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CURCUMIN: A WONDER THERAPEUTICAL DRUG

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ABSTRACT

Curcumin is the active ingredient in the traditional herbal remedy and dietary spice turmeric *(Curcuma longa)*. It has served an important role in many traditional cultures throughout the East, including being a revered member of the Ayurved. For the last few decades, extensive work has been done to establish the biological activities and pharmacological actions of turmeric and its extracts. Curcumin (diferuloylmethane), the main yellow bioactive component of turmeric has been shown to have a wide spectrum of biological actions. These include its antiinflammatory, antioxidant, anticarcinogenic, antimutagenic, antidiabetic, antibacterial, antifungal, antiprotozoal, antifibrotic, antiulcer, antiimunity and hypocholesteremic activities. At present the most important task for researchers, is to improve the bio-availability and stability of curcuminoids, inorder to create revolution in the field of medical science, therefore many synthetic analogue, nanocurcuminoids and similar compounds from plants are discovered and their properties, usefulness is compared with curcumin. Nanoparticles encapsulated curcumin like nanocurcumin are one of the major means that could be used to improve the bioavailability of curcumins.

Key word:- Curcumin, nanoparticle, bioavailability.

INTRODUCTION

The origin of the plant *Curcuma Longa L.*, which belongs to Zingiberaceae (Ginger, Zinzero, Gingembre, Jengibre, Gengibre) family[1] commonly named as Turmeric, jiang huang, haridra, Indian saffron, Scientificly known as Curcuma Longa Linnaeus. History of existence of tuermeric is very old and evidences have already proven that cultivation of turmeric plants began in Harappan civilization in 3000 BC and Susruta Samhita, dating back to 250 BC, highly recommends use of an ointment based on turmeric for relieving food poisoning effect. Turmeric was introduced to China from India by 700 A.D and has been said to be long used as a medicinal herb. The most useful component in Turmeric is curcumin, a bis-α β unsaturated β-diketone commonly known as diferuloyimethane, has recently gained a plenty of attention for its curative impact on number of diseases [8,13]**.** Curcumin acts as potent antioxidant, anti-inflammatoryand antiproliferative therapeutic agent [2-3]. Since from our Vedic period Tuermeric powder has also been used for healing wounds and in 1996, study from Uniformed Services University of the health sciences, Bethesda, MD, USA were first one to report the healing effect of curcumin by affecting angeogenisis, the growth of new blood vessels from preexisting ones [4]. Curcumin (1, 7-bis (4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione) is the most important compound in turmeric, poorly soluble in water, petroleum ether, and benzene; soluble in ethyl alcohols, glacial acetic acid, and in propylene glycol; very soluble in acetone and ethyl ether. Absorptive spectra of curcumin and curcuninoids are very similar, with their maximum values at 429 and 424 nm, respectively [6]. In addition, curcumin is considered a non-nutritive and non-toxic chemical, various animal models [9-10] or human studies [11-12] proved that curcumin is extremely safe even at very high doses. The essential oil (5.8%) obtained by steam distillation of *Curcuma Longa*, rhizomes has *a*-phellandrene (1%), sabinene (0.6%), cineol (1%), borneol (0.5%), zingiberene (25%) and sesquiterpines (53%) [5]. Curcumin (diferuloylmethane) (3–4%) is mainly responsible for the yellow colour in turmeric [1]. Demethoxy(17%) and bisdemethoxy(6%) derivatives, along with (77%) of curcumin have also been isolated [1]. Curcumin was first isolated in 1815 and almost it took 158 years to determine its chemical structure by Roughley and Whiting in 1973. It has a melting point at 176–177°C; forms a reddish-brown salt with alkali and is soluble in ethanol, alkali, ketone, acetic acid and chloroform. Curcumin's full pharmacological potential is limited owing to its extremely limited water solubility, but its solubility in water could be increased from 0.6 microg/ml to

7.4 microg/ml (12-fold increase) by the use of heat [14]. In Ayurveda more emphasis is given in traditional consumption of curcumin like adding with milk or processing with fats like *ghee*. The only problem associated with curcumin, is regarding its poor bioavalabilty, metabolism, and rapid elimination otherwise it could be extremely beneficial polyphenolic compound for humans. Some possible ways to overcome this problem could be some novel formulations, of nanocurcumin or finding some analogue of curcumin with almost similar Potentiality.

Habitat: In India Tamil Nadu and Andhra Pradesh are two states, where maximum cultivation of curcumin: (600,000 tons annually) is done. A part from India several other species of curcuma geneus grow wild in the forests of Southern Asia, Indonesia, Indochina, and some pacific Islands including Hawaii. In Pakistan Kasur district is the largest producer of turmeric. Turmeric was traditionally called "Indian saffron" because of its deep yellow-orange color and has been used throughout history as a condiment, healing remedy and textile dye. It has served an important role in many traditional cultures throughout the East, including being a revered member of the Ayurvedic pharmacopeia. While Arab traders introduced it into Europe in the 13th century, it has only recently become popular in Western cultures.

Medical science and Curcumin: Today, a large body of scientific evidence exists to indicate potential therapeutic benefits of *C. longa*. Several preclinical and clinical studies have investigated the pharmacological properties of *C. longa* and results indicate strong therapeutic potential for anti-inflammatory, antioxidant, antibacterial, anticancer and many other properties [26]. This review summarizes the scientific evidences showing the comparative development over the last thirty to forty years. Although the putative mechanism(s), molecular targets and range of therapeutic applications have been researched widely, further investigations are needed to explore the true therapeutic potential and future of curcuminoids as novel drug molecules in ophthalmic diseases.

[A] CANCER VS CURCUMIN: (Antiinflamatory): Extensive research over the last 50 years has indicated this polyphenol can both prevent and treat cancer[27]. The anticancer potential of curcumin stems from its ability to suppress proliferation of a wide variety of tumor cells, down-regulate transcription factors NF-kappa B, AP-1 and Egr-1; down-regulate the expression of COX2, LOX, NOS, MMP-9, uPA, TNF, chemokines, cell surface adhesion molecules and cyclin D1; down-regulate growth factor receptors (such as EGFR and HER2);

and inhibit the activity of c-Jun N-terminal kinase, protein tyrosine kinases and protein serine/threonine kinases. Curcumin inhibits a transcription factor, nuclear factor κB (NF-κB), by inhibiting inhibitor of κB kinase and subsequent IκBα phosphorylation [28-29]. As a result, curcumin down-regulates the expression of NF-κB-regulated gene products such as Bcl-2, Bcl-X_L, cyclin D1, matrix metalloproteinase-9, cyclooxygenase-2, and interleukin-6, resulting in cell cycle arrest, suppression of proliferation, and induction of apoptosis [29-30]. Second, curcumin inhibits the Akt/mammalian target of rapamycin (mTOR) pathway and phosphorylation of p70 ribosomal protein S6 kinase (p70S6K) and eukaryotic initiation factor 4E-binding protein, resulting in inhibition of proliferation and induction of apoptosis [30]. Other mechanisms of the antitumor effect of curcumin include down-regulation of transcription factors activator protein-1 [31] and Egr-1 [32]

(i) Prostate Cancer: Curcumin may help fight cancer, including prostate cancer. In prostate cancer, prostate gland cells produce PSA (prostate-specific antigen) majorly responsible for the cause. This study [34] consisted of both a laboratory experiment and a small clinical research trial with human volunteers. In the laboratory portion of this study, human prostate cancer cells were treated with soy isoflavones and curcumin. When these prostate cancer cells were treated with soy isoflavones and curcumin, the production of PSA by these cells was dramatically decreased. The results of this small and elegant research study do not prove that soy isoflavones and curcumin can actually prevent prostate cancer in humans; these results do suggest, at least, a biological mechanism whereby these dietary compounds might reduce the risk of developing prostate cancer, and might also have anti-cancer effects in patients with prostate cancer. A part from this, a combination of curcumin and resveratrol is also studied to prevent prostate cancer [33], even curcumin was also found to have anticancer effects on human Burkitt's lymphoma. Turmeric also blocks estrogen receptors and enzymes that promote cancer. And it's been found to stop the growth of new blood vessels in cancerous tumors - an important factor in keeping cancer from getting larger and spreading throughout the body[35]. Curcumin analog, ASC-J9, kills prostate cancer cells independent of androgen receptor (AR) status.[36]

(ii) Breast cancer: Breast cancer, is a malignant tumor in which cancerous cells get accumulate around breast area, mainly produced from the cells of the breast. According to recent studies in South Korea, Curcumin has been reported to have anti-cancer properties by modulating genes meant for multiple signaling pathways. Visfatin gene is affected by

curcumin in breast cancer cells. The results indicated that mRNA and protein levels of visfatin were down-regulated by curcumin in MDA-MB-231, MDA-MB-468 and MCF-7 breast cancer cells. Further, chromatin immune-precipitation analysis indicated the binding of p65 to the visfatin promoter which was blocked by curcumin. Many women use hormone replacement therapy to treat the symptoms of menopause, but this enhances more probability of breast cancer in them. Another study, explained that curcumin has been found to inhibit progestin-induced secretion of VEGF from breast cancer cell. So, by blocking the production of VEGF, the proliferation of breast cancer cells should be reduced, even Curcumin delays development of MPA-accelerated DMBA-induced mammary tumors[41]. In another research by Bharat Aggarwal, Department of Experimental Therapeutics at the University of Texas M.D. Anderson Cancer Center in Houston, found the cancer drug paclitaxel (sold under the brand name Taxol); or curcumin plus Taxol, lowered the rate of cancer spread. A comprehensive research [39] found, curcumin and piperine combination could be very effective in curing breast stem cells with the cancer. In the latest research, effect of two curcumin-derived compounds called FLLL31 and FLLL32 on a cell signaling chemical (called STAT3) shown to be important for breast cancer cell survival and drug resistance. The results of this cell culture study showed several positive effects of these curcumin-derived compounds, including: Inhibition of STAT3's ability to bind to cell DNA, this preventing multiple cancer processes, Initiation of programmed cell death of breast cancer cells, Reduction in the ability of breast cancer cells to form colonies and grow, and Working together with the chemotherapy drug doxorubicin to kill breast cancer cells. [38]. Another latest *vivo found*, the ability of curcumin to downregulate HER-2 oncoprotein and inhibit the signal transduction pathway of PI3K/Akt, MAPK, and NF-*κ*B activation may be important in the treatment of HER-2-overexpressed breast cancer.[42]

(iii) Curcumin in Colon Cancer: Curcumin, is known to inhibit proliferation of cancer cells by arresting them at various phases of the cell cycle and to induce apoptosis in tumor cells. Curcumin-induced apoptosis mainly involves the activation of caspase-3 and mitochondria-mediated pathway in various cancer cells of different tissue origin. In the present study, the induction of apoptosis and cytotoxicity by curcumin in colon cancer colo 205 cells was investigated by using flow cytometry. The results demonstrated that curcumin induced cytotoxicity and apoptosis dose and time-depedently. Curcumin induced the production of reactive oxygen species (ROS) and Ca^{+}, decreased the levels of mitochondria membrane potential and induced caspase-3 activity. Curcumin also promoted the expression of Bax,

cytochrome C, p53 and p21 but inhibited the expression of Bcl-2. These observations suggest that curcumin may have a possible therapeutic potential in colon cancer patients. In another research it is found that, curcumin impairs tumor suppressor p53 function in colon cancer cells [43]. In another rat model, Celecoxib and Curcumin Additively Inhibit the Growth of Colorectal Cancer.[44]

(iv)Curcumin and Its Role in Cancer Chemoprevention and Therapy: Curcumin, a natural component of the rhizome of curcuma longa has emerged as one of the most powerful chemopreventive and anticancer agents. Curcumin has been shown to possess anti-angiogenic properties and the angioinhibitory effects of curcumin manifest due to down regulation of proangiogenic genes such as VEGF [41] and angiopoitin and a decrease in migration and invasion of endothelial cells. One of the important factors implicated in chemoresistance and induced chemosensitivity is NFkB and curcumin has been shown to down regulate NFkB [46] and inhibit IKB kinase thereby suppressing proliferation and inducing apoptosis. Cell lines that are resistant to certain inducers and radiation become susceptible to apoptosis when treated in conjunction with curcumin. Besides this it can also act as a chemopreventive agent in cancers of colon, stomach and skin by suppressing colonic aberrant crypt foci formation and DNA adduct formation.[45]

[B].Spicing up of the Immune System by Curcumin: Curcumin has been shown in the last two decades to be a potent immunomodulatory agent that can modulate the activation of T cells, B cells, macrophages, neutrophils, natural killer cells, and dendritic cells. Curcumin can also downregulate the expression of various proinflammatory cytokines including TNF, IL-1, IL-2, IL-6, IL-8, IL-12, and chemokines, most likely through inactivation of the transcription factor NF-kappaB. Interestingly, however, curcumin at low doses can also enhance antibody responses. Many studies has already proven the beneficial impact of curcumin in many diseases, which is only due to its pure ability to modulate the immune system. Together, these findings warrant further consideration of curcumin as a therapy for immune disorders [2].

[C].Curcumin as an antioxidant in Alzheimr's: A growing body of evidence indicates that oxidative stress, free radicals, beta amyloid, cerebral deregulation caused by bio-metal toxicity and abnormal inflammatory reactions contribute to the key event in Alzheimer's disease. Study shows that curcumin, decreases the low-density lipoprotein oxidation and the free radicals that cause the deterioration of neurons, not only in AD but also in other neuron degenerative disorders such as Huntington's and Parkinson's disease [47]. In another study,

curcuma oil was given to rats and they found this has reduced the infarct volume, improved neurological deficit and counteracted oxidative stress [48], even a single injection of curcumin (1 and 2 mg/kg, i.v.) after focal cerebral ischemia/reperfusion in rats significantly diminished the infarct volume, improved neurological deficit, decreased mortality and reduced the water content in the brain.[49]. A study conducted at Jawaharlal Nehru University (India) demonstrated that the administration of curcumin significantly reduced lipid peroxidation and lipofuscin accumulation that is normally increased with aging [50]. Another study also shows that, curcumin improves memory and learning ability [51], It also increased the activity of superoxide dismutase, sodium-potassium ATPase that normally decreased with aging. In another study, curcumin has been shown to protect the cells from betaA (1-42) insult through antioxidant pathway [52]. Curcumin protects brain mitochondria against various oxidative stress [54]. In addition, when someone has AD, there is a lot of inflammation and reactive oxygen species in their brains, which destroys them. Curcumin has shown to successfully fight both inflammation and reactive oxygen species in the brain in mice. Curcumin achieves this is by blocking, or inhibiting, a pathway that causes inflammation called the NF-kB pathway.[30]

[D].Curcumin in gasteric Ulcer: *Curcuma longa* has been commonly used as a traditional remedy for symptoms such as, gastritis and gastric ulcer, main cause behind this is too much excretion of gastric acid. In the latest investigation, it was found that curcumin, lowers the different ulcerative effectors including gastric acid hypersecretion, total peroxides, myeloperoxiase (MPO) activity, IL6 and apoptotic incidence protects stomach during the acute chronic phase of gastric ulcer disease[55]. In another research *C. longa* extract has shown effect on gastric ulcers by blocking the H2 histamine receptor and ethyl acetate extract showed the most potent H2R antagonistic effect against dimaprit-induced cAMP production. However, curcumin, a major component of *C. longa* extract, showed no H2R blocking effect. *C. longa* ethanol extract and ethylacetate extract also blocked the binding of [3H]-tiotidine to membrane receptors on HL-60 cells. These findings suggest that the extract from *C. longa* specifically inhibits gastric acid secretion by blocking H2 histamine receptors in a competitive manner [54].

[E].Curcumin in rheumatoid arthritis: z Curcumin shows anti-inflammatory property and one compound in turmeric (curcumin) inhibits the synthesis of substances called prostaglandins in the body that are involved in pain. In another study, inflammatory

efficiency of curcumin was comapared with diclofenac sodium salt, in reducing joint swelling and joint pain. Overall curcumin showed better results than the potent inflammatory drug, and was found to be safer and did not relate with any adverse events [56]. Turmeric is largely non-toxic, and relatively free of side-effects. Turmeric's also showed better ability to reduce post-operative inflammation, as compare to the drug phenylbutazone and a placebo, and produced comparable improvement in duration of morning stiffness, walking time, and joint swelling among rheumatoid arthritis patients treated with phenylbutazone.

[F].Curcumin in liver diseases: Liver diseases are one of the major causes of mortality and morbidity worldwide, even drug-induced liver toxicity is another major problem of liver disorder.[57] Oxidative stress is considered as a mechanism in contributing to the initiation and progression of hepatic damage in a variety of liver disorders. A part from inflammatory properties, curcumin also inhibits proinflammatory induction. In a study ethanolic extract of *Curcuma longa* was investigated against paracetamol-induced liver damage in rats. Moreover, treatment of rats with only the ethanolic extract of Curcuma longa had no effects on the liver enzymes, while pretreatment of rats with the ethanolic extract of Curcuma longa prior to paracetamol dosing at statistically lowered the three serum liver enzyme activities. A research has shown curcumin, also prevents alcohol induced liver diseases [58]. Curcuminoids also prevents rat liver from high fat diet induced lipid accumulation *in vivo* [59].

[H].Curcuminoids as anti- HIV : *Curcuma Longa,* contains many active components like curcuminoids, turmerone, etc. Curcuminoids are proven to be very active component against anti–HIV activity.[62] demonstrated that curcumin has an antiviral activity, being a HIV-1 integrase inhibitor (IC_{50} = 40 μM) and suggested that curcumin analogs may be developed as anti-Aids drugs. In addition to reverse transcriptase and protease, HIV-1 integrase is being explored as a new target for the discovery of effective AIDS treatments. HIV-1 integrase is the enzyme that catalyzes the integration of the double-strained DNA of HIV into the host chromosome [62]. Curcumin inhibited this activity of HIV-1 integrase [62]. Other classes of compounds inhibited HIV-1 integrase in enzyme assays. Curcumin was reported to have moderate activity in cell-based assays, in addition to its activity in enzyme assays [63]. Data showed that curcumin inhibited the replication of HIV-1 integrase protein. In another research it was reported that curcumin was claimed for anti-HIV-1 and HIV-2 activities. Recently, its potential utility in autoimmune deficiency syndrome (AIDS) has been

demonstrated.[61] A latest research has found, curcumin-loaded apotransferrin nanoparticles are highly efficacious inhibitors of HIV-1 replication *in vitro* and promise a high potential for clinical usefulness.[60]

[I]. Curcumin as antimicrobial : Several research studies suggest that turmeric can help combat bacterial infections. In 2009, issue of the Journal of Pharmacology and Toxicology reported that aqueous extracts of turmeric showed good antimicrobial activity against such common bacteria as E. coli (common cause for food poisoning), Staphylococcus aureus, Klebsilla pneumoniae and Staphylococcus epidermidis. K. pneumoniae infections often affect those who are hospitalized for other reasons, but may also cause pneumonia outside the hospital. S. epidermidis is normally present on human skin, but it can make you sick if it gets to other parts of your body or if you have a weakened immune system. Turmeric may also help you fight viral and fungal infections. Turmeric helps you fight off infections by strengthening your immune system. Curcuminoids in turmeric significantly increase CD4 and CD8 counts. CD stands for "cluster of differentiation" and is a glycoprotein. CD4 and CD8 are subtypes of this glycoprotein found on the surface of different types of immune cells. They are both essential to your ability to deal with infections because they help activate and amplify your body's immune response.

Methodology

Many techniques are proposed for the isolation and purification of curcuminoids, but it is difficult to compare them with one another. Many solvents are used for extraction of curcminoids, isolation and purification by Column chromatography and purity analysis by HPLC, among different solvents acetone showed maximum yield of curcuminoids [20]. Studies also showns the feasibility of using supercritical fluid extraction (SFE) method and confirmed that ethanol could increase the recovery of curcumionoids in this method [16].

Another method, by pressurized liquid extraction, was found better but not simpler than the previous method [17]. In a comparative study, between various techniques, including hydro-distillation, low-pressure solvent extraction, Soxhlet extraction, and supercritical fluid extraction using carbon dioxide and co-solvents (e.g., ethanol, isopropyl alcohol, and their mixture in equal proportion) on the extraction of curcumin. It was found that the largest yield (27%) was obtained by the Soxhlet extraction using ethanol, while the lowest yield resulted from the hydrodistillation process (2.1%). [14].

Table 1: Yield percentage of curcumin with different solvent systems.

Solvent	Total Curcumin	Demethoxycurcumin	Bisdemethoxycurcumin	Total extract/gm
Acetone	22.8%	14.2%	6.5%	43.5%	3.49
Chloroform	19.7%	12.15%	5.05%	36.9%	3.09
Hexane	6.5%	1.03%	0.04%	7.57%	0.90
Methanol	15.68%	9.90%	4.73%	30.3%	4.31
Ethylacetate	18.76%	11.6%	.2%	35.5%	3.20
Hex/MeoH	18.1%	11.2%	6.1%	35.4%	3.62

Spectroscopy and curcumins: Spectrophotometric methods are mainly used for quantitative analysis of the curcuminoids. Usually, the detective wavelength was set at 420-430 nm, at which 6 curcuminoids have their maximal spectrophotometric absorption [18]. A linear relationship between the absorbance and curcumin concentration was obtained in the range of 0-15 µg/mL with a detective limit as low as 0.076 µg/mL [19]. Although the spectrophotometric method can quantify curcumin precisely within range mentioned above, it is not able to quantify each curcuminoid individually. Regarding the quantitative limitation of spectrophotometric method, high-performance thin-layer chromatography was suggested as an alternative method for the determination of individual curcuminoid in turmeric. However, TLC methods were restricted by their lower resolution than HPLC. The percentage composition of each curcuminoid was estimated by HPLC and the results are the average of three experiments. Curcuminoids are further separated by TLC using different solvent system but solvent system of chloroform : methanol at 95:5 showed comparatively better separation of R_f value at 0.75,0.55,0.27, as curcumin, demethoxycurcumin, bis-demethoxycurcumin [20]. Curcuminoids can be easily separated by reverse phase HPLC column under the following condition: using the reverse phase Supelcosil LC-18 column, and mobile phase A: 1% citric acid (pH adjusted to 3.0 with dilute NaOH) and B: acetonitrile [21]. A gradient mobile phase was controlled at 1 mL/min from 50% acetonitrile with an initial holding time of 10 min to 80% acetonitrile in 30 min. Although this method yielded good resolution and desirable peak shape, some components in the mobile phase (citric acid, NaOH) might clog the mass spectrometer interface leading to high back pressures, and thus contaminate the MS

ion source [17]. In another method, HPLC-PDA (photo-diode array) was used to determine curcuminoids and co-existing sesquiterpenes [22], While by using methanol as an additional mobile phase, which included solvents A: methanol; B: 2% acetic acid; and C: acetonitrile. Linearity was found in the concentration range between 0.0625 and 2.0 µg, with high reproducibility and accuracy [23]. In addition to the gradient method, acetonitrile at isocratic flow rate of 0.75 mL/min on LiChrosorb RP-8 column and ethanol:water (96:4) on Spheri-5 amino column were tested [24]. Both have demonstrated desirable resolution. Besides the methods mentioned above, capillary electrophoresis with amperometric detection (CE-AD) pretreated by solid-phase extraction (SPE) was also reported to quantify curcumin. CE-AD with SPE exhibited a low detection limit for curcumin extracted in light petroleum [25].

Another work performed by us which claims 99.06% yield of curcuminoids with purity more dan 99%. Rhizomes of *Curcuma longa* are dried and grounded to obtain a powder, which is extracted with a volatile solvent several times and concentrated into soft, mass which is filtered and precipitated and subjected to bed wash with solvent by using vacuum and dried and estimated. 1.5kg of turmeric rhizomes were dried and reduced to a size of 10 mesh followed by extraction for six times with 4.5L of chloroform each time at a temperature of 60^0C with an interval of 3 hours. All the extracts were mixed together and the chloroform is distilled out completely. The resulting soft mass was heated at a temperature of 60^0C with 270 mi 0f 10% of n-butanol in toluene having 2ml of glacial acetic acid and was allowed to stand at temperature of 3^0C for 2 hours followed by filtration. The precipitate thus obtained was provided a bed wash with 120ml of solvent mixture of 4% of glacial acetic acid in methanol at a temperature of 5^0C by using vacuum. The precipitate was then dried at 60^0C for 5 hours under vacuum and grounded to a size 40mesh to obtain 65.02 gm of curcuminoids having 99.06% purity. The preserved filtrate was concentrated to soft mass by using vacuum and the soft mass was refluxed for 30 mins with 45ml of 10% of n-butanol in toluene followed by cooling and filtration to form a precipitate. The precipitate so formed was dried at 65^0C for 8 hours and then reduced to size of 40 mesh to obtain 3.20 gm of curcuminoids having 99.32% purity as estimated by HPLC.

Mass Spectroscopy

Different spectrometric techniques are used for qualitative and quantitative analysis to charcaterise curcuminoids in a sample. A commercially obtained sample is subjected for mass spectroscopy. The mass analysis of this sample using time-of-flight reflectron mass

spectrometric techniques namely plasma desorption (PD), laser desorption (LD) and electrospray ionization (ESI) gave evidence for the presence of curcuminoids other than curcumin in the sample[20]. Mass spectrometry is a highly sensitive technique requiring only small amounts of material (typically 1µg) for analysis. The process of elucidating the mass and the structure of a substance can be expedited by using a high performance mass spectrometer. With the advent of "soft" ionization mass spectrometric techniques such as plasma desorption (PD)4, laser desorption (LD)5, and electrospray ionization (ESI)6 that produce protonated molecular ions with minimal or no fragmentation, pseudo-molecular ions of each eluting species can be readily produced. The ESI mass spectrometry6 is superior to others in this respect since structurally significant information can be elicited by collisional activation of the eluting species in the vacuum interface of the ESI source Table 1.

The peaks (m/z) in the PD mass spectrum of the curcumin sample are compared with the EI mass assignments of individual curcuminoids:

Table 2: Mass assignments in the EI mass spectrum for curcumin sample

peaks (m/z) in the PD mass spectrum of the curcumin sample	Mass assignments in the EI mass spectrum			Elementary composition of ions
	curcumin	Demethoxy curcumin	*Bis*demethoxy curcumin	
369	369	-	-	MH^+
339	-	339	-	$M'H^+$
309	-	-	309	$M''H^+$
298	298	-	-	$[M - C3H2O2]^+$
268	-	268	-	$[M'- C3H2O2]^+$
219	219	-	-	$[M – C9H9O2]^+$ $[M'- C8H7O]^+$
191	191	-	-	$[M – C10H9O3]^+$ $[M'- C9H7O2]^+$
177	177	177	-	$[M – C11H11O3]^+$ $[M'- C10H9O2]^+$
149	149	-	-	$[M – C12H11O4]^+$ $[M'- C11H9O3]^+$
147	-	147	147	$[M'- C11H11O3]^+$ $[M'' - C10H9O2]^+$
137	137	-	-	$[M – C13H11O4]^+$ $[M'- C12H9O3]^+$
107		107	107	$[M'- C13H11O4]^+$ $[M'' - C12H9O3]^+$

The PD-, LD-, and ESI-TOF mass spectra of the curcumin sample display the probable MH^+ peaks of demethoxycurcumin ($M'H^+$: m/z 339) and *bis*demethoxycurcumin ($M''H^+$: m/z 309). According to the electron impact ionization mass spectrum of curcumin[15] these peaks could not have arisen due to the fragments of curcumin. Therefore it implied that the presence of other curcuminoids in the curcumin sample might have given rise to these peaks. The presence of peaks at m/z 107, 147 and 268 that observed in the curcumin mass spectrum co-related to the fragment ion peaks of these curcuminoids. For example the peaks at m/z 107 and 147 correspond to the probable fragment ions respectively of either demethoxycurcumin or *bis*demethoxycurcumin. The peak at m/z 268 corresponds to the probable fragment of desmethoxycurcumin. These results gave further evidence for the presence of curcuminoids in the curcumin sample. All these techniques gave evidence for the presence of curcuminoids other than curcumin in the sample. An MS/MS study using the ESI-FT-ICR-MS has been used successfully to confirm the presence of these curcuminoids in the curcumin sample [20].

Future prospects

Turmeric has been used in ayurvedic medicine since ancient times, with various biological applications. Although some work has been done on the possible medicinal applications, no studies for drug-development have been carried out as yet. Although the crude extract has numerous medicinal applications, clinical applications can be made only after extensive research on its bioactivity, mechanism of action, pharmacotherapeutics and toxicity studies. However, as curcumin is now available in pure form, which shows a wide spectrum of biological activities, it would be easier to develop new drugs from this compound after extensive studies on its mechanism of action and pharmacological effects. Preclinical and clinical studies of curcumin have demonstrated its efficacy and tolerability in the treatment of cancer. Despite curcumin safety and efficacy, it has been hindered by low bioavailability. Different factors such as low serum level, tissue distribution, short half-life and rapid elimination from the body, limit its adequate concentration into the tissues. Several strategies have been explored to overcome its low bioavailability, which include concomitant administration and liposomal encapsulation of curcumin. Numerous curcumin analogues have been found to enhance its biological activity. However, future studies are likely to focus on a deeper understanding and knowledge of novel strategies, including those of nanoparticles, liposomes and phospholipid complexes for the administration of curcumin via different routes. Future trials should also include suitably planned pharmacodynamic studies. On behalf of such studies, one might be able to

gain insights into curcumin mechanisms at a clinical level and assess within a short period the potential success or failure of long-term interventions. However, contrary to the general perception that curcumin is quite safe there is some evidence suggesting that curcumin may cause toxic effects under specific conditions and these have been discussed in a recent review by Burgos-Mor'on et al. These include commonly reported side effects like stomach upset, nausea and diarrhea, an allergic skin reaction and anti-thrombosis activity interfering with blood clot formation. There is some evidence suggesting that high dose administration of curcumin in rodents for long-term duration can be tumourigenic. Although side effects have been limited in animal and Phase I short-term clinical studies, long-term, large scale and randomized clinical trials on humans are needed to establish the safety of curcumin at antioxidant and anti-inflammatory doses. These clinical studies are also necessary to determine the optimal dosage, bioavailability and bioefficacy of curcumin based drugs. The major challenge is to develop drugs based on curcumin with scientific evidence acceptable to the global community. An effective drug should exhibit adequate absorption, low toxicity, acceptable distribution, metabolism and excretion, and should be capable of treating the targeted disease with specificity and efficacy. The traditional medicinal system may need to adopt novel strategies such as combinatorial chemistry route combined with nanotechnology to develop curcumin-based drugs having enhanced bioavailability and efficacy. The challenges and technological prospects in realizing nano-curcumin based drugs for the future of medicine and health care. The time is not too fardistant, when curcumin will emerge as a promising therapeutic drug for the treatment of variety of diseases.

Nano-Curcuminoids

Today curcumin has been widely acknowledged globally as a "wonder drug of the future" because of its great potential abilities to prevent and treat a wide spectrum of incurable and chronic diseases. In addition, it has been proved to be remarkably safe in animal studies and in phase I clinical trials even at high doses (up to 12g/day). However, the major problem limiting the exploitation of its potentially valuable therapeutic effects is its low bioavailability. In practice, only very low or undetectable levels of curcumin can be achieved in blood by oral administration of curcumin. The low bioavailability of curcumin has been attributed to its very low aqueous solubility, tendency to degrade in the gastroinenstinal tract in the physiological environment, high rate of metabolism, and rapid systemic elimination. The low bioavailability of curcumin has so far limited its medical use. It has been suggested that a person is required to consume large doses (about 12-20g/day) of curcumin in order to

achieve its therapeutic effects on the human body. That means one has to swallow 24 to 40 curcumin capsules of 500mg each. These doses are considered to be too high, and therefore, not feasible to be incorporated in clinical trials due to unbearable after-taste to the palate, possibility of giving rise to nauseatic feeling and perceived toxicity issues. Therefore, to achieve the maximum response of this potentially useful chemopreventive agent, a number of approaches such as the use of adjuvants like piperine, synthetic analogues, chelating of curcumin with metals, combination with other dietary agents etc. have been investigated. Nanotechnology-based novel strategies are being aggressively explored worldwide to enhance curcumin's bioavailability and reduce perceived toxicity as they offer several other additional benefits such as improved cellular uptake, enhanced dissolution rates, excellent blood stability, controlled release functions, multifunctional design, enhancement in its pharmacological activities (e.g. antioxidant and antihepatoma activities) etc. In this pioneering work, researchers from Johns Hopkins University School of Medicine and the University of Delhi have jointly developed a polymer nanoparticle-encapsulated form of curcumin, "nanocurcumin", which can be readily dispersed in aqueous media. In this process, they have coated ordinary hydrophobic curcumin particles with hydrophilic polymer (N-isopropylacrylamide with N-vinyl-2-pyrrolidonne and poly(ethylene glycol) monoacryalate) nanoparticles. This nanocurcumin is soluble in water and can be readily absorbed into the bloodstream. It has already been tested *in vitro* on pancreatic cancer cells and it was shown to have equal or better effects than free curcumin on the human cancer cells, such as inhibition of NF-kB and downregulation of IL-6. Nanocurcumin was also given to mice, and did not show any evidence of undesirable effects. In addition to polymer-encapsulated curcumin, other nanobased drug delivery systems being employed for curcumin include curcumin nanocrystals, curcumin nanoparticles, nanoemulsions, nanoliposome-encapsulated curcumin, curcumin-loaded polymeric micelles, cyclodextrin/curcumin selfassembly, curcumin nanosuspension, solid-lipid nanoparticles etc.

The selected examples below highlight some of the ongoing R&D activities on nanotechnology-based curcumin across the globe.

Theracurcumin – A new curcumin formulation with markedly improved absorptivity[38)]

Japanese researchers have recently developed a new form of nanoparticle curcumin (Theracurcumin) containing 10% curcumin, 2% other curcuminoids and balance glycerin, gum ghatti and water. Its oral intake in rat model as well as humans shows 30 fold

improvements in bioavailability as compared to conventional curcumin. It shows excellent safety profile even at high dose levels. Theracurcumin can be used as a promising tool to evaluate the anti-cancer potential of curcumin in clinical trials.

Curcumin nanoparticles with enhanced antioxidant and antihepatoma activities[39] Curcumin-based nanoscale particle system (CURN) was developed by following a nanoprecipitation route with polyvinylpyrrolidone (PVP) as a hydrophilic carrier. The physiochemical properties including water solubility and drug release were improved by the reduction of particle size and formation of an amorphous phase with hydrogen bonding. In vitro studies clearly demonstrated that nanosized curcumin shows superior antioxidant and antihepatoma activities as compared to conventional curcumin.

Curcumin nanoparticles with highly potent antimicrobial properties[40]Water-soluble curcumin nanoparticles (2-40 nm) were prepared by wet milling method. These nanocurcumin showed marked improvement in their antibacterial and antifungal activities as compared to that of curcumin in DMSO. The antibacterial activity of nanocurcumin particles was attributed to their ability to penetrate inside the bacterial cell by breaking the cell wall, resulting to cell death.

Chitosan-PVA-Curcumin-Silver nanocomposite antimicrobial films for wound dressing[41]Chitosan-PVA-Silver nanocomposite antimicrobial films were fabricated by a chemical method in view of their potential applications in antimicrobial packaging and wound/burn dressing. Incorporation of curcumin into chitosan-PVA-silver nanocomposite films improve their therapeutic efficacy as anti-microbial agent. Curcumin-encapsulated chitosan-PVA-silver nanocomposite films show enormous growth inhibition of E-coli in comparison with curcumin or chitosan-PVA-silver nanoparticles film alone.

Curcumin/MPEG-PCL micelles for colon cancer therapy[42]Curcumin encapsulated into monomethoxy poly(ethylene glycol)-poly(-caprolactone) (MPEG-PCL) biodegradable micelles were prepared by a nano-precipitation technique. These curcumin-loaded micelles are an intravenously injectable formulation of curcumin. They were shown to supress the growth of colon carcinoma by inhibiting angiogenesis and killing the cancer cells.

Curcumin loaded PBCN nanoparticles for enhanced transport of curcumin to brain[43]Polybutylcyanoacrylate nanoparticles (PBCN) loaded with curcumin were

synthesized by modified anionic polymerization technique. Curcumin loaded PBCN shows enhanced transport of curcumin to the brain and has excellent potential to cross the blood-brain barrier. This novel delivery system will find applications for blocking brain tumor formation and curing Alzheimer's disease.

Curcumin loaded Lipo-PEG-PEI complex with enhanced antitumor effects on curcumin-sensitive/curcumin resistant cells[44)]A cationic liposome containing PEI and PEG as a carrier complex (LPPC) was developed to encapsulate curcumin for the treatment of cancer. It was found that curcumin/LPPC exhibits enhanced cytotoxicity and is able to rapidly penetrate curcumin-sensitive and resistant cells. It was observed that curcumin/LPPC is able to inhibit the colon/melanoma tumor growth in mice.

Nanoemulsion formulation and coadministration of Paclitaxel and curcumin to overcome multidrug resistance in tumour cells[45]Intracellular co-administration of Paclitaxel (mitotic inhibitor) and curcumin (NF-kB activity inhibitor) in the form of nanoemulsion exhibits remarkable enhancement in cytotoxicity in wild type (SKV3) and drug resistant (SKOV-3TR) human ovarian adenocarcinoma cells by promoting apoptotic response. This dual strategy shows great promise in the clinical management of refractory diseases (diseases that resist treatment) such as ovarian cancer.

Chemo/radio-sensitization in ovarian cancer cells using nano-curcumin[46)]Ovarian cancer cells are resistant both to radiation therapy and cisplatin-based drugs used in chemotherapy. Nano-enabled curcumin pretreatment strategy with enhanced efficacy and specificity was employed to induce chemo/radio sensitization in ovarian cancer cells. It was shown that this pretreatment with nano-curcumin improves in vivo therapeutic efficacy of curcumin, and thereby, inhibits the ovarian cancer cell growth.

Coformulation of Doxorubicin (DOX) and curcumin in the clinical management of leukemia[47)]The coadministration of DOX and curcumin in PLGA nanoparticle formulation can help in enhancing efficacy of DOX, thereby leading to cytotoxicity in erythroleukamia type K562 cells. The synergistic growth inhibition is clinically important and may provide combinatorial strategies in a variety of cancers, especially leukemia. In addition to the above approaches, a number of other unique nanotech-based techniques including a class of novel multifunctional hybrid nanogels amenable to photothermal therapy[48)], "nanodiscs" with phospholipids bilayers[49)], biocompatible thermoresponsive polymeric nanoparticles loaded with curcumin[50)], yeast cell-encapsulated-curcumin with high stability against heat, light and

humidity etc. are being developed[51] to enhance the bioavailability of curcumin combined with multifunctional attributes. A number of commercial nanotechnology based curcumin products with enhanced bioavailability have been developed by companies from the USA, India, Japan, and Canada. (These products and their manufacturers are listed in the original article in the July issue of the *Nanotech Insights* newsletter.) It is pertinent to note that the above mentioned products based on curcumin are treated as herbal/dietary supplements only[52] and are regulated by the US Food and Drug Administration (FDA), but not as pharmaceutical drugs. They fall under a category called dietary supplements. Manufacturers must follow good manufacturing practices (GMPs) to ensure that supplements are processed consistently and meet quality standards. Once a dietary supplement is on the market, the FDA is responsible for monitoring its safety. It is interesting to note that Johnson & Johnson has been marketing turmeric band-aids in India[53], which are being used as a traditional cure for cuts. It would be worthwhile to consider use of curcumin nanoparticles in place of turmeric for band-aids/dressings for cuts, wounds and other infections as they exhibit enhanced antibacterial/anti-infection properties.

CONCLUSION

The medicinal properties of curcumin and its analogs have been known to mankind for ages. Modern science has now provided a scientific basis to the numerous reports of the medicinal effects of these most inexpensive, yet pharmacologically safe, polyphenols. Extensive research in the last few years has indicated that most diseases are caused by the dysregulation of multiple signaling pathways, thus casting doubt on how effective monotherapy against single targets will prove to be. Curcumin and its analogs have been found to attack multiple targets, which provide the basis for their effectiveness in so many different diseases. Although most of the NSAIDS are now either withdrawn or survive with black box warnings, curcumin is one that is not known to show any adverse effects, even at doses as high as 8 g a day. Thus, a trip back to our “roots” to explore the “roots” of Curcuma longa as a source for better treatments will certainly prove productive. As Hippocrates said almost 25 centuries ago, “let food be thy medicine and medicine be thy food.”

Only mild side effects have been reported for *Curcuma longa*, dry mouth, flatulence, and gastric irritation. No serious side effects have been reported. Due to lack of data, the use of *Curcuma longa* in children under the age of 18 years cannot be recommended. As relevant data on the use during pregnancy and lactation is lacking, *Curcuma longa* can not be

recommended in these cases.

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