

Multifaceted Role of a Marvel Golden Molecule, Curcumin: a Review

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Moselhy, *et al.*: Multifaceted Role of Curcumin

Curcumin is chemically known as diferuloylmethane, which is an important nutraceutical obtained from the yellow spice *Curcuma longa*. It has been used traditionally as a folklore medicine in countries like India, China and Thailand for nearly 2000 years without any prior knowledge of the mechanism of action. Cell-based studies and clinical trials that have been reported so far have provided evidence that curcumin could be effectively used as antimicrobial, anticancer, antidiabetic, antiinflammatory, antimalarial and antioxidant. There are more than 9400 articles published on this “magical molecule” till date. Furthermore, nearly 100 clinical trials have been done using curcumin, which demonstrated safety, efficacy and prophylactic activity of curcumin. On the molecular level, curcumin has shown to modulate several crucial and significantly interlinked pathways in rendering an optimistic outcome against life-threatening diseases like cancer, diabetes, lupus nephritis, and other autoimmune and neurodegenerative diseases. In this communication, the chemical structure, biological properties and possible molecular targets of curcumin have been reviewed along with some recent developments in drug delivery systems of curcumin.

Key words: Curcumin, *Curcuma longa*, turmeric, antimicrobial, anticancerous, antiinflammatory, antioxidative, curcumin-delivery systems

Natural products and their derivatives have been the centre of attraction for researchers globally for the past few decades due to their wide therapeutic and clinical applications. This concept may seem recent to us but our ancestors have been benefiting from them since the time immemorial without any prior knowledge of the mechanisms involved or the bioactive components of the derivatives. There has been a spurt in the production of synthetic drugs and pharmaceuticals addressing many health disorders and diseases but the side effects and inefficiency caused due to them has craved the researchers to explore the properties of natural products, which are much more effective with minimized side effects than their synthetic counterparts.

Curcumin (CUR) is extracted from the rhizomes of a perennial herb, *Curcuma longa* (fig. 1). CUR has gained immense interest in the scientific community due to its antibacterial^[1], antifungal^[2] antiviral^[3], anticancer^[4], antiinflammatory^[5], antimalarial^[6], antioxidant^[7] and wound healing^[8] properties. Asian countries like India

and China have used turmeric as a traditional medicine for nearly 2000 y in the form of a paste or in oral form to treat various ailments of skin and illnesses successfully until the modern medicine found it prominent in the last two centuries. CUR was isolated in crystalline form in the year 1870 and the complete structure was elucidated in 1910.

PHYSIOCHEMICAL PROPERTIES OF CUR

Primary extracts from *C. longa* yielded 3 curcuminoids namely curcumin (PubChem CID: 969516), demethoxycurcumin (PubChem CID: 5469424) and bisdemethoxycurcumin (PubChem CID: 5315472) as depicted in fig. 2, all of which are polyphenols,

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Fig. 1: Morphology of *Curcuma longa* plant and its rhizome

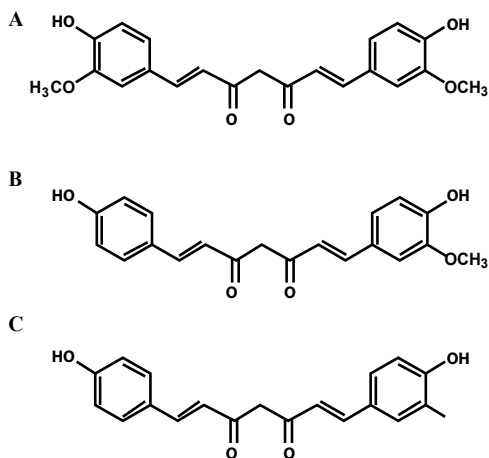


Fig. 2: Primary extracts of the *Curcuma longa* plant
(A) Curcumin (diferuloylmethane PubChem CID: 969516),
(B) demethoxycurcumin (PubChem CID: 5469424) and (C)
bisdemethoxycurcumin (PubChem CID: 5315472)

wherein the phenolic groups are inter-connected with unsaturated carbonyl groups.

CUR, chemically 1,7-Bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione is the most widely studied and active component, comprising of monocyclic sesquiterpenes and oxygenated derivatives with a melting point of 183^o[9]. CUR doesn't dissolve readily in water but dissolves in acetone, methanol and dimethyl sulfoxide. The absorption coefficient of CUR is 415-420 nm and 430 nm in acetone and methanol, respectively^[10]. In addition to the above-mentioned curcuminoids, turmeric also contains some volatile oils like tumerone, zingiberone, atlantone, proteins, sugars and resins but except CUR, no other constituent of turmeric was found to be antiproliferative and antiinflammatory.

CUR, A STRONG ANTIOXIDANT

The lipophilic nature of CUR made it an active antioxidant in radical scavenging of superoxide anions and DPPH. The antioxidant property of CUR is by virtue of its perfectly arranged structure, wherein the

two α , β unsaturated carbonyl groups arranged in stable enol form, interconnects the two methoxylated phenols. The bioactivity of CUR is attributed to its phenolic O-H and the C-H groups. CUR is also involved in the inhibition of lipid peroxidation using a polyunsaturated fatty acid-linoleate, which is later oxidized to form a fatty acid radical. CUR is also involved in the neutralization of lipid radicals and participate in the intermolecular Diels-Alder reaction by breaking the chain at the 3' position^[11]. Apart from lipid peroxidation inhibition, free radical scavenging activity of CUR has been demonstrated in *in vitro* and *in vivo* models by using peritoneal macrophages of a rat model^[12]. Macrophages produce various reactive oxygen species (ROS) like hydrogen peroxide, nitrite radicals and superoxide anions, which are actively scavenged by CUR.

The oxidative stress induced by the body due to the insults from the entry of pathogens or the other factors leads to the upregulation of inducible nitric oxide synthase (iNOS), which is commonly found in macrophages. iNOS produced large amounts of nitric oxide (NO), which further react with superoxide radicals in the surrounding oxidative environment to form peroxynitrite as a toxic product, which was found to be quite lethal to cells. CUR is reported to downregulate the activity of iNOS and reduces the levels of ROS in the cells. Additional studies pertaining to the microglial cells have proved that this antioxidant spice could protect the neural cells against oxidative damage by reducing the output of NO generation and also could reduce the neuroinflammation caused due to some chronic neurodegenerative disorders like Alzheimer's disease^[13].

CUR EXERTS CONSIDERABLE ANTIINFLAMMATORY EFFECT

The role of CUR as a potent natural antiinflammatory agent has been investigated in many chronic diseases like arthritis, diabetes, inflammatory bowel disease, cardiovascular diseases and Alzheimer's disease. CUR inhibited many inflammatory mediators as depicted in fig 3. Further, it modified the expression of tumour necrosis factor- α (TNF- α) by inhibiting p300/CREB-specific acetyltransferase, which in turn caused the repression of acetylation of histone or non-histone proteins resulting in the inhibition of transcription^[14]. Additionally, this lipophilic polyphenol also affected the methylation pattern of the TNF- α promoter^[15] and hence regulating the expression of TNF- α . The

BACTERIOCIDAL AND BACTERIOSTATIC EFFECTS OF CUR

Bacterial infections and diseases have given a tough time to the researchers worldwide and kept them on their toes to constantly develop new drugs to combat these dreadful diseases. However, after an extensive research of nearly 50 y, new antimicrobial drugs have been successfully isolated from different sources. Despite all the technological developments, the need to find new alternative sources still remains a necessity due to the rapid development of multi-drug resistant bacteria (MDR). Different extracts of CUR have demonstrated to exert a bacteriostatic or a bactericidal effect on many strains of bacterial species at different concentrations. The aqueous extract of *C. longa* was proven to be quite effective in the antibacterial study against *Klebsiella pneumonia* ATCC 10031, *Staphylococcus epidermis* ATCC 12228, *S. aureus* ATCC 25923 and *Escherichia coli* ATCC 25922 with an minimum bactericidal concentration value of 16 to 32 g/l and minimum inhibitory concentration (MIC) value of 4 to 16 g/l^[20]. The highest antimicrobial activity was evidenced with ethanol and hexane extract of CUR against 24 pathogenic bacteria, isolated from shrimps and chicken^[21].

In a different study, methanol extract of CUR was evaluated against *Bacillus subtilis* and *S. aureus* and it was concluded that the extract was quite effective even at minimal concentrations^[22]. In a separate study, bactericidal effects were observed with hexane and methanol extracts of *C. longa* against 13 species of bacteria, which included *B. subtilis*, *B. cereus*, *Vibrio cholera*, *V. harveyi*, *V. vulnificus*, *V. parahaemolyticus*, *V. alginolyticus*, *Aeromonas hydrophilia*, *Streptococcus agalactia*, *Staphylococcus aureus*, *S. epidermidis*, *S. intermedius* and *Edwardsiella tarda*^[23]. It has also been reported that CUR exhibited poor antimicrobial activity (5.9 %) in the elimination of *Helicobacter pylori* infection in patients as compared with OAM (omeprazole, amoxicillin and metronidazole) treatment (78.9 %)^[24]. The inflammation of gastric tissue due to *H. pylori* infection of the stomach was reduced by CUR due to the apparent blockage of NF-κB pathway activation and as a consequence, the release of IL-8 was inhibited, accompanied by the prevention of degradation of IB^[25].

Additionally, *in vitro* studies were carried out with three new compounds of CUR namely indium curcumin, diacetyl curcumin and indium diacetyl curcumin against

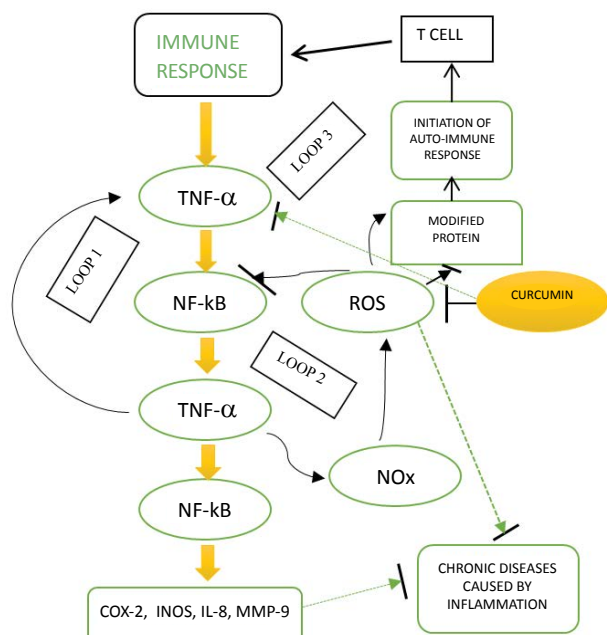


Fig. 3: Modulation of different inflammatory pathways by curcumin

lipopolysaccharide (LPS)-mediated induction of cyclooxygenase-2 (COX-2) expression is inhibited by the surface application of CUR, which reduced the formation of prostaglandin synthase E2. However, in macrophages, CUR raised the levels of COX-2, which was independent of LPS-mediated induction. It has also been demonstrated that CUR downregulated the secretion of inflammatory cytokines^[16] and hence minimized the toxic effects in adipocytes and exerted a cytoprotective effect in a dose-dependent manner. CUR also eased the inflammatory responses associated with asthma by down-regulation of expression of interleukin-1B (IL-1B), IL-6 and TNF-α by activating NrF2/HO-1^[16].

This antiinflammatory phytochemical also inhibited the expression of IL-6 and IL-1B, through many signalling pathways like mitogen-activated protein kinase and nuclear factor kappa-B (NF-κB) pathways in TNF-α treated HaCaT cells. It has also been found that CUR downregulated the expression of IL-8, IL-1B, MMP-8, TNF-α and acute phase proteins and hence protecting rats from paracetamol-induced cytotoxicity^[17]. Two novel synthetic analogues of curcumin-C66 and B06 have been reported recently, which prevented the activation of JNK/NF-κB signalling by downregulating the mRNA levels of COX-2, TNF-α, IL-6, IL-1 and iNOS, therefore reducing the production of NO and TNF-α in primary peritoneal macrophages stimulated by high glucose^[18,19].

E. coli, *P. aeruginosa*, *S. aureus* and *S. epidermis*. It was reported that the antibacterial activity of indium curcumin was far better than that of curcumin and diacetyl curcumin was found to be ineffective^[26]. To overcome the incidences of the development of drug resistance by different microbial strains, synergistic effects of the existing drugs with the combination of plant derivatives are being explored currently.

For instance, the resistance of *S. aureus* to penicillin is on the rise accompanied by adverse side effects like anaphylactic reactions and hyper sensitivity^[27]. Therefore, the synergistic studies of curcuminoids with ampicillin has resulted in a drastic reduction of MIC against *S. aureus* ATCC 25923 strain. Now with the development of nanotechnology, the use of strongly bound metal complexes and silver nanocomposite films against several strains of pathogenic species of bacteria has opened the gates of new avenues with high antibacterial effects in treating MDR infections

CUR: A POTENT ANTIMYCOTIC CHEMOPREVENTIVE

With the rise in the mortality and morbidity due to the rise in the fungal infections, there is an urgent need to explore alternative and new sources of drugs, which can inhibit the growth of these deadly pathogens. The resistance of pathogenic strains of fungus and ineffectiveness of the available drugs remains a problem that needs to be addressed. Many phytochemicals extracted from different natural sources have been tested successfully in *in vitro* and *in vivo* studies during the recent years. In a study conducted on the inhibitory effect of ethyl acetate extract of *C. longa*, it was observed that at a concentration of 0.001 g/ml, it inhibited the growth of *Puccinia recondite*, *P. infestans*, *Rhizoctonia solani* and *Botrytis cinerea*. At the same concentration of 0.001 g/ml, hexane extract of *C. longa* was found to be effective against some species of *Erysiphe graminis*, *Phytophthora infestans* and *R. solani*^[28]. However, the methanol extract showed appreciable antifungal activity at MIC values of 2.56 and 128 g/ml against *Candida albicans* and *Cryptococcus neoformans*, respectively^[22].

Turmeric oil has been proved to be effective in combating many plant fungal pathogens like *Helminthosporium oryzae* and *Fusarium solani*. In an interesting study conducted, the most effective inhibition was demonstrated at an IC₅₀ of 12.7 and 19.73 g/ml, respectively against *H. oryzae* and

F. solani^[29]. *Trichophyton rubrum* infected guinea pigs were chosen as the animal models for *in vivo* study to examine the healing effect of the topically applied turmeric oil. At a dilution rate of 1:80 it effectively cured the wounds within a week. The mechanism by which this antifungal effect is exerted is quite simple and involved the production of ROS leading to cell death due to rapid accumulation of biosynthetic precursors of ergosterol, via down-regulation of its production due to decreased turnover of $\Delta^{5,6}$ -desaturase (ERG3) enzyme^[30]. Apart from this, some other possible factors like changes in the membrane bound ATPase activity and reduction in the secretion of proteinase could be anticipated. Many species of *Candida* have become resistant to the excessive use of the existing drugs. Hence, finding new drugs with inhibitory effects against these fungal species have become the biggest challenge for the researchers.

In a clinical study, CUR has demonstrated to be an effective fungicide against 14 strains of candida including 4 ATCC strains with MIC values ranging from 250 to 2000 g/ml^[31]. In an intriguing study, the antifungal activity with CUR was effectual against some fluconazole resistant strains^[32]. The basis of the mechanism of action of CUR on candida is speculated to be intracellular acidification via inhibition of H⁺ extrusion leading to cell death^[32]. To enhance the efficacy of the existing fungicidal drugs, many combinations of CUR have been tried and tested successfully with an appreciable reduction in MIC values. The synergistic studies of CUR along with, itraconazole, voriconazole, miconazole, ketoconazole, fluconazole, nystatin and amphotericin B have shown a 10-35 fold reduction in the MIC values of the drugs against 21 clinical isolates of *C. albicans*^[33]. Indeed, the systemic fungal infections like candidemia and candidosis can be effectively treated with the different synergistic combinations of CUR with these fungicides saving the time and resources.

CUR CAN ACT AS AN ANTITUMOUR AGENT

During recent years, many researchers have reported affirmative results of CUR as an antitumour agent in *in vitro* and *in vivo* experiments against different tumours^[3,34]. The basis of the chemopreventive and anticarcinogenic effect of the CUR is attributed to its selective targeting of growth factors, transcription factors, apoptotic genes, adhesion molecules, angiogenesis regulators and cellular signalling

molecules. These different pathways modified by curcumin in different tumours are described in Table 1^[35-45].

CUR is reported to exert its antitumour effect by initiating either intrinsic (mitochondrial) or extrinsic (receptor-mediated) apoptotic pathways. The tumour suppressor p53 played a pivotal role in initiating a caspase cascade through the immediate activation of pro-apoptotic proteins of B-cell lymphoma 2 (Bcl-2) family like Bcl-2 associated X protein (Bax) and Bcl-2 homologous antagonist killer (Bak). These Bax and Bak perforate the mitochondrial membrane to release cytochrome c into the cytoplasm promoting mitochondria-mediated apoptosis. CUR also exhibited the ability to inhibit antiapoptotic proteins, Bcl-2 and B-cell lymphoma extra-large (Bcl-xL). Molecular docking studies reported by Luthra *et al.* confirmed the inhibition of Bcl-2 by direct binding of CUR to the second cavity of the protein, through the intermolecular interactions of amino acids^[46].

Guo *et al.* demonstrated that CUR inhibited the growth of colorectal carcinoma LoVo cells by initiating a caspase cascade at a significant concentration of 0-30 μ M. Moreover, the nuclear staining by Annexin V/PI was found to be positive, confirming the activation of apoptotic machinery^[47]. Recently, several reports have confirmed the antiproliferative action of CUR in cancers of breast, pancreas and lung through the down-regulation of epidermal growth factor receptor (EGFR), which is usually highly upregulated in tumour circumstances^[48].

The cell cycle is tightly regulated by a group of cell cycle regulatory proteins called cyclins and cyclin-dependent kinases (CDK), which regulate the proliferation of cells. But in tumours, these regulatory proteins are upregulated, leading to the rapid proliferation of cells.

However, CUR exerted its inhibitory effect on these regulatory proteins and inhibited the proliferation eventually^[49].

Accumulated evidence showed that CUR not only checked the proliferation of cancerous cells or inhibited ROS, but also promoted apoptosis via induction of expression of different secondary messengers like NO synthase, COX-2, matrix metalloproteinase-2 and matrix metalloproteinase-9 in tumour cells^[50]. Sethi and colleagues have reported that abnormal inflammatory signalling pathways also played a pivotal role in the advancement and growth of several cancers^[51]. NF- κ B is one such important inducible transcription factor, which can significantly regulate the inflammatory cytokines like IL-1 β , IL-6, IL-8 and TNF- α ^[52]. This NF- κ B signalling pathway is activated in most of the cancers and recently CUR has shown to inhibit this pathway gathering further interest of researchers towards the exploitation of this pathway in treating tumours^[53].

Additionally, several studies have reported that CUR acted as a chemosensitizer for tumour cells without affecting the normal cells at the molecular level. Global Clinical studies were performed on CUR to prove its efficacy in the treatment of patients with pre-invasive malignant or high-risk pre-malignant conditions. There are many studies, which showed that CUR has been effective against the cancers of breast, colon, stomach, pancreas, skin and oral cavity.

Pharmacodynamic studies were conducted by Garcea *et al.*^[54] with 12 patients suffering from colorectal cancer of different stages. It was concluded that after administration of varying doses of CUR from 450-3600 mg per day for seven days, there was a decrease in M₁G levels from 4.8 \pm 2.9 adducts per 107 nucleotides in malignant colorectal tissue to

TABLE 1: MOLECULAR TARGETS AND THE PATHWAYS MODIFIED BY CURCUMIN IN VARIOUS TUMORS

Molecular targets	Cell line/cancer	Reference
Apoptosis via PI3K/Akt pathway	SKOV3	[35]
Inhibition of NF κ B pathway	Colorectal cancer	[36]
Modulation of cell cycle	Ehrlich's ascites carcinoma (EAC)	[37]
Inhibition of EGF-mediated tyrosine kinase activity	A431	[38]
Increase in caspase-3 and caspase-9 activities	MCF-7	[39]
STAT-3 mediated down-regulation of Bcl-XL and survivin	NCI-H446 and NCI-1688	[40]
Induction of autophagy	SCC	[41]
G ₀ /G ₁ Cell cycle arrest	SK-MEL-37, MCF-7, Rh1, Rh30, PC-3, DU145 and HeLa	[3,42,43]
Inhibition of VEGF, c-jun-p, and MMP-2/-9	A549 cells	[44]
Inhibition of microtubule polymerization	B16-F10 skin cells	[45]

2.0±1.8 adducts per 107 nucleotides, without any change in the levels of COX-2 protein levels. Hence, they suggested a safe dosage of 3.6 g per day without any adverse effects^[54]. Braumann *et al.* presented a case report stating that good partial remission was observed in a 75-y-old patient with colon cancer metastatic to the liver, after administration of leucovorin, 5-fluorouracil and oxaliplatin in combination with 5 g of CUR daily, for five months^[55]. Hence, it can be conjectured from the on-going discussion that CUR can serve as an effective anticancer chemopreventive agent against different tumours.

CAN THESE BIOAVAILABILITY ISSUES OF CUR BE RESOLVED?

In a joint report released by the World Health Organization and Food and Agriculture Organization on food additives, it was recommended that the maximum daily intake of CUR without any possible adverse effects to be 0-1 mg/kg. An interesting chronic toxicity study has reported that the maximum daily dose of CUR can be up to 8 g when administered orally^[56]. In the *in vivo* studies conducted on rats, it was described that after administration of an oral dose of 1 g/kg, nearly 75 % of CUR was excreted in faeces and a considerable amount was seen in urine^[57].

While human pharmacokinetic studies have reported that the plasma levels of free CUR remained at 25 nmol when CUR complex was administered orally at a dose of 3.6-12 g daily for a week or longer^[58]. Whatever be the activity and the effect of a compound in *in vivo* system, the bioavailability always played a crucial role in determining the efficacy of the drug. While examining the properties of CUR, it was contemplated that the ineffectiveness of the CUR is exclusively due to low water solubility and poor intestinal permeability. Curcuminoids are insoluble in water and are excessively sensitive to pH, light, oxygen levels and also to the solvent system employed to dissolve them.

Aggarwal and colleagues reported in their research that the maximum solubility of CUR was as low as 11 ng/ml in an aqueous buffer with a pH of 5.0^[59]. While in a different study reported by Bernabé-Pineda *et al.*, it was concluded that, at high pH values (>11.7), there was an improvement in the stability of CUR^[60]. At a pH of 7.4, there was a rapid degradation of CUR. There was a steep decrease in the absorbance at 426 nm, from 50 % in 5 min to just 10 % after 10 min. New absorption coefficients were obtained

at 210 and 262 nm. Moreover, it was demonstrated that the final resulting solution was colourless, suggesting that the yellow conjugated system did not exist anymore in the degradation products. In addition, poor intestinal permeability has been a major obstacle in retaining the drug in the system for an extended period. In an interesting study, Ravindran and Chandrasekhara assessed that the poor permeability of CUR and the apparent permeability coefficients (Papp) using a Caco-2 cell line^[61]. For the basolateral-apical study, Papp was found to be $2.55 \pm 0.02 \times 10^{-6}$ cm/s and for apical-basolateral study, it was calculated to be $2.93 \pm 0.94 \times 10^{-6}$ cm/s. When further studies were done on lysed cells, it was revealed that more than 20 % of CUR was accumulated in the cells and nearly 11.78 % was metabolized during transport. Thus, it was concluded that the intracellular accumulation and first-pass metabolism in the intestine played a major role in decreasing the efficacy of CUR.

D'Souza and Devarajan suggested that the bioavailability largely depended on the stability of the drug in the gastrointestinal tract, which increased the absorption manifold. Hence, galectin-mediated absorption using galactose polysaccharides like arabinogalactan and kappa-carrageenan have been quite promising to enhance the bioavailability to nearly 25 %^[62].

CUR DELIVERY SYSTEMS

The retention of the drug for an extended period of time in the biological system and bypassing the first-pass metabolism is crucial in making any drug effective. To achieve this target, researchers have developed novel delivery systems, which aim at enhancing the bioavailability of CUR. With the increase in the pace of development of technology and incorporation of modern techniques in research, the use of solid CUR-loaded nanoparticles, hydrogels, microemulsions, transdermal delivery systems and implantable devices have gained momentum. Though there are many delivery systems in use, but in the following section, we have explored selected delivery systems of CUR, which are widely used currently.

Liposomes:

Liposomes are bilayered spherical vesicles possessing an aqueous interior, formed by the self-association of amphiphilic phospholipids and cholesterol molecules. The lipophilic part of CUR can be successfully trapped in the lipophilic core of the liposomes, hence, enhancing

the solubility significantly. Kusano *et al.* demonstrated that the oral administration of liposome-encapsulated CUR showed increased bioavailability, compared to nascent CUR^[63]. In another study, it was reported that silica-coated liposomes loaded with CUR and N-trimethyl chitosan chloride-coated CUR liposomes exhibited increased bioavailability compared to uncoated liposomes or suspension of CUR^[64].

In another distinguished study, Li and co-workers reported that a liposomal formulation of CUR using dimyristoyl-sn-glycero-3-phosphocholine (DGPC) was tested on human pancreatic cancer cells for the modification of pathways like apoptosis, angiogenesis, and proliferation. When this formulation was administered at 40 mg/kg for 3 times a week, it arrested the proliferation of MiaPaCa2 and BXP3 tumours in a xenograft murine model demonstrating the efficacy of liposomes as an effective delivery system^[65]. However, this delivery system has some disadvantages as well, like difficulty in sterilization, low drug loading, stability and poor batch to batch reproducibility^[66].

Microemulsions/self-emulsifying emulsions:

These are dynamic microstructures formed spontaneously by the combination of hydrophilic and lipophilic excipients in the presence of appropriate surfactants. These formulations are thermodynamically stable, transparent and optically isotropic and are regarded as ideal delivery systems with a faster rate of drug diffusion and high solubilisation capacity. Due to the lipophilic nature of CUR, it can not only pass through the cell membrane but also pass through the skin as reported by Teichmann *et al.*, that the oil in water microemulsions of CUR can penetrate up to the follicular infundibula via *stratum corneum*^[67].

Self-micro emulsions are more effective than emulsions when administered orally as they can form microemulsions with particle sizes of less than 100 nm under suitable gastrointestinal conditions. Self-micro emulsions are obtained by blending surfactants, co-surfactants, oil and the drug molecule to yield an isotropic mixture without a water phase, which renders it more stable.

When these microemulsions or self-micro emulsions are loaded with CUR, they deliver it in an absorbable form, enhancing the absorption and penetration to reach epithelial cells. Moreover, it has been demonstrated that the microemulsion droplets can be taken up by lymphatic tissues from the perfusion of the self-microemulsion. Bergonzi *et al.* formulated an

o/w emulsion to enhance the stability and solubility by using food grade components^[68]. They investigated the absorption potential of the oral CUR emulsion using parallel artificial membrane permeability assay in *in vitro* studies. This technique instantly measures the ability of the compound to passively diffuse through an artificial membrane. It was demonstrated that the permeation amount of the optimized microemulsion through the artificial membrane was 17.44 µg after 6 h and about 120.12 µg after 24 h with a solubility of 14.57 mg/ml. Whereas, the free curcuminoids dissolved in free PBS diffused at much lower speeds. But if buffer solution was used, the permeation amount was just 0.17 µg at 6 h and 1.66 µg after 24 h. It has been reported in various studies that the new self-microemulsifying systems in pellet and liquid forms are more stable and hence are being exploited by the researchers worldwide yielding promising results.

Sethacheewakul *et al.* studied the development and formulation of self-microemulsifying drug delivery systems (SMEDDS) in both pellet and liquid forms, which resulted in an increased solubility and stability in both *in vitro* and *in vivo* models^[69]. An optimized formulation of SMEDDS was prepared which comprised of 70 % mixtures of two surfactants, Labrasol and Cremophor EL (1:1) and 30 % mixtures of oil Capryol 90 and Labrafac PG (1:1) in both pellet and liquid forms with a particle size of 29.6-32.8 and 25.8-28.8 nm, respectively. These formulations were quite stable up to 6 mo under optimum and accelerated conditions. *In vivo* studies done on rats show that the pelleted forms and the liquid forms showed enhanced absorption, which was nearly 10- and 14-fold compared to the aqueous solutions of curcuminoids, respectively. Hence, self-microemulsifying systems hold immense potential in enhancing the bioavailability of CUR.

Polymeric micelles:

In the recent past, the use of mixed micelles has gained attention, which is formed by the mixing of two different surface active agents to yield better results than a single surfactant. Duan *et al.* performed a study using CUR-loaded phospholipid-sodium deoxycholate mixed micelles prepared by thin-film dispersion method followed by the optimization of central composite design-response surface method^[70]. It was concluded that the resultant micelles formed had a negatively charged colloidal surface, were smaller in size and spherical in shape. Moreover, the low critical micellar concentration of PC and SDC facilitated

the integrity of the micelles when administered parenterally. Further, the circulation of these micelles in blood was prolonged and the cytotoxicity on MCF-7 was higher when compared to free CUR. Due to the smaller particle size of the micelles, which varies from 20-100 nm in aqueous solution, it can be successfully absorbed in the intact form through endocytosis to the intestinal cells.

Letchford *et al.* prepared a polymeric micellar formulation of CUR-containing methoxy poly(ethyleneglycol)-block-polycaprolactone diblock copolymers (MePEG-b-PCL), which enhanced its solubility to nearly 13×10^5 fold^[71]. This was later verified by the pharmacokinetic studies conducted by Ma *et al.* that compared to free CUR the biological half-life of polymeric micelles was 60-fold higher in rats^[72]. All these findings suggest that the use of micelles as a successful drug delivery system for CUR is quite economic and can be exploited.

Transdermal drug delivery system (TDDS):

TDDS refers to the superficial or topical application of the drug on the *stratum corneum* layer of the intact skin for localized or systemic treatment. This delivery system has an advantage over the oral and parenteral routes of drug administration due to enhanced penetration, prolonged plasma circulation levels, better retention and bypassing the first-pass metabolism to address the problems of poor bioavailability. There are several well-documented studies, which have reported the use of hydroxy propyl methyl cellulose K4M (HPMC K4M) and ethyl cellulose (EC) for controlled release of drugs^[73,74]. In one such intriguing research, significant results were observed in antiinflammatory studies performed with different transdermal films prepared by incorporating CUR in the matrix of K4M (HPMC K4M) and EC with oleic acid as a permeation enhancer^[75].

The use of microneedle injections is sophisticated yet expensive; microneedle approach and other nanocarriers are already currently in use. However, due to limitations and disadvantages, there remains an indispensable demand to fill up the void by the development of novel strategies. Patra *et al.* reported the preparation of a new generation polyarginine containing nano-liposomes incorporated with carbon dots, which had better penetration ability than the conventional liposomes, owing to its small size and enhanced stability. This TDDS was effective in killing cancer cells when loaded with CUR and had

better permeation capacity which was confirmed by confocal fluorescence microscopic analysis^[76]. Further, many of the researchers have used the distinct form of carriers like ethosomes for TDDS. Ethosomes are spherical, malleable, soft vesicles comprising generally of phospholipids (phosphatidylserine, phosphatidylcholine and phosphatidic acid) accompanied by a high concentration of ethanol and water. These can be designed for the incorporation of active agents according to the requisite of the study involved.

In antiinflammatory studies reported by Madhavi *et al.* it was demonstrated that ethosomes incorporated with curcumin- β -cyclodextrin complex showed enhanced penetration (78.01 ± 0.22 %) compared to the aqueous (5.61 ± 0.263 %), ethanol (62.31 ± 0.263 %) and liposomal (59.3 ± 0.44 %) preparations, which could be attributed to the increased solubility of CUR in β -cyclodextrin complex^[77]. This approach of TDDS could be a hopeful strategy in the near future due to its increased bioavailability and efficacy in treating topical and systemic diseases.

Nanoparticle approach:

With the advancement in the frontiers of nanotechnology, several researchers have developed interest towards it owing to the prompt and effective results. The different nanodelivery systems are depicted in fig. 4. Mohanty and Sahoo designed a delivery system of nanoparticles by loading CUR in

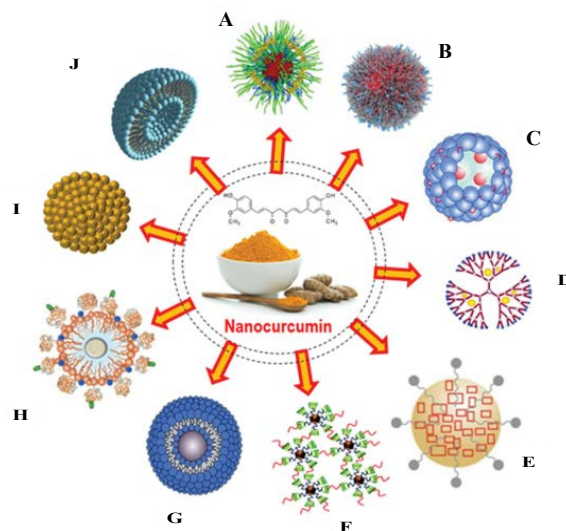


Fig. 4: Various nanocurcumin drug delivery systems currently in use^[62]

A. Polymeric micelles; B. polymer nanoparticles; C. nanogels; D. dendrimer; E. nanoemulsion; F. inclusion complex; G. phytosome; H. solid-lipid nanoparticles; I. curcumin nanoparticles; J. liposomes

glycerol monooleate/Pluronic F-127 particles using an emulsification technique by the successive addition of 0.5 % w/v polyvinyl alcohol. The resultant particles were spherically shaped with an average diameter of 192 ± 7 nm with an encapsulation efficiency of 90 ± 3 %, as determined by HPLC. The initial drug release experiments performed in *in vitro* model showed that nearly 46 % of the drug was released in 24 h and moreover, the remaining was released slowly up to a period of 10 d. The researchers found that the drug uptake was exclusively concentration-dependant; demonstrating better uptake and antiproliferative activity at low concentrations of CUR-loaded nanoparticles, than the unmodified CUR^[78].

In a unique study Sindhu *et al.* synthesized spherical gold nanoparticles using only CUR as a reducing agent. The average size of the particles was nearly 58 nm with a zeta potential of -23 mv. The particles were quite stable for nearly 6 mo at room temperature and no toxicity was reported in the *in vitro* studies so far^[79].

Many authors have demonstrated that the CUR-based nanoparticles are more effective in the chemotherapy for the treatment than the unmodified CUR due to its effective delivery to the target sites. Recently, animal studies were carried out using CUR-loaded magnetic nanoparticles on mice induced with pancreatic cancer. It was demonstrated that the formulation inhibited cancer effectively and moreover there was a 2.5 fold increase in the bioavailability as compared to native CUR. Hence, it can be speculated that the nanoparticle approach holds the solution to the treatment of cancer^[80].

Many studies have reported that the stability and solubility of CUR-loaded dextrin nano gels were much higher than the unmodified CUR. Cell culture studies were done successfully on Hela cell line to prove the efficacy of these formulations, which could be used in cancer therapy in near future^[81]. It has also been demonstrated in *in vitro* studies performed by using polymer-based CUR nanoparticles, that these forms of drug delivery systems are even effective to treat multiple brain tumours. A similar study by Lim *et al.* reported that these polymer-based nanoparticles could inhibit brain tumours arising from embryonal tumour-derived lines DAOY, D283Med and the glioblastoma neurosphere lines HSR-GBM1 and JHH-GBM14^[82]. However, the choice of delivery system depends on many factors like the site of action, economic

perspective, stability and safety with regard to the patient compliance.

In summary, curcumin has been used in traditional and complementary medicine for centuries and could be a promising drug candidate in the near future provided that it is delivered using an effective drug delivery system. The question that whether curcumin can be used as a drug alone or in a suitable formulation with an additional drug, which could enhance its potential on the frontiers of chemotherapeutic strategies is yet to be addressed. However, further studies and data are needed to understand the more precise and detailed mechanisms to enhance the antimicrobial, anticancer, antiangiogenic, antiinflammatory properties. Further, poor pharmacokinetic properties, poor solubility and low bioavailability still remain an area of research, which could be improved by employing emerging techniques bearing the economical aspect on the front. The new formulations in the form of transdermal implants, nanoparticles, nanoliposomes and nano gels are on the rise and efforts are being made to make them available within the reach of a commoner. The dictum “there is always room for improvement” is precisely in agreement with the pace of the ongoing developments to make curcumin as an effective drug candidate.

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Conflict of Interest:

The authors declare that they have no conflict of interest.

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