World Journal of Pharmaceutical and Life Sciences
WJPLS
www.wjpls.org
SJIF Impact Factor: 6.129

# CURCUMIN AS A POTENTIAL BIOACTIVE HOLISTIC UNIT FROM RHIZOME

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**Article Received on 21/02/2022** **Article Revised on 11/03/2022** **Article Accepted on 01/04/2022**

## ABSTRACT

Turmeric is a curry spice that originated from India, which has attracted great interest in recent decades because it contains bioactive curcuminoids Curcumin. In turmeric two other curcuminoids occur in lesser amounts namely, desmethoxycurcumin (DMC) and bis-desmethoxycurcumin (BDMC). Curcumin exerts a wide range of beneficial physiological and pharmacological activities, including antioxidant, anti-amyloid, anti-inflammatory, anti-microbial, anti-neoplastic, immune modulating, metabolism regulating effects. In spite of its benefit on inflammatory and antioxidant mechanisms, one of the major problems with ingesting curcumin by itself is its poor bioavailability which caused primarily due to poor absorption, rapid metabolism, and rapid elimination. Several strategies are been adopted to increase curcumin's bioavailability by addressing these various mechanisms. Most of them have been developed to block the metabolic pathway, increasing serum concentrations of curcumin in order to increase its bioavailability. For example: Piperine, Cyclodextrin, Liposomes, Phosphatidylcholine phytosome complex, di glutaric acid used as bioavailability enhancer by which can provide >100 folds better bioavailability than unformulated curcumin. How curcumin reacts with the body, how bioavailable is it, how well curcumin is absorbed and how it is metabolized, is the focus of this review.

**KEYWORDS:** Curcumin, Curcuminoids, Bioavailability, Solubility, Concentration, Control Release.

## INTRODUCTION

Turmeric is a spice that has received a lot of interest from each the medical & scientific worlds likewise as from the cookery world. Turmeric may be a stalk nonwoody perennial plant (*Curcuma longa*) of the ginger family.[1] The healthful properties of turmeric, the supply of curcumin, are better-known for thousands of years; but, the power to see the precise mechanism(s) of action and to see the bioactive elements have solely recently been investigated.[2] Curcumin (1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione), conjointly known as diferuloylmethane, is that the main natural polyphenol found within the rootstalk of *Curcuma longa* (turmeric) and in others genus Curcuma spp.[3] In addition to curcumin,[2] alternative curcuminoids occur in lesser amounts in turmeric, namely, desmethoxycurcumin (DMC) and bis-desmethoxycurcumin (BDMC). Removal of the methoxy teams yielding DMC and BDMC leads to completely different chemical and biological properties as compared with curcumin. Curcuminoids compose 2-4% of dry herb powder.[4-5] Curcumin may be administered as turmeric, concentrates of turmeric, primarily pure (95%) curcuminoids or curcumin alone. sadly, all of those separate, disparate entities are known as "curcumin", inflicting abundant confusion within the literature. Curcumin exhibits a large vary of useful effects as well as medication, inhibitor, chemoprotective, tissue protecting, medication, anti-fungal, antiviral, metabolism regulation, immuno-modulating, antineoplastic and anti-depressant properties[6-14] except its use as a curry spice, turmeric has been traditionally used as a natural colouring agent (food, cosmetics, and textiles), a repellent, and as an antimicrobial agent.[15] Despite its reported edges via inflammatory and inhibitor mechanisms, one in every of the main issues with ingesting curcumin by itself is its poor bioavailability sixteen, that seems to be primarily because of poor absorption, fast metabolism, and fast elimination Many agents are tested to boost curcumin's bioavailability by addressing these numerous mechanisms. Most of them are developed to damp the metabolic pathway of curcumin so as to extend its bioavailability.[16] For instance, piperine, a better-known bioavailability enhancer , is that the major active element of black pepper and is related to a rise of 2000% within the bioavailability of curcumin alternative reported delivery systems for curcumin embody micelles, liposomes, lipid complexes, microemulsions, nano-emulsions, emulsions, solid lipid nanoparticles, nanostructured lipid carriers, biopolymer nanoparticles and microgels, a proprietary curcumin- phosphatidylcholine phytosome complex named Meriva® is wide used.[17] They not solely

enhance efficacy however conjointly increase curcumin bioavailability by best permeation within the bowel and preventing the degradation within the GI tract.[19-24] This review, as compared to alternative curcumin-related reviews, summarizes the 3 broad formulation methods that are utilized to boost absorption and bioavailability, providing specific examples for every class. Finally, the potential health, well-being and therapeutic applications which will enjoy extremely bioavailable curcumin area unit summarized. during this review, developed curcumin product that give >100-fold higher absorption than unformulated curcumin area unit thought of extremely bioavailable because of the extent of the literature, we've got chosen to concentrate on the profit its related to some common health conditions and on profit its in healthy individuals instead of to review the in depth literature associated with cancer and alternative illness states.

## Curcumin

### *Chemistry of Curcumin*

Chemical composition of turmeric consists of approximately 70% carbohydrates, 13% moisture, 6% protein, 6% essential oils (phellandrene, sabinene, cineol, borneol, zingiberene and sesquiterpenes), 5% fat, 3% mineral (potassium, calcium, phosphorus, iron, and sodium), 3–5% curcuminoids, and trace amounts of vitamins (B1, B2, C, and niacin).[25-29] Among the curcuminoids (Figure 1), approximately CUR accounts for 77%, DMC accounts for 17% and BMC accounts for 3–6%.[26,30]

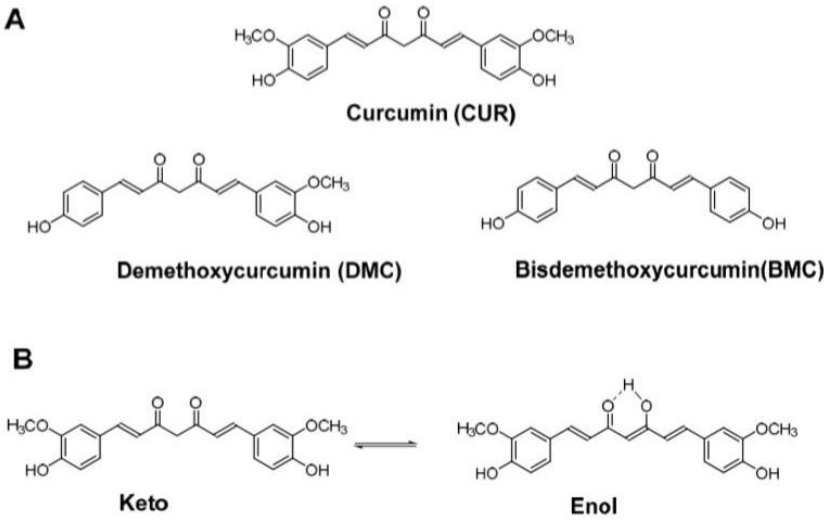


**Figure 1: A: Structure of Curcumin & structure of two minor curcuminoids. B:- Keto & Enol form of Curcumin.**

Curcumin has two tautomeric forms, keto and enol (Figure 1B). Curcumin is practically insoluble at room temperature in aqueous solutions at neutral and acidic pH. However, due to lipophilic nature with a log P value of ~3.0, it is soluble in organic solvents like methanol, ethanol, acetone, and dimethyl sulfoxide. Both at neutral and acidic pH, keto form is predominant, however, enol tautomer is exclusively present in alkaline conditions, which can be rationalized by the intramolecular hydrogen bonding in enol form.[28,31,32] The solubility of curcumin in aqueous solution increases under alkaline conditions, but CUR degrades rapidly under both neutral and alkaline conditions.

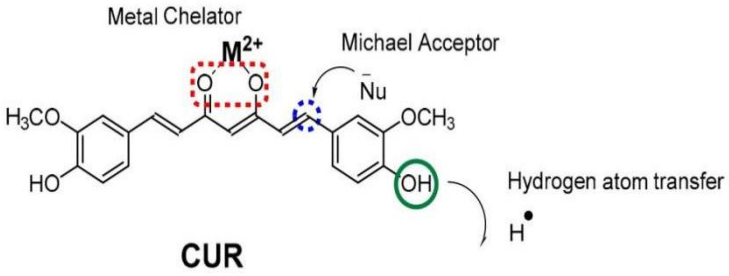


**Figure 2: Chemical reactivity sites in curcumin which contribute to its activity and bioavailability.**

Curcumin shows maximum absorption at 430 nm in methanol and 415–420 nm in acetone.[25,33] In alkaline conditions (pH > 10), CUR is fully deprotonated and shows maximum absorbance at 467 nm.

CUR primarily has three reactive sites, as illustrated in Figure2, hydrogen atom donor, Michael acceptor, and a metal chelator.[27,28,34] Theα,β-unsaturatedβ-diketone portion of CUR is an excellent metal chelating agent and forms complexes with several known metal ions. The metal chelating ability of CUR has shown great promise as a therapeutic agent against diseases like Alzheimer's, cancer, depression, and arthritis.[28,35-38] CUR forms complexes with all the metals such as $Al^{3+,}$ which are involved in Alzheimer's, or direct binding to the small β-amyloid species to prevent aggregation and fibril formation Curcumin reduces heavy metal-induced toxicity (oxidative stress) by forming stable complexes with heavy metals like copper (Cu), chromium (Cr), arsenic (As), mercury (Hg), lead (Pb) and cadmium (Cd).[39-47]

***Bioactivity of Curcumin***

CUR has an ability to affect multiple biological targets and has been shown to exhibit activity against various diseases, including cancer, cardiovascular disease, neurological and autoimmune diseases) CUR can modulate several biological targets (including transcription factors, growth factors, inflammatory mediators, cytokines, cell cycle proteins, enzymes, protein kinases, and apoptotic proteins) and cellular pathways For instance, CUR modulates tumor growth via regulating multiple signaling pathways, including cell survival, tumor suppressor, caspase pathways, protein kinase, and death receptor pathways.[26,48,50,52]

CUR can inhibit the activation of the transcription factor nuclear factor kappa B (NF-$_{K}$B), which is responsible for cell survival, cytokine production, and other cellular functions. CUR down regulates the signal transducer and activation transcription (STAT) proteins, which are essential for cell growth, differentiation, and survival STAT proteins are also involved in immune system development, function, and clearance. Curcumin upregulates a leucine zipper protein NrF2, which regulates the expression of antioxidant properties that protect the cells from oxidative stress Curcuminoids therapeutic effect in treating some of the medical conditions/ diseases and related mode of action have been discussed below.[34,48,52]

Curcumin has been shown to improve systemic markers of oxidative stress There is evidence that it can increase serum activities of antioxidants such as superoxide dismutase (SOD).[51-53]

Curcumin's result on free radicals is meted out by many completely different mechanisms. It can scavenge different forms of free radicals, such as reactive oxygen and nitrogen species (ROS and RNS, respectively)[52] it can modulate the activity of GSH, catalase, and SOD enzymes active in the neutralization of free radicals; also, it can inhibit ROS-generating enzymes such as lipoxygenase/cyclooxygenase and xanthine hydrogenase /oxidase.[55,56]

Tumor necrosis factor (TNF-α) is a major mediator of inflammation in most diseases, and this effect is regulated by the activation of a transcription factor, nuclear factor (NF)-κB. Whereas TNF-α is a most potent NF-κB activator, the manifestation of TNF-α is also regulated by NF-κB. In addition to TNF-α, NF-κB is also activated by most inflammatory cytokines; gram-negative bacteria; various disease-causing viruses; environmental pollutants; chemical, physical, mechanical, and psychological stress; high glucose; fatty acids; ultraviolet radiation; cigarette smoke; and other disease-causing factors. Therefore, agents that down regulate NF-κB and NF-κB–regulated gene products have potential efficacy against several of these diseases. Curcumin has been shown to block NF-κB activation increased by several different inflammatory stimuli Curcumin has also been shown to suppress inflammation through many different mechanisms beyond the scope of this review, thereby following action as a potential anti-inflammatory agent.[57] Sahebkar reported that curcuminoids might reduce circulatory C-reactive protein levels, which is a predictor and independent risk factor of cardiovascular disease Curcumin has also shown to be effective against myocardial infarction and atherosclerosis CUR also has shown to decrease triglycerides levels, LDL (low-density lipoprotein), and total cholesterol Murugan and Pari in 2007 observed that decreased levels of plasma total protein, albumin, globulin, and albumin/globulin ratio in diabetic rats were brought back to near normal after CUR administration.[17,47,59,58]

***Bioavailability of curcumin***

The therapeutic potential of CUR is mainly circumvented by its low bioavailability and poor pharmacokinetic profile (ADME; absorption, distribution, metabolism, and excretion) and short half-life time in the gastrointestinal (GI) tract.[27,29] Another challenge for CUR as a potential therapeutic agent is its poor stability under physiological conditions. For instance, at 37 ◦C and neutral pH (7.2), curcumin $t_{1/2}$ was reported less than 10 min. CUR degradation occurs in two pathways: solvolysis and photodegradation ·Solvolysis involves the nucleophilic substitution or elimination by solvent molecules. The nucleophile attack occurs on α,β-unsaturated ketone part of CUR (Michael addition).[29]

In aqueous alkaline buffer, solvolysis of heptadienone chain results in 90% of CUR degradation to generate vanillin, ferulic acid, ferulic aldehyde, and other products CUR degradation occurs upon exposure to sunlight which is commonly observed by quick removal of turmeric stains when exposed to sunlight. Photochemical degradation of CUR occurs in solid as well as solubilized forms to ferulic acid, ferulic aldehyde, vanillin, and vanillic acid.[27-29]

First time Wahlstrom and Blennow in 1978 reported that after oral administration of 1 g/kg of curcumin in Sprague-Dawley rats, negligible amounts of curcumin in

blood plasma of rats was observed which could be its poor absorption from the gut. Later several studies conducted on bioavailability of curcumin and found that certain amount of curcumin are bioavailable in serum of animals. In a study, when curcumin was given orally at a dose of 2 g/kg to rats, a maximum serum concentration of 1.35±0.23 µg/mL was observed at time 0.83 hours, whereas in humans the same dose of curcumin resulted in either undetectable or extremely low (0.006±0.005 µg/mL at 1 hour) serum levels [61,62]

A very recent study by Sun et al. showed that intravenous administration of unformulated curcumin to rats showed better availability of curcumin in blood plasma. The concentration was 6.6 µg/mL of blood plasma when administered 2 mg/kg through tail vain.[63]

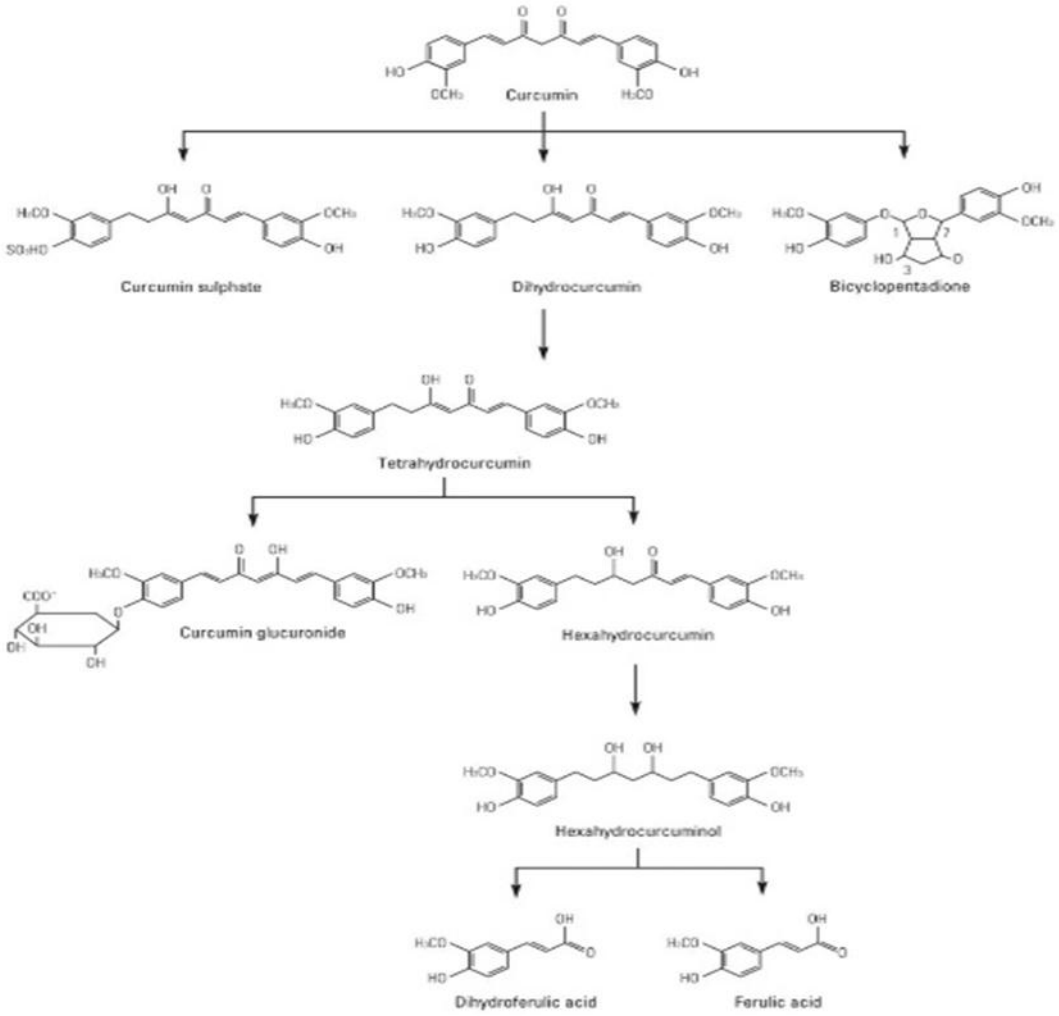


**Figure 3:- Metabolism of Curcumin.**

***Metabolism of Curcumin***

CUR metabolism mainly occurs via reduction and conjugation. After p.o. dosing, curcumin undergoes metabolic O-conjugation to curcumin glucuronide and curcumin sulfate and bioreduction to tetrahydrocurcumin, hexahydrocurcumin, octahydrocurcumin, and hexahydrocurcuminol in rats and mice *in-vivo* and in suspensions of human and rat hepatocytes Reduced curcumin also subjected to glucuronidation into curcumin glucuronide, dihydrocurcuminglucuronide, tetrahydrocurcumin-glucuronide, and curcumin sulfate.[64-66] Holder et al. reported that the major billiary metabolites of curcumin are glucuronides of tetrahydrocurcumin and hexahydrocurcumin in rats.[67] A fraction of biliary metabolite was dihydroferulic acid together with traces of ferulic acid. Numerous studies have revealed that curcumin metabolites have antioxidative, anti-inflammatory and anticancer activities. Tetrahydrocurcumin (THC) inhibits radiation-induced lipid peroxidation and induced antioxidant enzymes *in-vitro.* Hexahydrocurcumin, another metabolite, has reduced ability to inhibit COX-2 expression compared to curcumin.[65,68] Hexahydrocurcumin also induce cell cycle arrest in human colorectal cancer SW480 cells Pan et al. has shown that another metabolite, octahydrocurcumin, has very less NF-κB suppressive activity compared to curcumin.[70,71]

Beside these, we have recently showed that none of curcumin mono or di glucuronide showed biological activity such as anti inflammatory or antiproliferative activity compared to curcumin. Curcumin sulfate inhibits prostaglandins E2 activity very poor than curcumin. [65]

**Various Formulation Strategies**

Various types of chemical modification of CUR (which include use of liposomes, nanoparticles, micelles, phospholipid complexes, polymers, adjuvants) have been developed to improve curcumin solubility, bioavailability, longer circulation time, targeted delivery and ADME profiles.[29,75-77] Nano-, micro-formulations have gained a great focus because of the advantages associated with them, including increased solubility, improved cellular uptake, target specificity, decreased degradation, increased bioavailability, circulation times, and ADME profiles.[73,74] Curcumin is fat soluble, and therefore consuming curcumin with a fatty meal enhances absorption. Early approaches to enhancing absorption were the addition of turmeric oil (BCM-95®; BioCurcumax®; Curcugreen™) a small amount of piperine (Curcumin C3 Complex®) to stimulate the digestive system and forestall flow of curcumin, or as a turmeric natural resin (Curcugen™) that have resulted in tiny progressive will increase in curcumin absorption.[82,85]

**Table 1: Curcumin Formulation Strategies to Enhance Absorption.**

| Technical approaches. | Commercial products | PK Studies | Hydrolysis |
|---|---|---|---|
| **Turmeric oil**[86,87] | BCM-95® BioCurcumax® | Yes | Yes |
| **Piperine**[83,85] | Curcumin C3 Comples® | Yes | Yes |
| **Turmeric oleoresin** | Curcugen® | No | NA |
| **Gama-Cyclodextrin**[86] | Cavacurmin® | Yes | Yes |
| **Microcrystalline cellulose/Lecithin**[17,80,88-90] | Meriva® | Yes | Yes |
| **Cellulosic derivatives**[21] | CurcuWIN® | Yes | Yes |
| **Silicon dioxide/triacetin/Panodan®**[91] | Micronized Curcumin | No | NA |
| **Carbohydrates/protein/oil/Fiber**[20] | Cureit®; Acumin® | Yes | No |
| **Whey protein** | CurcuminPro™ | No | NA |
| **Rice flour/ silica/magnesium/Stearate** | Curcufresh™ | No | NA |
| **Gelucire®/Polysorbate 20**[13] | BioCurc® | Yes | No |
| **Galactomannan fiber**[91] | CurQfen® | Yes | Yes |
| **Gelucire®/Labrasol®**[92] | No | No | NA |
| **Ghatti gum/glycerin/Lipids/hydroxymethyl**[93] | Theracurmin® | Yes | Yes |
| **Cellulose/sodium alginate**[94] | MicroActive Curcumin™ | No | NA |
| **Surfactants/polar lipids Solvents**[95] | HydroCurc™ | No | NA |
| **Docosahexaenoic acid/Lecithin/stearic acid**[96] | Longvida® | Yes | No |
| **Sod. Caseinate/Tween 80**[24] | No | No | NA |
| **Proprietary microcapsules Curcushine™** | Curcushine™ | No | NA |
| **Acacia gum/quillaia/sunflower oil** | TurmiPure® | No | NA |

Among the multiple curcumin-formulations, the phytosomal formulation of CUR (Meriva), which is a complex of curcumin with phosphatidylcholine, is one of the well-studied curcumin-formulation Meriva is prepared by adding phospholipids to the hydroalcoholic extract of turmeric rhizomes under reflux conditions Meriva has shown improved bioavailability and pharmacokinetic prof I les than the uncomplexed curcumin There have been several studies focusing on the effIcacy of phytosomal curcumin in treating conditions such as cancer, inflammatory diseases, and diabetes. The data suggest that the phytosomal curcumin formulation has excellent properties as a delivery system[97]

**Table 2: Several curcumin formulations using Meriva® and their clinical or in-vivo outcomes.**

| Disease/Curcumin Activity | Formulation | Outcome |
|---|---|---|
| **Solid Tumor**[98] | Meriva®(Patented and commercialized); a complex of curcumin with phosphatidylcholine | Suppression of systemic inflammation via reduction of inflammatory mediators and biomarkers (TNF-α, CGRP, substance P, MCP-1, hs-CRP, and IL-6) |
| **Diabetes**[99] | Meriva® | Significant improvement in the venoarteriolar response and a decrease in the peripheral oedema |
| **Osteoarthritis**[100] | Meriva® | Improvement of both the clinical and biochemical endpoints |
| **Central serous chorioretinopathy**[101] | Meriva® | Reduction in neuroretinal or retinal pigment epithelium detachment |
| **Osteoarthritis**[102] | Meriva® | Clinically effective in osteoarthritis treatment and management, while treatment costs were reduced signifIcantly |
| **Diabetes**[103] | Meriva® | Decrease in skin flux and edema |
| **Solid Tumor**[23] | Meriva ® | Signs of reduced side effects of cancer chemo- and radiotherapy treatment which are attributed to an anti-oxidant and anti inflammatory activity of curcumin |

Clinical studies is been done with more than 100 patients and it's found to be effective with most of them

**Theracurmin**, another CUR formulation consisting of dispersed curcumin with colloidal nanoparticles, was studied for improved bioavailability and its efficacy in treating osteoarthritis compared to turmeric powder itself. Theracurmin was shown to own larger bioavailability than turmeric powder by 40 fold in rats and 27 fold higher in humans A clinical study conducted by Nakagawa et al. finished that Theracurmin was found to be effective in decreasing pain while not inflicting any adverse effects.[105-107]

***Prodrug Approach***

A curcumin-diglutaric acid (CurDG) prodrug was synthesized by conjugation of curcumin with glutaric acid via associate organic compound linkage. The water solubility, partition constant, unleash characteristics, and antinociceptive activity of CurDG were compared to those of curcumin. The aqueous solubility of CurDG (7.48 µg/mL) is significantly greater than that of curcumin (0.068 µg/mL). A study in human plasma showed that the CurDG utterly releases curcumin at intervals two h, suggesting the power of CurDG to function a prodrug of curcumin. A hot plate test in mice showed the highest antinociceptive ef f ect dose of curcumin at 200 mg/kg p.o., whereas CurDG showed the same effect at an effective dose of 100 mg/kg p.o., indicating that CurDG significantly enhanced the antinociceptive effect compared to curcumin.The enhanced antinociceptive effects of CurDG may be due to improved water solubility and enhanced oral bioavailability compared to curcumin [108-109]

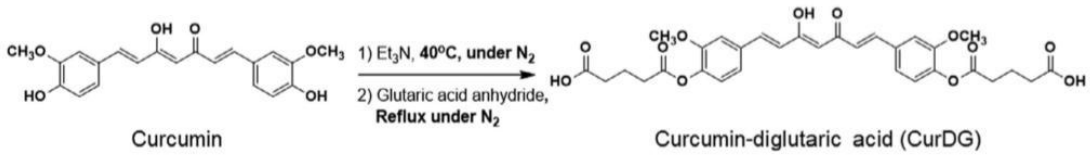


**Figure 4: Synthesis of CurDG.**

***Synthesis of CurDG***

In synthesis of CurDG (Figure 4), curcumin (1.47 g, 4 mmol) and triethylamine (1.26 mL, 9 mmol) were dissolved in dichloromethane, followed by gradual addition of glutaric anhydride (1.03 g, 9 mmol) in dichloromethane at 40 °C under a nitrogen atmosphere. The reaction mixture was refluxed under nitrogen for 2 h. After the reaction was complete based on monitoring with TLC, 0.1 N HCl and water were used to remove triethylamine hydrochloride and excess hydrochloric acid, respectively. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. The crude product was purified by crystallization from methanol to give CurDG (2.03 g, 85%) as a yellow solid; melting point 158–161 °C.

***Bioavailability of Curcumin in different Formulations Approaches***

***Nanocurcumin:-*** To increase the bioavailability of curcumin different formulations have been made. Among them, nanoglobules. Based nanoemulsion formulation has been prepared to evaluate the potential for the solubility enhancement of curcumin. During *ex vivo* study, the release of curcumin from nanoemulsion was

found much higher than curcumin suspension. This indicated the enhancement of solubility of curcumin in aqueous solution Another study showed an encapsulating the curcumin into the hydrogel nanoparticles yielded a homogenous curcumin dispersion in aqueous solution compared to the free form of curcumin.[108] Also, the in vitro release profile showed up to 95% release of curcumin from the developed nano-microparticulate systems.[109] The colloidal nanoparticles, named as 'theracurmin' showed AUC after the oral administration more than 40-fold higher than that of curcumin powder in rats. In healthy human volunteers, **theracurmin** (30 mg) when administered orally resulted 27-fold higher AUC than that of curcumin powder Another curcumin-loaded apotransferrin nanoparticles (nanocurcumin), prepared by sol-oil chemistry, releases significant quantities of drug gradually over a fairly long period, ~50% of curcumin still remaining at 6 hours of time. In contrast, intracellular soluble curcumin (sol-curcumin) reaches a maximum at 2 hours followed by its complete elimination by 4 hours Thus, nanocurcumin enhances bioavailability of curcumin in animals as well as in humans.[23,110]

***Poly Lactic Co- Glycolic Acid:-*** To improve the pharmacokinetics of curcumin with enhancing its bioavailability other effective formulation PLGA encapsulated curcumin was prepared. In vitro study showed that PLGA-curcumin has very speedy and more efficacious cellular uptake than curcumin. Intravenous administration of either curcumin or PLGA-curcumin (2.5 mg/kg), exhibited almost twice as high serum concentration of PLGA-curcumin than curcumin.[111] Another formulation PLGA and PLGA-polyethylene glycol (PEG) (PLGA-PEG) mixed nanoparticles containing curcumin were made. The PLGA and PLGA-PEG nanoparticles increased the curcumin mean half-life in approximately 4 and 6 hours, respectively, and the C(max) of curcumin increased 2.9- and 7.4-fold, respectively. Compared to the curcumin liquid suspension, the PLGA and PLGA-PEG nanoparticles inflated the curcumin bioavailability by 15.6- and 55.4-fold, respectively. Thus these formulations are potential carriers for the oral delivery of curcumin Other study showed that curcumin encapsulated in low and high molecular weight PLGA have relatively different oral bioavailability of curcumin. It has been found that the relative bioavailability of high molecular weight PLGA conjugated curcumin has 40-fold higher than that of low molecular weight PLGA conjugated curcumin and conventional curcumin, respectively It has been also observed that PLGA-curcumin enhances two and six fold increases in the cellular uptake performed in cisplatin resistant A2780CP ovarian and metastatic MDA-MB-231 breast cancer cells, respectively, compared to free curcumin.[112-114]

***Liposomal encapsulation:-*** Liposomes are considered as effective drug carriers because of their ability to solubilize hydrophobic compounds and to alter their pharmacokinetic properties. In rat oral administrations of liposome-encapsulated curcumin (LEC) showed high bioavailability of curcumin. In order to, a faster rate and better absorption of curcumin were observed as compared to the other forms. Oral LEC gave higher C(max) and shorter T(max) values, as well as a higher value for the AUC, at all time points In order to facilitate the intracellular delivery of curcumin, a new type of liposomes-propylene glycol liposomes (PGL) were prepared. It has been observed from cell experiment in vitro, PGL exhibited the highest uptake of curcumin compared with that of conventional liposomes and free curcumin solution. These studies indicate that liposome conjugated curcumin increases the bioavailabllity of curcumin.[115,116]

***Cyclodextrin(CD):-*** CD, cyclic oligosaccharides, has been also used in order to improve curcumin's delivery and bioavailability via its encapsulation with CD. It has been found that CD encapsulated curcumin (CDC) had a greater cellular uptake and longer half-life in the cancer cells compared with free curcumin indicating CDC has superior attributes compared with free curcumin for cellular uptake In addition, the improvement of CUR permeability acrossed animal skin tissue was observed in CD encapsulated curcumin and was about 1.8-fold when compared with the free curcumin. Thus, these studies shows that CDC has improved in vitro and in vivo bioavailability and chemotherapeutic efficacy compared to curcumin alone.[117,118]

***Piperine:-*** Besides these natural compounds have been also used to increase the bioavailability of curcumin. One of them is piperine, a major component of black pepper, known as inhibitor of hepatic and intestinal glucuronidation and is also shown to increase the bioavailability of curcumin.[16] This effect of piperine on the pharmacokinetics of curcumin has been shown to be much greater in humans than in rats. In humans, curcumin bioavailability was increased by 2,000% at 45 minutes after co-administering curcumin orally with piperine, whereas in rats, it has been found that concomitant administration of piperine 20 mg/kg with curcumin 2 g/kg increased the serum concentration of curcumin by 154% for a short period of 1-2 hours post drug. 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 absorption of curcumin was also found relatively higher when administered concomitantly with piperine, and it stayed significantly longer in the body tissues. In view of these findings, curcumin-piperine (Cu-Pi) nanoparticles has been prepared by various methods. The bioavailability, cellular uptake and biological effects of this nanoparticles are being tested.[23,119,120]

***Prodrug with di-glutaric acid:-*** The water solubility of CurDG was found to be approximately 100 times higher than that of curcumin. At 25 °C, curcumin was found to

have a maximum concentration of 0.068 µg/mL in water, while that of Cur DG was 7.48µg/mL.The solubility as a function of pH study showed that the most concentrations of CurDG in 0.1 M HCl and acetate buffer pH 4.5 were less than 0.025 µg/mL whereas the concentration in phosphate buffer pH 6.8 was 1.43 µg/mL after 1.5 h.In addition, the partition coefficient was reported as log $P_{o/w.}$ In this study, the log $P_{o/w}$ of CurDG was 1.79. In the stability in buffers study, the quantity of curcumin and CurDG were measured after incubation in 0.1 N hydrochloric acid (pH 1.2), acetate buffer (pH 4.5), and phosphate buffer (pH 7.4) at 37 °C. Semi-logarithmic plots of the concentration of curcumin and CurDG versus time were linear indicating that the degradation kinetics are pseudo first order.

***Meriva®:-*** Meriva (developed by Indena, S.p.A.) tablets were prepared by Sigmar Italia S.p.A. (Almè, Italy). The treatment consisted of two 500-mg tablets daily, one after breakfast and one after dinner (1,000 mg/day, corresponding to 200 mg curcumin/ day). The composition of the test material was a natural curcuminoid mixture (20%), phosphatidylcholine (40%), and microcrystalline cellulose (40%). However, few successful clinical studies of curcumin have been reported because of its poor oral bioavailability. Unrealistically high dosages (>10 g/day) are often required to achieve plasma concentrations corresponding to those suggested by the preclinical studies To overcome these issues, a phytosome was developed, complexing curcumin with phosphatidylcholine In the wake of studies showing promising data for hydrolytic stabilization at physiological pH (unpublished), approximately 20-fold improvement of oral absorption compared to noncomplexed curcumin in animal and human pharmacokinetic studies, and nutrigenomic veterinarian evidence of anti-inflammatory activity.

| Formulation | Properties | Inference |
|---|---|---|
| Nanocurcumin:- | | |
| Theracurmin(30mg) | In oral Administration it gives 27 fold higher bioavailability than free curcumin. | Among nanocurcumin Theracurmin shows maximum Bioavailability |
| Apotransferin (Curcumin loaded nanoparticles) | Higher elimination half-life than sol-curcumin<br>Apotransferin:- $t_{1/2}$:- 6 Hours<br>Sol Curcumin:- $t_{1/2}$:- 2-4 Hours | |
| Poly Lactic Co-Glycolic Acid:- | | |
| PLGA Curcumin | It increases Curcumin half life by 4hours<br>It gives 2.9 fold higher Cmax<br>It gives 15.6-fold higher bioavailability than aqueous curcumin. | |
| PLGA PEG Curcumin | It increase Curcumin half life by 6 Hours.<br>It increase 7.4 fold Cmax than unformulated curcumin.<br>It increase 55.4 fold bioavailability than aqueous curcumin. | |
| High Molecular weight PLGA conjugated Curcumin. | It increase 40 fold higher bioavailability than conventional curcumin and other PLGA conjugated Curcumin. | Among PLGA conjugated Curcumin High Molecular weight PLGA conjugated Curcumin shows maximum increase in bioavailability. |
| Lipsome:- | | |
| Liposome Encapsulated Curcumin(LEC) | It has higher Cmax and shorter Tmax and shows a higher bioavailability. | |
| Propylene Glycol Curcumin (PGL) | Shows higher cellular uptake than LEC and Conventional Curcumin. | Among all Liposome encapsulated curcumin PGL curcumin shows better bioavailability than conventional curcumin. |
| Cyclodextrin:- | | |
| Cyclodextrin conjugated Curcumin | It has a greater cellular uptake long half life in cancer cells.<br>It increase Curcumin bioavailability by 1.8 fold. | It increase Curcumin bioavailability and chemotherapeutic efficacy than normal curcumin. |
| Piperine:- | | |
| Curcumin- Piperine nanoparticles. (CU-Pi | In oral administration it increase Curcumin bioavailability 2000% at 45 | Piperine complex not just increase its bioavailability but it also increase its |

| | | |
|---|---|---|
| complex) | minutes than free curcumin.<br>It also inhibit the intestinal and hepatic glucoronidation of curcumin. | Absorption and increase serum concentrations.<br>It shows maximum increase Curcumin efficacy among all nanoparticles |
| Prodrug:- | | |
| Combined with Di- Glutaric acid<br>Cur-DG complex | At 25°C Curcumin have maximum concentration 0.068ug/ml in water<br>But CurDG complex shows 7.48ug/ml.<br>And it's Shows better stability in high pH<br>In Phosphate buffer pH 6.8 CurDG shows 1.63ug/ml after 1.5h | It shows 100 times higher solubility than unformulated curcumin.<br>And a better stability in intestinal pH |
| Meriva®:- | | |
| Phosphatidylcholine phytosome complex | 20 fold improvement in oral administration than noncomplexed curcumin. | It shows better efficacy in osteoarthritis patients, diabetes patients. |

## CONCLUSION

Curcumin has received worldwide attention for its multiple health advantages, that seem to act primarily through its anti-oxidant and anti inflammatory mechanisms. Trendy science has delineated the molecular basis for the pharmaceutical uses of curcumin. Multiple studies over the past decade have indicated the protection and effectivity of curcumin within the management of aerobic and inflammatory conditions, metabolic syndrome, arthritis, anxiety, and hyperlipidemia. Despite of this effectivity the bioavailability of curcumin is that the major concern. But in tries to enhance the bioavailability of curcumin, many ways are explored like modulation of route and medium of curcumin administration, interference of metabolic pathways by concominant administration with alternative agents, and conjugation and structural modifications of curcumin, like piperin, Cyclodextrin, Liposomes, conjugation with phosphatidylcholine phytosome complicated Meriva®, prodrug with di-glutaric acid. Proof from literatures indicated its multiplied bioavailability and effectivity in numerous experimental models with these ways. The existence of extremely bioavailable styles of curcumin currently permits the exploration and determination of the total health-promoting advantages of curcumin.

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