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Nano Curcumin: Making it useful for Human Therapy

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Abstract

Curcumin, the polyphenolic pigment from turmeric has excellent therapeutic potential but due to poor aqueous solubility and metabolic instability, it has not yet been possible to use it as a drug. Structural studies have revealed that depending upon ambient pH, curcumin can remain in keto- enol tautomeric forms. The keto form is generated at acidic pH and due to the presence of the β-diketone motif in the molecule, the methylene group gets activated and can donate a hydrogen atom to reactive oxygen species which is responsible for its anti-oxidative properties. The enol form of curcumin which is present at alkaline pH becomes a planar molecule due to extensive delocalization of electrons from one aromatic ring to the other through the pi orbital of C=C bonds in the heptadione linkage. At alkaline pH, curcumin gets degraded to smaller molecules which have interestingly been shown to have therapeutic activity. Molecular interaction studies have identified the methylene group in the β-diketone domain and the methoxy as well as the phenoxy group on the aromatic rings of curcumin molecule to be the contact points with enzymes and signaling molecules and may be involved in inactivating them. The bioavailable forms of curcumin cited in this review have been formulated using curcumin entrapped or bound to polymeric nanoparticles, liposomes, phospholipid complexes, nanoemulsions, or polymeric micelles and have been tested against chronic inflammatory conditions in animal models or cell lines.

Keywords: Nano Curcumin, Nanoparticles, Liposomes, Neurodegenerative Diseases.

Introduction

Turmeric prepared from the rhizome of *Curcuma longa* plant has been used in Indian traditional systems of medicine for centuries for healing wounds, reducing pain, and as an anti-bacterial agent. But no one had any idea about the bioactive component of turmeric until the yellow pigment in the pure form was isolated by Vogel Jr.in 1842. This led to the elucidation of its chemical structure and naming it as curcumin by Milobedzka and Lampe [1]. Subsequently, fractionation by Srinivasan in 1953 showed that it consisted of three different molecules namely curcumin, demethoxycurcumin, and bis-demethoxycurcumin [2]. Recently by using better chromatographic techniques, suitable resins, and solvent systems a fourth molecule called cyclocurcumin has been added to this list **(Figure 1)** [3].

The development of sensitive methods of separation and mass spectroscopic analysis has revealed that turmeric has many more molecules with potential therapeutic activity. Except for very few none of those molecules has been studied extensively [4]. Once the method for isolation of curcumin from *Curcuma longa* extract was established, it became commercially available and many laboratories from different parts of the world got involved in evaluating its potential as a therapeutic agent against various pathogens and cancer cells in culture or in animal models. This generated a large body of interesting data. Knowing that curcumin has the potential to reduce inflammation, efforts are on to find whether curcumin can be developed into an adjunct drug to be used in chronic inflammatory diseases like cancer, neurodegenerative diseases, and arthritis in humans. However, for this to happen it would require determination of its pharmacokinetics and short term as well as long term toxicity in animals so that clinical trial in humans could be started to assess its safety and efficacy. To date, more than 200 clinical trials have been conducted using natural curcumin and it has been declared as "Generally Recognised as Safe" (GRAS). Thus it was found that an individual can take 12 grams of natural curcumin per day without any toxicity [5]. But curcumin is very poorly soluble (600ng/ml) in water and is metabolically unstable [6]. Therefore it could not fulfill the pharmaceutical requirement of proper absorption, distribution, metabolism, excretion, and toxicity (ADMET) to be developed into a drug. To overcome the disadvantages of poor bioavailability and metabolic instability of curcumin one has the option of either synthesing curcumin analogues with better aqueous solubility and resistance to enzymatic degradation and use them as drugs or prepare

nanotechnology enabled formulations of curcumin with increased bioavailability (Cmax) and sustained circulation in the blood (AUC, Area under the curve) and use them. Most researchers have preferred the nanotization approach so that nano curcumin can be prepared and administered orally for better bioavailability longer circulation in the blood and lesser toxicity [7]. It is apparent that Nanotechnology-based drug delivery systems can provide solutions for some of these problems. Analysis of published papers and the patents which have been filed shows how intense efforts are being made to find solutions to prevent or treat chronic inflammatory diseases like cancer, cardiovascular disorders and neurological disorders. These activities are being pursued worldwide, especially in USA, India, China, Europe and South Korea.

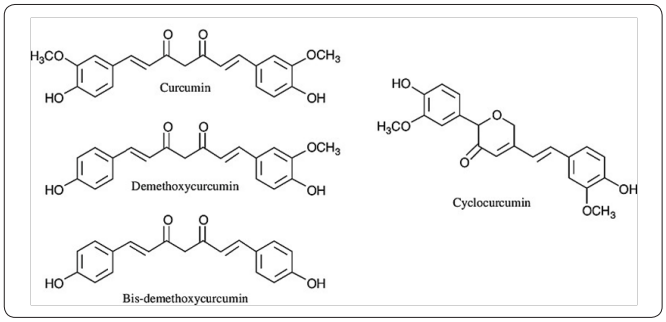

Figure 1: Molecules present in Curcumin.

It is observed that only Universities, Research Institutes and some small pharma companies are involved in doing research on nano curcumin and patenting them. No major pharma companies are involved in promoting nano curcumin yet. The first patent on nano-based curcumin was filed on November 7, 2000 [8] and the first research paper on nano-based curcumin for medicinal applications was published in the year 2005 [9].

In this review, we will very briefly present curcumin's chemistry and pharmacology and highlight efforts that have gone into making it into nano form with better bioavailability, so that its activity can be tested using cell lines and animal models. Our review has a special emphasis on how to develop it into a formulation that can be useful to humans. Since literature is vast and many excellent reviews have been published recently, we would mostly focus on nano-formulations which have been used with some success in disease models involving cell lines and animal models. We will also touch upon the structural features of curcumin which make it a unique molecule, its pharmacological properties, and the role its degradation products may be playing in curcumin's therapeutic activity.

Curcumin the Molecule

Structure-activity Relationship

Curcumin, IUPAC ID (1E, 6E)-1,7-bis (4-hydroxy-3-methoxyphenyl) -1,6- heptadiene-3,5- dione, is a bright yellow-orange powder with the molecular formula: C21H20O6, molecular mass: 368.38 g/mol, and melting point 183°C. Its two structural features namely a β-diketo domain with an active methylene group in between and two aromatic rings with phenolic and O- methoxy groups linked with a heptadiene linker. Extensive research during the past decades has provided evidence for the role of these different functional domains in the observed biological activities of curcumin [10]. Due to the presence of the methylene group with two active hydrogen atoms flanked by two keto groups, the hydrogen atom attached to the carbon atomcan migrate to the oxygen atom of the keto group generating the keto-enol tautomeric forms (**Figure 2**).

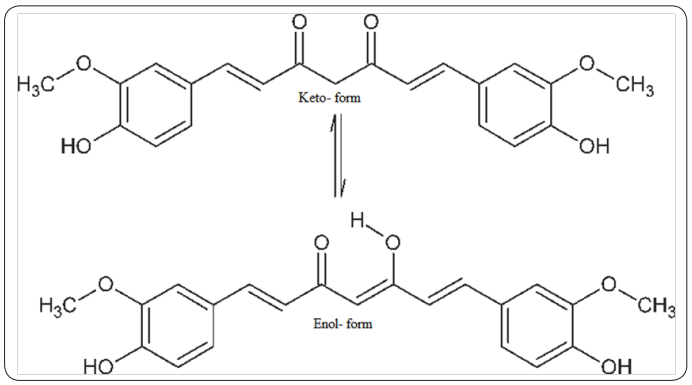

Figure 2: Keto-enol tautomerism of Curcumin

The keto form is found mostly embedded into the lipid bilayer of the membranes when the pH is between 3 to 7 and the enol form is found around pH 8. This keto-enol-enolate equilibrium of curcumin determines its physicochemical and antioxidant properties [12]. It is interesting to note here that when curcumin is present in the enol form both the aromatic rings present at either end of the molecule can interact with each other through extensive delocalization of electrons through the pi orbital of C=C bonds in the heptadiene linkage. Due to these structural constraints, the aromatic rings at either end of the molecule will have to be in the same plane and the whole molecules becomes planar. Such a molecule will have the propensity to bind to a large number of proteins circulating in the blood [13]. The keto form will be flexible due to the freedom of rotation of c-c bonds present in the molecule (**Figure 1**).

The two aromatic rings with hydroxyl and O-methyl groups can be in different planes and can interact with other molecules independent of each other. The keto form shows different physiological properties while the enol form which is constrained to be planar undergoes degradation fast.

When curcumin in the native form is administered into the body either orally or by intraperitoneal injection it is rapidly eliminated from the body because of its low solubility which leads to diminished absorption and extensive systemic clearance due to its degradation or metabolic conversion to more water-soluble molecules which are secreted rapidly. Curcumin is enzymatically converted to more soluble forms like glucuronide and sulfate conjugates or reduced to tetrahydrocurcumin and hexahydrocurcuminglucuronides in the gut [14] (**Figure 3**).

The basic antioxidant activity of curcumin is directly dependent on the presence of hydrogen on the phenolic groups or the central-

methylene groups.

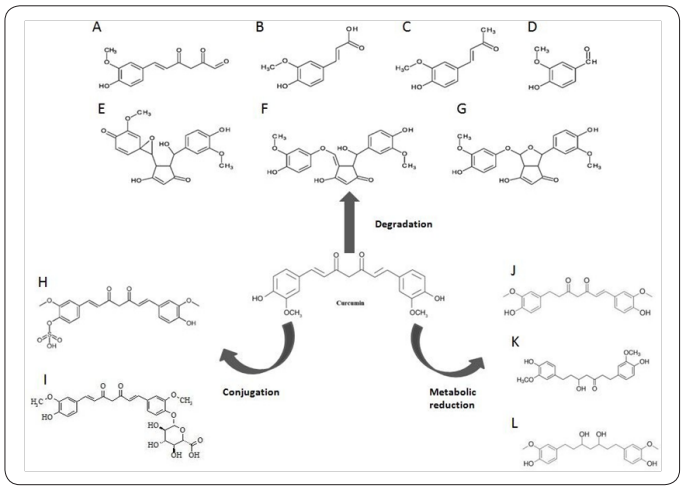

Figure 3: Degradation products of Curcumin A) Trans-6-(4-hydroxy-3-methoxyphenyl)-2, 4-dioxo-5-hexanal B) Ferulic acid C) Feruloyl methane D) Vanillin E) Spiroepoxide F) Vinylether G) Bicyclopentadione H) Curcumin sulfate I) Curcumin glucuronide J) Tetrahydrocurcumin K) Hexahydrocurcumin L) Octahydrocurcumin.

A phenoxy-radical can be generated from the phenolic groups present in the curcumin molecule by loss of a proton and similar reactions can generate a carbon radical from the central methylene group. The stability of the phenoxy-radical is higher than that of the carbon-radical, but experimental data where curcumin has been used, indicate that both the phenoxy radicals as well as the carbon radicals contribute to the biological activity of curcumin (10). The phenoxy or the carbon radicals generated in the curcumin molecules are resonance stabilized and could be inter-converted through extensive conjugation through the heptadiene linker. Therefore curcumin can act as a powerful scavenger of different reactive oxygen species (ROS), such as the hydroxyl radicals, hydrogen peroxide, singlet oxygen, superoxide anion, etc., thereby preventing damage to macromolecules in circulation in the blood or present in the tissue. Therefore, phenolic groups or the active methylene groups are one of the most important parts of the curcumin molecule which contribute to its bioactivities [15].

Pharmacology of Curcumin Molecule

Role of Degradation Products

Curcumin is poorly bioavailable and unstable under the physiologic conditions prevalent in the tissue. So it is very likely that the metabolically transformed products of curcumin which are relatively more water-soluble may be responsible for the observed health benefits ascribed to curcumin. Wang et al. found that 90% of curcumin degraded within 30 minutes in phosphate buffer (pH 7.4) into various products, identified as trans-6-(4**β**-hydroxy-3**β**- methoxyphenyl)-2,4-dioxo-5- hexenal, ferulic aldehyde, ferulic acid, feruloyl methane, vanillin, and few others [16] (Figure 3). Besides, it is not clear how curcumin exerts inhibitory effects against so many enzymes, whose binding pockets cannot bind specifically to curcumin. By analyzing the similarities between the biological activities of curcumin and its degradation products against diseases such as Alzheimer's and cancer, as well as the preferential inhibition of some enzymes by these products, it appears that the bioactive degradation products may contribute to the pharmacological effects of curcumin. But when curcumin enters the blood, it binds to proteins like albumin, fibrinogen, etc., and gets stabilized [13]. Therefore the degradation of curcumin which is observed in the absence of proteins may not happen that rapidly in the blood. This possibility should be examined in greater detail for elucidating the pharmacology of curcumin against various diseases.

Nanoparticles

Nanoparticles are usually defined as particles of 1–100 nm in diameter that possess unique physical, chemical, and biological properties that can be used for drug delivery. Even particles of slightly bigger size can be considered as long as they are suitable for both controlled and targeted drug delivery purposes. If a drug can be nanotized, it is excellent but otherwise, the intended drug can be encapsulated inside nanoparticles which can enhance the pharmacokinetics and solubility of the drug, help in targeted delivery, and control the release of the drug. In recent times, there has been an increase in the approved nano-based pharmaceutical products which are therapeutic agents themselves, or which act as vehicles to carry different active pharmaceutical agents to specific parts of the body. Chang et al. studied the molecular mechanisms activated by curcumin loaded-PLGA nanoparticles in CAL27 cisplatin resistant cancer cells (CAR cells). Experimental data suggested that curcumin loaded-PLGA nanoparticles controlled the activity of multiple drug resistance protein 1 (MDR1) and the development of reactive oxygen species (ROS) in CAR cells by activating the intrinsic apoptotic pathway. Besides, curcumin loaded PLGA nanoparticle is more effective against the treatment of CAR cells along with enhanced bioactivity under in vitro condition and better bioavailability in in-vivo condition compared to the native curcumin [17]. Curcumin silk fibroin (CUR-SF) nanoparticles provided a more stable delivery to colon cancer cells and produced a strong anticancer effect than it's freeform in HCT116 cells. This study concluded that controlled release of CUR-SF can improve cellular uptake of curcumin into cancer cells and reduce the cytotoxicity to normal cells [18]. In recent years, gold nanoparticles synthesized with plant extracts have been widely used for therapeutic purposes [19]. Stability due to colloidal form of these particles prevents the physicochemical properties from changing. Thus, it leads to stability of the biological activity of the particles. Sanoj et al. demonstrated that curcumin-encapsulated chitosan-graft-poly (N-vinyl caprolactam) nanoparticles containing gold nanoparticles (Au-CRC-TRC-NPs) could be employed in targeted delivery of drug and inducing apoptosis in colon cancer cells [20].

Liposomes

Liposomes are vesicular structures consisting of an aqueous core surrounded by single or multiple phospholipid bilayers. They may vary in their charge, dimensions, and composition which is facilitated by the use of different types of phospholipids. Liposomes can be multilamellar consisting of several concentric bilayers of phospholipids or unilamellar consisting of only one phospholipid bilayer. Liposomes can be ideal delivery systems for biologically active substances. Targeting of liposome-encapsulated drugs to particular cells or tissues can be achieved by covalent attachment of target cell-specific monoclonal antibodies.

Many studies have shown that liposomes solubilize curcumin in the phospholipidic bilayer and allow curcumin to be distributed over the aqueous medium so that it can be delivered into the target cell after fusion of the liposome with the cell. Extensive studies showed that liposomal curcumin was the most suitable vehicle to treat various cancers. Dhule et al. showed that liposomal curcumin inhibited the growth of the KHOS OS cell line and MCF-7 breast cancer cell line and exhibited a strong anticancer effect in both in vitro and in vivo conditions [21]. Tefas et al. prepared the liposomes coencapsulating doxorubicin and curcumin and the formulation reduced the cell proliferation in C26 murine colon cancer demonstrating a better cytotoxic activity than free curcumin [22]. Similarly, liposomes co-encapsulating curcumin and resveratrol showed a lower particle size, polydispersity index, and high encapsulation efficiency [23].

Micelles

Amphipathic molecules like lipids and detergents having both polar and nonpolar regions, spontaneously aggregate in an aqueous solution above a critical concentration (CMC) to form micelles. While forming micelles, the polar region of the amphipathic molecule forms the outer layer and remains in contact with water while the nonpolar tails are sequestered in the interior, and in this process, they can trap hydrophobic molecules inside. The nature and length of the nonpolar tail, the nature and size of the polar head, the temperature at which the aggregates are formed, the salt concentration, and the pH of the aqueous suspension determine what kind of aggregates will be formed. Micelles therefore can trap hydrophobic drugs inside and move them across a hydrophilic environment. They have been used to deliver poorly water-soluble drugs like curcumin into the tissue. The carrying ability of micelles can be altered if parameters determining their size and shape are changed. Liu et al. used a one-step solid dispersion approach to make curcumin encapsulated polymeric micelles (Cur-M) and studied the effectiveness of Cur-M in a breast tumor model. It was seen that, compared with unformulated curcumin, Cur-M was successful in obstructing the growth of breast tumors and spontaneous pulmonary metastasis to the lungs [24]. Curcumin-poly (ethylene glycol) methyl ether (MPEG-PCL) micelles solid dispersion enhanced the anti-angiogenesis and anti-tumor effect of curcumin. Results from this study also proposed that curcumin micelles may be useful in pulmonary carcinoma treatment [25]. Chang et al. evaluated the outcome of various sizes of curcumin encapsulated micelles on human colon carcinoma cells under in vitro conditions by determining their cellular uptake, and cytotoxicity. The results suggest that small sized curcumin loaded micelles have potential to induce better cytotoxicity effect on the human colon carcinoma cells than larger micelles. The study therefore highlighted that drug loading, micelle size and uptake/ release kinetics are important considerations for determining the drug efficacy as it affects nanoparticle drug delivery [26].

Solid Dispersions

Poor aqueous solubility of drugs leading to low bioavailability is the main problem of making effective drug formulations for therapy. Solid dispersion has become an attractive way to tackle this problem where a hydrophilic matrix is used to disperse a hydrophobic drug in the solid-state to improve its bioavailability. Solid dispersions are usually made through fusion and melt or solvent-based methods and the bound drugs are released by making nano range colloidal particles from the solid dispersion in an aqueous media which improves the oral bio-distribution of the drug. Therefore suitable solid dispersions can be used for oral delivery of curcumin. Li et al. prepared a curcumin–Eudragit® PO solid dispersion through a solution mixing technique to increase the solubility and stability of curcumin in water [27]. In another study, curcumin- Gelucire®50/13 solid dispersion prepared by spray drying showed better solubility (3,600-fold) in water compared with the native curcumin. Besides, the bioavailability and anti-inflammatory activity of curcumin were highly improved by solid dispersion as a consequence of an increased gastrointestinal absorption [28]. Similarly, curcumin solid dispersion-encapsulated temperaturesensitive in situ hydrogels (CSDG) are effective for treatment for vaginal bacterial infection by stable and sustained release of curcumin [29].

Conjugates

The use of hydrophilic polymers to disperse a drug molecule to improve the bioavailability of the drug, which is known as solid dispersion is quite popular in the pharmaceutical industry. But the methods of making hydrophilic-hydrophobic polymer nano-conjugates and hydrophobic drug-hydrophilic polymer nano-conjugates have been developed as alternate strategies for drug development. The conjugation process induces the formation of structures wherein in an aqueous environment the poorly water-soluble drug is reduced to nanosize particles leading to enhanced bioavailability. It has been shown that conjugation of curcumin to small molecules or hydrophilic polymers increases its solubility and oral bioavailability. Therefore curcumin conjugates will be quite effective in delivering curcumin to its target site. Manju and Sreenivasan reported conjugation of curcumin with hyaluronic acid improves curcumin's aqueous solubility and stability [30]. Singh et al. demonstrated that curcumin conjugates with piperic acid and glycine, prepared by esterifying the phenolic hydroxyls of the two aromatic rings, increase its bioavailability and trigger apoptosis in MCF-7 and MDA-MB-231 cell lines through a mitochondrion based pathway [31]. Similarly, Muangnoi et al. prepared glutaric acid conjugate of curcumin, curcumin-glutaric acid (CurDG) prodrug through ester linkage and tested it in mice. It revealed that solubility and antinociceptive properties were increased for CurDG compared to curcumin [32]. Recently, the gold nanoparticle–PVP–curcumin conjugate (PVP–C– AuNP) found to have obstructed the amyloid Ab (1-6) aggregation with high degree of curcumin bioavailabilty, loading efficiency (80%), and prolonged drug release.

Nanospheres and Microcapsules

Another alternative to solid dispersion or conjugates is polymer-based Nanocapsules which have been widely studied as potential drug delivery systems for hydrophobic drugs with poor bioavailability. Nanocapsules provide a unique nanostructure, consisting of a liquid/ solid core and a polymeric shell which has an important role in drug delivery applications. Using curcumin, this method has been shown to

be quite effective. Arunraj et al. synthesized the surfactant-free curcumin nanospheres (CNSs) and detailed the evidence of CNSs anticancer effect on breast cancer and osteosarcoma cell lines [33]. Curcumin was successfully encapsulated into the poly(ethylene glycol)-poly(lactic acid) (PEG-PLA) nanospheres and delivered to HeLa and MDA-MB-231 cancer cells. This formulation improved curcumin solubility and stability than native curcumin and showed better cytotoxic effects against cancer cells [34]. Huo et al. synthesized the selenium nanoparticles (Se NPs) encapsulated poly-lactide-co-glycolide (PLGA) nanospheres with curcumin. It decreased the amyloid-b load in Alzheimer's disease in mice, and greatly improved the memory deficiency of the model mice due to effective and targeted drug delivery [35].

Miscellaneous Nanoformulations

Besides what we have discussed till now, other nanoformulations like nanogels and metal- complexes of curcumin can be used to enhance curcumin's biological activities. A nanogel is formed by either physical or chemical cross-linking of curcumin with a polymer under controlled conditions. It can become a structure for storing curcumin and protecting it from degradation while curcumin can be released slowly to exert its biological efficacy. Reeves et al. synthesized and examined a colloidal nanogel carrier system for encapsulation of curcumin to enhance its solubility. This curcumin-nanogel formulation was able to kill the tumor cells more efficiently as compared to curcumin alone [36]. Similarly, curcumin loaded into gold nanoparticles-chitosan nanogels showed greater extent of cellular uptake and better cytotoxic effects on huh7 and MCF7 cell lines compared to native curcumin [37]. Ghosh et al. was first to used nanodisk in order to boost the solubility and targeted the release of curcumin [38]. Effstathia et al. demonstrated that curcumin could be loaded into the Saccharomyces cerevisiae cell membrane that resulted in microcapsules containing about 35.8 ± 0.86% w/w curcumin that integrated in the plasma membrane, and also interacted with constituents of the cell wall network [39]. In another research, Paramera et al. determined the stability of yeast cell–loaded curcumin, which showed that yeast cells protected curcumin from environmental factors (i.e., light, humidity, and heat) [40].

Therapeutic use of Nanocurcumin in Different Disease Models

Cardiovascular Diseases

Wang et al. designed a self-assembled amphiphilic carbo-methylhexanol chitosan (CHC) nano matrix with demethoxycurcumin (DMC), with an approach to inhibit the proliferation and migration of vascular smooth muscle cells (VSMCs); a process that is associated with response to vascular injury and atherogenesis [41]. In this approach, DMC and CHC were solubilized in an organic solvent:aqueous mixture, from which the organic solvent was slowly removed under reduced pressure using a rotary evaporator, at room temperature. The modified amphiphilic chitosan used in the preparation demonstrated the ability to self-associate in contact with an aqueous medium to form polymeric nanoparticles and hydrogels and encapsulating the DMC present in the solution. The drug encapsulated nano matrix prepared this way was then tested and found to be successful in cellular internalization and exerting a cytotoxic effect on the growth and migration of VSMCs. Carlson et al. demonstrated the preparation of a polymeric micellar delivery system of curcumin which could mitigate the severe cardio-toxicity associated with Doxorubicin (DOX) treatment, by reducing apoptosis and reactive oxygen species (ROS) levels in vitro [42]. Pramanik et al. further confirmed that the curcumin entrapped nano-micellar formulation led not only to the amelioration of doxorubicin-associated cardiomyopathy but also successfully aided in overcoming multidrug resistance in cancer cells [43]. The mitigation of cardiopathy observed in this study was attributed to the reduction of DOX-induced intracellular oxidative stress in cardiac tissue brought about by the activity of curcumin present in the nanoformulation. In another study, a preparation comprising of curcumin loaded onto poly (ester amine) nanoparticles was tested by Ding et al. for enhancement of hydrophilic characteristics and improvement of therapeutic efficacy, against angiogenesis in a transgenic zebrafish model. The study demonstrated the effectiveness of poly (ester amine) nanoparticles as a suitable curcumin delivery system for efficient anti-angiogenesis therapy [44].

Neurodegenerative Diseases

The dysfunctioning of the central nervous system (CNS), brain, or the spinal cord is at the root of several complex diseases that are observed in humans. Drug delivery at these anatomical sites for effective therapy requires overcoming the complexity of the blood-brain barrier (BBB). Given the neuroprotective benefits that curcumin is known to exert, one of the more successful strategies in the attempt for delivering curcumin across the BBB for therapeutic purposes has been to synthesize apolipoprotein-E (ApoE)-derived peptide nanoparticles and incorporate curcumin or suitable derivatives of curcumin into the synthesized peptide nanoparticles as demonstrated by Re et al. [45]. Curcumin has also been found to possess anti-amyloid-**β** activities, which can help prevent the pathological manifestations associated with the development of Alzheimer's disease (AD). As a result, the successful delivery of curcumin to targeted sites has received great attention. In this context, Doggui et al. attempted to encapsulate curcumin into biodegradable PLGA–nanoparticles and deliver it to neuronal cells to facilitate entry of the molecule into the cell. The formulation was observed to exert neuroprotective effects against H_2O_2- induced elevation of ROS. The curcumin encapsulated PLGA nanoparticles used in this study were demonstrated to be able to prevent Nrf2 induction in the presence of H2O2, thereby conferring protection against oxidative damage [46]. Apart from PLGA, curcumin has been formulated using coupling to polyethylene glycol (PEGylated), biodegradable poly(alkyl cyanoacrylate) [47], PEG liposomes with anti-transferrin [48], lipid conjugated liposome [49], nanoliposomes [50], and click-chemistry-based nanoliposomes [51] and demonstrated to inhibit aggregation of A**β** and A**β** associated cytotoxicities observable in AD. Potent anti amyloidogenic effects in Tg2576 with reduced amyloid plaque density and improved bioavailability [52]. Apolipoprotein E3-mediated poly (butyl) cyanoacrylate nanoparticles containing curcumin (ApoE3-C-PBCA) had potent anti-amyloidogenic activity over the free form of curcumin and possible in the treatment

of bamyloid- induced cytotoxicity [53]. Mathew et al. described that conjugation of Tet-1 peptide to curcumin-PLGA nanoparticles showed the anti-amyloid effect against AD. It was seen that formulated curcumin had a strong affinity toward neurons by easily crossing the blood-brain barrier, and it has assisted the better obliteration of the amyloid aggregates, exhibiting its capability to treat AD [54].

Inflammatory Diseases

Inflammatory diseases include a vast array of disorders and conditions which have inflammation as a common basis. Curcumin, for a long time, has been regarded as a strong anti-inflammatory agent and hence several attempts have been made to develop it into a suitable formulation that can be employed to treat a variety of inflammation-related ailments. In a rat model of inflammation, gold nanoparticle formulated curcumin was demonstrated to successfully suppress lipopolysaccharide (LPS)-induced inflammation and cytotoxicity [55]. In another study curcumin loaded onto PLGA-Eudragit(®) S100-based nanoformulation was observed to significantly reduce TNF-**β** secretion by LPS-activated macrophages (J774 cells) [56]. Shukla et al. [57] showed that treatment with nanoemulsion of curcumin inhibited TNF-**β** levels, oxidative stress, and LPS-induced lung- and liver-associated injury by minimizing neutrophil migration in rats. Sun et al. demonstrated exosome-mediated delivery as an approach for delivering curcumin efficiently to activated myeloid cells for reducing inflammatory damage in vivo, as well as in lipopolysaccharide (LPS)-induced septic shock mouse model [58]. Curcumin-loaded solid lipid nanoparticles were observed to be beneficial in the treatment of sepsis [59] and for providing hepato-protection [60]. Arora et al. [61] established an effective curcumin-loaded solid lipid nanoparticle formulation for Complete Freund's adjuvant-induced arthritic rat model. The results in the arthritic rat model showed that treatment with curcumin loaded solid lipid nanoparticles significantly ameliorated several symptoms that were associated with arthritis in rats which support the protective effects exerted by this particular form of curcumin nanoformulation. Nehra et al. [62] demonstrated the therapeutic efficacy of pure curcumin nanoparticles (200 nm average size) in ameliorating hyperbaric hypoxia-induced lung injury by modulation of the Akt/Erk signaling pathway in rat lungs. Similarly, nanocurcumin enhances oral bioavailability and increases effectiveness over the native form in the prevention of streptozotocin (ST) induced diabetes at least partly, by the suppression of inflammation and pancreatic beta-cell apoptosis in rats [63]. In another report, it was seen that loss of NF-kb activation leads to the down-regulation of COX-2 and iNOS expression, obstructing the inflammatory response and tumorigenesis. The experimental study demonstrated that the curcumin-loaded PLGA nanoparticles (CUR-NP) decrease the pro-inflammatory mediators in Staphylococcus aureus affected mammary tissues by affecting NF-kb signaling [64].

Infectious Diseases

Several investigations have demonstrated activities against different types of bacteria, fungi, viruses, and parasites. A parenteral administration of lipid-based curcumin nanoparticles in an in vivo model was demonstrated to result in a 2- fold increase in anti-malarial activity over free curcumin [65]. Furthermore, a novel PEGylated liposome-based curcumin nanoformulation was observed to provide therapeutic benefit to Plasmodium berghei NK-65-infected mice [66]. Curcumin bound to chitosan nanoparticles was demonstrated to inhibit hemozoin synthesis indicating its potential to be developed as a potent anti-malarial compound [67]. One of the major complications of malaria in humans is the development of cerebral malaria which results in severe neurological impairments, coma, and death. The pathophysiology of human cerebral malaria is largely mimicked in murine models of cerebral malaria. The efficacy of curcumin in preventing cerebral malaria in mice was demonstrated by Dende et al.[68] who showed that entrapping curcumin into PLGA nanoparticles and orally administering to mice infected with P. berghei ANKA prevents disease pathology in infected mice at fifteen fold lower concentration as compared to free curcumin. This enhancement in efficacy is caused by an increase in the bioavailability of curcumin when formulated into PLGA nanoparticles. Gandapu et al. [69] developed apotransferrin tagged curcumin nanoparticles by sol–oil chemistry for improved uptake by T cells through transferrin-mediated endocytosis, which showed a higher anti - HIV activity of nano curcumin. Tousif et al. [70] demonstrated the preparation of 200 nm size nanoparticles using pure curcumin and their use in curing Mtb infected mice and reducing hepatotoxicity arising out of isoniazid treatment in M.tb infected mice. Ahmed et al. [71] demonstrated the use of the same pure curcumin nano formulation in enhancing the capacity of BCG to induce central memory T cells of Th1 and Th17 lineages that result in augmentation of host protective responses against TB infection. It was found that silver decorated polymeric micelles encapsulated with curcumin exhibited strong antibacterial activity to P. aeruginosa and Staphylococcus aures [72]. Similarly, Zaharieva et al. reported that curcumin loaded micelles enhance the alkylphosphocholines erufosine and miltefosine antibacterial activities against pathogenic S. aureus strain [73].

Cancer

Cancer is one of the leading causes of human deaths. The most commonly used treatment options include surgery, chemotherapy, radiotherapy, targeted therapy, hyperthermia, photothermic therapy, and other alternative therapies. For metastatic tumors, chemotherapy is the usual choice of treatment but it is associated with adverse effects to healthy tissues, leading to organ damage. The use of curcumin and its nanoformulations therefore can play a significant role in enhancing the effectiveness of anticancer drugs by chemo-sensitization of cancer cells. Curcumin nanoformulations significantly internalize inside cancer cells through receptor-mediated endocytosis and release curcumin for it to exert its biological effects [74]. Dextran–Curcumin nanoparticles have been demonstrated to be taken up significantly by HeLa cells in a selective manner with respect to normal cells [75]. Maitra et al. have engineered a curcumin nanoformulation (NanoCurc™) [76-78], developed by random copolymerization of N-isopropyl acrylamide with N-vinyl-2-pyrrolidone, poly(ethylene glycol)–monoacrylate in the presence of N, N**β**methylene bisacrylamide, 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. The formulation was demonstrated to possess high systemic bioavailability in plasma and tissues over free

curcumin [76-78]. This formulation was demonstrated to inhibit tumor growth by significantly reducing activation of nuclear factor kappa B (NF-βB), inhibiting the expression of matrix metalloproteinase-9 (MMP-9) and cyclin D1 in animal models [79-82]. Newer approaches for delivery of curcumin with augmented activity include 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) which successfully block the hepatocyte growth factor-induced signaling in the breast cancer cell line, MDA-MB-231 [83]. Curcumin encapsulation in Eudragit S100 polymer nanoparticles, which dissolve at colonic pH, (6.1-7.5) was shown to influence cellular uptake of curcumin and exhibit a two-fold superior to ordinary curcumin anti-cancer potential in HT-29 human colorectal cell line [84]. Hossain et al. demonstrated that nanoparticles of pure curcumin prepared by a modified solvent co-precipitation method exhibit better bioavailability as compared to ordinary curcumin and cause a reversal of tumor-shed TGF-β-induced Treg cell augmentation in the tumor microenvironment [85]. Over to native curcumin, curcumin encapsulated in monomethoxy poly (ethylene glycol)-poly(3-caprolactone) (MPEG-PCL) micelles hindered the proliferation of colon carcinoma cells at in vivo condition [86]. Chen et al. synthesized the curcumin-loaded liposomes nanoparticles (CLNP) and then examined for the anticancer activity in B16BL6 melanoma cells. It revealed that the proliferation activity of the B16BL6 melanoma cells severely hindered by CLNP [87]. Basniwal et al. studied the effect of anticancer properties of curcumin nanoparticles in the lung (A549), liver (HepG2), and skin (A431) cancer cell lines. It was seen that curcumin nanoparticles showed a much better effect on the cancer cells compared to native curcumin under physiologic conditions [88]. HIF-1 and NF- kB are both indispensable for the improvement of cancer cell progression. PLGA nanoparticles (NP), loaded with curcumin (cur-PLGA-NP) elevated the HIF-1 and NF-kB subunits (HIF- 1a and nuclear p65 (Rel A) expression in breast and lung cancer cells at the hypoxic microenvironment [89]. Dendrosomal nanocurcumin and exogenous p53 can act together to produce anticancer effects against TNBC cells [90].

Summary

Numerous attempts to develop formulations comprising of curcumin being embedded into polymeric nanoparticles or trapped into liposomes, phospholipid complexes, nanoemulsions, or polymeric micelles which have been referred to as 'Nanocurcumin' have been made and tested in cell lines and animal disease models Nano curcumin of average size 200 nm prepared from pure curcumin without any carrier has also been shown to be effective in preventing growth of tumours in mice , in curing Mtb infected mice in the presence of INH and modulating T central memory cell response against BCG in mice. All these formulations will have to be tested in chronic diseased conditions of humans to test its efficacy and suitability for long term use. The degradation products of curcumin that have shown therapeutic potential have not yet been tested enough. Nano formulations made out of pure curcumin or its degradation products that are bioactive could provide better alternatives for human therapy than those made using polymeric nano particles and other carriers.

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