EXPERT OPINION

Emerging role of nanocarriers to increase the solubility and bioavailability of curcumin

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Introduction: Curcumin is a safe, affordable and natural bioactive molecule of turmeric (*Curcuma longa*). It has gained considerable attention in recent years for its multiple pharmacological activities. However, its optimum pharmaceutical potential has been limited by its lack of aqueous solubility and poor bioavailability. To mitigate the above limitations, recently various nanostructured water-soluble delivery systems were developed to increase the solubility and bioavailability of curcumin.

Areas covered: Major reasons contributing to the low bioavailability of curcumin appear to be owing to its poor solubility, low absorption, rapid metabolism and rapid systemic elimination. The present review summarizes the strategies using curcumin in various nanocarrier delivery systems to overcome poor solubility and inconsistent bioavailability of curcumin and describes the current status and challenges for the future.

Expert opinion: The development of various drug delivery systems to deliver curcumin will certainly provide a step up towards augmenting the therapeutic activity of curcumin thereby increasing the solubility and bioavailability of curcumin. However, the future of such delivery technology will be highly dependent on the development of safe, non-toxic and non-immunogenic nanocarriers.

Keywords: absorption, bioavailability, curcumin, metabolism, nanocarrirer, poor solubility

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1. Introduction

Curcumin is a low molecular weight, bioactive polyphenol isolated from the rhizome of the turmeric plant (*Curcuma longa*). Chemically, it is a *bis*-α,β-unsaturated β-diketone and show signs of keto-enol tautomerism. It has a predominant keto form in acidic and neutral solutions and a stable enol form in alkaline media (**Figure 1**) [1,2]. Commercial curcumin is a mixture of curcuminoids, containing approximately 77% diferuloylmethane, 18% demethoxycurcumin and 5% *bis*-demethoxycurcumin (BDMC) [3]. Preclinical and clinical studies suggest that curcumin has prospective therapeutic significance against most chronic diseases including cancer, neurological, cardiovascular, pulmonary, metabolic and psychological diseases [4,5]. Extensive research within the last half century on curcumin has proven that it is a molecule with anti-oxidant, anti-inflammatory and antitumorigenic properties [6,7]. These pleiotropic activities of curcumin attributed to its aptitude to modulate multiple signaling pathways at multiple levels such as transcription factors (nuclear factor-kappaB (NF-κB) and activator protein 1 (AP-1)), enzymes (cyclooxygenase-2 (COX-2), matrix metalloproteinases (MMPs)), cell cycle arrest (cyclin D1), cell proliferation (EGFR and Akt), survival pathways (β-catenin and adhesion molecules), cytoprotective pathways (Nrf2), etc. [7,8]. Additionally, curcumin is also known to downregulate the intracellular levels of three major ABC drug transporters, P-glycoprotein (P-gp), MRP-1 and

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Article highlights.

- The optimum pharmaceutical potential of curcumin has been limited by its lack of aqueous solubility and poor bioavailability.
- To mitigate the above limitation, current trends in curcumin research mainly focus on adjuvant therapy and the use of curcumin analogs.
- Different nanostructure water-soluble delivery systems for curcumin provide promising prospects for improving the solubility and bioavailability of curcumin.
- These carrier systems are actively engaged in improving the stability, solubility, absorption and therapeutic action of the curcumin within the disease tissue and permit long-term release of the drug at the target site.
- Systematic investigations on physicochemical, physiological properties and non-toxicity issue may lead to the introduction of different novel formulations of curcumin for clinical applications against various diseases.

This box summarizes key points contained in the article.

ABCG2 that are important in multidrug resistance (MDR) [9]. Systemic toxicity at high dose renders other therapeutic drug unsuitable for disease treatment conversely; various animal models and human studies interestingly established the fact that curcumin is extremely safe even at very high doses of treatment [10].

The pharmacological safety and efficacy of curcumin rendered it a prospective compound for the treatment and prevention of wide variety of human diseases. In spite of its efficacy and safety, it has shown limited pharmaceutical role because of its extremely low aqueous solubility, rapid systemic elimination, inadequate tissue absorption and degradation at alkaline pH, which severely curtails its bioavailability [2,11]. Some proof-of-concept studies have demonstrated that aqueous solubility of curcumin is very low (i.e., 0.0004 mg/ml at pH 7.4) and it is extremely sensitive at physiological pH. The authors including others have extensively shown the low solubility, instability and low bioavailability of curcumin after systemic administration. Irrespective of the route of administration, curcumin has been showing poor bioavailability both in animals and human [12,13]. In this regard, Wahlstrom and Blennow demonstrated that administration of 1 g/kg curcumin orally to rat results in rapid excretion of 75% curcumin in the feces along with a marginal amount in urine and blood plasma [14]. Concurrent to above study, the animal studies conducted by the authors also demonstrated undetectable range of curcumin from serum (~ 0.006 µg/ml) following 6 h intravenous systemic administration of native curcumin at a dose of 30 mg/kg in mice [12]. In summary, the relative solubility and bioavailability of curcumin has been highlighted as a major problem which hinders the use of such novel drug to exert its maximum therapeutic activity against various diseases.

To this end, current trends of curcumin research have been engaged to find out a solution to overcome the drawbacks associated with conventional curcumin delivery, such as low solubility and low systemic bioavailability. In this regard, various strategies such as adjuvant therapy and the use of curcumin analogs have been launched in scientific research [15,16]. Leaving behind the alternative strategies, nanotechnology offers various unprecedented smart drug delivery systems for curcumin that have been actively engaged in improving the solubility, stability, absorption and therapeutic action of curcumin against various diseases and additionally permit long-term release of drug for effectual therapeutic activity [17-20]. In this context, nanoengineered delivery systems for curcumin such as liposome, micelles, dendrimers, nanoparticles (NPs), magnetic nanoparticles (MNP), solid lipid NPs (SLNs), nanoemulsion and hydrogel NPs have already been developed for successful treatment against various diseases (**Figure 2**) [21-24]. Moreover, enhancement of solubility and bioavailability of curcumin by the advent of various nanodelivery systems is currently subjected to several novel formulations for commercialization (**Table 1**). Some of other commercially available nanoformulations of curcumin have been reported earlier by Yallapu *et al.* [25]. Thus, the purpose of the current review article is to discuss the common challenges associated with conventional curcumin delivery and address the current novel nanocarriers used for curcumin delivery with an evidence of increased solubility and bioavailability and the novel applications for step-up therapy.

2. Disease targets of curcumin

Traditional medicine serves as a fertile ground for the source of modern medicines [26]. The plant product curcumin, a yellow coloring agent present in the spice turmeric (*C. longa*), falls into this category. Curcumin, the active component of turmeric has been reported to play a major role in preventing various diseases [5]. For instance, curcumin was found to correct cystic fibrosis (CF) through opening of the cystic fibrosis transmembrane-conductance-regulator channels (CFTR) [27]. CF is caused by loss-of-function mutations in the CFTR chloride channel. The most common mutation entails the deletion of a phenylalanine in position 508 ($\triangle$F508) that causes protein misfolding and abnormal CFTR processing [28]. Curcumin, is a non-toxic low-affinity SERCA (sarco endoplasmic reticulum calcium ATPase) pump inhibitor and studies have shown it to be capable of correcting the defect in cell lines and mice expressing mutant $\triangle$F508 CFTR [27]. Another life-threatening disease getting beneficial effect from curcumin is inflammatory bowel disease (IBD). Targeted therapy with infliximab have shown success in treating IBD, however, widespread use of infliximab is limited because of many adverse effects associated with it [29,30]. In this setting, curcumin has shown tremendous improvement in the treatment of IBD [30]. Holt *et al.* conducted a small, open-label, pilot study of curcumin in five patients with ulcerative colitis and five patients with Crohn's disease, in which they documented an improved response of

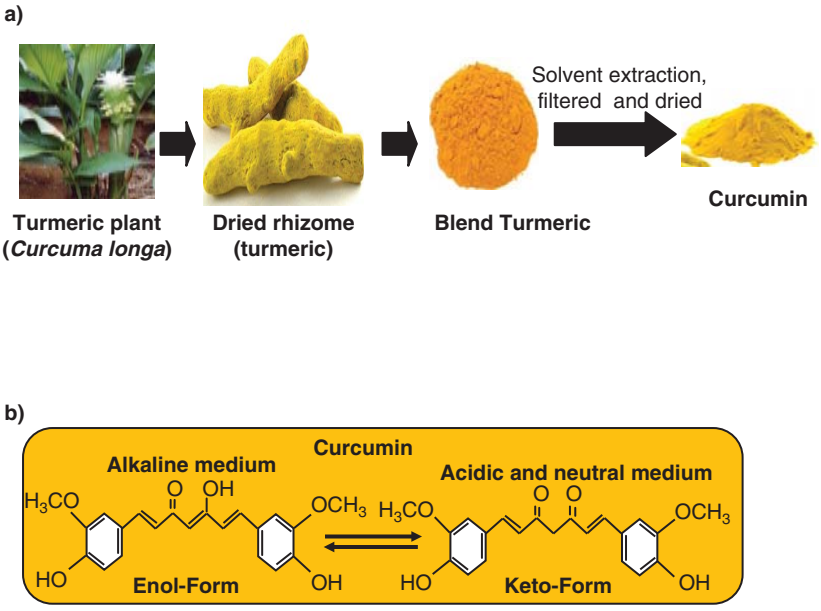

Figure 1. A. Extraction of curcumin from the rhizome of the turmeric plant (*Curcuma longa*). **B.** The chemical structure of curcumin showing keto-enol tautomerism at different medium.

the patient towards curcumin treatment with lower relapse rate [31]. Curcumin's ability to prevent myocardial infarction and other cardiovascular diseases has also been demonstrated [32-34]. The effects of curcumin in cardiovascular diseases are linked to its ability to i) inhibit platelet aggregation, ii) inhibit inflammatory response, iii) inhibit fibrinogen synthesis and iv) inhibit oxidation of low-density lipoprotein (LDL) [35]. The beneficial effect of curcumin has also been documented in various neurological disorders [36]. Parkinson's disease (PD), an age-associated neurodegenerative disease, arises due to selective degeneration of dopaminergic neurons in the substantia nigra of the ventral midbrain thereby depleting the dopamine levels in the striatum. Most of the current pharmacotherapeutic approaches in PD aim to replenish the striatal dopamine, however, it lacks neuroprotective effect. Consequently, novel therapies involving natural antioxidants and plant products/molecules with neuroprotective properties have been exploited for adjunctive therapy. Several studies in different experimental models of PD, strongly support the clinical application of curcumin in this neurological disorder. In light of this, Gadad *et al.* synthesized curcumin-glucoside (Curc-gluc), a modified form of curcumin and demonstrated that addition of Curc-gluc inhibits aggregation of α-synuclein, whose aggregation is centrally implicated in PD [37]. Alzheimer's disease (AD), a progressive neurodegenerative brain disorder, is affecting more and more elderly all around the world [38]. Amyloid-β (Aβ) plaques, widely accepted as the key pathological feature of AD, are mainly constituted by aggregation of the Aβ peptide derived from the amyloid precursor protein (APP). In a mutant APP transgenic plaque-forming animal model, curcumin has been shown to reduce amyloid plaques and accumulated Aβ [39]. Curcumin has also been shown to play a role in diabetes mellitus type II, in which the patients develop a resistance to insulin [40-42]. Several animal studies have demonstrated that curcumin can overcome insulin resistance [43]. Besides, curcumin has been shown to be effective against different skin diseases including psoriasis, scleroderma and dermatitis [44]. Cancer is a life overwhelming thereat that needs serious attention. Chemotherapeutic treatment regimens are frontiers in cancer treatment; however, multifaceted side effects associated with most of the chemotherapeutic agents limit their therapeutic ability. In this setting, studies are being carried out to exploit the therapeutic capability of many phytochemicals to establish a therapeutic approach with less or limited toxicity. In view of this, curcumin holds tremendous potential, as this molecule is well known for its ability to suppress cellular transformation, proliferation, invasion and metastasis [45]. Various *in vitro* studies conducted by the authors and *in vivo* studies performed by others clearly reveal the therapeutic benefits of curcumin in diverse cancer types [17,46-50]. Development of drug resistance against most of the available chemotherapeutic agents represents a foremost hurdle in cancer treatment. In this setting, Misra and Sahoo documented the use of curcumin as chemosensitizer to potentiate the efficacy of doxorubicin in leukemia therapy [50]. All these preclinical data indicate that curcumin has potential therapeutic value against diverse chronic diseases.

3. Problems associated with curcumin delivery

Ongoing research over the last half century has demonstrated that curcumin shows restrictive pharmacological activity in

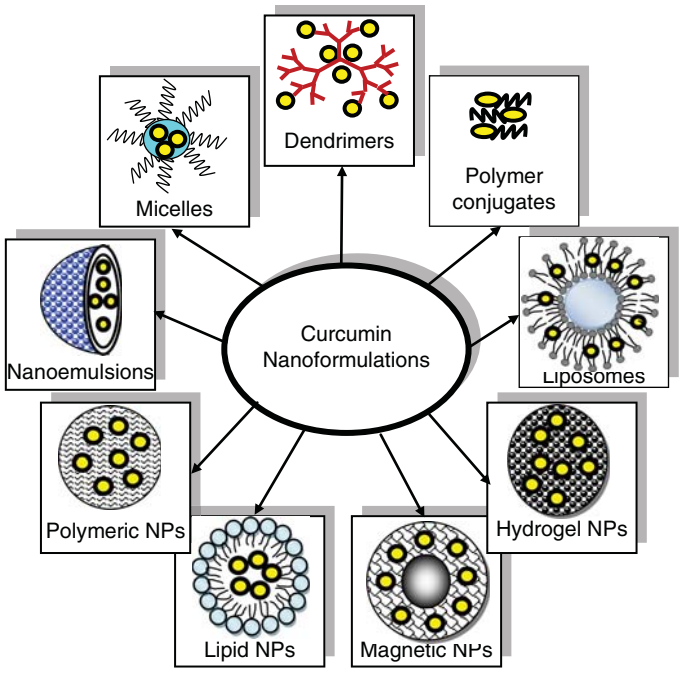

Figure 2. Schematic representation of different nanotechnology-based delivery systems for curcumin. Curcumin-loaded polymeric nanoparticles (NPs) are small colloidal particles encapsulated with curcumin in polymer matrix. Curcumin-loaded lipid NPs are made up of solid lipids, coated with surfactant (for stabilization) and encapsulate curcumin within its core. Magnetic NPs are nanometer-sized ferrite or magnetite (Fe_3O_4)-based spherical particles, coated with various hydrophilic polymers for entrapment of curcumin. Curcumin-loaded hydrogel NPs are the combination of a hydrogel system (e.g., hydrophilicity and extremely high water content) with curcumin. Curcumin-loaded liposomes are lipid bilayer structures in which curcumin can be loaded. Curcumin polymer conjugate system is a polymeric drug carrier in which curcumin covalently conjugates to polymer thereby increasing its stability and solubility. Curcumin-loaded dendrimers are monodispersed symmetric macromolecules, where curcumin can be loaded in internal cavity or can be conjugated with the reactive end groups. Curcumin-loaded polymeric micelles made up of block copolymer with an inner hydrophobic core containing curcumin. Curcumin-loaded nanoemulsions are of 50 – 200 nm size range oil-in-water type of emulsion containing curcumin.

clinical setting owing to its poor solubility, poor absorption and rapid metabolism, which consequently curtails its bioavailability. A clear concept regarding the limitation allied with conventional curcumin delivery and its consequent reduced therapeutic efficacy in clinical set-up has been schematically illustrated in **Figure 3**. Due to the immense interest in curcumin over the past decade, enough data have been accumulated on these limiting parameters from studies performed on animal and human subjects. This section briefly describes the major limitations associated with conventional curcumin delivery.

3.1 Solubility and degradation

Aqueous solubility of any therapeutically active substance is a key property, as it governs dissolution, absorption and thus the *in vivo* efficacy. As a hydrophobic polyphenol, curcumin shows limited solubility in water (i.e., 0.0004 mg/ml at pH 7.4), though it is slightly soluble in methyl alcohol, and highly soluble in dimethyl sulfoxide (DMSO) and chloroform [5,11,51]. So, owing to its extremely low solubility in water, curcumin has not yet shown its expected therapeutic efficacy at clinical level. In this regard, Tonnesen *et al.* prepared cyclodextrin complexes of curcumin to improve the water solubility and the hydrolytic and photochemical stability of the compound. They demonstrated complex formation that resulted in an increase in water solubility at pH 5 by a factor of at least 10^4 times [52]. Moreover, various novel drug-delivery approaches, including microemulsions, nanoemulsions, micelles and self-microemulsifying drug-delivery systems have been used to enhance the bioavailability and tissue-targeting of curcumin [25]. These attempts have revealed promising results for enhanced bioavailability and targeting to the disease site. However, curcumin has also shown poor stability to light. On exposure to light it decomposes and degrades into vanillin, vanillic acid, ferulic aldehyde and ferulic acid [53]. Beside poor solubility and low stability in light, the other major challenges of curcumin are its instability and biodegradation in physiological pH. The alkaline degradation and instability of curcumin has recently been investigated by the authors. It was observed that native curcumin

Table 1. A list of several commercially available curcumin-loaded nanoformulations to treat different diseases.

Brand name	Company name	Delivery system	Disease
Theracurcumin™	P.L. Thomas & Co., Morristown, NJ, USA	NPs	Cardiovascular, digestive and bone health
NanoCurcuminoids™	Life Enhancement Products, Inc., Petaluma, CA, USA	SLNs	Anti-inflammatory and anti-oxidant
Genus Serum Curcumin	X-Lab (S) Pte. Ltd., Singapore	NPs	Anti-inflammatory and arthritis treatment, anti-oxidant Cardiovascular diseases
N-Curcumin	Roxbury London Remedies	NPs	Colon cancer and Alzheimer's disease

NPs: Nanoparticles; SLNs: Solid lipid nanoparticles.

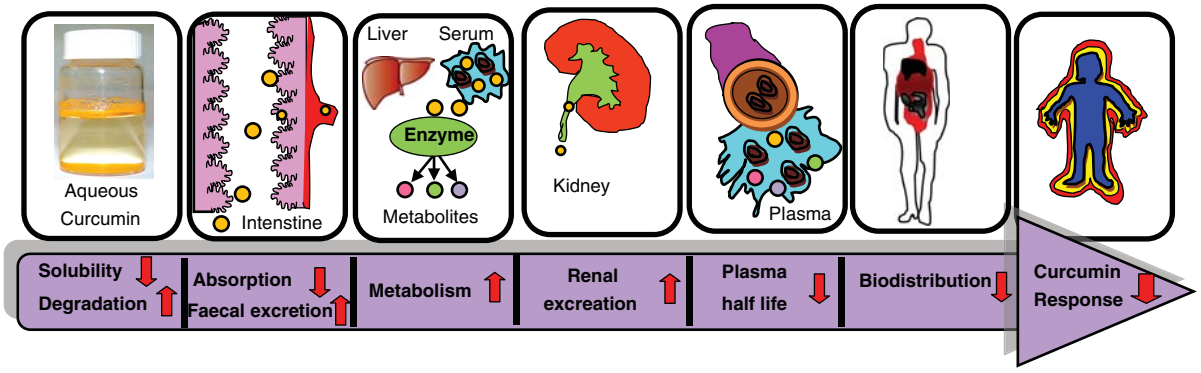

Figure 3. Schematic diagram showing the hurdles associated with delivery of native curcumin and these drawbacks promote low drug response in clinical set-up. Native curcumin is sparingly soluble in water and highly degradable in alkaline medium. On therapeutic application, it is not properly absorbed in the intestine and results in maximum fecal excretion. The proportion of curcumin absorbed by our body undergoes rapid metabolism and exerts maximum renal excretion. This results in low bioavailability and short half-life of curcumin in plasma which ultimately leads to its low biological activity.

underwent rapid degradation in phosphate-buffered saline (PBS) (0.01 M, pH = 7.4) and after 6 h incubation only 6% of curcumin was detected, as quantified by high-performance liquid chromatography (HPLC) analysis [12]. Generally, curcumin degrades rapidly within 30 min of placement in phosphate buffer systems of basic pH to *trans*-6-(4′-hydroxy-3′-methoxy-phenyl)-2,4-dioxo-5-hexanal, ferulic acid, feruloylmethane and vanillin [54]. It was further reported that the major degradation product of curcumin was *trans*-6-(4-hydroxy-3-methoxy-phenyl)-2,4-dioxo-5-hexenal and the minor degradation products were vanillin, ferulic acid and feruloyl methane [55]. In this regard, immense studies on curcumin conclude the fact that the optimum potential of curcumin is being limited due to its lack of solubility, stability and high degradation at physiological condition.

3.2 Metabolism and half-life

In vivo low bioavailability of curcumin in various animal studies supports the fact that curcumin undergoes metabolism on systemic administration. Once it is absorbed by the body, it starts rapid metabolism via conjugation (glucuronidation and sulfation) and reduction followed by fast systemic elimination [56]. The conventional mode of curcumin administration, formation of major metabolites and different elimination pathways are schematically represented in **Figure 4**. The biodistribution study on rat conducted by Wahlstrom and Blennow reported for the first time that the rapid metabolism of curcumin takes place when given orally [14]. It is now almost certain that the intestinal tract plays an imperative role in the metabolic disposition of curcumin. The first evidence to support the fact was conducted by Ireson *et al.* In their study, [^{3}H]-labeled curcumin was incubated with inverted rat gut sacs and observed that curcumin underwent extensive metabolic conjugation and reduction in the gastrointestinal tract [57]. Fast elimination/clearance of curcumin from the body also holds major pitfall that results in relatively low biological activity. Scientific research over the past decade has shown that oral route of administration of curcumin rapidly eliminates large quantities of curcumin and its glucuronidated, sulfated metabolites in urine. Furthermore, curcumin on intraperitoneal or intravenous administration is found to be excreted primarily in bile, mainly as tetrahydrocurcumin and hexahydrocurcumin glucuronides [2,58,59]. However, it is still ambiguous whether curcumin metabolites are as active as curcumin itself, since most studies indicate that curcumin glucuronides are

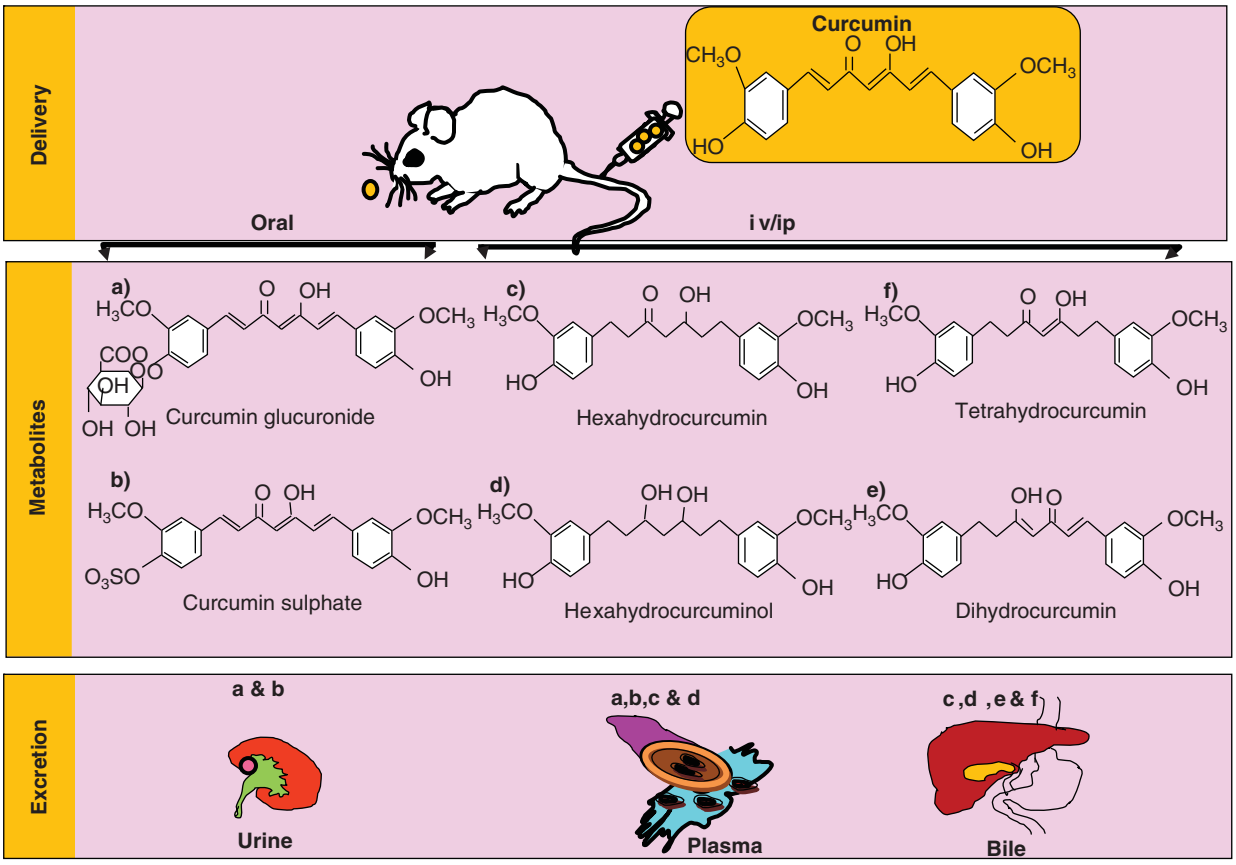

Figure 4. Metabolites and possible excretion pathways of curcumin. Oral route of administration of curcumin rapidly eliminates large quantities of curcumin and its *glucuronidated, sulfated* metabolites in urine. Furthermore, curcumin on intravenous or intraperitoneal administration is found to be excreted primarily in bile mainly as hexahydrocurcumin, hexahydrocurcuminol, tetrahydrocurcumin, dihydrocurcumin and their glucuronides. The metabolites like curcumin glucuronide, curcumin sulfate, hexahydrocurcumin and hexahydrocurcuminol are also found in plasma.

less active than curcumin [3,57]. Similarly, other studies also suggest that they may be more active than curcumin [60].

3.3 *In vivo* bioavailability

One of the greatest challenges of curcumin delivery involves defining its bioavailability and accessibility to disease tissue. Numerous publications have indicated that the inferior *in vivo* bioavailability of curcumin is owing to its poor solubility, poor absorption, high rate of metabolism, inactivity of metabolic products, rapid elimination and high clearance rate from the body. In a human clinical trial, patients received a daily dose of 8 g curcumin via oral route and a steady-state level of curcumin 22 – 41 ng/ml in plasma was evident by day 3 [13]. A recent study by Anand *et al.* showed that 2.5 mg/kg of curcumin given to mice by i.v. and after 30 min the maximum serum curcumin level was found to be ~ 320 ng/ml [61]. In a Phase I clinical trial involving curcumin dose escalation (from 0.5 to 8 g/day) study, no trace of curcumin was found in plasma of human patients. However, only trace amounts were detected in a minority of patients on 10 – 12 g of curcumin intake per day [10]. Further, low bioavailability of curcumin has also been well imparted in tissue biodistribution study. In a recent study, Pan *et al.* demonstrated insignificant amount of curcumin in the liver, kidneys, spleen, brain and intestines of mouse after 1 h administration of curcumin at a safety dose of 0.1 g/kg i.p. administration [62]. Study conducted by Kundu *et al.* using a mice model, a curcumin dose of 25 mg/kg via i.v. route showed a trace amount, that is, ~ 0.44 µg/g in brain tissue after 1 h of administration. These studies suggest that irrespective of the route of administration, the poor solubility of curcumin results in low absorption and consequently low bioavailability of curcumin at serum as well as at tissue level [17].

4. Different approaches and implications of nanotechnology platform to increase the solubility and bioavailability of curcumin

Some of the issues that are often considered central to the efficacy and usefulness of adopting a therapeutic regimen are its absorption, metabolism and eventual bioavailability in the target organs within the body. Although curcumin has

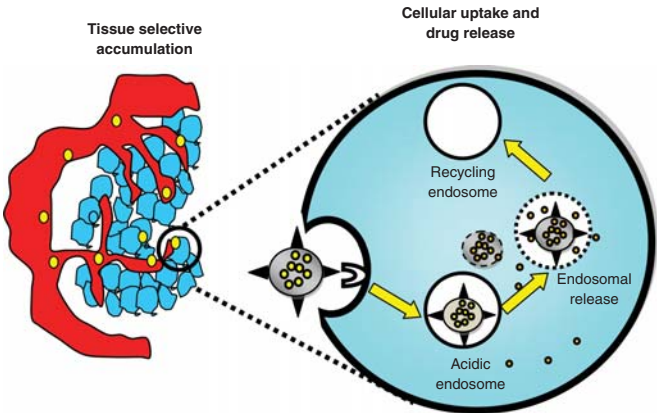

Figure 5. Schematic representation showing specific accumulation in targeted cells and internalization of drug-loaded NPs by receptor-mediated endocytosis. When the endosomal compartment acidifies, it gets accumulated in the cytosol and consequent sustained release of drug from NPs promotes stable accumulation and enhanced bioavailability of drug inside the cells.

been shown to modulate several targets that have been linked with cancer and various other chronic diseases, one of the most important limitations with curcumin is its poor bioavailability [11,16,47]. Whether performed in animals or human, studies have shown that when administered orally, curcumin is poorly bioavailable. The low bioavailability of curcumin is either due to i) hydrophobic nature of the molecule, ii) poor absorption, iii) rapid metabolism, iv) fast elimination [3,54,57]. Considering the relative importance of this natural molecule in diverse diseases, numerous approaches have been undertaken to enhance the bioavailability. These approaches involve i) the use of adjuvants, ii) use of curcumin derivatives, iii) the use of structural analogs of curcumin, iv) curcumin nanoformulations.

4.1 Adjuvant therapy

A major aspect in enhancing curcumin bioavailability is the use of adjuvant, which blocks its metabolic pathways. For instance, Shoba *et al.* examined the effect of piperine on the pharmacokinetics of curcumin in animals and human volunteers [15]. Their result clearly indicates an improved bioavailability, enhanced absorption and reduced clearance of curcumin when administered with piperine in comparison with only curcumin. In another study, Antony showed that in comparison with native curcumin in human volunteers, curcumin prepared from a formulation of curcuminoid with the essential oil of turmeric showed enhanced bioavailability [63]. With a view to improve the bioavailability of curcumin, the same group developed a formulation of curcuminoid and sesquiterpenoids present in turmeric (Biocurcumax™), and investigated its bioavailability in comparison with native curcumin and curcumin–lecithin–piperine formulation in human volunteers. The results of the study clearly indicate seven- and sixfold increase in bioavailability of Biocurcumax ™ compared with native curcumin and curcumin–lecithin–piperine formulation, respectively. Further, they also noted an improved absorption of curcumin in the form of Biocurcumax ™, than that of native curcumin or curcumin–lecithin–piperine formulation [64].

4.2 Curcumin derivatives

The chemical structure of curcumin plays a pivotal role in its biological activity. For instance, isomerization has been proved to have an influence on antioxidant activity of curcumin [65]. Thus, researchers hope to achieve improved biological activity of curcumin by its structural modifications. Synthesis of curcumin derivatives is one such approach that has been investigated extensively to improve the stability and pharmacokinetics of curcumin. Compounds that retain the basic structural features of curcumin, such as the two dioxy-substituted benzene rings, the –C=C––CO––CH_2–CO–C=C-linker and the oxy substituents on the benzene rings, are designated as curcumin derivatives. The curcumin derivatives are generally synthesized by derivatization, starting from curcumin. For example, the phenolic hydroxy group may be acylated, alkylated, glycosylated, demethylated and amino acylated [66-70]. Recently, Pana *et al.* synthesized a novel curcumin analog (B06) that exhibited an improved pharmacokinetic and enhanced anti-inflammatory activity compared with curcumin in rat model [71]. Their findings suggest that the novel derivative B06 might be a potential therapeutic agent for diabetic complications via an anti-inflammatory mechanism. Traumatic brain injury (TBI) is a chronic disease associated with broad pathological abnormalities and there are no current efficient treatments available to counteract this disease. Recently, Wu *et al.* studied the neuroprotective ability of a curcumin derivative (CNB-001) to reduce the effects of experimental TBI [72]. Their findings suggest that curcumin derivative has protective role in animal models of neurodegenerative diseases, with enhanced brain absorption and biological

Table 2. Representation of different molecular targets modulated by various curcumin-loaded nanoformulations to treat different diseases.

Curcumin-loaded nanoformulation	Disease	Molecular target	Ref.
NPs	Pancreatic cancer	NF-κB	[12,61,113]
NPs	Glioblastoma	STAT3	[17]
MNPs	Leukemia	Bcr-Abl	[120]
PEGylated curcumin analogs	Inflammatory disease	Nrf2	[129]
Polymeric NPs	Brain tumor	Hedgehog path way	[130]
PLGA NPs	Alzheimer's disease	Nrf2	[131]
PLGA NPs	Leukemia	MDR (P-gp)	[50]
PLGA NPs	Retinoblastoma	MDR (MDR-associated protein, lung resistance-related protein)	[46]
PLGA NPs	Leukemia	Bcr-Abl	[132]

MDR: Multidrug resistance; MNPs: Magnetic nanoparticles; NF-κB: Nuclear factor-kappaB; NPs: Nanoparticles; P-gp: P-glycoprotein; PLGA: Poly(D,L-lactide-co-glycolide).

activity. In a recent investigation, Kim *et al.* developed a curcumin derivative named BDMC and studied its barrier protective activity in comparison with native curcumin [73]. Interestingly, the barrier protective activities of BDMC were better than that of curcumin, and the result suggests that it can be used as efficient therapeutic candidate for various systemic inflammatory diseases.

4.3 Curcumin analogs

Structural modification of curcumin represents a strategy to improve its stability and bioactivity. In this context, numerous structural analogs of curcumin have been developed till date to improve its bioavailability. Based on the previously reported literature, curcumin analogs can be broadly categorized as natural analogs and synthetic analogs. However, both of the structural modifications have resulted in its improved bioavailability.

4.3.1 Natural analogs

Turmeric contains three important analogs: curcumin, demethoxycurcumin (DMC) and BDMC [16]. Collectively called curcuminoids, the three compounds differ in methoxy substitution on the aromatic ring. Curcumin, DMC and BDMC exhibit cardioprotective, antidiabetic and nematocidal activities. Several *in vitro* and *in vivo* comparisons of therapeutic activity of curcuminoids have been reported in various disease conditions [3,74]. For instance, *in vivo* studies have shown that curcuminoids can act as an inhibitor of lead acetate Pb(II)-induced neurotoxicity in primary hippocampal neurons and the result clearly indicates that curcumin was the most effective as compared with others in neutralizing lead acetate-induced neurotoxicity [75]. A lesser known curcuminoid from turmeric is cyclocurcumin, first isolated and characterized by Kiuchi *et al.* [76]. Structurally, cyclocurcumin differs from curcumin in the β-diketone link. Studies have been performed to evaluate the beneficial effect of cyclocurcumin, however, not many biological studies on this molecule have been reported [77].

4.3.2 Synthetic analogs

During the last decade, synthetic modifications of curcumin, which were aimed at enhancing its bioactivities, have been intensively studied. The modification of the basic structure of curcumin can be achieved by acetylation, alkylation and glycosylation of the phenolic hydroxyl group as well as by alterations of the number of carbons in the middle linker chain. Glycosylation of the curcumin aromatic ring provides a more water-soluble compound with a greater kinetic stability and a good therapeutic index [78]. Recently, Liang *et al.* synthesized a series of β-diketone-excluding mono-carbonyl analogs of curcumin which exhibited enhanced stability *in vitro* and greatly improved pharmacokinetic profiles *in vivo* [79]. Their findings suggest that the analogs lacking the β-diketone moiety were more stable in neutral pH and the stability of curcumin could be enhanced through deleting the β-diketone moiety. Shibata *et al.* synthesized new analog of curcumin named GO-Y030 [(1*E*,4*E*)-1,5-*bis*-(3,5(*bis*-methoxymethoxyphenyl) penta-1,4-dien-3-one], which showed 30-fold greater growth suppression in colorectal cancer cell lines SW480, HT-29 and HCT116 [80]. The bioavailability of this analog was examined by *in vivo* studies using a mouse model harboring the germline mutation of Apc, and the result documented an augmented antitumor activity of GO-Y030 with concurrent increase in survival rate as compared with native curcumin. Mosley *et al.* prepared glutathione conjugates of curcumin named as EF-24-GSH having enhanced water solubility. However, anticancer potential of the new analogs remains more or less similar to that of parent molecule [81]. Recently, Al-Hujaily *et al.* investigated the antibreast cancer properties of novel curcumin analog 5-*bis*(4-hydroxy-3-methoxybenzylidene)-*N*-methyl-4-piperidine (PAC). Interestingly, PAC exhibited higher stability in blood and greater biodistribution and tumor bioavailability than curcumin in mice model [82].

4.4 Nanotechnology platform

Nanotechnology plays a crucial role in disease treatment and provides a solution to the problems involved in conventional

therapy. Nanomaterials are at the cutting edge of the rapidly developing era of nanotechnology and several decades of biomaterials research have lead to a progressively heightened interest in the use of biodegradable and biocompatible nanovehicles for drug delivery applications [22,24]. Recently, nanodelivery systems have received much attention to resolve the problems like solubility, bioactivity and bioavailability issues associated with most of the therapeutic agents. Various types of NPs, such as polymeric NPs, micelles, liposomes/phospholipids, nano-/microemulsions, nanogels, SLNs, polymer conjugates, self-assemblies and so on, are suitable for the delivery of an active form of curcumin to various disease tissues (**Figure 2**) [83]. Research efforts during the past decades demonstrate the significant exploitation of these carrier systems in improving the between solubility and pharmacokinetics, of curcumin, some of which has been discussed here.

4.4.1 *Solid lipid nanoparticles*

Among the most popular drug delivery systems, SLNs have emerged as promising approaches for poorly soluble drugs during the recent years [84]. Advantages of SLNs include their lipid composition from biodegradable and biocompatible materials, controlled release of payloads, protection of drugs from chemical degradation and enhanced drug solubility [85,86]. Use of SLNs to improve the bioactivity and bioavailability of various pharmaceuticals including curcumin has been documented in recent years. In this setting, Kakkar *et al.* tried to improve the bioavailability of curcumin by formulating a lipid-based nanoformulation and their findings reveal 39-fold enhancement in its oral bioavailability when incorporated in SLNs to that of native curcumin [87]. Recently, curcuminoids were reported to have a prominent antimalarial activity in both *in vitro* (chloroquine resistance and sensitive *Plasmodium falciparum* lab strains) and *in vivo* (*Plasmodium berghei*) studies [88,89]. To implement use of curcuminoids with enhanced bioavailability in malaria treatment, Nayak *et al.* formulated curcuminoid-based nanolipid carrier and their findings suggest a twofold increased survival of *P. berghei*-infected mice treated with curcuminoids-loaded lipid NPs as compared with native curcumin [90].

4.4.2 *Nanosuspensions*

Interest of pharmaceutical industry in nanosuspensions has resulted in several nanosuspension products in the market for poorly soluble drugs [91]. Nanosuspensions are submicron colloidal dispersions of nanosized drug particles stabilized by surfactants [92]. The advantages of nanosuspensions include: i) ability to enhance the solubility and bioavailability of drugs, ii) higher drug-loading capability, iii) ability to enhance the physical and chemical stability of drugs, iv) provides a passive drug targeting, vi) small-sized nanosuspensions render the possibility of intravenous administration [93]. Till date, nanosuspensions have been extensively developed for a wide range of drugs and interestingly, they have proven to be a better alternative over other approaches available for improving bioavailability of drugs with low solubility [91]. In this scenario, Gao *et al.* documented a novel nanosuspension of curcumin (CUR-NS) and studied its bioactivity and pharmacokinetics. The result clearly indicates that the solubility and dissolution of CUR-NS were significantly higher than those of native curcumin [94]. Pharmacokinetics and biodistribution results of CUR-NS after intravenous administration in rabbits and mice showed that CUR-NS presented a markedly improved pharmacokinetic property as compared with the native curcumin.

4.4.3 *Nanoemulsions*

Nanoemulsions are a class of extremely small droplets, usually in the range of 50 – 200 nm [95]. They have garnered considerable attention in research as well as in therapeutics due to their advantages like i) thermodynamic stability which provides significantly better stability over unstable dispersions, such as conventional emulsions and suspensions, ii) optical clarity, iii) ease of preparation and iv) unique property of behaving as super-solvent for solubilizing both hydrophobic and hydrophilic solutes. Further, because of the small droplet sizes, any drug molecules entrapped within nanoemulsions can be transported through the cell membranes much more easily, resulting in an increased therapeutic concentration in plasma and subsequently increase the bioavailability [96]. Since poor bioavailability is often cited as the major limitation for the use of curcumin, various research groups have tried to improve its bioavailability and activity via nanoemulsions. To develop soluble formulations of curcumin with enhanced solubility, bioavailability and photostability, nanoemulsions of curcumin (NE-Cur) were formulated by Onoue *et al.* [97]. In comparison with native curcumin, curcumin nanoemulsions exhibited marked improvement in solubility and ninefold enhancement of bioavailability in plasma following oral administration in rat model. In another investigation, Lin *et al.* explored nanoemulsions carrier system to improve the oral bioavailability of dibenzoylmethane (DBM), a β-diketone analog of curcumin in rat model.

The findings suggest an improved pharmacokinetic behavior of DBM, administered as nanoemulsions to that of conventional emulsions [98]. Recently, Yu and Huang developed an organogel-based NE-Cur, curcuminoid and documented the improved solubilization profile of curcumin *in vitro* and enhancement of plasma bioavailability in mice model [99].

4.4.4 *Hydrogel nanoparticles*

In recent years, hydrogel NPs have received considerable attention as one of the most promising nanoparticulate drug delivery systems owing to their unique potential via combining the characteristics of a hydrogel system (e.g., hydrophilicity and extremely high water content) with NPs (e.g., very small size). Several polymeric hydrogel nanoparticulate systems have been prepared and characterized, based on both natural and synthetic polymers. Hydrogels have been

attempted extensively to achieve ideal drug delivery systems with desirable therapeutic features [100]. In a recent investigation, Dandekar *et al.* formulated hydrogel NPs using a combination of hydroxyl propyl methyl cellulose and polyvinyl pyrrolidone to enhance absorption and delay in rapid clearance of curcumin [101]. Further, they tested the therapeutic efficacy of the curcumin nanoformulations as antimalarial system. *In vivo* antimalarial studies revealed significant superior action of curcumin-loaded nanoformulations as compared with native curcumin and indicated the potential of the formulation to be used as an adjuvant therapy for the treatment of malaria, along with the standard therapy. A vast exploitation of hydrogel NPs for improving the bioactivity and bioavailability of curcumin is lacking till date and further use of such carrier system is warranted in near future.

4.4.5 Phospholipid complex

Complexion of phospholipids with numerous therapeutic cargoes has provided dramatic bioavailability enhancement, faster and improved absorption [102,103]. With a view to improve the absorption profile and bioavailability, complexion of curcumin with phospholipid complex has been worked out in recent years. In this setting, complexation of curcumin with phosphatidyl choline (CU-PC) has been used by Gupta and Dixit to improve the pharmacokinetics and pharmacodynamics of curcumin [104]. The complex showed enhanced bioavailability, improved pharmacokinetics and increased solubility as compared with native curcumin. Recently, Marczylo *et al.* developed a phospholipid complex of curcumin (Meriva®) and a comparison of systemic bioavailability of curcumin with that of Meriva® was performed in rat model [56]. The results clearly indicate a fivefold increase of plasma bioavailability of curcumin in rat administered with Meriva® than that of native curcumin. Further in another investigation, Cuomo *et al.* explored the improved absorption and plasma bioavailability profiles of curcuminoid with Meriva® than that of unformulated curcuminoid mixtures [105].

4.4.6 Liposomes

Liposomes are simple, self-assembling systems that consist of a bilayer membrane surrounding an aqueous interior compartment. They are generally formed from naturally occurring phospholipids and cholesterol, rendering them readily biodegradable [106]. Liposomes have been designed to modulate properties such as elimination half-life, permeability, biodistribution, cellular penetration and targeting specificity [90,107]. Currently, most traditional anticancer drugs/therapeutic agents have been encapsulated in liposomes using different technologies and many of them have entered clinical trials or being marketed for human use [108]. In the context for improving the bioavailability and bioactivity of curcumin, recently Agashe *et al.* developed a liposomal carrier system for curcumin analog named CLEFMA (4-[3,5-*bis*(2-chlorobenzylidene-4-oxo-piperidine-1-yl)-4-oxo-2-butenoic acid]) and their result indicates an improved antitumor activity and bioavailability of CLEFMA-loaded nanoformulations than that of native curcumin [109]. Systemic administration of liposomal curcumin has shown an increase in bioavailability and tumor-suppressing effect in various cancers [110]. In a recent *in vivo* studies by Wang *et al.*, inhibitory effect of curcumin in liposomal formulation in xenograft tumor model was documented following intravenous administration [111].

4.4.7 Micelles

The widespread use of micellar drug delivery systems in recent times has shown significant contribution for delivery of curcumin. Micelles are made up of a hydrophobic core and a hydrophilic corona or shell. The hydrophobic core is meant to entrap and solubilize the hydrophobic drug like curcumin. In this system, curcumin can be partitioned in the hydrophobic domain and the outer hydrophilic layer can form a stable dispersion in aqueous media. In this regard, recently the authors developed a curcumin-encapsulated methoxy poly (ethylene glycol) (MePEG)/poly-ε-caprolactone (PCL) diblock copolymeric micelle and it has shown to increase the solubility and enhanced cytotoxicity compared with native curcumin in a panel of cancer cell lines *in vitro* [20]. Similarly, Bisht *et al.* formulated a curcumin-loaded *N*-isopropylacrylamide (NIPAAM), with *N*-vinyl-2-pyrrolidone (VP) and poly (ethyleneglycol)monoacrylate (PEG-A) micelle, which demonstrated enhanced bioavailability of curcumin in animal model due to its successful aqueous dispersion and enhanced cellular uptake [112,113]. Ma *et al.* in their study used curcumin-loaded poly(ethylene oxide)-*b*-PCL (PEO-PCL) amphiphilic block copolymer micelles and demonstrated comparatively better solubilization, stabilization and controlled release of curcumin in comparison with native curcumin [18]. In another study, the same group demonstrated increased *in vivo* bioavailability as well as tissue biodistribution after treatment with curcumin entrapped in polymeric micelles compared with that of solubilized curcumin in a rat model [114]. Song *et al.* also formulated a curcumin-loaded poly(D,L-lactide-co-glycolide)-*b*-poly(ethylene glycol)-*b*-poly(D,L-lactide-co-glycolide) (PLGA-PEG-PLGA) micelles and their study showed polymeric micelles increased the half-life of curcumin and higher amount of it was found to be distributed in lung and brain compared with the native curcumin treatment [115]. As polymeric micelles could solubilize the curcumin and provide better aqueous dispersion, recently different novel micellar carrier systems were formulated to extend its application to improve the bioavailability of curcumin and make the drug amenable to parenteral administration.

4.4.8 Dendrimers

Recently, dendrimers have gathered significant interest for prospective curcumin delivery. It is a novel macromolecular compound and possesses highly branched three-dimensional

polymer. It consists of an inner core and outer series of branches containing large number of terminal groups to which drug molecules can be attached. Recently, Abderrezak *et al.* prepared several dendrimers of different compositions mPEG-PAMAM (G3), mPEG-PAMAM (G4) and PAMAM (G4) to load hydrophilic drug (cisplatin) and different hydrophobic drugs like (resveratrol, genistein and curcumin). It has demonstrated that dendrimers with a hydrophobic interior and hydrophilic chain ends are able to solubilize hydrophobic compounds like curcumin effectively in aqueous solutions [116]. In another study, Shi *et al.* formulated a water-dispersed cystamine core PAMAM dendrimers conjugate with curcumin. Their preliminary *in vitro* biological studies demonstrated that the formulation efficiently stained and dissolved the amyloid fibrils in human heart tissue containing intercellular amyloid. It is to be noted that amyloid-β peptide (Aβ) aggregation is suspected to play an important role in Alzheimer's disease and amyloid deposits are also implicated in amyloid heart disease [117].

4.4.9 Nanoparticles

Recent trends of curcumin delivery mainly focus on the development of novel biodegradable NPs for effectual delivery. The recent reports have confirmed that curcumin-loaded glyceryl monooleate-based NPs could afford solubility as well as enhanced bioavailability of curcumin after systemic administration in mice. Encapsulation of curcumin in the formulated polymeric NPs resulted in an excellent aqueous solubility. On administrating curcumin intravenously at a dose of 30 mg/kg in mice, the results demonstrated nanoparticulate curcumin to be ~ 32- and ~ 1000-fold more bioavailable compared with native curcumin after 30 and 60 min administration [12]. The extension work further demonstrated that the mucoadhesive properties of the formulated lipid NPs could cross the blood–brain barrier and enhance the bioavailability of curcumin in brain tissue in comparison with native curcumin in a rat model [17]. Similarly, the study conducted by Suwannateep *et al.* showed that mucoadhesive curcumin nanosphere showed a dose-dependent *in vitro* cytotoxic effect toward MCF-7 human breast adenocarcinoma and HepG2 hepatoblastoma cells. Furthermore, the *in vivo* evaluation of their adherence to stomach mucosa and enhanced oral bioavailability prop up its applicability against various diseases [118]. Recently, Mazzarino *et al.* prepared curcumin-loaded lipid nanocapsules which demonstrated better efficacy in reduction of tumor volume in an animal model owing to its superior bioavailability [119]. The strength of nanodrug delivery systems lies in their ability to alter the pharmacokinetics and biodistribution of the drugs. Besides the successful applicability of various nanoparticulate drug delivery systems for therapeutic exercise, in recent years, different drug delivery system including NPs have been coupled to a variety of ligands for providing targeted treatment modality. These multifunctional NPs can be utilized for simultaneous targeting, imaging and therapy of diseases. Numerous NPs-based targeted or non-targeted curcumin delivery systems have been developed or are currently under development. The precise and selective binding of ligand to the receptors that are overexpressed on targeted tissue provides cell-specific delivery and could limit the toxicity and dose of drug administration for effective treatment. The ligand-based targeting of curcumin to disease tissue is illustrated schematically in **Figure 5**. In this regard, Mathew *et al.* recently developed curcumin–loaded PLGA NPs conjugated with Tet-1 peptide. Their study showed the ligand-conjugated NPs demonstrated effective delivery of curcumin to neuron and inhibited the amyloid aggregates, owing to anti-oxidative property of curcumin [19]. To date, numerous attempts have been made for disease-specific drug delivery and targeting, including the use of antibodies, aptamers, small molecules, etc. With regards to targeted curcumin delivery, few reports have come up; however, it is still an unexplored area and needs attention in near future to increase the bioavailability of curcumin thereby increasing site-specific targeted delivery.

4.4.10 Magnetic nanoparticle

Recently, significant attention has been given to superparamagnetic iron oxide NPs for diverse biomedical applications, such as contrast agents in magnetic resonance imaging, local hyperthermia and magnetic carriers in drug delivery systems. Moreover, the implementation of external magnet-based tissue targeting delivery was mostly successful in several animal studies. Recently, the authors developed an aqueous-based formulation of glycerol monooleate-coated magnetic NPs (MNPs) loaded with curcumin and surface conjugated with transferrin ligand. On *in vitro* condition, it has demonstrated better solubility and enhanced cellular uptake with higher cytotoxicity as compared with native curcumin in K562 cell line [120]. In a recent study, Yallapu *et al.* formulated MNPs by chemical precipitation method and loaded curcumin using diffusion technique. The formulated MNPs exhibited potent anticancer activity along with a contrast agent for magnetic resonance imaging in comparison with native curcumin, suggesting its importance in cancer treatment and cancer imaging in the near future [121].

4.4.11 Other nanoformulations of curcumin

Microemulsions are optically isotropic, stable mixtures of oil, water and surfactant in combination with a cosurfactant. Hydrophobic drugs like curcumin solubilizes mainly in oil droplets of oil-in-water microemulsions. It has many advantages which includes high solubilization potential, stability, improved drug dissolution and high permeability owing to the added surfactant. Recently, Setthacheewakul *et al.* formulated different self-microemulsifying drug delivery systems of curcumin. These formulations showed improved solubility and stability and demonstrated enhanced pharmacokinetics of curcumin following oral administration of the formulations compared with native curcumin in a rat model [122]. To increase the solubility and bioavailability of curcumin,

recently many attempts were done including curcumin self-assembly formation with cyclodextrin and other derivatives. In this regard, Yadav *et al.* prepared a cyclodextrin-complexed curcumin and their *in vitro* study demonstrated superior attributes of the formulation in KBM5 cell lines owing to its enhanced solubility and cellular uptake compared with free curcumin [123]. Cyclodextrin–curcumin complexes have demonstrated improved water solubility, stability and these have been effectively applied in medical, pharmaceutical and nutraceutical products [25]. Similarly, solid dispersion is another promising approach to increase the solubility and bioavailability of hydrophobic drugs such as curcumin. It is a solid product consisting of at least two different components that is a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. With a view to increase the physicochemical and pharmacokinetics profile of curcumin, the crystal and amorphous solid dispersion have also been designed by wet milling and subsequent freeze-drying method. Recently, Onoue *et al.* prepared water-soluble formulations of curcumin, including crystal/amorphous solid dispersions. Pharmacokinetics study in rat model after oral administration showed enhanced plasma curcumin concentration with high photochemical stability compared with native curcumin [97]. In another study, curcumin solid dispersion using Solutol® HS15 was prepared and the formulation has shown increased solubility as well as stability of curcumin. Also, in an animal study, it has demonstrated significant improved plasma bioavailability after oral administration [124].

5. Novel curcumin nanoformulations with improved solubility and bioavailability

Development of novel curcumin-based nanoformulations has emerged as putative approach for improving the stability, bioavailability and bioactivity of native curcumin. The sustained enhanced uptake and bioavailability of curcumin from these nanoformulations have been documented to regulate different signaling pathways that play central role in various diseases (**Table 2**). Further, several research efforts have been undertaken in this line and few are under clinical trials. For instance, in a recent study by Agashe *et al.*, curcuminoid CLEFMA entrapped liposomal formulation was prepared to improve the bioavailability of curcuminoid [109]. In nude rats bearing a H441 xenograft, about 94% reduction in tumor volume was evident following intravenous administration with CLEFMA liposomes. Further, the above formulations were devoid of any apparent toxicity issues in liver, lung, kidney, etc. as evident from histopathological examination. In a similar approach, Chin *et al.* formulated curcumin-based silica MNPs with cell-specific targeting ability [125]. Their findings suggest a 14- and 2.5-fold enhancement in mean residence time and bioavailability of curcumin, following intravenous administration of curcumin-entrapped MNPs compared with native curcumin in rat model. Kakkar *et al.* initiated to improve the bioavailability of curcumin by synthesizing lipid-based nanoformulations and their findings disclosed 39-fold enhancement in its oral bioavailability when incorporated in SNPs to that of native curcumin [87]. A novel CUR-NS was developed to increase the solubility, dissolution, pharmacokinetics and biodistribution of curcumin [94]. Further, complexation of CU-PC has shown improved pharmacokinetic and pharmacodynamic properties [104]. The complex showed enhanced bioavailability, improved pharmacokinetics and increased solubility as compared with native curcumin. In recent clinical trials in human volunteers, novel formulations of curcumin NPs (Theracurcumin™) have improved the pharmacokinetic properties of curcumin to many folds [126]. In the present scenario though, several novel curcumin nanoformulations have been documented for their putative role in improving the solubility, stability and pharmacokinetics of native curcumin; still a high-throughput research activity to develop more efficient curcumin-based nanocarriers are needed for better therapeutic approach.

6. Conclusion

Over the last few years, there has been an increased interest and extensive research on curcumin owing to its diverse pharmacological efficacy with no systemic toxicity even at a higher dose of administration. Despite its safety and efficacy, the short biological life and low bioavailability of free curcumin continue to be the major reasons for hindering the successful application of this molecule in clinical settings. Rapid development of new formulations of curcumin with the implementation of nanotechnology, currently play a unique and increasingly important role to enhance the solubility and bioavailability of curcumin. So far, various novel avenues of curcumin-loaded nanoparticulate delivery systems have been testified as competent nanoformulations to increase the solubility and bioavailability of curcumin. It is evident from the preceding discussion that these carrier systems are actively engaged in improving the stability, solubility, absorption and therapeutic action of the curcumin within the disease tissue and permit long-term release of the drug at the target site. Furthermore, the successful surface modifications and conjugation of targeting ligand will certainly enhance the solubility and bioavailability of this promising natural molecule for treatment of various diseases in near future.

7. Expert opinion

Over the past few decades, preclinical and clinical evidences suggest that the pathological mechanisms involved in chronic diseases are multifactorial and these conditions could be better addressed with a multitargeted rather than a monotargeted therapy. Natural products like quercetin, resveratrol, genistein, curcumin have already shown tremendous potential as multifaceted agent that can be used as next-generation

multitargeted therapeutic molecules in chronic diseases. Among these natural molecules, curcumin has been well investigated in diverse diseases by various groups and shown its potency in array of preclinical and clinical trials. In short, no compound better than curcumin exemplifies the biomedical relevance of multitargeted natural molecules in chronic diseases. Curcumin features a unique blend of Michael acceptor, metal chelating, anti-oxidant, antiproliferative, anti-apoptotic properties which make this molecule unique for various therapeutic purposes. However due to limited solubility, poor pharmacokinetic properties, poor bioavailability and low retention in the target tissue, the therapeutic usefulness of this novel molecule has been somewhat limited. Considering this, agents that can modulate multiple cellular targets and strategy that can achieve better therapeutic indices for these multitargeted molecules are now considered as attractive research leads. To this end, researches in diverse directions are actively undergoing to achieve a therapeutic approach that can overcome the shortcoming associated with native curcumin. For instance, various strategies like use of adjuvants, or development of novel curcumin analogs are under trial, however, a concrete solution to achieve an improved bioactivity, solubility and bioavailability for this novel molecule is not yet achieved. So, with a view to conquer the hurdles associated with curcumin, researchers have now started exploring nanotechnology-based different drug delivery systems. Curcumin-based nanoformulations have improved its solubility and pharmacokinetics properties and some of the nanoformulations are under clinical trials. This clearly indicates the tremendous possibility for improving solubility, bioactivity and bioavailability of natural drugs like curcumin by exploring nanodrug delivery vehicles. As some of the curcumin analogs have efficiently increased the bioavailability of curcumin, a combinational approach delivering curcumin analog by nanodrug delivery systems could result in better therapeutic approach. Targeted drug delivery of curcumin has not been well explored yet, therefore, surface functionalization of curcumin-loaded nanoformulations may pave a new way to achieve tissue-specific drug delivery. Though, nanotechnology-based delivery approach for curcumin to achieve improved bioavailability, solubility profile has shown tremendous potential in clinical settings, issues like safety, non-specific side effects and toxicity with respect to nanodrug delivery vehicles need to be addressed. For instance, two recent reports explored the carcinogenic risk of carbon nanotube on *in vivo* subjects, which revealed that on long-term use it might impair the biological system [127,128]. The interaction of nanodrug delivery systems with cells and tissues, and the potential toxicity mainly depends on the formulation of NPs and its composition. It is oblivious that the ideal candidate that constitutes the drug delivery system should be biodegradable, have appropriate degradation rate and the degradation product should be excreted from the body. Various components constituting the nanoparticulate delivery systems are still under investigation. Many carrier systems, which vary from biological substances like albumin, gelatin, phospholipids for liposomes and substances of chemical nature like various polymers and solid metals, are mainly under investigation. In this regard, there are still many unanswered questions about the fate of NPs introduced into the living body. These will require further studies before some of the products can be approved for clinical application.

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