes is an indication found in humans in which blood glucose levels are high. Curcumin has been effective against diabetes-related complications, including heart, kidney, and liver disease. Therefore, it is believed that delivering curcumin in the form of nanoparticles and lipid/liposomes could improve therapeutic outcomes (99). Self-nanoemulsifying drug delivery system containing curcumin was evaluated in male Sprague-Dawley rats for diabetic neuropathy (100), and the results showed greater neuroprotective function as confirmed by various parameters such as nerve function and inflammatory proteins (NF- κ B, IKK- β , COX-2, iNOS, TNF- α , and IL-6). Diabetes is also linked to

increased levels of free radicals and systemic proinflammatory cytokines that can alter lipid profiles. In a recent study, an employed PLGA–curcumin nanoformulation in streptozotocin-induced diabetic rats demonstrated reduced C-reactive protein levels, IL-6, and TNF that lead to significant reduction in plasma triglycerides and total cholesterol and an increase in high-density lipoprotein cholesterol (101). In a leptin-deficient (*ob/ob*) mouse with steatosis model of insulin resistance, treatment with liposome nanoparticles inhibited proinflammatory pathways in hepatic tumor necrosis factor, inducible nitric oxide synthase-producing dendritic cells, and adipose tissue macrophages (ATMs), which can reverse insulin resistance, an indication for targeting inflammatory approach for type 2 diabetes (102).

Lung Diseases

Inflammation is an ultimate event in the development of lung diseases, including asthma, chronic obstructive pulmonary disease, severe acute respiratory syndrome, lung cancer, granulomatous lung diseases, and so on. The effective delivery of curcumin to the lung depends on the physiology of the lungs and a number of factors such as type of formulation, mode of delivery, and its mode of action. Conventional poly(lactic acid) (PLA)-containing curcumin showed an improvement in the anti-inflammatory activity of curcumin even at 1/8 dose, i.e., 50 vs. 400 mg/kg free curcumin (103). A self-assembled anisotropic (Janus particles) curcumin formulation delivered through local inhalation in an orthotopic mouse model of human lung cancer resulted in accumulation and retention of most of the nanoparticles in the lungs of mice for at least 24 h for inducing its effects (104).

Upon administering curcumin solid lipid nanoparticles in mice, maximum nanoparticles reached the lung and liver (105). More importantly, in ovalbumin-induced allergic rat model of asthma, this formulation effectively (i) suppressed airway hyperresponsiveness, (ii) suppressed inflammatory cell infiltration, and (iii) inhibited the expression of T-helper-2-type cytokines (IL-4 and IL-13) in bronchoalveolar lavage fluid, indicative of a promising candidate for asthma therapy (105). The more popular curcumin formulation, NanoCurc™, can maintain intrahepatic curcumin levels in hepatocytes and nonparenchymal cells, which can help to inhibit carbon tetrachloride-induced liver injury (38). Another study confirmed significant anti-inflammatory activities of curcumin-loaded polyvinylpyrrolidone induction in the lung epithelial cells of TNF- α -treated mice (106).

Delivering drugs to the small airways, terminal bronchioles, and deep lung is difficult. A chitosan-based curcumin nanoparticle formulation delivers effectively to the deep lung *via* extratesticular Sertoli cells (107). These swellable hydrogel-based microparticle pressurized metered dose inhaler formulations can also be used as potential delivery vehicles for nanoparticle therapeutics. (108). Inhibition of methicillin-resistant *Staphylococcus aureus* (MRSA) *in vitro* and *in vivo* (MRSA-induced pneumonia in mice) was achieved by upconversion of near infrared light nanoparticles conjugated with curcumin due to activated effects under NIR photosensitizer (109).

Anti-Microbial and Wound Healing

Curcumin has been known for centuries as a household remedy that can be extended to anti-microbial activity (110). In addition, curcumin has proven wound healing properties which helps in enhanced granulation tissue formation, collagen deposition, tissue remodeling, and wound contraction (111). An aqueous dispersion of wet milling nanocurcumin exhibited potent activity against a number bacteria (*S. aureus*, *Bacillus subtilis*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Penicillium notatum*, and *Aspergillus niger*); however, it was more effective against Gram-positive bacteria than Gram-negative bacteria (112). Curcumin nanovesicles efficiently bind to the surface of bacteria and reduce their counts from 5 log CFU mL⁻¹ to an undetectable level, suggesting a novel approach for controlling microbial growth, cross-contamination, and biofilm formation (113).

A high curcumin-loaded and biodegradable *in situ* gel formulation is capable of inducing well tissue adhesiveness and releasing curcumin in a sustained manner that is suitable for wound healing application (114). This formulation proved to have *in vivo* wound healing activity that was determined by higher tensile strength and thicker epidermis. In addition, this gel formulation confirmed an increase in collagen content, granulation, wound maturity, and catalase while a decrease in superoxide dismutase. In a recent study, curcumin-encapsulated nanoparticles exhibited a dose-dependent inhibition of methicillin-resistant *S. aureus* and *P. aeruginosa* (115). The same formulation showed inhibited MRSA growth and enhanced wound healing activity in a murine wound model. A combination of curcumin nanoparticles with silver and chitosan formulation was successful in eradicating parasite from stool and intestine in *Giardia lamblia* cyst rat model (116). More importantly, this treatment did not show any signs of undesirable toxicity.

Ophthalmic

Beneficial effects of curcumin on several ocular diseases, including dry eye syndrome, glaucoma, age-related macular degeneration, and diabetic retinopathy suggest its implementation for ophthalmology (117). Initial studies were confirmed that curcumin in albumin or pluronic polymers (F127 and F68) have sol–gel transition with sustained curcumin release characteristics and were found to have no eye irritation in rats (118). This work prompted implementation for its ocular application. Pradhan *et al.* (119) successfully proved that retention of curcumin in the cornea can be accomplished with curcumin-loaded PEG-PCL nanoparticles. Curcumin formulation also suppressed the expression of vascular endothelial growth factor, inflammatory cytokines, and matrix metalloproteinases. Altogether, this study confirms a potential approach for prevention of corneal neovascularization.

Skin Diseases

Curcumin has been used since ancient ages as a beauty product, which suggests its implication in skin-related diseases. A β -cyclodextrin–curcumin nanoparticle complex improved permeability across skin model tissue in gel form 1.8-

fold over the free CUR gel (120). Another curcumin encapsulated in PVA nanoformulation showed no improved penetration in pig skin dermis *via* hair follicle (121). Ethyl cellulose and methylcellulose blended curcumin nanoparticles can be used to transport curcumin effectively into the porcine ear skin (122). Biocompatible curcumin-loaded phospholipid vesicles can counteract on phorbol ester 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced lesions and inflammation (123). This was confirmed by an extensive re-epithelization of the TPA-damaged skin. Additionally, this formulation was proven to form skin lesion abrogation, which causes epithelial loss and skin damage. Furthermore, an encapsulated curcumin nanoparticle formulation penetrates into the skin and subsequently reduces UVB-irradiation-induced radical formation more than free curcumin (124).

Malaria

The World Health Organization estimates that about half a million deaths occur due to malaria, which is caused by a parasite called *Plasmodium* (transmitted *via* the bites of infected mosquitoes). Parenteral administration of lipid-based curcumin nanoparticles in an *in vivo* model resulted in a 2-fold increase in anti-malarial activity over free curcumin (125). Furthermore, a novel PEGylated liposome-based curcumin nanoformulation provided the most pronounced and statistically significant therapeutic benefit in *in vivo Plasmodium berghei* NK-65-infected (murine model of malaria) mice (126). Chitosan-bound curcumin nanoformulation inhibited hemozoin synthesis, which is lethal for the parasite (127) suggesting its anti-malarial activity. The mice infected with a lethal strain survive for five more days upon treatment with this nanoformulation.

Cystic Fibrosis

Cystic fibrosis is also a common life-threatening disease and has evolved mainly due to mutations in the gene encoding (primarily $\Delta F508$) the cystic fibrosis transmembrane conductance regulator (CFTR), which causes retention of $\Delta F508$ -CFTR in the endoplasmic reticulum and frontrunners for absence of CFTR Cl⁻ channels. This phenomenon can be corrected by curcumin treatment (128,129). A PLGA-based curcumin nanoparticle formulation has been able to correct the defects associated with cystic fibrosis in two different mouse strains (130). A formulation with a blend of PLGA-*b*-PEG-triphenylphosphonium is capable of targeting mitochondria and demonstrates its adaptability for mitochondrial-associated diseases (81).

Osteoporosis

Cyclodextrin-conjugated gold nanoparticles self-assembled with curcumin formulation significantly inhibited osteoclast formation of bone marrow-derived macrophages *via* suppression of the receptor activator of nuclear factor- κ B ligand-induced signaling pathway (131). The *in vivo* results in an ovariectomy-induced osteoporosis model demonstrate that this formulation improved bone density and prevented its loss.

Human immunodeficiency virus (HIV)

Incompatibility of rigid implants and the soft brain tissue results in oxidative stress that leads to the neurodegenerative reactive tissue response. Curcumin-releasing softening polymer implants not only cause minimal implant neuroinflammation but also utilize a new concept of localized curcumin delivery (132). Sankar *et al.* (133) further proved that curcumin nanoformulation significantly decreased the lipid peroxidation and increased the enzymatic and nonenzymatic anti-oxidants (glutathione content, superoxide dismutase, catalase, glutathione peroxidase, and glutathione reductase) in brain and prevented arsenic-induced oxidative damage. A simple and direct nose-to-brain delivery of curcumin nanoformulation with poly(*N*-isopropyl acrylamide) has been developed (134). Gandapu *et al.* (135) developed apotransferrin tagged curcumin nanoparticles by sol-oil chemistry for improved uptake in T cells through transferrin-mediated endocytosis, which shows a higher anti-HIV activity nanocurcumin (IC₅₀) <1.75 μ M compared to sol-curcumin (IC₅₀)=5.1 μ M). This is attributed to prominent inhibition of HIV-1-induced expression of Topo II α , IL-1 β , and COX-2 and blocking the synthesis of viral cDNA in the gag region.

EXPERT OPINION

Although curcumin is a food additive that is widely consumed worldwide on daily basis, there are concerns about its bioavailability, a suboptimal pharmacokinetics, and minor side effects. It is important to improve these features and overcome those unforeseen side effects by encapsulating or by adding ingredients or excipients that help curcumin's overall stability. However, an investigational new drug application is required for conducting any clinical trials. Since parent curcumin is widely consumed by humans, there may not be any major restriction by USFDA. Food-based curcumin nanotechnology is likely to be approved as an alternative therapeutic modality in the near future and may have a significant impact in daily lifestyles. The clinical translation of curcumin nanoformulations can be possible with expertise from various disciplines, e.g., biologists, nanotechnologists, pharmaceutical scientists, and pre-clinical and clinical personnel. However, the goal is that such renewed interest in curcumin nanotherapeutic approaches will lead toward generation of new formulations for various disease treatments with minimal adverse effects.

The overall aim of the development of curcumin nanoformulations is to either prevent or slow down the development, which potentially lowers the incidence and burden, of disease. It is also important to understand the molecular mechanisms of curcumin nanoformulations in addition to the native curcumin molecule. It is also advised to examine and compare the therapeutic outcome of curcumin nanoformulations with the existing conventional therapeutic modality.

A comparative mechanistic approach should be implemented to learn how these curcumin nanoformulations enhance the therapeutic activity and control the progression, recurrence, metastases, and disorder of diseases. All these preliminary examinations will be helpful in identifying a

suitable curcumin nanoformulation that has predicted optimal loading, release, and targeting capacity. Many physiological barriers certainly hinder the penetration of curcumin nanoformulations deep inside the disease area and performance of its activities. Often, such circumstances lead to limited drug supply and accumulation, which cause cells to develop resistance. In the case of a highly fibrotic condition, design of curcumin nanoformulations composed of collagen or fibrotic tissue dissolution agent/inhibitors or tumor-penetrating peptides along with an antibody-guided targeted manipulation helps to deliver curcumin deep into disease tissue in a step-wise manner. Additionally, recent developments have revealed that multiple drugs or a drug with siRNA/miRNA molecule delivery through nanoparticles modulates the microenvironment and offers a better therapeutic index. Therefore, developing such novel composite systems would help to improve patient compliance by reducing side effects and increasing potential benefits.

CONCLUSION

Curcumin is an inexpensive polyphenol extracted compound from *curcuma longa* that is abundantly available and nontoxic with exhibited medicinal opportunities. A number of *in vitro*, *in vivo*, and clinical trial investigations have provided evidence for the bioactive role of curcumin in the prevention and treatment of various human diseases. Several curcumin nanoformulations discussed in this review efficiently tackle various signaling pathways that are linked to various human diseases. Most of these studies have been conducted only in pre-clinical animal models, and therefore, a main shortcoming is our lack of understanding of curcumin nanoformulation risks in humans. Clinical trials confirm that curcumin nanoformulations improve curcumin bioavailability and are systemically safe. However, testing of these formulations as therapeutic modalities is highly desirable and is crucial for future clinical trials and for human use. In addition, implementation of curcumin nanoformulations as combination agents is appropriate for reducing the dose of the main therapeutic agent, which can result in enhanced therapeutic efficacy while reducing systemic toxicity.

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Conflict of Interest Authors declared no conflicts of interest.

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