CURCUMIN: A REVIEW

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The main objective of this review article is to overcome or to improve the problems related with curcumin with the help of new technologies or modifications to make a promising therapeutic agent which gives a good therapeutic response. Curcumin, a known natural polyphenolic compound obtained from dietary spice turmeric, possesses pharmacologic effects including anti-inflammatory, antioxidant, and many other activities. Clinical trials on curcumin have shown its safety and efficacy even at high doses in humans. But inspite of that it shows poor bioavailability (oral bioavailability) which is one of the major problems regarding curcumin. There are other reasons contributing to the low plasma and tissue levels of curcumin appear to be due to poor absorption, rapid metabolism, and rapid systemic elimination. To improve the bioavailability of curcumin, numbers of approaches have been undertaken. These approaches involve, first, the use of adjuvant like piperine that interferes with glucuronidation; second, the use of liposomal curcumin; third, curcumin nanoparticles; fourth, the use of curcumin phospholipids complex; and fifth, the use of structural analogues of curcumin.

Key words: Curcumin; bioavailability; adjuvant; liposome, nanoparticles, phospholipids

INTRODUCTION

Phytochemicals a naturally occurring substance obtained from plants. There has been wide use of phytochemicals which is obtained from nutritional component to heal human diseases [1, 2]. Curcumin (*Curcuma longa*) an active ingredient of a much known spice ,turmeric, used in cooking in whole India and also other regions of Asia[3, 4] which belongs to ginger family (Zingiberaceae)[5] having number of pharmacological effects including anti-inflammatory, antioxidant, anti proliferative and antiangiogenic activities. Commercially curcumin contains approximately 77% diferuloylmethane, 17% demethoxycurcumin, and 6% bisdemethoxycurcumin. [6, 7]

CHEMISTRY

Curcumins are polyphenols responsible for yellow color. Curcumin have several functional groups. Polyphenols are attached with two alpha and beta unsaturated carbonyl group which forms an aromatic ring. The two carbonyl groups form a diketone. The diketone form stable enols or are easily deprotonated and form enolates, while the alpha, beta-unsaturated carbonyl undergoes nucleophilic addition [5]. Curcumin is unstable at basic pH, and degrades in 30 min to Trans-6-(40-hydroxy-30-methoxyphenyl)-2, 4- dioxo-5-hexanal, ferulic acid, feruloylmethane and vanillin [8, 9]. The presence of foetal calf serum or human blood, or addition of antioxidants such as ascorbic acid, N-acetylcysteine or glutathione completely blocks the degradation in culture media or phosphate buffer above pH 7. Under acidic conditions, the degradation of curcumin is much slower, with less than 20% of total curcumin decomposed at 1 h. [8, 10]

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PHARMACOLOGICAL ACTIVITIES

Inflammation [12]

Curcumin inhibits the enzyme which is related to activation of inflammatory substances. Curcumin shows natural anti inflammatory activity as same as steroidal drugs and some of steroidal drugs. It has also effective like phenylbutazone which is used in treatment of post operative inflammation and arthritis.

Cancer

Curcumin shows its efficiency in many types of human cancers such as melanoma of head and neck, breast, colon, pancreatic, prostate and ovarian cancers. It helps in targeting various levels of regulations in the processes of cellular growth and apoptosis. [13-24]

The current position of curcumin's potential against various cancers is synergistically analyzed and

presented below under different headings. Breast cancer is the most common and normally diagnosed cancer in women. In oesophageal cancer curcumin inhibit cytokinin induced activation oesophageal endothelial cells [25, 26]. 5-Fluorouracil shows inhibition of growth of gastric carcinoma cells in gastric cancer. In intestinal cancer, in vivo studies in mouse models showed that curcumin is responsible for the modification of apoptosis resistance, leading to the inhibition of tumour formation and the prevention of adenoma development in the intestinal tract [25, 27]. 0.45-3.6 dose of curcumin were administered daily radiologically stable disease was observed in 2 out of 15 patients for up to 4 months of treatment [25, 26]. Curcumin shows its potential in many other cancers.

Inspite of that it is already proved that curcumin shows low bioavailability. To overcome these problems, advanced drug delivery needs to design which gives good and prolonged therapeutic effect. Various drug delivery systems like Nanoparticles (polymeric and solid lipid NP, solid lipid nanoparticles), liposome (formulation of curcumin for parentral administration), microemulsion/ microencapsulation, implantable drug delivery systems [28, 36] can be formulated.

Polymeric and solid lipid NP formulation

Nanoparticle proved its efficiency in targeting tumors because of vascular leakiness due to huge production of cytokinines and angiogenesis cascade at these sites. In various tumors the permeability ranges are between 380-780 nm but in normal it ranges from 2-4 nm. This large difference helps in targeting of tumors and accumulation of resulting enhanced permeation. Being lipophillic curcumin encapsulated in polymers or phospholipids not only enhances its bioavailability but also increase its stability. [28, 37-41]

Curcumin as an Antioxidant [12]

Free radicals can originate from environmental chemicals, tissue injury, infections and auto-immune processes. Antioxidant protects the body from damage from free radicals. One study showed that curcumin is 8 times more powerful than vitamin E in preventing lipid per oxidation.

Curcumin's Antimicrobial Effects [12]

Several studies in animal models showed that turmeric extract and curcumin inhibits the growth of a variety of bacteria, parasites and pathogenic fungi. Turmeric reduced the lesions caused by intestinal parasites, pathogenic fungi and various other organisms. Topical applications of curcumin extract were also effective.

Liposomal formulation for Parenteral administration

Liposomes shows greater encapsulation efficiency especially DMPC and DPPC of particle size 100-150 nm which inhibit 70% -80% cellular proliferations of human prostate LNcaP and c4-2Bcancer cell .[28, 42-46]

Micro emulsion/Microencapsulation

Mostly carrier or technique used is micro emulsion/microencapsulation giving high drug entrapment efficiency with long term stability. These thermodynamically stable, transparent formulations are characterize by a dynamic microstructure resulting mixing lipophillic and hydrophilic excipients in the presence of suitable surfactants. This not only helps in delivering lipophillic compound like curcumin across lipophillic cell membranes but also through skin. [28, 47-51]

Implantable drug delivery systems

Implants with homogeneous entrapment of drugs in this type of system a polymeric matrix achieve sustained localized delivery showing desired bioavailability into systemic circulation by slowly releasing the encapsulated drug at the site of implantation. [28, 52-55].

PHARMACOKINETICS [56]

Asai A. & Miyazawa T. (2000) investigated the absorption and metabolism of orally administered curcuminoids (curcumin, demethoxycurcumin and disdemethoxycurcumin) in rats. High performance

liquid chromatography (HPLC) and Liquid Chromatography Mass Spectrometry (LS-MS) analysis after enzymatic hydrolysis, showed that the predominant metabolites in plasma following administration were glucuronides and glucoronide/ sulfates (conjugates with both glucuronide and sulfate) of curcuminoids. The plasma concentrations of conjugated curcuminoids reached a maximum one hour after administration. The conjugative enzyme activities for glucuronidation and sulfation of curcumin were found in liver, kidney and intestinal mucosa. There results indicate that orally administered curcuminoids are absorbed from the alimentary tract and present in the general blood circulation after largely being metabolized to the form of glucuronide and glucuronide / sulfate conjugates.

Various studies performed in animal models or human models [6, 57, 58, 59-62] proved that curcumin is extremely safe even at very high doses. For example, phase I clinical trials indicated that curcumin, when taken high dose as 12 g per day, is well tolerated. [6,60,62] In the same way, the effectiveness of curcumin in various diseases including cancer has also been well established [6,63] Several clinical studies dealing with the efficacy of curcumin in humans can also be cited The pharmacological safety and efficacy of curcumin makes it a possible compound for treatment and prevention of a wide variety of human diseases. In spite of that the efficacy and safety of curcumin has not yet been approved as a therapeutic agent, and the relative bioavailability of curcumin has been highlighted as a major problem for this. The purpose of this review is to discuss in detail the bioavailability, factors controlling bioavailability, and means to improve the bioavailability of curcumin. [6, 64-65]

BIOAVAILABILITY OF CURCUMIN

The reasons for low bioavailability of any agent inside the body are low intrinsic activity, poor absorption, and high rate of metabolism, inactivation of metabolic products and/or rapid elimination and clearance from the body. There are various studies which is related to absorption, distribution, metabolism and excretion of curcumin, exposed poor absorption and rapid metabolism that strictly curtails its bioavailability [6, 66] resulting low serum levels, limited tissue distribution and short half-life. Regarding the distribution of curcumin, it showed its accumulation in the intestine, colon and liver, so this is one of the major reasons why it is showing most promising in vivo effects in gastrointestinal diseases when compared with other organ systems. The liver, and to a lesser extent the intestinal mucosa are the major organs responsible for metabolism of curcumin. On absorption, curcumin gets converted into metabolite form i.e., glucuronides and sulfates or it is reduced to hexahydrocurcumin. To overcome these problems, there is no clear understanding whether these curcumin metabolites are pharmacologically as active as curcumin or whether these conjugates have effects that differ from those of curcumin [62, 67, 68]

The direct studies showed the low systemic bioavailability in humans on taking oral dose. First phase I clinical trial of curcumin was done in 25 patients [69, 70]. In this if the first dose shows no toxicity, then the dose was increased to another level, but the large volume of the drug was unacceptable to the patients beyond the recommended dose. In this experiment the scientist reported that the serum concentration of curcumin usually peaked at 1–2 h after oral intake of curcumin and slowly declined within 12 h. Urinary excretion of curcumin was invisible. [69, 71]. The original data prepared by Wahlstorm and Blennow showed that after oral administration of 1 g/kg curcumin to rats, more than 75% of curcumin was excreted in feces and small amount was detected in urine. How to improve the bioavailability of curcumin is also an issue. The roles of adjuvant [69, 62] which can block metabolic pathways of curcumin is one of the major means that are being used to improve its bioavailability. Nanoparticles, liposome, micelles, and phospholipids complexes are other promising new formulations, which appear to provide

longer circulation, better permeability, and resistance to metabolic process. [6, 62.]

ROLE OF BIOEHANCERS

There is a worldwide use of herbal medicines as compared to synthetic drugs. Curcumin is one of them but the only problem is its bioavailability as compared to other herbal drugs. So to increase its bioavailability most of the pharmaceutical industries prefer enhancers as a possible way. There are various natural bioenhancers for curcumin's oral bioavailability i.e. piperine, quercitine and epigallactocatechin-3-gallate. [72]

Piperine, a known inhibitor of hepatic and intestinal glucuronidation, was evaluated on the bioavailability of curcumin in rats and healthy human volunteers. It is considered that if curcumin was given alone, it takes longer time to achieve moderate serum concentrations. Relatively the administration of piperine increased the serum concentration of curcumin in less time. Time to maximum was significantly increased while elimination half life and clearance significantly decreased, and the bioavailability was increased, this experiment is performed on rats. In humans if curcumin is given alone, serum levels were either undetectable or very low. Additional administration of piperine produced much higher concentrations; the increase in bioavailability was more as compared to rats. According to the scientists who performed this experiment shows that the bioavailability was increased 154% in rats and in human it is increased upto 2000%. The study shows that in the dosages used, piperine enhances the serum concentration, extent of absorption and bioavailability of curcumin in both rats and humans with no adverse effects [62].

Quercetin is a flavonoid found in citrus fruits. Quercetin increases drugs' bioavailability is from the inhibition of the metabolizing enzyme, CYP3A4 in the intestinal mucosa [73]. In case of epigallocatechin-3-gallate, it also works like quericitine when it is combining with curcumin [74].

ROLE OF DRUG DELIVERY SYSTEM

The main goal of any drug delivery system is to achieve desired concentration of the drug in blood or tissue, which is therapeutically effective and non toxic for a prolonged period [75].

Liposome

"A colloidal, vesicular structured composed of one or more lipid bilayers containing aqueous compartments known as liposome". In case of conventional dosage form when it reaches in circulatory system achieves therapeutic level for short time due to metabolism and excretion. So therapeutic level of drug encapsulated in liposome is for longer period and release of drug occurs before metabolism and excretion. [76, 77, 78]

The overall problem of oral bioavailability is pretty fascinating. Over time, there are some developed simple ways of increasing the bioavailability of the various things we eat, mostly through heating them and concentrating them into more potent oils and tinctures, this is where a closely related technology comes into play: encapsulation. Encapsulation slows down the absorption of substances and allows them to spend more time in our bodies, increasing bioavailability. In researching curcumin, there are some papers which describes , combination of some relatively simple ingredients (curcumin, modified starch) in a relatively simple way to increase the oral bioavailability of curcumin by more than 1700 times. The new technique involves encapsulating substances in liposome [79]. Encapsulation puts the drug in shattered or cryptic form and thus rate of metabolism of encapsulated drug is less than that of free drug. This may be beneficial in cases where metabolic degradation occurs [80].

Nanoparticle

The main aim of selecting nanoparticles as a delivery system is to control particle size, surface properties and release of pharmacologically active agents in order to achieve the site-specific action of the drug at the therapeutically optimal rate and dose regimen [81].

Nanoparticle based delivery systems mainly used for hydrophobic agents having poor aqueous solubility such as curcumin. A recent study is (Bisht *et al*.) reported the application of a polymer-based nanoparticle of curcumin namely "nanocurcumin" with less than 100 nm size. It was found to have similar in Vitro activity as that of free curcumin in pancreatic cell lines. [82] An in vivo study with healthy volunteers showed the improved efficiency of a topical application cream containing curcuminoid loaded SLNs over that containing free curcuminoids [6,51]. Overall, nanoparticle based systems for curcumin delivery is still needs much progress in this area.

Micelles

Micelles can develop the gastrointestinal absorption of natural drugs, so giving higher plasma levels and lower kinetic elimination resulting improved bioavailability [6, 83].Pharmacokinetic studies by Ma et al. also verified that a polymeric micellar curcumin gave a 60-fold higher biological half-life for curcumin in rats compared to curcumin solubilized in a mixture of DMA, PEG and dextrose [6,84].

Phospholipid complexes

Complexation is another possible way for increasing the bioavailability of curcumin. Complex of curcumin and phosphotidylcholine increases the bioavailability and absorption also due to its ampiphillic nature of complex can increases water and lipid solubility. [85]

Derivatives and Analogues

The chemical structure of curcumin plays a pivotal role in its biological activity [6, 86]. A curcumin analogue EF-24 was reported to be a lead compound displaying increased antitumor action invitro and in vivo in comparison to curcumin. Another analogue of curcumin i.e.; symmetrical 1,5- diarylpentadienone compounds whose aromatic rings possess two alkoxy substitutes were synthesized and screened for anticancer activity.[6,87]

POTENTIAL RISKS AND SIDE EFFECTS

Various reports proved the synergistic effect of curcumin with chemotherapy which shows the administration of (2.5% w/w) of curcumin [69] disrupt the antitumor action of chemotherapeutic agent such as cyclophosphamide in treating breast cancer. [5]. The major drawback of the study was very short duration (3 days) of treatment of mice with curcumin. It has been reported that curcumin exhibit both antioxidant and prooxidant activities due to activation of opposing activities of it [69].

Contraindications

Restriction for the patients with bile duct obstruction, gallstones, and GI disorders (including stomach ulcers and hyperacidity disorders) should not take this supplement. [5]

Curcumin drug interaction

Turmeric may increase the risk of bleeding or potentiate the effects of warfarin or other blood thinning therapies [5].

RECENT ADVANCEMENT AND FUTURE ASPECTS

MERIVAR is the patented complex of soy phospholipids obtained with the phytosome technology which mainly works on osteoarthritis .This is the first time curcumin shows efficacy at low and realistic dosage form. It is published by Italian researchers on 26th of July, 2010.in Panminerva Medica. [88]

Development and Clinical Application of THERACURMIN^R

Oral bioavailability is one of the major challenges which limit the clinical application of curcumin [89, 90]. Therefore nanoparticulation technique was used to develop THERACURMIN^R highly absorbable curcumin formulation that is easily dispersible in water. On studying absorption of THERACURMIN^R in rats and human after oral administration found that rate of

curcumin in blood was increased in both rats and human, while AUC was more than 30 fold higher in humans compared to that of curcumin bulk powder. [89, 91]

LONGVIDA™ is the another name of curcumin it is a drug under clinical trials another patented complex obtained from natural phytosome constituents by Verdure Sciences company which shows efficacy at low and realistic dosage form. It has antioxidant, anti-inflammatory, antiviral, antibacterial, antifungal, and anticancer activities. It has also a major role on Alzheimer disease which shows limited permeability in brain. [92]

Clinical Application of Curcumin: Current status and future

In future ,it will be necessary to focus attention on the clinical application of curcumin in neurodegenerative disease ,cardio vascular disease and diabetes because many experiments have clarified the potential value of curcumin in these areas As a diet derived agent curcumin has no severe toxicity except for minor G.I side effects up to the dosage of 8gm for 3 months .However, curcumin has a low bioavailability, so it is imperative to improve the bioavailability of curcumin in its clinical application .[93]

CONCLUSION

In this whole subject it can be concluded that curcumin has the ability to stand against dreadful diseases by giving desired action but there is one major drawback which is also highlighted i.e., solubility and bioavailability which is a challenge for all of us. Various strategies has now being explored in attempts to improve the bioavailability of curcumin such as, modulation of route and medium of curcumin administration, blocking of metabolic pathways by concomitant administration with other agents, and structural modifications . However there are also some novel delivery strategies including nanoparticles, liposomes and defined phospholipids complexes help in enhancement of the bioavailability and improvement of its medicinal value, and application of this interesting molecule from Mother Nature.

REFERENCES

1. Sharma R.A, Geschay A.J, Steward W.P. Curcumin: The story so far; European Journal of Cancer; 2005, 41; 1955-1968.
2. Brouk B. Plants consumed by man; New York; Academics press 1975:331.
3. Rajasekaran S.A.Therapeutic potential of curcumin in gastrointestinal diseases. World Journal of Gastrointestinal Pathophysiology; 2011; 15, 2(1):1-14.
4. Kim J; Lee K.W. Naturally occurring phytochemicals for the prevention of Alzheimer's diseases; J. Neurochem 2010: 1415-1430.
5. Curcumin. Available from: http:// www.healthoracle.org.
6. Anand P, Kunnumakkara A.B, Newman R.A, Aggarwal B.B .Bioavailability of curcumin: Problem and promises, Review article; molecular pharmaceutics, 2007, 4 (6): 807-818.
7. Aggrawal B.B, Kumar A, Bharti A.C. Anticancer potentials of curcumin, preclinical and clinical studies, anticancer research 2003; 23(1):363-398.
8. Sharma R.A, Geschay A.J, Steward W.P. Curcumin: The story so far; European journal of Cancer; 41, 2005:1955-1968.
9. Lin J.K, Pan M.H, Shiau S.Y.L. Recent studies on the biofunctions and biotransformation of Curcumin, biofactors 2000, 13:153-158.
10. Wang Y.J, Pan M.H, Cheng A.L. Stability of curcumin in buffer solutions and characterization of its degradation products; J Pharm Biomed Anal 1997, 15: 1867-1876.
11. Pharmacopoeia of India, Published by the controller of Publication, Delhi, 3rd edn, II 1985:177.
12. Akram M, Shahab-Uddin, Ahmed A, Khan U, Hannan A, Mohiuddin E, Asif M .Curcuma longa and Curcumin: A review article, Rom J.Biol- Plant Biol, 55(2):65-70.

13. Wilken R, Veena M.S, Marilene B .Wang, Srivastaw E.S. Curcumin: A Review of anticancer properties and therapeutic activity in head and neck squamous cell carcinoma; Molecular cancer.2011, 10:12:1-19.
14. Stell P.M, Vokes E.E, Weichselbaum. Survival time in end-stage head and neck cancer. Eur J SurgicalOncol 1989, 15: 407-410.
15. Altekruse S.F, Kosary C.L, Krapcho M, Neyman N, Aminou R, Waldron W,Ruhl J, Howlader N, Tatalovich Z, Cho H, Mariotto A, Eisner M.P, Lewis DR, Cronin K, Chen HS, Feuer E.J, Stinchcomb D.G, Edwards B.K: Seer Cancer Statistics Review 1975-2007.
16. Aggarwal S,Takadar V, Singh S, Myers J.N, Aggarwal B.B. Inhibition of growth and survival of human head and neck squamous cell carcinoma cells by curcumin via modulation of nuclear factor kB signaling Int .cancer 2004; 111:679-692.
17. Lo Tempio M.M, Veena M.S, Steele H.L, Ramamurthy B, Ramalingam T.S, Colen A.N, Ch-krabati R, Srivatsan E.S, Wang M.B. Curcumin suppress growth of head and neck and sqamous cell carcinoma; clinical cancer; Res 2005; 11:6994-7002.
18. Wang D, Veena M.S, Sterenson K, Tang C, Ho B; Suh J.D, Duarte V.M, Faull K.F, Mehta K Srivatsan E.S, Wang M.B. Liposome encapsulated curcumin suppress growth of head and neck squamous cell carcinoma invitro and in xenografts through the inhibition of nuclear factor kappa B by an AKT independent pathway; clin cancer Res 2008; 14:6228-6236.
19. Mukhopadhay A, Bueso-Ramos, Chatterjee P, Pantazis P, Aggarwal B.B. Curcumin down Regulates cell survival mechanism in human prostate cancer cell lines, oncogenes 2001; 20: 7597-7609.
20. Mehta K, Pantazis P, Mcqueen T, Aggarwal B.B. Antiproliferative effect of curcumin against Human breast tumor cell lines; anticancer drugs 1997; 8:470-481.
21. Hanif R, Qiao L, Scniff S.J, Rigas B. Curcumin a natural plant phenolic food additive, inhibit Cell proliferation and induces cell cycle changes in colon, adenocarcinoma cell lines by a Prostaglandin independent pathway; J Lab clin Med 1997, 130:576-584.
22. Elattar T.M, Virji A.S.The inhibitory effect of curcumin, genistein, quercitine and cisplatin on the growth of oral cancer cell in vitro; anticancer Res 2000; 20:1733-1738.
23. Lin Y.G, Kunnumakkara .A.B, Nair A, Merritt W.M ,Han L.Y, Amaiz Pena G.N, Kamat A.A, Spanmuth W.A, Gershanson D.M, Lutgendorf S.K, Aggarwal B.B, Sood A.K. Curcumin inhibit tumor growth and angiogenesis in ovarian carcinoma by targeting the nuclear factor Kappa B pathway clin cancer Res 2007, 13:3423-3430.
24. Siwak D.R, Shishodia S, Aggarwal B.B, Kuzrock R, Curcumin induced antiproliferative and proapoptotic effects in melanoma cells are associated with suppression of kappa B kinase and an independent of the B rat/mitogen activated/extracellular signal regular proteins kinase pathway and Akt pathway cancer 2005; 104:879-890.
25. Anand P, Sundaram C, Jhurani S, Kunnumakkara A.B, Aggarwal B.B, Curcumin and cancer: An ‘‘old-age” disease with an ‘‘age-old” solution Cytokine, 2008 ,267 ,2008 :133–164.
26. Rafiee P, Ogawa H, Heidemann J, Li M.S, Aslam M, Lamirand T.H, Fisher P.J, Graewin S.J, Dwinell M.B, Johnson C.P, Shaker R, Binion D.G. Isolation and characterization of human esophageal microvascular endothelial cells: mechanisms of inflammatory activation, Am. J. Physiol. Gastrointestinal. Liver Physiol. 285, 2003:1277–1292.
27. Aggarwal B.B, Bhatt I.D, Ichikawa H, Ahn K.S, Sethi G, Sandur S.K, Sundaram C, Seeram N, Shishodia.S. Curcumin – biological and medicinal properties, 200:297–368.

28. Bansal S.S, Goyal M, Aquil F,Vadhanam M.V, Gupta R.C. Advanced Drug Delivery Systems of curcumin for cancer chemoprevention. Cancer Prev Res, 2011 4: 1158.
29. Bansal S.S, Vadhanam M.V, Gupta R.C. Development and invitro-in vivo evaluation of polymeric plants for continuous systemic delivery of curcumin Pharm Res 2011, 28:1121-30.
30. Ma Z Haddadi A,Malavio, Lavasanifar A, Lai R, Samuel J; Micelles of poly (ethylene oxide) –b-poly (epsilon- caprolactone) as vehicle for the solubilization, stabilization and controlled delivery of curcumin, J Biomed Mater Res A 2008:86:300-10.
31. Thangapazaham R.L, Puri A, Tele S, Blumenthal R, Maheshwari R.K. Evaluation of a nanotechnology based carrier for delivery of curcumin in prostate cancer cells Int J Oncology 2008; 32:1119-23.
32. Anand P, Nair H.B, Sung B, Kunnumakkara A.B, Yadav V.R, Tekmal R.R. Design of Curcumin loaded PLGA nano particles formulation with enhanced cellular uptake and increased bioactivity in vitro and superior bioavailability in vivo. Biochem Pharmcol 2010; 79: 330-8.
33. Bisht S, Feldmann G, Soni S, Ravi R, Karikar C, Maitra A, Polymeric nanoparticle encapsulated curcumin (nanocurcumin), novel strategy for human cancer therapy, J Nanobiotechnology 2007; 5: 3.
34. Shaikh J, Ankola D.D, Benival V, Singh D, Kumar M.N. Nanoparticle encapsulation improves oral bioavailability of curcumin by at least 9 folds when compared to curcumin ad- ministered with piperine as absorption enhancer, Eur.J.Pharm Sci 2009; 37:223-30.
35. Ganta S, Amji M. Co administration of paciltaxel and curcumin in nanoemulsion formula- tion to overcome multidrug resistance in tumour cells.Mol.Pharm 2009; 6:928-39.
36. Maiti K, Mukherjee K, Gantait A, Saha B.P, Mukherjee P.K. Curcumin- phosphoplipid Complex, preparation, therapeutic evaluaton and pharmacokinetic study in rats; Int J Pharma 2007; 330:155-63.
37. Grabovac V, Bernkop.Schmuch. A Development and in vitro evaluation of surface modified Poly (lactide-co-glycolide) nanoparticle with chitosan -4 thiobutyl amidine. Drug Dev Ind Pharm 2007; 33: 767-74.
38. Hobbs S.K, Monsky W.L, Yuan F, Roberts W.G, Griffith L, Torchilin V.P. Regulation of transport pathways in tumor vessel: role of tumor type and micro-envoirnment.1998; 95:4607-12.
39. Yuan F, Dellian M, Fukumuua P, Leunig M, Berk D.A, Torchillin V.P. Vascular per-meability in a human tumor xenograft molecular size dependence and cut off size cancer Res 1995; 55:3752-6.
40. Gerlowski L.E, Jain R.K. Microvascular permeability of normal and neoplastic tissue Micr-ovase Res 1986; 31:288-305.
41. Birnboin S A, Del Vecchio P.J, Cooper J.A, Blumenstock F.A, Shephard J.M, Malik A.B. Molecular sieving characterstics of the cultured endothelial monolayer J Cell Physiol 1987; 132:111-7.
42. Thangapazaham R.L, Puri A, Tele S, Blumenthal R, Maheshwari R.K. Evaluation of a nan-otechnology based carrier for delivery of curcumin in prostate cancer cells Int J Oncology 2008; 32:1119-23.
43. Li L, Braiteh F.S, Kurzrock R. Liposome encapsulated curcumin, in vitro and in vivo effects on proliferation apoptosis, signaling and angiogenesis cancer 2005; 104:1322-3.
44. Jung S, Otberg N, Theide G, Richter H, Sterry W, Panzer S . Innovative liposomes as a transfollicular drug delivery system: penetration into porcine hair follicles .J invests Dermatol 2006; 126:1728:32.
45. Wattanakrai P, Suwanachote S, Kulkollakarn S, Rajatanavin N. The study of human skin irritation of a novel herbal skin care product and ingredients by human single closed patch testing. J Med Assoc Thai 2007; 90:1116–22.

46. Campbell RB, Ying B, and Kuesters GM, Hemphill R. Fighting cancer: from the bench to bedside using second generation cationic liposomal therapeutics. J Pharm Sci 2009; 98:411– 29.
47. Lee MH, Lin HY, Chen HC, Thomas JL. Ultrasound mediates the release of curcumin from microemulsion Langmuir2008; 24:1707-13.
48. Santos P, Watkinson AC, Hadgraft J, Lane ME. Application of micro emulsions in dermal and transdermal drug delivery. Skin Pharmacol Physiol 2008; 21:246–59.
49. Teichmann A, Heuschkel S, Jacobi U, Presse G, and Neubert RH, Sterry W .Comparison of stratum corneum penetration and localization of a lipophilic model drug applied in an o/w microemulsion and an amphiphilic cream. Eur J Pharm Biopharm 2007; 67:699–706
50. Boriwanwattanarak P, Ingkaninan Khorana N, Viyoch J.Development of curcuminoids hydrogel patches using chitosan from various sources as controlled-release matrix. Int J 05–18.
51. Tiyaboonchai W, Tungpradit W, Plianbangchang P. Formulation and characterization of curcuminoids loaded solid lipid nanoparticles. Int J Pharm 2007; 337:299–306.
52. Domb AJ, Israel ZH, Elmalak O, Teomim D, Bentolila A. Preparation and characterization of carmustine loaded polyanhydride wafers for treating brain tumors. Pharm Res 1999; 16:762– -5.
53. Jain JP, Modi S, Domb AJ Kumar N. Role of polyanhydrides as localized drug carriers. J Control Release 2005; 103:541–63.
54. Langer R. Drug delivery and targeting. Nature 1998; 392:5–10.
55. Dash AK, Cudworth GC 2nd. Therapeutic applications of implantable drug delivery systems. J Pharmacol Toxicol Methods 1998; 40:1–12.
56. Asai A, Miyazawa T., Occurrence of orally administered curcuminoid as glucuronide and glucoronide / sulfate conjugates in rat plasma, Life-Sci. 2000; 67(23):2785-93.
57. Shankar T. N, Shantha N. V, Ramesh H. P, Murthy I. A, Murthy, V. S. Toxicity studies on turmeric (Curcuma longa): acute toxicity studies in rats, guinea pigs & monkeys. Indian J. Biol. 1980, 18 (1): 73–5.
58. Qureshi, S, Shah A. H, Ageel, A. M .Toxicity studies on Alpinia galanga and Curcuma longa. Planta Med. 1992, 58 (2): 124–7.
59. Lao, C. D, Demierre, M. F, Sondak, V. K. Targeting events in melanoma carcinogenesis for the prevention of melanoma. Expert ReV. Anticancer Ther. 2006, 6 (11): 1559–68.
60. Lao, C. D, Ruffin, M. T, Normolle, D, Heath, D. D, Murray, S. I, Bailey, J. M, Boggs, M. E., Crowell, J, Rock, C. L., Brenner, D. E. Dose escalation of a curcuminoid formulation. BMC Complement Altern. Med. 2006, 6:10.
61. Cheng A. L, Hsu C. H., Lin J. K, Hsu M. M, Ho Y. F, Shen T. S, Ko J. Y, Lin J. T, Lin B. R., Ming-Shiang W, Yu H. S, Jee S. H, Chen G. S, Chen T. M, Chen C. A, Lai M. K., Pu Y. S, Pan M. H, Wang Y. J, Tsai C. C, Hsieh C. Y. Phase I clinical trial of curcumin, a chemopreventive agent, in patients with high-risk or pre-malignant lesions. Anticancer Res. 2001, 21 (4):2895–900.
62. Shoba. G, Joy. D, Joseph. T, Majeed. M, Rajendran. R, Srinivas P. S. Influence of piperine on the pharmacokinetics of curcumin in animals and human volunteers. Planta Med 1998, 64(4):353–6.
63. Aggarwal B. B, Sundaram C, Malani N, Ichikawa H. Curcumin: the Indian solid gold. AdV. Exp. Med. Biol. 2007, 595:1–75.
64. Aggarwal, B. B, Kumar A, Bharti A. C. Anticancer potential of curcumin: preclinical and clinical studies. Anticancer Res. 2003, 23 (1):363–98.
65. Hsu, C. H, Cheng A. L. Clinical studies with curcumin. AdV.Exp. Med. Biol. 2007, 595:471–80.
66. Wahlstrom, B, Blennow, G. A study on the fate of curcumin in the rat. Acta Pharmacol.Tox- -icol. (Copenhagen) 1978, 43 (2): 86–92.

67. Rajasekaran SA. Therapeutic potential of curcumin in gastrointestinal diseases. World J Gastrointest Pathophysiol 2011; 2(1): 1-14
68. Anand P, Kunnumakkara AB, Newman RA, Aggarwal BB. Bioavailability of curcumin: problems and promises. Mol Pharm 2007; 4: 807-818.
69. Aggarwal B.B, Harikumar B.Kuzhuvelil, Potential therapeutic effects of curcumin the anti inflammatory agent, against neurogenerative, cardiovascular, pulmonary, metabolic autoimmune and neoplastic diseases; 2008,41:40-59.
70. Cheng AL, Hsu CH, Lin JK, Hsu MM, Ho YF, Shen TS. Phase I clinical trial of curcumin, a chemo preventive agent, in patients with high-risk or pre-malignant lesions. Anticancer Res 2001; 21:2895–900.
71. Lao CD, Ruffin M.T.T, Normolle D, Heath DD, Murray SI, Bailey JM. Dose escalation of a curcuminoid formulation. BMC Complement Altern Med 2006; 6:10.
72. Shishu, Maheshwari M. Comparative bioavailability of curcumin, turmeric and BiocurcumaxTM in traditional vehicles using non-everted rat intestinal sac model. J Func Foods 2010; 2: 60-65.
73. Kang MJ, Cho JY, Shim BH, Kim DK, Lee J. Bioavailability enhancing activities of natural compounds from medicinal plant. J Med Plants Res 2009; 3: 1204-1211.
74. Balasubramanian S, Eckert RL. Green tea polyphenol and curcumin inversely regulate human involucrin promoter activity via opposing effects on CCAAT/enhancer-binding protein function. J Biol Chem 2004; 279: 24007-24014.
75. Chiao CS, Robinson JR. Sustained- Release Drug Delivery Systems. 1995: (2):1660-75.
76. Kant Shashi, Kumar Satinder, Prashant Bharat. A complete Review on: Liposome; ISSN 2230-8407: 10-16.
77. Crommelin D.J.A, Lasic D.D, papahadjopoulos D. Liposome, revisited Science 1995 267: 1275-1276.
78. Emanuel N, Kedar E, Bolotin E.M, Smorodinsky N.I, Barenhotz V, 1996.Preparation & Characterization of doxorubicin loaded stearically stabilized immunoliposomes Pharm Res 13: :352-359.
79. DIY Scientist. Increasing the bioavailability of curcumin through Liposomal Encapsulation June 1, 2011.
80. Vyas S.P, Khar R.K. Targeted & Controlled Drug Delivery; section II Carrier concepts in Drug Delivery, chapter 5, liposomes; CBS publishers &Distributers first edition 2002:173-248.
81. Vila A, Sanchez A, Tobio M, Calvo P, Alonso MJ. Design of biodegradable particles for protein delivery. J Control Release 2002; 78: 15-24.
82. Karikar C, Maitra A, Bisht S , Feldmann G , Soni S , Ravi R. Polymeric nanoparticle encapsulated curcumin ("nanocurcumin"): a novel strategy for human cancer therapy. J. Nanobiotechnol. 2007, 5: 3.
83. Suresh D, Srinivasan K. Studies on the in vitro absorption of spice principles—Curcumin, capsaicin and piperine in rat intestines. Food Chem. Toxicol. 2007, 45 (8):1437–42.
84. Ma Z, Shayeganpour A ,Brocks D. R , Lavasanifar A , Samuel J. High-performance liquid chromatography analysis of curcumin in rat plasma: application to pharmacokinetics of polymeric micellar formulation of curcumin. Biomed. Chromatogr. 2007, 21 (5):546–52.
85. Gupta NK, Dixit V.K. Bioavailability enhancement of curcumin by complexation with Phosphatidylcholine; 100(5):1987-95.
86. Shen, L, Ji H. F. Theoretical study on physicochemical properties of curcumin.Spectrochin. Acta A Mol. Biomol. Spectrosc. 2007, 67 (3–4):619–23.
87. Ohori, H , Yamakoshi H, Tomizawa M , Shibuya M , Kakudo Y , Takahashi A , Akashi S, Kato S, Suzuki T, Ishioka C, Iwabuchi Y, Shibata H. Synthesis and biological analysis of new curcumin analogues bearing an enhanced potential for the

medicinal treatment of cancer. Mol. Cancer Ther. 2006, 5 (10): 2563–71.

88. Belcaro G, Cesarone M.R, Dugall M. Product-evaluation registry of Meriva®, Curcumin-phosphadidylcholine complex, for the complementary management of osteoarthritis, Panminerva Medica 2010 Giugno; 52,2 (1):55-62.
89. Shimatsu A, Kakeya H, Imaizumi A , Morimoto T, Kanai M, Maeda S . Clinical Application of "Curcumin", a Multi-Functional Substance, 2012:75-82.
90. Anand P, Kunnumakkara AB, Newman RA. Bioavailability of curcumin: problems and promises. Mol Pharm 2007, 4(6); 807-18.
91. Sasaki H, Sunagawa Y, Takahashi K,. Innovative preparation of curcumin for improved oral bioavailability. Biol Pharm Bull 2011, 34(5): 660-5.
92. Frautschy SA, 2011.
93. Fan X, Zhang C, Liu DB, Yan J, Liang HP .The clinical applications of curcumin: current state and the future, Curr Pharm Des. 2013; 19(11):2011-31.

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