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Curcumin Nanoconjugates- A Restitutive Therapeutics

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Abstract
Curcumin is a natural polyphenol and essential curcuminoid derived from the rhizome of the medicinal plant *Curcuma longa* (*L*.). Inspite of being wonder drug with lots of advantages, its low aqueous solubility and poor stability remain major barriers for clinical efficacy. Nanoformulation of curcumin is emerging as a novel substitute for their superior therapeutic modality. Formulation of curcumin with various conjugates in enhances its aqueous solubility and attains targeted delivery to the tissue of interest that prompts to enhance the bioavailability, better drug conveyance, and more expeditious treatment. This review conglomerates various curcumin nano formulations, together with therapeutic benefits.

Keywords
Curcumin, nano formulations, conjugates, polymers

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INTRODUCTION
Nano conjugates are the emerging drug-delivery vehicles for their multimodular structures enabling them to actively target discrete cells, pass through biological barriers and simultaneously carry multiple drugs of various chemical nature.

Among a large number of components isolated from turmeric, Curcumin was found to be the most active polyphenol extracted and evidenced by enormous citations in the literature so far (Tyagi *et al,*2015). Curcumin([1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione]) is a naturally yellow-colored phenolic antioxidant. Curcumin possesses many beneficial properties as antioxidant (Pizzo *et al,*2010,Sugiyama et.al.,1996), anti-cancer (Lee *et al,*2009), anti-arthritic, anti-microbial (De *et al,*2009)antidiabetic (Srimal *et al,*1973) and anti-inflammatory activities(Aggarwal *et al,*2009) and avails in the treatment of many ailments including tendinitis, liver cirrhosis, Alzheimer's disease, heart attack, hypoglycemia, gastrointestinal problems, worms, swelling, cancer, skin and ocular perceiver infections (Morimoto *et al,*2008 and Wang, 2009).

Inspite of being wonder drug with lots of advantages, its low aqueous solubility and poor stability remain major barriers for clinical efficacy. It was reported that curcumin solubility in aqueous buffer (pH5.0) was only 11ng/mL. Another reason that limits clinical application of curcumin is that curcumin degrades quickly in neutral or alkaline buffer solution (Ling *et al,*2016). So thus, curcumin in the form of Nano conjugates, metallic nanoparticles, liposomes, micelles, cyclodextrin, curcumin nano suspensions are upcoming stream of curcumin vehicles inorder to exploit the beneficial therapeutic effects of curcumin. This review conglomerates various curcumin nano formulations, together with therapeutic benefits.

Nanoconjugates for improving solubility and stability of curcumin
In order to improve the solubility and stability, formulation of curcumin in the form of nano particles has gained immense importance. The most

commonly used polymers in the design of nano particles include natural polymers chitosan, dextran, dextrin, pullulan, mannan, proteins, hyaluronic acid]; synthetic polymers [N-(2-hydroxypropyl) methacrylamide (HPMA) copolymer, poly(ethyleneimine) (PEI), ploy(acroloylmorpholine) (PAcM), poly(vinylpyrrolidone) (PVP), polyamidoamines, divinylathermaleic anhydride/acid (DIVEMA) copolymer, poly(styrene-co-maleic acid/anhydride (SMA), polyvinyl alcohol (PVA)] and pseudosynthetic polymers [polyglutamic acid (PGA), poly(L-lysine), poly(malic acid), poly(aspartamides), poly((N-hydroxyethyl)-L-glutamine) (PHEG)]. The factors important to for selection of a suitable polymer should be inherently biodegradable, non-toxic and non-immunogenic. It should exhibit low poly dispersity (high homogeneity) with one reactive group for protein conjugation to avoid crosslinking and many reactive groups for small active molecules to achieve appropriate drug loading (conjugation efficiency) and longer residence time for prolonged action or to allow effective drug distribution (Greco F & Vicent MJ ,2009, Kaneda Y *et al,*2004, Kamada H *et al*,2000, Yasukawa T *et al,* 1999, Chipman,2006, Ljubimova JY *et al*,2008).

Yang et al, 2012 attempted organo gel-based nanoemulsions and bovine serum albumin for improving the bioavailability of curcumin and its implications on the stability and antioxidant property. Manju *et al,* 2012 reported synthesis of water-soluble gold nanoparticles in curcumin-polymer conjugate and studied it for blood compatibility and targeted drug delivery onto cancer cells. Silica nanoparticles have also been immensely explored due to their interesting properties such as hydrophilic surface favouring protracted circulation, versatile silane chemistry for surface functionalization, excellent biocompatibility, ease of large-scale synthesis and porosity. These have been projected to be one of the safest (non-toxic) candidates for DNA-conjugation, drug-delivery and many other applications (Sreelakshmi *et al,*2013).

Naksuriya *et al*,2015 explores the advantages of polymeric micelles composed of block copolymers of methoxypoly(ethylene glycol) (mPEG) and N -(2-hydroxypropyl) methacrylamide (HPMA) modified with monolactate, dilactate and benzoyl side groups to enhance solubility and stability of nanoparticles. Polymeric micelles can serve as transporters of water-insoluble drugs such as curcumin, which can augment the drug's efficiency by targeting definite cells or organs; therefore, fewer drugs accumulate in healthy tissues and their toxicity reduces, and occasionally higher doses can be administered (Jones MC and Leroux JC *et al,*1999). Casein-dextran nanoparticles (CDNs) were prepared from casein-dextran conjugates by heating in a dry/wet state and then adjusting the pH to the isoelectric point of the protein (pH 4.6) to investigate their physicochemical characteristics. The CDNs were spherically shaped and uniformly dispersed, as confirmed by atomic force microscopy.

Liposomes can encapsulate drugs with widely varying solubility or lipophilicity, entrapped either in the aqueous core of the phospholipid bilayer or at the bilayer interface. Sun *et al,* (2010) developed a cationic liposome containing Polyethyleneimine-Polyethylene glycol as a carrier encapsulate curcumin with enhanced anti-tumor effects on colon/ melanoma tumor growth in mice. Kundu *et al,* (2012) reported curcumin-loaded lipid nanoparticles and investigated anti-glioma activity in encephalon tissue for effective glioblastoma therapy resulting in enhanced bioavailability.

The cyclodextrin-based nanosponges of curcumin cross-linking with dimethyl carbonate were synthesized by Darandale et al, (2013) which significantly enhanced the stability as well as solubility compared to free curcumin. Also, the in vitro drug release efficacy of curcumin was found to be highly controlled over a prolonged duration and found to be non-hemolytic. In another study conducted by Mangalathillam *et al,* (2012) reported curcumin loaded chitin nano gels comprised of cross-linked polymer network tested in vitro on breast cancer cell lines and observed an amelioration in bioavailability, anticancer effects, better-controlled release and enhanced stability.

Magnetic nanoparticles (MNPs) have attracted special attention in various biomedical applications, such as molecular detection, drug delivery, hyperthermia, magnetic resonance imaging (MRI), and bioengineering. The major requirements for MNPs to be suitable for biomedicine are non-toxicity biocompatibility, monodispersity, stability in colloidal media, high magnetic moment. Among MNPs, superparamagnetic iron-oxide nanoparticles (Fe3O4 or -Fe2O3) have emerged as the most promising biomedical candidates as they are biocompatible, non-toxic, simple to fabricate, and remanence-free particles with high magnetic moment (Figuerola *et al,* 2010, Chertok *et al,* 2008, Columo *et al,* 2012). Patra *et al,* (2015) designed a dual (magnetic and thermal) responsive nanoparticles using advanced nano innovative applications for effective delivery and enhanced efficacy of curcumin. A system with combination of

cyclodextrin with magnetic nano particles gives synergistic advantage of both enhanced bioavailability of drug and magnet responsive transport respectively. The design of such system was possible due to presence of hydroxyl groups on both the moieties, which can be linked to isocyanate form polyurethane (PU) polymer (RadosławMrówczyn´ski *et al,*2018).

Niosomes can provide a container for drug molecules with a wide range of solubilities due to presence of hydrophilic, amphiphilic, and lipophilic moieties in the constitution. These systems distinguish themselves between size, drug entrapment, repose angle, hydration rate, and vesicular stability under different storage settings. Results showed that proniosomes are very stable and promising prolonged delivery systems for curcumin (Kumar K & Rai AK 2011).

When subjected to a mild physical stress, curcumin is seen to internalize within the miceller hydrophobic core of Oleic Acid Sophorolipid resulting in the formation of Curcumin-Sophorolipid Nanoconjugates (CurSL). These bio-composite, shows enhanced retention time and increased bioavailability of curcumin in Rat models. In presence of gold salts, CurSL acts as a potent reducing and capping agents, resulting in the synthesis of monodispersed, spherical gold nanoparticles (CurSL-GNPs) of 8-10nm size (Priti A. Darne *et al*,2016). Sophorolipids is a class of extracellular biosurfactants produced by a non-pathogenic yeast *Candida bombicola* (ATCC 22214).

The dendrimer structure, consisting of a core, branched interiors, and numerous surface functional groups, serves as a platform to which additional substrates can be added to this spherical molecule in a highly controlled manner. Debnath *et al,* (2013) generated dendrimer curcumin conjugate, a water-soluble and effective cytotoxic agent against breast cancer cell lines. Unlike other biodegradable polymers, chitosan is the only one exhibiting a cationic character due to its primary amino groups that responsible for various effects in drug delivery systems (Bernkop-Schnrch A and Dunnhaupt S,2012**)**. It displays particular properties, for example, solubility in various media, polyoxy salt creation, polyelectrolyte behavior, metal chelations, and structural uniqueness. Another formulation included a novel folate-conjugated, curcumin-loaded human serum albumin nanoparticles (F-CM-HSANPs) prepared by the chemical conjugation of folate to the surface of curcumin loaded human serum albumin nanoparticles injected in vitro results in sustained drug release at desired site and prolonged retention time with specific targeting in vivo after the intravenous injection of F-CM-HSANPs in current clinical tribulations (Song *et al,*2016). Polymeric materials like Poly (lactic-co-glycolic) acid (PLGA), Polyethylene glycol (PEG), surfactant copolymers were also used for encapsulating the nanoparticles (Gupta and Gupta,2005).

Preparation of nano particles

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

Characterisation of nano particles

These nano formulation of any particle ranges from 1 nm to 1000 nm, reduction in the size of the material results in an exponential increase in surface area to volume ratio. This may increase the extent of distribution among the tissues. The surface charge of the nanoparticle is also an important feature. The negatively charged particles have reduced adsorption rate of serum proteins, resulting in longer circulation half-lives as compared to the positively charged particles (Alexis *et al,*2008). Particle shape is another essential property of nanoparticles that plays a pivotal role in various biological processes associated with its therapeutic activity the tailoring of nanoparticle shape and dimension also has improved the efficacy of tumor therapy

Differential scanning colorimetry is used to study thermal transition and to study the physical change of drug from one state to other state, the electric charge at the surface of the particles, indicating the stability of nanoparticles determined by zeta potential, drug entrapment efficiency for samples and solubility of curcumin was determined using dissolution apparatus.

On one hand, the design of nanomaterials as drug carriers should address the following key issues: (i) sufficient biocompatibility and biodegradability; (ii) good stability in physiological conditions; and (iii) high drug loading capacity and low toxicity and finally scale up to the industry is also an important one.

PROSPECTS AND CONCLUSIONS

Several types of NP have been found to be suitable for the encapsulation or loading of curcumin to improve its effects in cancer therapeutics. The characteristics of these curcumin nanoformulations

can be tailored according to the specific requirement for inducing cellular death by various mechanisms. Therefore, future studies should concentrate on the traditional drugs which has a rich repository of medicines utilising them in a novel formulations inorder to overcome their disadvantages.

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