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A REVIEW ON PREPARATION & METHODS OF CURCUMIN NANOPARTICLES AND ITS APPLICATION

Vijaya Lakshmi Jampala * and Swarupa Arvapalli

Joginpally B. R. Pharmacy College, Moinabad, Hyderabad - 500075, Telangana, India.

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Correspondence to Author:
Vijaya Lakshmi Jampala

Student,
Joginpally B. R. Pharmacy College,
Moinabad, Hyderabad - 500075,
Telangana, India.

E-mail: avrv2910@gmail.com

ABSTRACT: Curcumin is a highly potent, nontoxic, bioactive agent found in turmeric and has been known for centuries as a household remedy to many ailments. The main active ingredient of turmeric is curcumin, a polyphenol that helps prevent and control neurological, respiratory, cardiovascular, metabolic, inflammatory and autoimmune diseases and some cancers. The major drawbacks of curcumin are low absorption and poor bioavailability. Curcumin nanoparticles possess remarkable antibacterial, antiviral and antiprotozoan activity. Cancer is the second leading cause of death in the world and one of the significant public health problems. Despite the great advances in cancer therapy, cancer incidence and mortality rates remain high. This review mainly focuses on the preparation & methods of Curcumin nanoparticles and their applications. Therefore, the quest for more efficient and less toxic cancer treatment strategies is still at the forefront of current research.

INTRODUCTION: Curcumin [chemicalname: (E, E)-1,7-bis(4-hydroxy-3-methoxy phenyl)-1,6-heptadiene-3,5-dione] is the active ingredient in the traditional herbal remedy and dietary spice turmeric. It has a molecular formula $C_{21}H_{20}O_6$, a molecular weight (MW) 368.38, and a melting point of 179–183 C. Curcumin is more soluble in ethanol, dimethyl sulfoxide (DMSO), methanol, and acetone than in water. Curcumin is a brightly yellow-colored compound derived from the popular Indian spice of turmeric, a member of the ginger family (Zingiberaceae) [1]. Curcumin is a highly potent, nontoxic, bioactive agent found in turmeric and has been known for centuries as a household remedy to many ailments.

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Curcumin is a natural product that possesses several pharmacological properties. Especially, it has been demonstrated to be a superior anticancer agent against several types. These activities have been demonstrated after parenteral or oral administrations in animal models or using *in-vitro* assays. In animals, curcumin reduced carcinogen-induced tumorigenesis and inhibited the growth of implanted human tumors. Curcumin is a polyphenolic compound that is found in turmeric *Curcuma longa* has many varieties of pharmacological activities, including anti-inflammatory, anticancer, antibacterial, antioxidant.

Curcumin acts as a promising agent for Alzheimer's disease. Nanotechnology is a field of modern applied science that aims to develop materials and devices with unique and inherent, in their size of1−100nm, at least in one dimension. Nanoparticles are defined as particulate or solid dispersion with the size lying 10-100nm range. By designing nanoparticles, control release of active agents, surface properties, and particle size can be

manipulated. An antiviral drug, tenofovir disoproxil fumarateen capsulated with chitosan nanoparticles, can potentially be used as a drug delivery system with hepatic targeting and controlled release properties. Nanoparticles-loaded anti-retroviral drugs may be a new promising drug delivery system for managing HIV-1 infected patients [2]. It is found mostly in tropical and sub-tropical regions throughout the world. It is commonly cultivated in Asian countries, mostly in India and China. It is extensively used in Ayurveda, Unani and Siddha systems of medicine as one of the household therapies for all deviate different diseases. These obstacles of curcumin can be eliminated by synthesizing curcumin nanoparticles, liposomes, micelles, and phospholipid complexes, which can be used for longer circulation, permeability and increased resistance to metabolic processes.

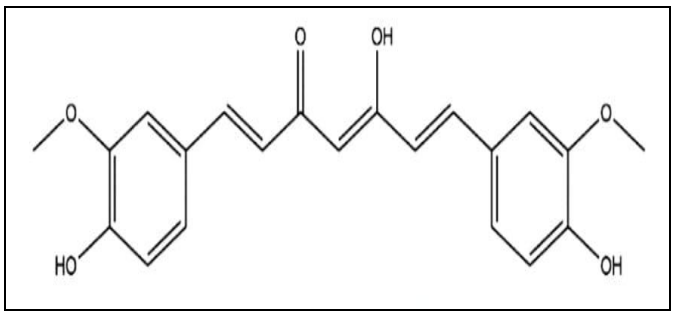


FIG. 1: CHEMICAL STRUCTURE OF CURCUMIN

MATERIALS AND METHODS:

Apparatus and Materials: Dichloromethane used to prepare nanoparticles was of analytical grade. The ultrasound device used during preparation was an ultrasonic cleaner TPC-25 from Roop Telesonic. Buchi rotavapor (R- 210) was used to remove the solvent. Thin-layer chromatography (TLC) analysis was performed on silica gel (Merck, Germany) coated on an alumina sheet, and 1% methanol in chloroform was used as the developing solvent. All of the chemicals and Petri plates used for microbial studies were procured from HiMedia, Ltd., Mumbai, India [3].

Extraction of Curcumin from Turmeric: Various approaches have been followed to extract or isolate curcumin from turmeric.

- Solvent extraction (the most conventional method).
- Supercritical CO_2 extraction.
- Ultra-sonic irradiation (40% curcumin yield).
- Microwave extraction (68.75% curcumin yield).
- Water-soaked irradiation (71.42% curcumin yield) [4].

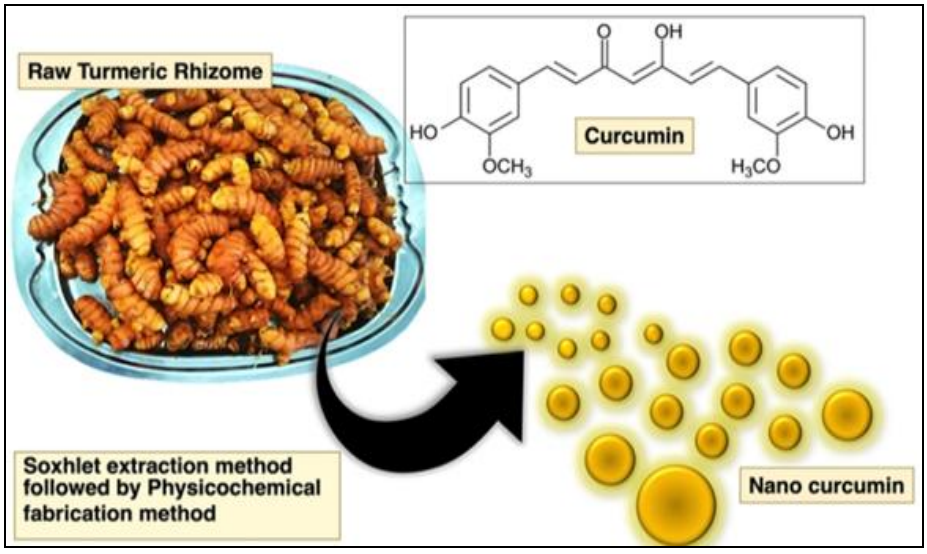


FIG. 2: EXTRACTION OF CURCUMIN

Synthesis of Curcumin: A century after its isolation from turmeric, Lampe's first paper on curcumin synthesis was reported in 1918. The method involved five steps starting from carbomethoxyferuloyl chloride and ethyl acetoacetate. Later, Pabon reported a simple method for synthesizing curcumin in high yields using acetyl acetone and substituting aromatic

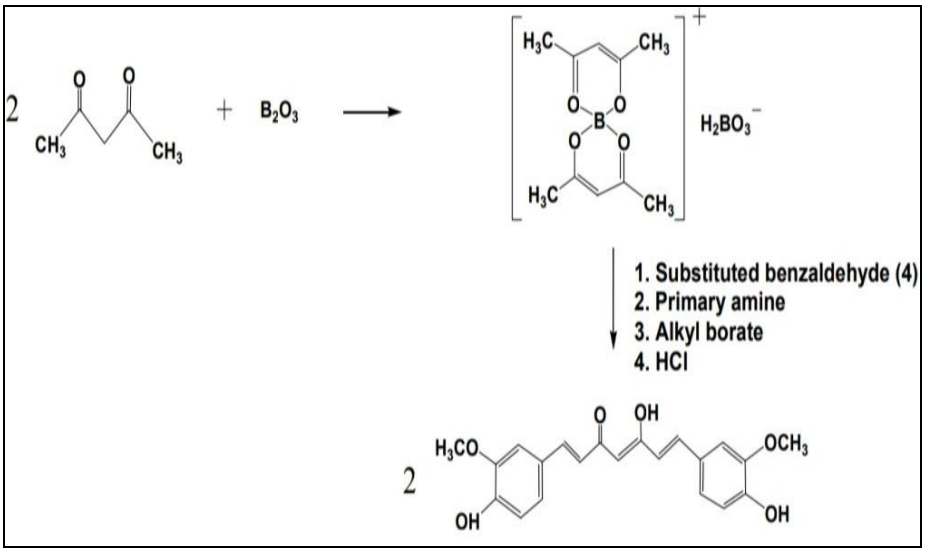
aldehydes in the presence of boron trioxide (B_2O_3), trialkyl borate and n-butylamine and with slight modifications several research groups have adopted this method by Pabon for practically all subsequent curcumin syntheses.

Some patents indicate the utilization of B2O3, trialkyl borate and n-butylamine along with inert organic amide solvents to improve the yields. Attempts to replace boric oxide with boric acid did not prove to be successful.

Rao and Sudheer proposed using trifluoroboronite and produced stable curcuminoid trifluorboronites that can be hydrolysed in aqueous methanol at pH 5.8 to get curcumin. In all these methods the primary step is the reaction of 2,4-diketones with suitably substituted aromatic aldehydes. To prevent participation of the diketone in Knoevenagel condensations, it is complexed with boron. Anhydrous conditions and polar aprotic solvents, where curcumin can be separated easily from the reaction mixtures are suitable for these reactions.

Primary and secondary amines are used as catalysts to provide the necessary basicity to deprotonate the alkyl groups of the diketone. To remove the water produced during the condensation reaction, scavengers like alkyl borates are employed.

If removed, the water can react with the diketone complex, reducing the curcumin yield. The boron complex dissociates into curcumin under slightly acidic conditions. Curcumin from this reaction mixture can be separated by washing and repeated precipitation followed by coloumn chromatography.



SCHEME 1: SYNTHESIS OF CURCUMIN BY THE GENERAL METHOD PROPOSED BY PABON

Structural Characteristics of Curcumin: Curcumin is a symmetric molecule known as diferuloyl methane. The IUPAC name of curcumin is (1E, 6E)-1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione, with chemical formula C21H20O6, and molecular weight of 368.38.

Its structure has three chemical entities: two aromatic ring systems containing o-methoxy phenolic groups, connected by a sevencarbon linker consisting of an α, β-unsaturated β-diketone moiety. The chemical structure of curcumin is given in Scheme 2. The diketo group exhibits keto-enol tautomerism, which can exist in different types of conformers depending on the environment.

In the crystal state, it exists in a cis-enol configuration, where it is stabilized by resonance-assisted hydrogen bonding. The structure consists of three substituted planar groups interconnected through two double bonds.

In most non-polar and moderately polar solvents, the enol form is generally more stabilized than the keto form by 5 to 8 kcals/mol, depending on the nature of the solvent. Due to extended conjugation, the π electron cloud is all along the molecule. In solution, it exists as cis-trans isomers where the trans-form in which the two phenolic-methoxy groups are on the curcumin backbone is slightly more stabilized than the cis-form, where the

phenolic methoxy groups are in the same side up the backbone. The computed dipole moment of curcumin in the ground state is 10.77 D. It is a hydrophobic molecule with a logP value of ~3.0. It is almost insoluble in water and readily soluble in polar solvents like DMSO, methanol, ethanol, acetonitrile, chloroform, ethyl acetate, *etc*.

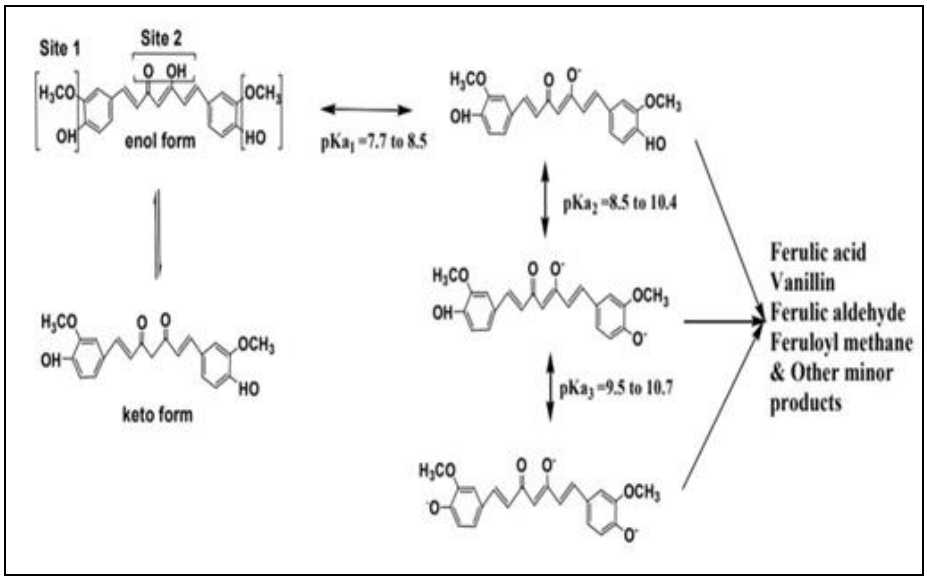
It is sparingly soluble in hydrocarbon solvents like cyclohexane and hexane. The absorption spectrum of curcumin has two strong absorption bands, one in the visible region with a maximum ranging from 410 to 430 nm and another in the UV region with maximum at 265 nm. The molar extinction coefficient of curcumin in methanol is 55,000 dm3·mol−1·cm−1 at 425 nm.

Curcumin is a weak Bronsted acid with three labile protons; accordingly, three pKa's have been estimated to correspond to three prototropic equilibria (Scheme 2). Both NMR and absorption spectrometry have been used to estimate the pKa. The first pKa in the pH range of 7.5 to 8.5 changes curcumin from yellow to red.

The chemical reactivity and solubility of the anionic curcumin, *i.e.*, in the basic pH range, increases, and this curcumin is more water soluble than the neutral form. The absorption maximum of fully deprotonated (red) curcumin in alkaline pH (>pH 10) is at 467 nm, and the molar extinction coefficient is 53,000 dm3 $mol^{-1}cm^{-1}$.

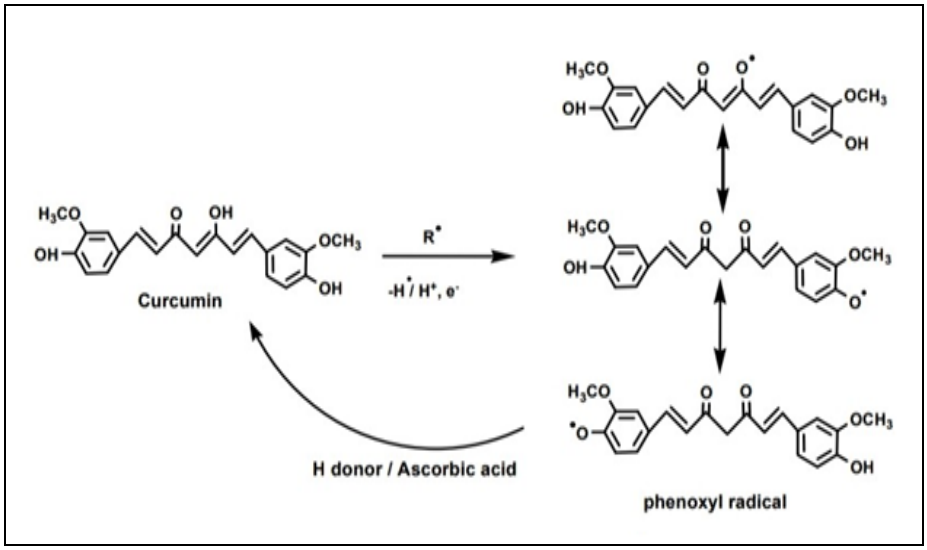
There is still a debate about which one of the three, *i.e.*, the enolic OH or the phenolic OH is the most acidic. Although calculations indicate that the enolic OH is the most acidic group, the pH-dependent spectral changes are difficult to distinguish between the two protons. From 1H-NMR studies, Borsari *et al.* proposed a pKa of 12.5 for the deprotonation of the enolic proton and another pKa at 13.6 for the phenolic protons.

However, these values for enolic protons differ significantly from those reported by other methods. With the availability of other spectroscopic techniques, it should be possible to resolve these differences in estimating pKa's in the future.



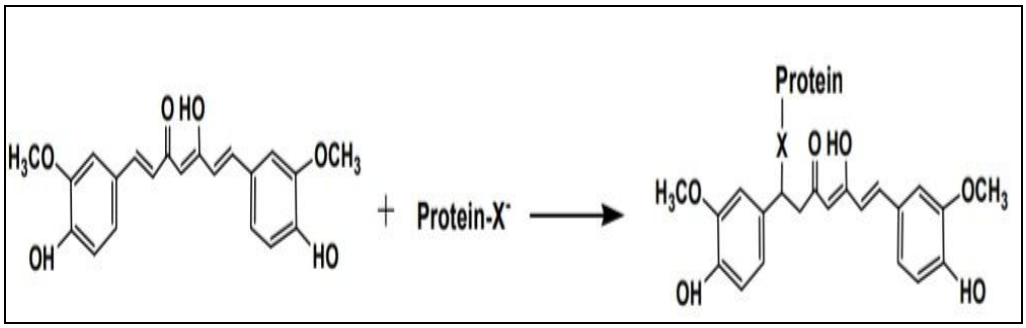
SCHEME 2: KETO-ENOL TAUTOMERISM PROTOTRIPIC EQUILIBRIA AND DEGRADATION PRODUCTS OF CURCUMIN

Curcumin has been found to be an excellent scavenger of most ROS, a property that bestows curcumin with antioxidant activity in normal cells. ROS consists of both free radical oxidants and molecular oxidants; free radical oxidants participate in hydrogen abstraction and also in electron transfer reactions. All three active sites of curcumin can undergo oxidation by electron transfer and hydrogen abstraction. Detailed investigations by different groups have confirmed that during free radical reactions, the most easily abstract able hydrogen from curcumin is from the phenol-OH group, resulting in formation of phenoxyl radicals, which are resonance stabilized across the keto-enol structure.



SCHEME 3: POSSIBLE SITES OF ATTACK OF FREE RADICAL OXIDANTS WITH CURCUMIN AND STABILIZATION OF PHENOXYL INTERMEDIATE AND ITS REGENERATION BY ASCORBIC ACID

Nucleophilic Addition Reaction: The α,β-unsaturated β-diketo moiety of curcumin participates in nucleophilic addition reactions. This reaction, known as the Michael addition, occurs between the unsaturated ketone as an acceptor and anions of –OH, –SH, –SeH as donors. It is a 1,4-addition reaction, and the resultant product formations are mostly irreversible, but they can be made reversible under oxidizing and basic conditions. Since the anions only act as nucleophiles, pH conditions are very important for this reaction. At physiological pH, both –OH and –SH are protonated but –SeH can easily undergo deprotonation, therefore, it acts as a better nucleophile. This reaction has been reported to be extremely useful in explaining the biological chemistry of curcumin in living cells; of special interest has been the reaction of biological thiols like glutathione having –SH groups. Indeed curcumin-glutathione conjugates have been isolated in different systems. Formation of this additional product would lead to the depletion of the intracellular glutathione levels in cells, thereby reducing the overall antioxidant defense. Although a few reports suggest that this is a reversible reaction, it is not yet confirmed, under the conditions present in living cells, whether the such reaction is reversible or not. Reversibility of the reaction can be expected under oxidizing conditions and at basic pH. A similar reaction has been observed during curcumin's inhibition of thioredoxin reductase. Thioredoxin reductase is a crucial enzyme involved in maintaining cellular redox homeostasis. The active center of this enzyme is selenocysteine. The selenol of selenocysteine, a stronger nucleophile at physiological pH, easily undergoes 1,4-addition with curcumin, forming covalently bonded species. This reaction is speculated to be mainly responsible for the effective inhibition of the thioredoxin reductase enzyme by curcumin. Scheme 4 shows the structure and the chemical reaction product of curcumin with protein thiols and selenols by Michael addition [5].



SCHEME 4: MICHAEL ADDITION PRODUCTS OF CURCUMIN WITH PROTEIN THIOLS AND SELENOLS WHERE, X= S OR SE

Preparation of Curcumin Nanoparticles: Curcumin (100mg, 0.27mmol) was taken in dichloromethane (20 mL) and 1 mL of this solution was sprayed into boiling water (50mL) dropwise with a flow rate of 0.2 mL/min in 5 min under ultrasonic conditions, with an ultrasonic power of 100 W and a frequency of 30 kHz. After sonication for 10 min, the contents were stirred at 200-800 rpm at room temperature for about 20 min when a clear orange-colored solution was obtained. The solution was concentrated under reduced pressure at 50 C and then freeze-dried to obtain an orange powder. A co-TLC of the powdered sample with standard curcumin showed both to have the same Rf values. Further, the lyophilized powder's 1H NMR and ultraviolet (UV) spectra confirmed it to be curcumin. The choice of the solvent was crucial because spraying of curcumin solution prepared in other organic solvents, such as methanol or acetone, resulted in particle aggregation, and nanoparticles could not be isolated. Further, maintaining the drop flow was significant for forming nanoparticles and maintaining uniformity in their size. It was seen that the addition of the entire curcumin solution to water in one lot led to particle aggregation [3].

Methods of Preparation of Curcumin:

- 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 synthesis method, the polymer is dissolved in an organic solvent (e.g., dichloromethane, ethyl acetate, or acetonitrile), and an herbal drug (curcumin) is suspended directly in polymeric solution, and it is allowed to homogenize properly. Nanoparticles are collected by centrifugation. It is an inexpensive method. The main drawback of this method is that it requires a large amount of solvent. Chirio et al., 2011 formulated curcumin-loaded nanoparticles by using this technique.

Nanoprecipitation Techniques: Nanoprecipitation method is also known as the Solvent displacement method. In this method, the desired polymer is suspended in a suitable solvent to form a polymeric solution, and a herbal drug (curcumin) is added. After that, this drug-polymer solution is added into water under continuous stirring, resulting 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 synthesis method, curcumin and polymer are dissolved in the same solvent or solvents. Chin *et al.,* 2014 prepared starch nanoparticles for the controlled release of curcumin.

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.,* 2010 fabricated curcumin-encapsulated PLGA nanoparticles.

Single Emulsion Method: The single emulsion method is the conventional method for synthesizing curcumin nanoparticles. This method prepares curcumin nanoparticles by dispersing them 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-co-glycolic acid) (PLGA) nanoparticles can also be prepared. Sari *et al.,* 2013 produced curcumin nanoparticles by this method.

Solvent Evaporation Method: The 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. The advantage of this method is that the low temperature required for evaporation of the solvent and thermal deposition can be prevented. Disadvantages are: (I) the reagents used in this method are quite expensive, (ii) the selection of proper solvent is somehow difficult, and evaporation of the organic solvent is a time-consuming process. PLGA (Poly (lactic acid-co-glycolic acid) this technique synthesizes loaded curcumin nanoparticles. Liemann *et al.,* 2013 formulated PHBV nanoparticles by a solvent evaporation method.

Microemulsion: Microemulsion is considered an ideal method for nanoparticles fabrication. The surfactants used in this method are hydrophobic for water-soluble drugs and hydrophilic in nature for oil-soluble drugs. A 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. The microemulsion technique is affected by certain parameters like temperature and pH variation. Lin *et al.,* 2009 formulated phospholipid-based curcumin-encapsulated microemulsions.

Wet Milling Method: Curcumin nanoparticles can be synthesized from a wet-milling method. Curcumin is suspended in an appropriate dispersing solvent. The obtained solution is further agitated under the ultrasonication method. Distilled water is used for the synthesis of curcumin nanoparticles. The obtained solution is then centrifuged and the formed nanoparticles are collected. Giat *et al.,* 2014 fabricated nanocurcumin by wet milling method.

Thin Film Hydration Method: In this synthesis method, herbal drugs (curcumin) and surfactants are allowed to mix in a suitable organic solvent under sonication conditions. The solvent is allowed to evaporate under certain pressure. After that, distilled water is added to the sonication condition, and the obtained nanosuspension is then centrifuged to obtain curcumin nanoparticles. Moorthi *et al.,* 2012 demonstrated curcumin nanoparticles synthesis by this method of synthesis.

Solid Dispersion Method: The matrix and hydrophobic drugs like curcumin are mixed in this method. The matrix can be amorphous or crystalline form. This method can be used to dissolve the insoluble hydrophobic drug. This is a fast and readily scalable method used for curcumin nanoparticle synthesis. Moorthi *et al.,* 2012 synthesized curcumin nanoparticles by solid dispersion method.

Emulsion Polymerization Method: Organic and continuous phase are two emulsion techniques that can be used to synthesize 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.,* 2012 reported the synthesis of curcumin nanoparticles by using this method, and piperine was used along with curcumin to increase the biological activity of synthesized curcumin nanoparticles.

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

Ionic Gelatin Method: Hydrophobic drug such as curcumin is dissolved in a proper solvent that shows complete solubility of curcumin in it, and then this solvent is added to polymeric solution under constant stirring conditions. This method

depends on the cross linking of polymer along with drugs such as curcumin. This polymer improved the solubility and stability of curcumin nanoparticles.

Ultrasonication: This method is generally employed for less water-soluble drugs. By this technique, curcumin is first dissolved in an organic solvent. The resulting solution is then added to the polyelectrolye solution under ultrasonication for several intervals and the formed curcumin nanoparticles are collected. Zhang *et al.,* 2011 synthesized curcumin nanoparticles using this ultrasonication technique.

Antisolvent Precipitation Method: Antisolvent precipitation is the method of synthesis of the poorly water-soluble drug. In this synthesis method, curcumin is dissolved in an organic solvent followed by adding this solution into the deionized water under constant stirring. Hence, curcumin nanoparticles can be synthesized by this method. Yadav *et al.,* 2014 used this method to synthesize curcumin nanoparticles. The advantage of this synthesis method is that it is suitable for synthesizing poorly soluble curcumin nanoparticles [6].

Different Types of Curcumin Delivery Systems Used In Cancer Therapy: Various delivery systems for curcumin have been formulated using different nanotechnologies to improve curcumin properties and target ability. For the rational design of the nanoformulations, several factors should be considered in order to enhance the efficacy and improve the cellular targeting of the anticancer agents.

These factors include the nanoparticle size and shape, surface properties, and nanoparticle targeting ligands, as illustrated in Figure. The summary of the most commonly used curcumin delivery systems is introduced in this section.

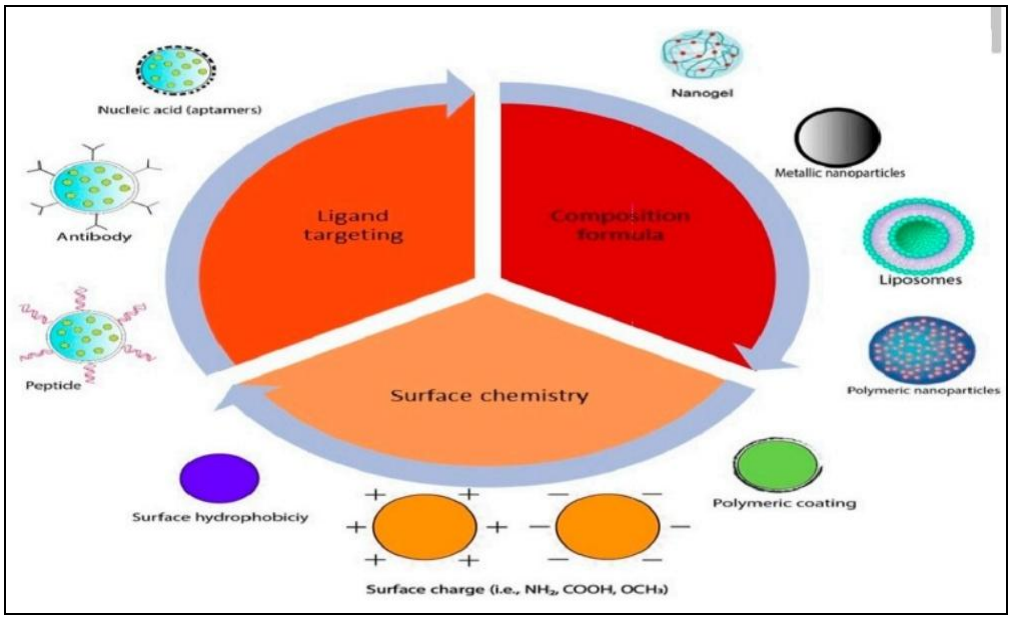


FIG. 3: EXAMPLES OF CURRENT NANOPARTICLE DESIGN STRATEGIES USED TO IMPROVE TARGETING

Polymeric Nanoparticles: Various polymers have been utilized to prepare nanoformulations for curcumin drug delivery to improve its biological activity. Biocompatible and biodegradable polymers are preferred in drug delivery systems due to the lower risk of toxicity. Therefore, biodegradable synthetic polymer delivery systems due to lower risk of toxicity. Therefore, biodegradable synthetic polymers such as PLGA (poly (D, L-lactic-co-glycolic acid) and natural polymers such as silk fibroin and chitosan have become widely used in drug delivery. PLGA-curcumin nanoformulation was found to be as effective as curcumin at 15-fold lower concentration in inhibiting mRNAs for inflammatory cytokines (CXCR3 and CXCL10) and increasing anti-inflammatory cytokine interleukin-10 (IL-10) in the brain.

In-vivo study in rats showed that the bioavailability of curcumin-PLGA nanospheres was increased

nine-fold in comparison to unprocessed curcumin administrated with alkaloid compound piperine. However, curcumin/piperine coadministration enhanced curcumin activity by inhibiting hepatic and intestinal deactivation. Another study compared the anticancer activity of curcumin-loaded PLGA nanoparticles (CUR-NPs) and curcumin-loaded PLGA nanoparticles conjugated to anti-P-glycoprotein (P-gp) (CUR-NPs-APgp). The latter formulation showed significantly more specific binding to cervical cancer cells KB-3-1 but lower entrapment efficiency CUR-NPs. Spherical PLGA nanospheres were also developed to encapsulate dimethyl Curcumin (ASC J9) and tested in breastcancer cells. The PLGA nanospheres were capable of releasing ASC-J9 intracellularly, leading to growth inhibition of estrogen-dependent MCF-7 cancer cell [7]. Curcumin nanoparticles inhibit the growth of brain tumor cells. Curcumin nanoparticles inhibit the growth of brain tumor cell lines via programmed cell death and G2 /M cell cycle arrest. Nanocurcumin treatment caused a dose-dependent decrease in cell growth as measured by MTS assay in multiple malignant brain tumor cell lines. After 3 days of treatment using 10 μM curcumin, we noted a statistically significant 35% growth reduction in adherent DAOY medulloblastoma cells. A second non-adherent line, D283Med, had growth inhibited by 87% over a somewhat longer period. To investigate the specificity of the observed inhibitory effects, we also examined NIH-3T3 cells. Although free curcumin concentrations above 30 μM had been previously shown by Jiang *et al.* 17 to be toxic in NIH-3T3 cells, the doses of nanocurcumin (up to μM) used in this study slowed or arrested brain tumor growth resulted instead in the increased growth rate of NIH-3T3 cells. This suggests that the effects are somewhat selective and do not inhibit cellular proliferation and growth in all cells at these doses [8].

Curcumin as a Traditional Therapeutic agent: In Indian and Chinese medicine, for centuries, curcumin has been used as a wound healing agent and in curing many diseases. Curcumin has been recognized as one of the most active therapeutic agents of turmeric due to its anti-inflammatory, antioxidant, anticancerous, and antimicrobial effect. Reported curcumin as a potential agent in the therapy of Alzheimer's disease, rheumatoid arthritis, metabolic syndrome, neurodegenerative and cardiovascular diseases, *etc* [9].

Role of Curcumin in the Treatment of Chronic Inflammatory Diseases: In various chronic illnesses in which inflammation is known to play a major role, curcumin has been shown to exhibit therapeutic potential. These diseases include Alzheimer's disease (AD), Parkinson's disease, multiple sclerosis, epilepsy, cerebral injury, CVDs, cancer, allergy, asthma, bronchitis, colitis, rheumatoid arthritis, renal ischemia, psoriasis, diabetes, obesity, depression, fatigue and AIDS [10].

Different Properties of Curcumin [11]:

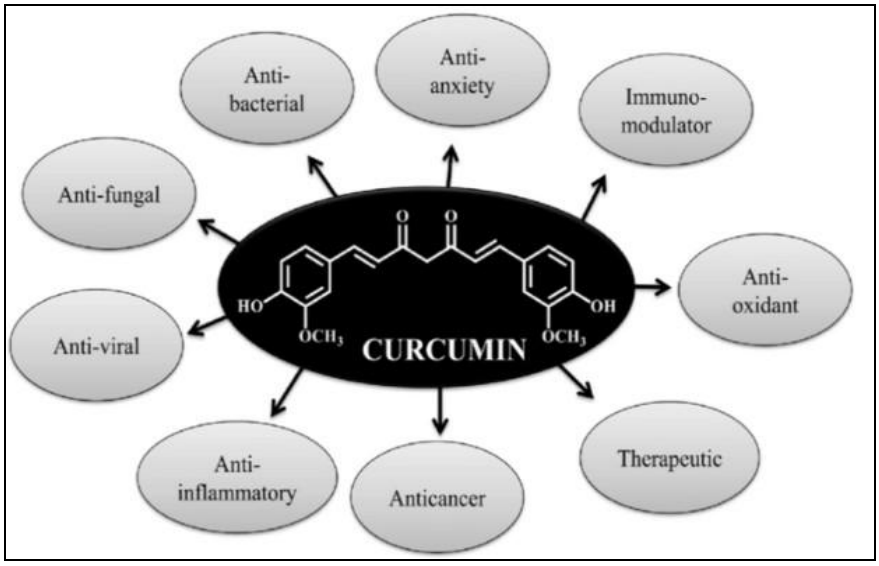


FIG. 4: DIFFERENT PROPERTIES OF CURCUMIN

Anti-oxidant Properties of Curcumin:

- Curcumin is known to protect bimembranes against peroxidative cell membrane damage (free radical-mediated chain reaction)

- Free-radical-mediated peroxidation of membrane lipids and oxidative damage of DNA and proteins are believed to be associated with a variety of chronic pathological complications such as cancer, atherosclerosis, and neurodegenerative diseases; curcumin is thought to play a vital role against these pathological conditions [12].

Anti-bacterial Activity: Bacterial infections are among the important infectious diseases. Hence, over 50 years of extensive research have been launched for achieving new antimicrobial medicines isolated from different sources. Despite progress in the development of antibacterial agents, there is still a need to find new antibacterial agents due to the development of multidrug-resistant bacteria. The antibacterial study on aqueous extract of *C. longa* rhizome demonstrated the MIC (minimum inhibitory concentration) value of 4 to 16 g/L and MBC (minimum bactericidal concentration) value of 16 to 32 g/L against S. epidermis ATCC 12228, Staph. aureus ATCC 25923, *Klebsiella pneumoniae* ATCC 10031, and *E. coli* ATCC 25922. The methanol extract of turmeric revealed MIC values of 16 µg/mL and 128 µg/mL against *Bacillus subtilis* and *Staph. aureus*, respectively.

Anti-viral Activity: The lack of effective therapeutics for most viral diseases, the emergence of antiviral drug resistance, and the high cost of some antiviral therapies necessitate finding new effective antiviral compounds. Additionally, the existing antiviral therapies are not always well-tolerated or quite effective and satisfactory.

Hence, the increasing requirement for antiviral substances will be highlighted. Plants, as a rich source of phytochemicals with different biological activities, including antiviral activities, are interesting to scientists. It has been demonstrated that as a plant derivative, curcumin has a wide range of antiviral activity against different viruses. Inosine monophosphate dehydrogenase (IMPDH) enzyme due to rate-limiting activity in the de novo synthesis of guanine nucleotides, is suggested as a therapeutic target for antiviral and anticancer compounds. Among the 15 different polyphenols, curcumin, through inhibitory activity against IMPDH effect in either a noncompetitive or competitive manner, is suggested as a potent antiviral compound via this process. The study of different bioconjugates of curcumin, namely, di-O-tryptophenylphenylalanine curcumin, di-O-decanoyl curcumin, di-O-pamitoyl curcumin, di-O-bis-(γ,γ) folyl curcumin, C4-ethyl-O-γ-folyl curcumin, and 4-O-ethyl-O-γ-folyl curcumin, against variety of viruses including parainfluenza virus type 3 (PIV-3), feline infectious peritonitis virus (FIPV), vesicular stomatitis virus (VSV), herpes simplex virus (HSV), flock house virus (FHV) and respiratory syncytial virus (RSV) assessed by MTT test showed the potent antiviral activity of curcumin and its bioconjugates against different viral pathogens for further studies. Also, di-O tryptophanylphenylalanine curcumin and di-O-decanoyl curcumin revealed remarkable antiviral activity against VSV and FIPV/FHV with EC50 values of 0.011 µM and 0.029 µM, respectively. However, bioconjugates did not exhibit significant antiviral activity against IIIB and ROD strains of type 1 human immunodeficiency virus (HIV-1) in MT-4 cells].

Anti-fungal Activity: Substances and extracts isolated from different natural resources, especially plants, have always been a rich arsenal for controlling fungal infections and spoilage. Due to the extensive traditional use of turmeric in food products, various researches have been done to study turmeric and curcumin to control fungal-related spoilage and fungal pathogens. The study of adding turmeric powder in plant tissue culture showed that turmeric at 0.8 and 1.0 g/L had appreciable inhibitory activity against fungal contaminations.

The methanol extract of turmeric demonstrated antifungal activity against Cryptococcus neoformans and *Candida albicans* with MIC values of 128 and 256 µg/mL, respectively. The study of hexane extract of *C. longa* at 1000 mg/L demonstrated antifungal effect against *Rhizoctonia solani*, *Phytophthora infestans*, and *Erysiphe graminis*. It was also shown that 1000 mg/L of ethyl acetate extract of *C. longa* exhibited an

inhibitory effect against *R. solani*, *P. infestans*, *Puccinia recondita* and Botrytis cinerea. Curcumin at 500 mg/L also showed antifungal activity against *R. solani*, *Pu. recondita*, and *P. infestans. Curcumin* and turmeric oil exert antifungal effects against two phytophagous fungi, namely, *Fusarium solan*i and *Helminthosporium oryzae*. Turmeric oil exhibited the most effective antifungal activity against *F. solani* and *H. oryzae* with IC_{50} of 19.73 and 12.7 µg/mL, respectively. The crude methanol extract of *C. longa* has an inhibitory effect against some clinical isolates of dermatophytes [13].

Immunomodulatory activity of Curcumin: The effect of curcumin on the development of T cell-mediated immunological responses largely remains unknown. In this study, we have investigated the effect of curcumin on mitogen/antigen-induced proliferation of splenic lymphocytes, induction of cytotoxic T lymphocytes (CTLs), lymphokine activated killer (LAK) cells, and the production of cytokines by T lymphocytes and macrophages. We found that mitogen, interleukin-2 (IL-2) or alloantigen-induced proliferation of splenic lymphocytes and development of cytotoxic T lymphocytes is significantly suppressed at 12.5-30 micromol/L curcumin.

The generation of LAK cells at similar concentrations was less sensitive to curcumin's suppressive effect than the generation of antigen-specific CTLs. Curcumin irreversibly impaired the production of these immune functions since lymphoid cells failed to respond to the activation signals following 8h pretreatment with curcumin. Curcumin also inhibited the expression/production of IL-2 and interferon-gamma (IFN-gamma) by splenic T lymphocytes and IL-12 and tumor necrosis factor-alpha (TNF-alpha) by peritoneal macrophages irreversibly. Curcumin inhibited the activation of the transcription factor nuclear factor kappaB (NF-kappaB) without affecting the levels of constitutively expressed NF-kappaB. The latter result suggests that curcumin most likely inhibits cell proliferation, cell-mediated cytotoxicity (CMC), and cytokine production by inhibiting NF-kappaB target genes involved in the induction of these immune responses [14].

Neurodegenerative Alzheimer's and Brain diseases: Many human diseases evolve in the central nervous system (CNS), brain, or spinal cord. Delivery of curcumin at these sites requires overcoming the blood-brain barrier (BBB) complexity. A promising strategy is functionalizing apolipoprotein E (ApoE)-derived peptides (residues 141–150) to nanoparticles. Alzheimer's disease (AD) progresses with the accumulation of β-amyloid peptide (Aβ) in senile plaques, which is toxic to species in monomeric and fibrillary form and is a hallmark lesion of AD. Curcumin is a molecule that can target amyloid pathology; therefore, curcumin delivery has received great attention, and its imaging capacity offers diagnostic capabilities.

Advantages and Disadvantages of Nanoparticles [16, 17]:

TABLE 1: ADVANTAGES AND DISADVANTAGES OF NANOPARTICLES

Types	Advantages	Disadvantages
Gold nanoparticles	Increased contrast less invasive. No photo bleaching	Biocompatibility. Optical signal not strong. Toxicity. Tumor targeting efficacy low.
Quantum dots	Multiple molecular targets simultaneously Fluorescence of high quality and energy	Toxicity effect of metal core
Nanocapsule	Effecient drug accumulation at site sustained drug release for weeks	Large dispersion of encapsulated actives
Carbon nanotubes	Less cytotoxic	Currently the process is relatively expensive to produce nanotubes
Liposomes	Biocompatibility biodegradability Isolation of drug from surrounding environment Ability to entrap both hydrophilic and hydrophobic drugs	Leakage and fusion of encapsulated drugs/ molecules Fewer stables. High production costs Short half-life. Low solubility

Biodegradable PLGA–curcumin nanoformulations exhibit nontoxicity in human neuroblastoma SK-N-SH cells and protect H_2O_2- induced elevation of ROS. This formulation can prevent the induction of the redox-sensitive transcription factor Nrf in the presence of H_2O_2, indicative strategy to protect

neurons against oxidative damage commonly observed in AD. Additionally, curcumin formulations containing biotin coupling poly (ethylene glycol) ylated (PEGylated), biodegradable poly (alkyl cyanoacrylate), PEG liposomes with the anti-transferrin lipid conjugate liposome nanoliposomes PEG–polylactic acid block co-polymer and click-chemistry-based nanoliposomes have shown aggregation inhibition of Aβ and toxicity rescues Aβ, indicative of AD treatment and diagnosis [15].

CONCLUSION: Curcumin nanoparticles have been proven effective against various diseases like cancer, alzhemiers, diabetes, strokes, *etc*.

They also possess potential immunomodulatory activity; being obtained from a natural source, they offer added advantages like minimal side effects and increased bioavailability. This review suggests curcumin nanoparticles as promising delivery systems and recommends further study for future prospectives.

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