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VARIOUS APPROACHES TOWARDS ENHANCEMENT OF BIOAVAILABILITY OF CURCUMIN – A POTENT PHYTOCHEMICAL

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ABSTRACT

Herbal medicine is the oldest form of health care known to mankind. Turmaric (Curcuma longa Linn), a nature's precious and most popular Indian spice belonging to family zingiberaceae is cultivated throughout the Indian sub continent because of its excellent medicinal properties. Curcumin is a specially gifted molecule provided by Mother-Nature to protect humans from chronic health problem. Although curcumin has shown therapeutic efficacy against many human ailment, one of the major problems with the curcumin is its poor bioavailability, which appears to be primarily due to poor absorption, rapid metabolism and rapid systemic circulation. Nanotechnology is an innovative idea that can be used to overcome the problems associated with curcumin solubility, stability and bioavailability. In this review, the various problems, methods of preparation, various types of curcumin nano-drug delivery system of curcumin nanoparticles and its novel approach are discussed. The introduction of gold and silver nanoparticles, Liposomes, Niosomes and so on provides a solution towards increased bioavailability of curcumin. Design and development of herbal nanoparticles has become a frontier research in the nanoformulation arena. However, most of the known activities of curcumin are based only on *in vitro* and *in vivo* studies and this nanotechnology-based medicine may become a reality in clinical applications.

KEYWORDS: Curcumin, Nanoparticles, Liposomes, enhancement of bioavailability.

INTRODUCTION

Scientific research spanning over more than four decades has confirmed the diverse pharmacological effects of curcumin and established its ability to act as a chemopreventive

agent as well as a potential therapeutic agent against several chronic diseases.[1] Curcumin is a lipophilic phenolic substance with a characteristic yellow color derived from the rhizome of the plant turmeric (Curcuma longa, Family-Zingiberaceae).[2] Turmeric has also been used for centuries in Ayurvedic medicine, which integrates the medicinal properties of herbs with food.[3] This compound consists of 3 components. (i) curcumin, (ii) demethoxycurcumin and (iii) bisdemethoxycurcuminoids with ratio 77:17:3 and recently cyclocurcum.[4] Curcumin has wide range of applications such as anti-bacterialactivity, antiinflammatory, antioxidant, pro-apoptotic, chemopreventive, chemotherapeutic, antiproliferative, wound healing, anti-nociceptive, antiparasitic, anti-malarial, diabetes, obesity, neurologic, psychiatric disorders and cancer, as well as chronic illnesses affecting the eyes, lungs, liver, kidneys, and gastrointestinal and cardiovascular systems.[5] Curcumin is a potent phytomolecule with a wide range of biological activities.[6] but its clinical applications are limited largely due to its poor solubility, rapid metabolism and rapid systemic elimination, which results in poor bioavailability. Curcumin is characterized with extremely low solubility in water (11ng/ml) and significant presystemic biotransformation, mainly via glucuronide and sulfate conjugation.[7] Therefore, efforts have been made to improve curcumin's bioavailability by improving these features. The promising approaches to increase the bioavailability of curcumin include the use of nanoparticles, liposomes, micelles, phospholipid complexes and structural analogues.[5] Notably, natural polymers such as starch, chitosan, casein, cellulose are being investigated as delivering materials for curcumin which can enhance efficiency of curcumin usage.

With the ongoing development of nanotechnology, the nanoparticles have its own importance in novel drug delivery system. Nanoparticles exhibit special features like large surface area, quantum effect and ability to bind and carry compounds like drugs. The physical, chemical, optical and electronic properties of the nanoparticles depend on the size, shape and surface morphology. The application of nanoparticle mainly in medicine like drug delivery, probing of DNA structure, detection of protein, tissue engineering, detection of pathogens, destruction of cancer cells and phagokinetic studies, will deliver new approaches for enhancement of solubility, stability, bioavailability and pharmacological activity and ability to avoid physical and chemical degradation.[8] Therefore introduction of nanotechnology in curcumin provides a solution towards increased bioavailability and therapeutic efficacy. Considering the number of reviews in many related fields of curcumin, in the present manuscript, only some of the

important recent findings in curcumin chemistry bioavaibality have been reviewed that have contributed to its potential applications in the development of curcumin- based drugs.

PROBLEMS OF CURCUMIN BIOAVAILABILITY

The reasons for reduced bioavailability of curcumin within the body are low intrinsic activity, poor absorption, high rate of metabolism, inactivity of metabolic products and/or rapid elimination and clearance from the body.[9]

Serum Concentration: One of the major observations related to curcumin studies involves the observation of extremely low serum levels.

Tissue Distribution: Uptake and distribution of curcumin in body tissues is obviously important for its biological activity.

Metabolites: Various studies have evaluated the metabolism of curcumin in rodents and in humans. Once absorbed, curcumin is subjected to conjugations like sulfation and glucuronidation at various tissue sites.

Causes of Low Bioavailability

- First pass metabolism
- Poorly water soluble, slowly absorbing aral drugs
- Insufficient time for absorption in GIT
- Poor dissolution (highly ionoized and polar)
- Age, stress, disorders, surgery etc
- Chemical reaction
- Metabolism by luminal microflora.

Approaches

- Coacervation techniques
- Nanoprecipitation method
- Spray drying method
- Single emulsion method
- Solvent evaporation method
- Microemulsion
- Wet milling method

- Thin film hydration method
- Solid dispersion method
- Emulsion polymerization method
- Fessi method
- Ionic gelation method
- Ultrasonication
- Antisolvent precipitation method.

Coacervation techniques: In this method of synthesis, the polymer is dissolved in organic solvent (e.g. dichloromethane, ethyl acetate, or acetonitrile) and herbal drug (curcumin) is suspended directly in polymeric solution and it is allowed to homogenize properly. Nanoparticles are collected by centrifugation. It is inexpensive method. The main drawback of this method is that it requires large amount of solvent. Chirio et al., formulated curcumin loaded nanoparticles by using this technique.[10]

Nanoprecipitation method

Nanoprecipitation method is also known as Solvent displacement method. In this method, desired polymer is suspended in the suitable solvent to form polymeric solution and herbal drug (curcumin) is added into it. After that this drug- polymer solution is added into water under continuous stirring which results in precipitation. After that the solvent is allowed to evaporate by hot air flow. Spray drying resulted in the formation of drugs in the amorphous state, which may get partially crystallized during processing. In this method of synthesis, curcumin and polymer are dissolved in same solvent or mixture of solvents. Chin et al.,prepared starch nanoparticles for controlled release of curcumin.[11]

Spray drying method: Curcumin nano-crystals can be formulated by spray drying method. For that Curcumin nano-suspensions, having a drug concentration of 10% (w/w), are dried with a Mini spray-dryer. The spray – dried curcumin nanocrystals are directly collected after the process. Yallapu et al., fabricated curcumin encapsulated PLGA nanoparticles.[12]

Single emulsion method: Single emulsion method is the conventional method for the synthesis of curcumin nanoparticles. In this method, curcumin nanoparticles are prepared by dispersing it in a suitable solvent, followed by high speed homogenization or ultrasonication to form the emulsion. Further the solvent from the emulsion is evaporated by continuous magnetic stirring at room temperature or under reduced pressure. The solidified nanoparticles

are ultrasonicated and collected, followed by washing with distilled water to remove additives and lyophilized to get nanoparticles. Curcumin loaded poly (lactic-coglycolic acid) (PLGA) nanoparticles can also be prepared. Sari et al., produced curcumin nanoparticles by this method.[13]

Solvent evaporation method: Solvent evaporation method includes two major steps: (i) preparation of drug-polymeric solution (ii) evaporation of dispersing solvent used for dissolving curcumin. It results in the formation of solid mass. The emulsion formed is then converted into nanoparticles suspension by evaporation of the solvent. Advantage of this method is that low temperature required for evaporation of solvent and thermal deposition can be prevented. Disadvantages are: (i) the reagents used in this method are quite expensive (ii) selection of proper solvent is somehow difficult and evaporation of organic solvent is time consuming process. PLGA (Poly (lactic acid-co-glycolic acid) loaded curcumin nanoparticles are synthesized by this technique. Liemann et al., formulated PHBV nanoparticles by solvent evaporation method.[14]

Microemulsion: Microemulsion is considered as an ideal method for nanoparticles fabrication. The surfactants used in this method are hydrophobic in nature for water soluble drugs and hydrophilic in nature for oil soluble drugs. Microemulsion is formed when a small amount of surfactant is stirred and curcumin is added in it along with oil and water. It results in the formation of turbid solution which generally appears like small droplets. Various types of surfactants are used to increase the surface stabilization of curcumin nanoparticles. This method is easy and can be effectively used for drug delivery with less energy expenditure. Microemulsion technique is affected by certain parameters like temperature and pH variation observed in formulation of phospholipid-based curcumin encapsulated microemulsions.[15]

Wet milling method: Curcumin nanoparticles can be synthesized from wet-milling method. Curcumin is suspended in an appropriate dispersing solvent. The obtained solution is further agitated under ultrasonication method. Distilled water is used for the synthesis of curcumin nanoparticles. The obtained solution is then allowed to centrifuge and the formed nanoparticles are collected. Giat et al.,[16] fabricated nanocurcumin by wet milling method.

Thin film hydration method: In this method of synthesis, herbal drug (curcumin) and surfactants are allowed to mix in a suitable organic solvent under sonication condition. Solvent is allowed to evaporate under certain pressure. After that distilled water is added in

sonication condition and the obtained nanosuspension is then centrifuged to obtain curcumin nanoparticles. Moorthi et al., demonstrated curcumin nanoparticles synthesis by this method of synthesis.[17]

Solid dispersion method: In this method, the matrix and hydrophobic drugs like curcumin are mixed. Matrix can be in the amorphous or in crystalline form. This method can be used to dissolve the insoluble hydrophobic drug. This is fast and readily scalable method used for curcumin nanoparticles synthesis by solid dispesion method. as reported by Moorthi et al.

Emulsion polymerization method: Organic and continuous phase are two types of emulsion techniques which can be used for the synthesis of curcumin nanoparticles. By this method, the surfactant is dissolved in pure water by ultrasonication, then curcumin is dissolved in an organic solvent and finally the solution is added to the surfactant. Moorthi et al have reported synthesis of curcumin nanoparticles by using this method and piperine was used along with curcumin to increase the biological activity of synthesized curcumin nanoparticles.[17]

Fessi method: In this method of synthesis, curcumin is dissolved in suitable solvent under sonication condition. The solution thus obtained is further added in pure water along with certain surfactant with constant stirring. Curcumin nanoparticles can be spontaneously synthesized by this method. Moorthi et al., 2012 have used this method for fabrication of curcumin nanoparticles. This is easy and simple method of nanoparticles synthesis.

Ionic gelation method: Hydrophobic drug such as curcumin is dissolved in proper solvent which showed complete solubility of curcumin in it and then this solvent is added in polymeric solution under constant stirring condition. This method depends on the cross linking of polymer along with drug such as curcumin. Chabib et al., 2012 reported synthesis of curcumin nanoparticles and used chitosan as a polymer.[18] This polymer improved the solubility and stability of curcumin nanoparticles.

Ultrasonication: This method is generally employed for the drugs which are less water soluble. By this technique, curcumin is first dissolved in an organic solvent and the resulting solution is then added into the polyelectrolye solution under ultrasonication condition for several intervals of time and the formed curcumin nanoparticles are collected. Zhang et al., 2011 have synthesized curcumin nanoparticles by using this technique of ultrasonication.[19]

Antisolvent precipitation

Antisolvent precipitation is the method of synthesis of the poorly water soluble drug. In this method of synthesis, curcumin is dissolved in an organic solvent followed by the addition of this solution into the deionized water under constant stirring. Hence, curcumin nanoparticles can be synthesized by this method. Yadav et al.,[20] used this method for synthesis of curcumin nanoparticles. Advantage of this method of synthesis is that it is suitable technique for synthesis of poorly soluble curcumin nanoparticles.

Type of Curcumin Nano Drug Delivery System to Increase Bioavailability

Curcumin is highly unstable in acidic pH of the stomach and degraded at alkaline pH before reaching to the blood and other constituents might be metabolized by the liver. Resulting, the optimum quantity of the curcumin may not reach the blood resulting in no/less therapeutic effect. Nanocarriers applying to curcumin will carry optimum amount of the drug to their site of action bypassing all the barriers such as acidic pH of stomach, liver metabolism and increase the prolonged circulation of the drug into the blood due to their small size. So curcumin was selected as feasible drug candidate for delivery through a nano delivery system because of the following properties.

- To improve the solubility.
- To enhance the bioavailability
- To reduce the dose.
- To target the site of action.
- To control the release of the drug.

Types of curcumin nano drug delivery systems

- Liposomes
- Polymeric Nanoparticles
- Solid lipid nanoparticals
- Polymeric micelles
- Magnetic nanoparticals
- Nanogels
- Gold Nanoparticles
- Silver Nanoparticles
- Niosomes
- Cyclodextrin

- Implant delivery system
- cur-PLGA-NPs.

Liposomes: Liposomes are nanosize artificial vesicles of spherical shape that can be produced from natural phospholipids and cholesterol. These vesicles have been reported to serve as immunological adjuvants and drug carriers. Liposomes are increasingly used by the pharmaceutical industry to deliver certain drugs, vaccines and enzymes for the prevention or treatment of a variety of diseases. Liposomes have been investigated for delivery of chemotherapeutic agents for cancer treatment, vaccines for immunological protection, radiopharmaceuticals for diagnostic imaging and nucleic acid–based medicines for gene therapy.[21] Liposomes are closed spherical vesicles consisting of a lipid bilayer that encapsulates an aqueous phase in which drugs can be entrapped.[22] With the advantages of high biocompatibility, easy preparation, chemical versatility, and simple modulation of their pharmacokinetic properties by changing the chemical composition of the bilayer components, they have been used to improve the therapeutic activity and safety of drugs for many years.[23] So, liposomes have found wide application in enhancing curcumin's bioavailability and efficacy. In this regard, to enhance the solubility of curcumin, Rahman et al., prepared beta-cyclodextrin curcumin inclusion complexes that entrapped both native curcumin and the complexes separately into liposomes. All curcumin-containing formulations were effective in inhibiting cell proliferation in in vitro cell culture.[24] Chen et al., reported the effects of different liposomal formulations on curcumin stability in phosphate buffered saline, human blood, plasma, and culture medium. Liposomal curcumin showed a higher stability than free curcumin in phosphate buffered saline (PBS).[25] The formulation silica-coated flexible liposomes loaded with curcumin (CUR-SLs) and curcumin-loaded flexible liposomes (CUR-FLs) without silica-coatings have been designed and found that the bioavailability of CUR-SLs and CUR-FLs was 7.76- and 2.35-fold higher, respectively, than that of curcumin suspensions.[26] The fluidity of the lipid bilayers and the relatively small size of the liposomes greatly facilitate oral absorption.[27]

Liposome Preparation: Different total lipid curcumin ratios (weight/weight) ranging from 10:1 to 4:1 were tested before settling on a fixed ratio of 10:1. The lyophilization procedure involved several steps. First, curcumin was dissolved in 50 mg/mL DMSO. The lipid (e.g., DMPC) was dissolved in 20 mg/mL tert-butanol. The 2 solutions were mixed and filtered through a 0.22 M filter for sterilization. Aliquots of this solution were placed in lyophilization

vials. The vials were frozen in a dry ice acetone bath and lyophilized for 24 hours to remove all DMSO and tert-butanol. The vials were stored at 20°C. The lipid formulation included DMPC or DMPC/ DMPG in some experiments.[28]

Polymeric Nanoparticles: NPs range in size from 10 to 1000 nm and can be synthesized from lipids, proteins and carbohydrates, as well as several natural and synthetic polymers. For delivery, a drug is dissolved, entrapped, encapsulated or attached to an NP matrix. Depending upon the method of preparation, NP, nanospheres or nanocapsules can be obtained. NP systems are being explored for a variety of biomedical applications. Their use to improve the therapeutic index of encapsulated drugs either by protecting them from enzymatic degradation, altering pharmacokinetics, reducing toxicity, or providing controlled release over extended periods of time has gained enormous acceptance of NP systems in the last decade, as reviewed recently. Due to the small size and excellent biocompatibility, polymeric nanoparticles can circulate in the bloodstream for a longer time; thus, specific therapy can be achieved. The widely researched synthetic polymers include chitosa, poly(D,L-lactideco-glycolide) (PLGA), and PEG for the cucrcumin nanoparticle formation. Moreover, polymers can be combined to form copolymers, which could be a promising drug carrier for the site targeting and sustained action.[26]

Solid Lipid Nanoparticles (SLNs): SLNs are made of natural or synthetic lipid or lipoid, such as lecithin and triglycerides, which are solid at human physiological temperature. SLNs offer unique properties such as smaller size, larger surface area, interaction of phases at the interfaces, and these are attractive for their ability to improve performance of neutraceuticals, pharmaceuticals and other materials. Solid lipid nanoparticles possess a solid lipid core matrix that can solubilize Lipophilic molecules. The lipid core is stabilized by surfactants (emulsifiers). For pharmaceutical applications, all formulation excipients must have Generally Recognized as Safe (GRAS) status to achieve and maintain a solid lipid particle upon administration, the lipid nanoparticles melting point must exceed body temperature (37°C). Kakkar et al., prepared curcumin-loaded solid lipid nanoparticles (C-SLNs) for the improvement of its oral bioavailability. Dadhaniya et al., examined the adverse effects of a new solid lipid curcumin particle in rats.[29]

Polymer Micelles: Micelles are lipid molecules that arrange themselves in a spherical form in aqueous solutions with a very narrow range from 10 to 100 nm in size, which makes them more stable towards dilution in biological fluids. The functional properties of micelles are

based on amphiphilic block copolymers, which come together to form a nanosized core/shell structure in aqueous media.[30] 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.[31] In this regard, to overcome the poor water solubility of curcumin, Liu et al., prepared curcumin loaded biodegradable self-assembled polymeric micelles for sustained release.[32] In addition, the preparation of curcumin-loaded micelles based on amphiphilic Pluronic/ polycaprolactone block copolymer was investigated by Raveendran et al., which proved to be efficient in enhancing curcumin's aqueous solubility.[33] Thus the micellar system is efficient for solubilization, stabilization, and controlled delivery of curcumin.

Magnetic Nanoparticles: Magnetic drug targeting, in which a drug is conjugating with a magnetic material under the action of the external magnetic field. Drug-loaded magnetic nanoparticles can accumulate in target tissue areas under the action of the external magnetic field; the drug then releases from the particles in a controllable way. Yallapu et al.,[34] introduced magnetic drug carriers with a pluronic polymer (F127) shell for controlled delivery of curcumin. A nanosized magnetofluorescent water dispersible Fe_3O_4-curcumin conjugate with chitosan or oleic acid asits outer shell and entrapped curcumin was designed by Tran et al.,. The Fe_3O_4-curcumin conjugate exhibited a high-loading cellular uptake that was distinctly observed by magnetic and fluorescent methods and was also shown to be a good candidate for a dual (optical and magnetic) imaging probe.[35]

Nanogels: Nanogels are cross-linked three dimensional polymer chain networks which are created through covalent linkages and can be customized to gel networks with biocompatible and degradable properties. Nanogels demonstrate excellent potential for systemic drug delivery that should have a few common features including a smaller particle size (10–200 nm), biodegradability and/or biocompatibility, prolonged half-life, high stability, higher amount of drug loading and/or entrapment, and molecules protection from immune system. Goncalves et al., applied a self assembled dextrin nanogel as curcumin delivery system by using dynamic light scattering and fluorescence measurements. Various nanogel properties can be attained by altering the chemical functional groups, cross-linking density, and surface active and stimuli-responsive elements.[36] It designed a class of water-dispersible hybrid nanogels for intracellular delivery of hydrophobic curcumin.

Gold nanoparticles: With the optical and electrochemical uniqueness, gold nanoparticles have proven to be a potent apparatus in nanomedicinal requests.[1] Moreover, the stability of AuNPs and their capability to combine with biomolecules are their other outstanding properties. AuNPs are studied broadly as imperative drug delivery vectors due to some of their characteristic aspects, such as low cytotoxicity, tunable surface features, and stability in in vivo conditions, and can be easily synthesized and functionalized. Rajesh et al.[37] used polyvinyl pyrrolidone (PVP) as a proven drug carrier to curcumin conjugation with AuNPs to enhance solubility of curcumin. In a study by Singh et al.[38] curcumin was bound on the surface of AuNPs in order to increase the bioavailability of it. Manju and Sreenivasan[39] also formulated a simple method for the fabrication of water-soluble curcumin conjugated AuNPs to target various cancer cell lines. AuNPs also cause targeting and sustained release of curcumin and an excellent antioxidant activity.

Silver Nanoparticles: Silver is usually utilized as an incredibly efficient material for antimicrobial utility.[40] Silver nanoparticles are identified for their brilliant optoelectronic properties originated from surface plasmon resonance. They have shown excellent antimicrobial activity compared to other available silver antimicrobial agents. Sodium carboxylmethyl cellulose silver nanocomposite films were attempted for antibacterial applications, so, to improve their applicability, novel film-silver nanoparticle curcumin complexes have been developed.[41] In addition, silver nanoparticles could protect cells against HIV1 infection and help with the wound healing process and also have essential function as an anti-inflammation, an antiviral, and an anticancer agent.[42] So, the combination of silver nanoparticles and curcumin, besides prolonged therapeutic outcomes and sustained release, has several other useful effects such as anti-inflammatory, anti-infection, anticancer, and wound healing.

Niosomes: Niosomes are microscopic lamellar structures, which are formed on the admixture of nonionic surfactant of the alkyl or dialkyl polyglycerol ether class and cholesterol, with subsequent hydration in aqueous media.[43] They resemble liposomes in their architecture and can be used as an effective alternative to liposomal drug carriers.[44] Niosomes are a promising vehicle for drug delivery, and since they are non-ionic, they are less toxic and improve the therapeutic index of drugs by restricting their action to target cells. The characteristics of the vesicle formulation are variable and controllable. Altering vesicle composition, size, lamellarity, trapped volume, surface charge and concentration can control

vesicle characteristics. The vesicles may act as a depot, releasing the drug in a controlled manner.Niosomes are osmotically active, stable and increase the stability of the entrapped drug. They improve oral bioavailability of poorly absorbed drugs and enhance skin penetration.[21]

Cyclodextrin: Cyclodextrins (CDs) are unique molecules with 'pseudo-amphiphilic' structure, and several members of this family are used industrially in pharmaceutical and allied applications. The enzymatic degradation of starch by glucosyltransferase generates cyclic oligomers of α-1,4D-glucopyranoside, or CDs. CDs with lipophilic inner cavities and hydrophilic outer surfaces are capable of interacting with a large variety of guest molecules to form noncovalent inclusion complexes.[45] CDs have an internal hydrophobic domain that can accommodate poorly water-soluble molecules, while the outer hydrophilic surface facilitates its solubility in the aqueous environment.[46,47] They have been widely exploited for drug delivery and used in the preparation of various delivery vehicles, such as liposomes, microspheres, microcapsules and NPs.

CDs enhance bioavailability of insoluble drugs by increasing drug solubility and dissolution. They also increase the permeability of insoluble, hydrophobic drugs by making the drug available at the surface of the biological barrier (e.g., skin and mucosa) from when it partitions into the membrane without disrupting the lipid layers of the barrier. In such cases, it is important to use just enough CD to solubilise the drug in the aqueous vehicle since an excess may decrease drug availability.[48] Cyclodextrins can also enhance drug bioavailability by the stabilization of drug molecules at the biomembrane surface. For example, CD-enhanced insulin bioavailability after nasal administration is partly due to this stabilizing effect.[49] Sublingual drug delivery is one of the most efficient ways to bypass hepatic first-pass metabolism,[50] whereby the drug enters the systemic circulation by dissolving in the mucosa. In the sublingual formulations, the complexation of poorly water-soluble drugs with cyclodextrin has been shown to increase the bioavailability of various lipophilic drug.[51]

Implant delivery system: Implants of drug-loaded polymers, either as millirods, pellets or microspheres, are able to deliver drugs for prolonged periods. The benefits of this subcutaneous implantation include greater assurance of patient compliance, which then leads to better therapeutic outcome, particularly for chronic medication.[52,53] This approach is well recognized for contraception and hormonal therapy. Two types of polymeric delivery systems are being used: no degradable and biodegradable polymeric matrices. Non-degradable

biometrics are composed of either silicone or poly(ethylene-co-vinyl acetate).[54] The Norplant delivery system uses this approach for contraception.[55] Vadhanam et al. have used the system to deliver ellagic acid in a mammary tumorigenesis model and shown effectiveness while delivering 130-fold less compound via silastic implants compared to dietary route (500 ppm), during a 28-week treatment period.[56] Even though this approach has the potential to deliver over prolonged time periods, risks include mechanical failure that may lead to dose dumping, in the case of reservoir systems, and continuous dose drops, in the case of solid-drug distributed matrices. The other issue related to this system is the potential for fibrous growth around the implants, sometimes making it difficult to remove them at the end of the treatment period.

Therapeutic Application of Curcumin

Anticancer activity: Cancer is the most common devastating disease diagnosed throughout the world. Conventional treatments like chemotherapy, radiation therapy and surgery cause adverse side effects. Recently, curcumin nanoformulations with enhanced bioavailability, solubility and specific tumour cell targetting were used as novel therapy for cancer.

Breast cancer: Breast cancer is a prevalent disease mainly affecting women worldwide. The *in vitro* studies of curcumin micelles showed increased bioavailability, cytotoxicity and longer half-life in triple negative breast cancer (TNBC) xenografts. The combination of curcumin-encapsulated nanoparticles with electroporation technique in MCF-7 human breast cancer cells depicted better anticancer activity.[8]

Ovarian cancer: Ovarian cancer comprises different types of cancer depending on the cells from which they form. The major interruption in treating advanced ovarian cancer is chemoradiotherapy resistance. Paclitaxel and curcumin-encapsulated nanoemulsion showed anticancer activity against drug resistant SKOV3 and SKOV3 (taxol-resistant) human ovarian adenocarcinoma cells by promoting apoptotic response. Curcumin nanoemulsion suppressed the nuclear factor kappa B (NFκB) activity and down-regulated P-glycoprotein expression.

Pancreatic cancer: Bisht et al., synthesised curcumin-loaded polymeric nanoparticles using the co-polymers N-isopropylacrylamide, N-vinyl-2-pyrrolidone and poly (ethylene glycol) monoacrylate. It acts as a potential agent to inhibit the tumour growth in xenograft models of human pancreatic cancer.[57]

Prostate cancer: Prostate cancer is a disease which develops in the prostate gland of the male reproductive system. Gradually, it may spread to other parts of the body like bones and lymph nodes.[58] Curcumin-loaded poly (lactic-co-glycolic acid) (PLGA) nanoparticles prepared by Yallapu et al., demonstrated the anticancer activity of curcumin nanoparticles against prostate cancer.[59]

Antimicrobial activity: Micro-organisms play a major role in causing numerous infections to humans. Traditionally, turmeric has been used as an antimicrobial agent. Curcumin nanoparticles were used as they are known to possess superior antimicrobial activity than the normal curcumin. Bhawana et al., reported the antibacterial and antifungal activities of nanocurcumin prepared by wet-milling technique. The nanocurcumin was more water dispersible in the absence of any surfactants and highly active against Staphylococcus aureus, Bacillus subtilis, Escherichia coli, Pseudomonas aeruginosa, Penicillium notatum and Aspergillus niger. The nanocurcumin formulation was more reactive against Gram-positive bacteria than the Gram-negative bacteria.[58]

Anti-HIV activity: Human immunodeficiency virus (HIV) attacks the immune system by destroying CD^{4+} T cells. The progressive failure of the immunity finally leads to acquired immunodeficiency syndrome (AIDS).[59] It is reported that curcumin-loaded apotransferrin nanoparticles prepared by sol-oil technique was very potent to prevent HIV-1 replication by transferrin-mediated endocytosis.

Antimalarial activity: Malaria is caused by parasites and carried by female Anopheles mosquitoes. The *in vivo* studies of curcumin-loaded hydrogel nanoparticles reported by Dandekar et al., showed antimalarial activity. The toxicity studies proved the oral safety and cytotoxic effects of the nanoformulations. Curcumin-loaded chitosan nanoparticles cured the mice infected with Plasmodium yoelii by blocking the hemozoin synthesis.[60]

Anti-inflammatory activity: In ancient Indian medicine, turmeric has been used as an anti-inflammatory agent Curcumin-encapsulated exosomes were studied for their potency in lipopolysaccharide-induced septic shock mouse model. In that experiment, curcumin delivered by exosome demonstrated more stability, target specificity and they were found in high concentrations in blood.[61]

Curcumin enhances immunity: Curcumin can also help the body fight off cancer should some cells escape apoptosis. When researchers looked at the lining of the intestine after ingestion of curcumin, they found that CD4+ T-helper and B type immune cells were greater in number.[62]

Alzheimer's disease: Alzheimer's disease (AD) is a progressive neurodegenerative disorder that occurs all over the world. It is a common type of dementia associated with memory loss and gradual death of brain cells. PLGA-coated curcumin nanoparticles in conjugation with Tet-1 peptide possess anti-amyloid and antioxidant property and it can be used as a potential drug for treating AD.

Antioxidant Effects: Water- and fat-soluble extracts of turmeric and its curcumin component exhibit strong antioxidant activity.

Hepatoprotective Effects: Turmeric has been found to have a hepatoprotective characteristic similar to silymarin. Animal studies have demonstrated turmeric's hepatoprotective effects from a variety of he-patotoxic insults, including carbon tetrachloride (CCl4), galactosamine, acetaminophen (paracetamol), and Aspergillus aflatoxin.

Cardiovascular Effects: Turmeric's protective effects on the cardiovascular system include lowering cholesterol and triglyceride levels, decreasing susceptibility of low density lipoprotein (LDL) to lipid peroxidation, and inhibiting platelet aggregation. These effects have been noted even with low doses of turmeric.

Gastrointestinal Effects: Constituents of Curcuma longa exert several protective effects on the gastrointestinal tract. Sodium curcuminate inhibited intestinal spasm and p-tolymethylcarbinol, a turmeric component, increased gastrin, secretin, bicarbonate, and pancreatic enzyme secretion.[63]

CONCLUSION

Herbal medicine is the oldest form of health care known to mankind. Curcumin is a specially gifted molecule provided by Mother-Nature to protect humans from chronic health problem. Nanotechnology is an innovative idea that can be used to overcome the problems associated with curcumin solubility, stability and bioavailability. In this review, the various problems, methods of preparation, various types of curcumin nano-drug delivery system of curcumin nanoparticles and its novel approach are discussed. However, most of the known activities of

curcumin are based only on *in vitro* and *in vivo* studies. Curcumin has yet not been approved for treatment of any human disease. Therefore, the promise of nanotechnology-based medicine may become a reality with sufficient efforts and further researches. Human trials need to be conducted to establish curcumin's effectiveness in clinical applications.

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