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. Commerically curcumin contains approximately 77%
diferuloylmethane, 17% demethoxycurcumin, and 6%
bisdemethoxycurcumin.[6, 7]

CHEMISTRY
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]

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

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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. 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. 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. Curcumin shows its potential in many other cancers.

In spite 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 parenteral administration), microemulsion/microencapsulation, implantable drug delivery systems 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.

**Curcumin as an Antioxidant**
Free radicals can originate from environmental chemicals, tissue injury, infections and autoimmune 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**
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 c4-2B cancer cell.

**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.

**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.

**PHARMACOKINETICS**
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 glucuronide/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 hexahydropicrocurcumin. 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, 65] 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 quercitine 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. 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. 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. 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.

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 amphiphilic nature of complex can increases water and lipid solubility.

Derivatives and Analouges
The chemical structure of curcumin plays a pivotal role in its biological activity. A curcumin analogue EF-24 was reported to be a lead compound displaying increased antitumor action invivo 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.

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 disrupt the antitumor action of chemotherapeutic agent such as cyclophosphamide in treating breast cancer. 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.

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

Curcumin drug interaction
Turmeric may increase the risk of bleeding or potentiate the effects of warfarin or other blood thinning therapies.

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.

Development and Clinical Application of THERACURMIN®
Oral bioavailability is one of the major challenges which limit the clinical application of curcumin. Therefore nanoparticulation technique was used to develop THERACURMIN® highly absorbable curcumin formulation that is easily dispersible in water. On studying absorption of THERACURMIN® 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.

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