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CURCUMIN: TRANSFORMING THE SPICE TO A WONDER DRUG

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ABSTRACT: Turmeric is a spice obtained from the dried rhizomes of *Curcuma longa*, family Zingiberaceae. It has been extensively used in traditional Indian (Ayurveda) and Chinese medicine for various ailments such as anti-inflammatory, blood purifier and even as a cosmetic. Curcumin, the chief constituent in turmeric has been isolated centuries ago, has been found to have a wide range of pharmacological actions such as antioxidant, anti-inflammatory, anticancer, antimicrobial and much more. Thus curcumin and its analogues have immense therapeutic potential for use in rheumatoid arthritis, Crohn's disease, cancer, diabetes, cardiovascular disease, HIV-I and Alzheimer's disease. Phase I clinical studies have shown that high doses of curcumin is well tolerated in man. Despite its safety, curcumin still evades clinical use due to poor bioavailability. Novel formulations of curcumin with piperine, soluble fibres of fenugreek, liposomes, micelles, nanoparticles, cyclodextrin and turmerone have shown enhanced bioavailability to some extent, each one having its own limitations. Recent formulation of curcuminoid with 45% turmerone seems to be promising. Further research in this direction is imperative to realize the clinical use of this promising molecule.

INTRODUCTION: The age old spice, turmeric contains 5% of curcuminoids and 6% essential oil as the yellow colouring matter. Curcumin, the chief constituent makes up 60% of curcuminoid [1], others are demethoxycurcumin, bisdemethoxycurcumin and AR- turmerone [1]. Curcumin, a hydrophobic, polyphenol called diferuloylmethane is an antioxidant more powerful than *alpha*- tocopherol [2].

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Turmeric has been used traditionally as antiinflammatory, stomachic, choleretic, cholagogue, blood purifier and as cosmetic [1]. Extensive research has revealed that curcumin acts on multiple molecular targets, receptors, proinflammatory enzymes, protein kinases, adhesion molecules, transcription factors, antiapoptotic proteins and cell cycle-related gene expression [3]. Modulation of these targets is the basis of numerous pharmacological actions such as antioxidant [1], anti-inflammatory [4], antimicrobial [5, 6, 7], anticancer [8], hepatoprotective [9], antidiabetic [10], antithrombotic[11], anti HIV-I[12] and in Alzheimer's disease[13]. Three different clinical trials indicate that curcumin is well tolerated in man at doses as high as 12g/day [14]. This review intends to have an

overview of curcumin chemistry, structure - activity relationship, molecular targets, pharmacological actions, problems of bioavailability and various curcumin formulations designed to achieve improved bioavailability so as to realize the safe clinical use of this versatile molecule.

Chemistry &Structure-Activity Relationships (SAR) of Curcuminoids:

Curcuminoids, the main components in *Curcuma* species, share a common unsaturated alkyl- linked biphenyl structural feature and are responsible for their major pharmacological effects. Curcumin,the chief constituent of curcuminoids is an orange–yellow crystalline powder practically insoluble in water and ether but soluble in ethanol, dimethylsulfoxide and acetone. Curcumin is 1, 6-heptadiene - 3, 5 – dione - 1, 7 – bis (4-hydroxy-3-methoxyphenyl)-(1E, 6E) or Diferuloylmethane. The feruloylmethane skeleton of curcumin was confirmed in 1910 by Lampe [15, 16].

Chemically, curcumin is a bis-α, β-unsaturated β-diketone and exists in equilibrium with its enol tautomer (**Fig. 1**). The bis-keto form predominates in acidic and neutral aqueous solutions as well as in the cell membrane due to the heptadienone linkage between two methoxyphenol rings containing a highly activated carbon atom.Curcumin has a unique conjugated structure including two methylated phenols linked by the enol form of a heptadiene-3,5-diketone that gives the compound a bright yellow color [17].

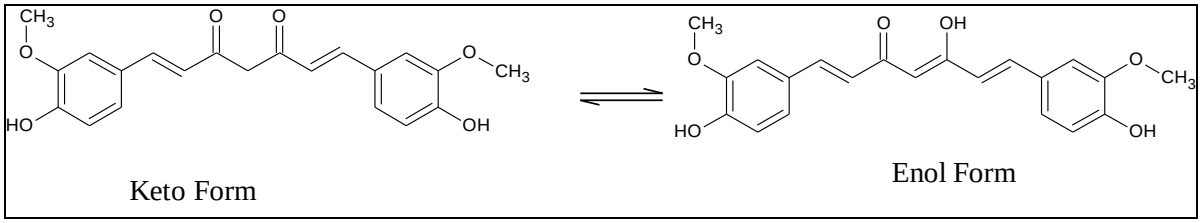


FIG. 1: KETO-ENOLTAUTOMERISM IN CURCUMIN.

Curcuminoids in *C.longa* and other *Curcuma* species are mainly curcumin, bis-demethoxycurcumin and demethoxycurcumin (**Fig. 2),** among which curcumin is the most studied and shows a broad range of biological activities.

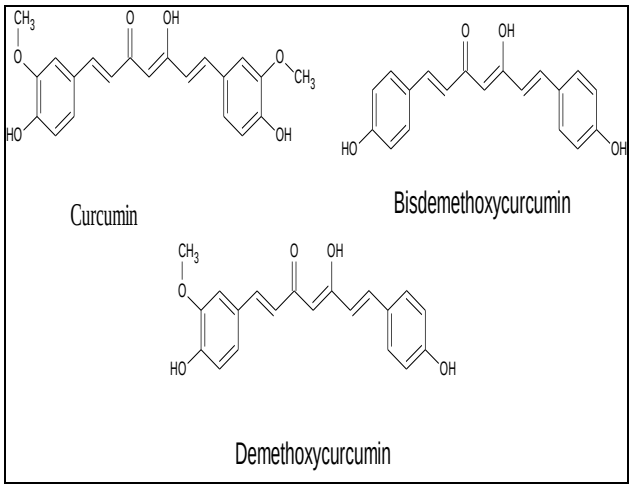


FIG. 2: CURCUMINOIDS IN *C. LONGA*

Structure-Activity Relationships(SAR):

Synthetic bioactive curcumin analogs were developed from the natural compound based on the structure-activity relationship (SAR) studies and optimization of compounds as drug candidates in their relation to different activities, including anti-inflammatory, anti-oxidant, anti-HIV and anti-cancer, as well as possible mechanisms of actions.

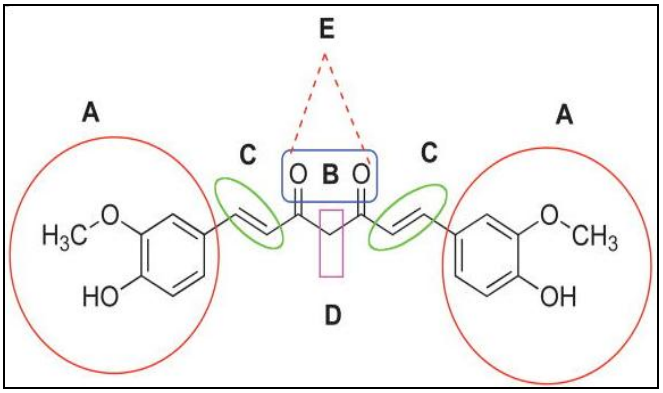


FIG. 3: BASIC NUCLEUS OF CURCUMIN

Structural possibilities for modification of curcumin - Aryl side chain modification **(A)**, Modification of diketo functionality **(B)**, Modification of double bond **(C)**, Modification of active methylene functionality **(D),** Metal complexes of curcumin **(E)** and Appended

curcumin mimics/structural analogs of curcumin **(F).**

Anti-inflammatory SAR:

The active constituents of *C. Longa* are curcuminoids, including curcumin, demethoxycurcumin and bisdemethoxycurcumin[18] (**Fig.1**), among which curcumin is the most potent anti-inflammatory agent [19]. In addition to these natural curcuminoids, sodium curcuminate and tetrahydrocurcumin (**Fig. 4**) showed potent anti-inflammatory activity at low doses in carrageenin-induced rat paw edema and cotton pellet granuloma assays [20]. Other semi-synthetic analogs of curcumin were screened for anti-inflammatory activity in the same assays; diacetylcurcumin and tetrabromocurcumin (**Fig. 4**) were the most potent [21, 22, 23]. The presence of the β-diketone moiety as a linker between the two phenyl groups was deemed important for the anti-inflammatory activity.

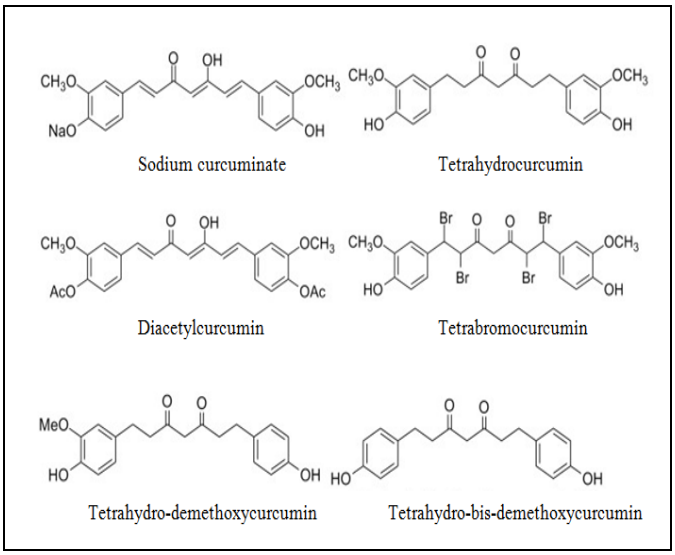


FIG. 4: STRUCTURES OF SEMI-SYNTHETIC ANALOGS TESTED FOR ANTI-INFLAMMATORY ACTIVITY

Antioxidant SAR:

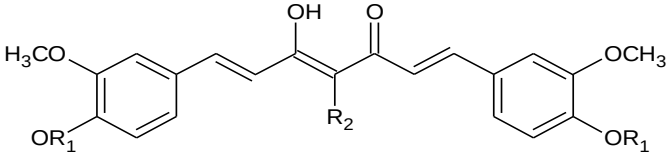
It was found that the phenolic analogs were more active than the non- phenolic analogs [24]. The highest antioxidant activity was obtained when the phenolic group was sterically hindered by the introduction of two methyl groups at the ortho position. The phenolic group is essential for free radical scavenging activity, and the presence of the methoxy group further increases the activity [25]. The structural features that enhance the antioxidant properties of phenols are optimized in curcumin to a significant extent [24]. Curcumin and tetrahydrocurcumin had the strongest anti-oxidant activity among the natural and hydrogenated curcuminoids respectively [26, 27, 28]. Among all compounds, tetrahydrocurcumin showed the highest potency, implying that hydrogenation of curcuminoids increased their anti-oxidant ability. Absence of one or both methoxy groups resulted in decreased anti-oxidant activity in both natural curcuminoids and tetrahydrocurcuminoids. Tetrahydrocurcumin and curcumin showed comparable antioxidant activity. This result suggests that enhanced electron delocalization of the double bonds may not be essential to anti-oxidant activity of curcuminoids.

Anticancer SAR:

Simon *etal* [29], found that the presence of the diketone moiety in the curcumin molecule seems to be essential for its ability to inhibit the proliferation of MCF-7human breast tumor cells. The aromatic enone and dienone analogs of curcumin were demonstrated to have potent antiangiogenic properties in an *in vitro* SVR assay [30].

Certain curcumin analogs including **1** (JC-9), **2 (**4-methoxycarbonyl curcumin, MCECu) and **3** (LL-80) showed potent *in vitro* cytotoxic activity against LNCaP and PC-3 human prostate cancer cell lines (**Table1**). Among them, compound **4** showed the most potent activity, suggesting that introducing a conjugated side chain in the enol-ketone linker may stabilize the enol-ketone form as the predominant tautomer, which may contribute to the anti-prostate cancer activity [32].

TABLE 1: CYTOTOXIC ACTIVITY DATA OF CURCUMIN DERIVATIVES AGAINST PC-3 AND LNCAP PROSTATE CANCER CELL LINES



Compound	R_1	R_2	PC-3 IC_{50} (µM)*	LNCaP IC_{50} (µM)*
1	H	H	7.7	3.8
2	CH_3	H	1.1	1.3
3	H	CH_2CH_2COOEt	5.1	1.5
4	CH_3	CH=CHCOOEt	1.0	0.2

IC_{50} values are mean concentrations that inhibit cell growth by 50% (variation between replicates was less than 5%).

IC_{50} values are expressed as 'means'.

It has been found that curcumin loses its activity instantaneously in a reducing environment. Enol form was found to be responsible for the rapid degradation of the compound. To increase the stability of curcumin, several analogues were synthesized in which the diketone moiety of curcumin was replaced by isoxazole (compound **5**) and pyrazole (compound **6**) groups. Isoxazole and pyrazolecurcumins were found to be extremely stable at physiological pH, in addition to reducing atmosphere, and they can kill cancer cells under serum-depleted condition. Molecular modeling has shown that both compounds **5** and **6** could dock to the same site of tubulin as the parent molecule, curcumin. Interestingly, compounds **5** and **6** also show better free radical scavenging activity than curcumin. Altogether, these results strongly suggest that compounds **5** and **6** could be good replacements for curcumin in future drug development [32].

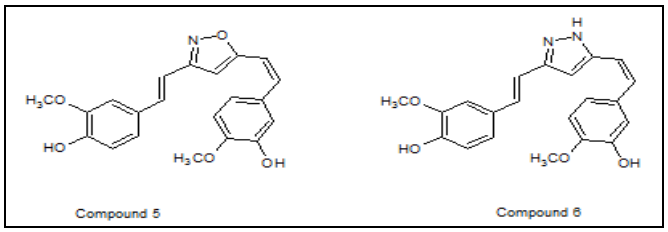


FIG. 5: SYNTHETIC CURCUMIN ANALOGUES HAVING ANTICANCER ACTIVITY

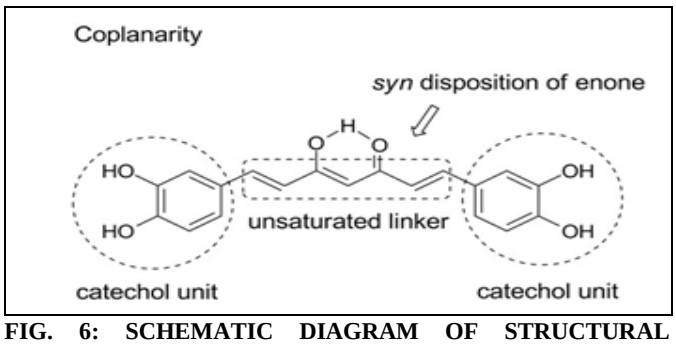


FIG. 6: SCHEMATIC DIAGRAM OF STRUCTURAL FEATURES FAVOURING ANTI-HIV-1 INTEGRASE ACTIVITY [33].

In the further SAR investigation of curcumin analogs as inhibitors of HIV-1 integrase, a syn disposition of the C=C-C=O moiety in the linker and a coplanar structure were found to be important to the integrase inhibitory activity of curcumin analogs [34].

Pharmacological Actions:

Curcumin's capacity to modulate multiple molecular targets forms the basis of its numerous pharmacological actions such as antioxidant [1],anti-inflammatory [4], anticancer [8], nephro& hepatoprotective [9], cardioprotective [35], antidiabetic [10] and antirheumaticactions [36]. It has also been found to be effective in Alzheimer's disease [13] and against HIV-I [12].

Antiinflammatory and antioxidant properties:

Curcumin has been found to be a potent antioxidant[37] and anti-inflammatory agent[4]. Curcumin has been shown to suppress the expression of COX 2, 5-LOX, and iNOS that are pro inflammatory enzymes through suppression of transcription factor, NF-κB. Curcumin inhibits inflammation by blocking the adhesionof monocytes to endothelial cells by inhibiting the activation of the cell adhesion molecules ICAM-1, VCAM-1, and ELAM-1 [3] Most of the activities of curcumin seem to be due to its ability to suppress inflammation [38].Free-radical-mediated peroxidation of membrane lipids, oxidative damage of DNA and proteins and inflammation [39, 40] are associated with a variety of chronic pathological conditions such as cancer, atherosclerosis, and neurodegenerative diseases. Hence curcumin is thought to play a vital role against these pathological conditions [38]. Curcumin also functions as a pro-oxidant under certain conditions[41] most likely as a result of electrontransfer to molecular oxygen to generate reactive oxygen species(ROS)[42].

Anticancer action:

Multiple studies have shown that curcumin can reduce the growth of cancerous cells in the laboratory and inhibit the growth of tumors in test

animals [43, 44]. Curcumin has been shown to inhibit the proliferation of a wide variety of tumor cells, through suppression of various transcription factors including NF-κB, STAT3, Egr-1, AP-1, PPAR-γ, and betacatenin activation. Suppression of protein kinases, induction of apoptosis and modulation of cell- cycle related gene expression are other mechanisms for its anticancer action [3].

Cardio protective action:
Endothelial dysfunction is the underlying cause of heart diseases. Curcumin has been found to improve the functions of the endothelium thereby exerting cardio protective action [45].

Anti – Diabetic action:
Curcumin has shown beneficial effects in diabetic rats[3].

Anti-rheumatic action:
There are many different types of arthritis, most of which involve inflammation of joints. Curcumin being a potent anti-inflammatory agent could alleviate rheumatoid arthritis[46].

Alzheimer's disease:
Oxidative damage, inflammation, cognitive deficits, and amyloid accumulation associated with Alzheimer's disease are suppressed by curcumin[47].

Anti HIV-I action:
Curcumin was found to be a potent and selective inhibitor of human immunodeficiency virus (HIV-1) long-terminal repeat-directed gene expression, which governs the transcription of type 1 HIV-1 provirus [48].

Nephro and hepato –protective action:
Curcuminoids have shown nephro and hepatoprotective action [49].

Bioavailability:
In-vitro studies have shown that curcumin has strong intrinsic activity and efficacy on various disease targets. However, unfavourable pharmacokinetic properties, particularly poor bioavailability have been identified as the major hurdle in approving it as a therapeutic agent. Poor absorption, inadequate tissue distribution, rapid first pass metabolism in the liver and intestinal wall [50], and short half life are the factors that result in extremely low serum and tissue levels.

Several bioavailability studies have shown that curcumin was poorly absorbed from the gut and higher serum levels were attained when curcumin was administered by i.p route in rodents than the oral route. However, data from human clinical trials suggest the role of initial oral dose on achievable serum levels of curcumin[50, 51, 14, 52].

Irrespective of the dose, the percentage of curcumin absorbed (60-66% of the given dose) remained constant [53, 54]. The serum levels of curcumin in rats and in human are not directly comparable. When curcumin was administered in mice by i.p route, maximum amount was seen in intestine, moderate amounts in spleen, liver and kidney, only trace amount was found in brain[55, 56].

Metabolites:
Various studies have evaluated the metabolism of curcumin in rodents and in humans. Once absorbed, curcumin is subjected to conjugations like sulfation and glucuronidation at various tissue sites. The first bio distribution study reported the metabolism of major part of curcumin orally administered to rats. Liver was indicated as the major organ responsible for metabolism of curcumin[51, 57, 58]. Holder et al. reported that the major billiary metabolites of curcumin are glucuronides of tetrahydrocurcumin (THC) and hexahydrocurcumin (HHC) in rats. A minor biliary metabolite was dihydroferulic acid together with traces of ferulic acid [59].

In addition to glucuronides, sulfate conjugates were found in the urine of curcumin treated rats[53]. Hydrolysis of plasma samples with glucuronidase by Pan et al. Showed that 99% of curcumin in plasma was present as glucuronide conjugates. Curcumin is absorbed from the alimentary tract and present in the general blood circulation after largely being metabolized to the form of glucuronide/sulfate conjugates [60, 61]. Curcumin sulfate and curcuminglucuronide were identified in the colorectal tissue of colorectal cancer patients who ingested curcumin capsules [57, 58].

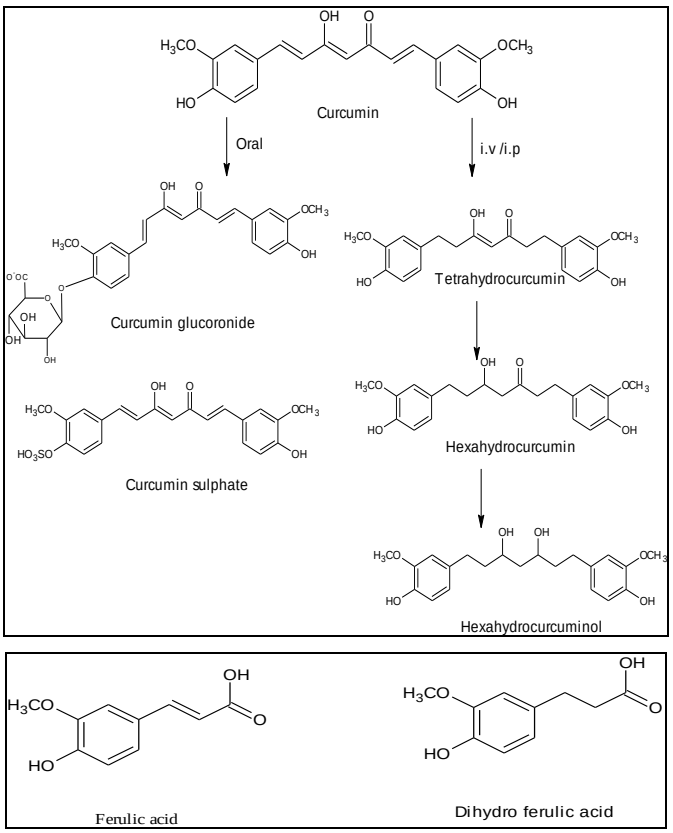


FIG. 7: METABOLITES OF CURCUMIN

The pharmacokinetics of curcumin has been extensively studied in animals, but to a lesser extent in humans. Majority of the studies have demonstrated that curcumin exhibits extremely poor gastrointestinal absorption/ oral bioavailability and undergoes metabolism to form several chemical species, including curcuminglucuronide and curcumin sulfate[62].Attempts to avoid rapid metabolism has met with little success. Further research is warranted in this direction as available literature is unable to give clear evidence.

Measures to improve bioavailability:

Considerable effort has been taken to develop curcumin derivatives, curcumin analogs, and curcumin-drug vehicle combinations that display enhanced absorption and systemic bioavailability as compared to the parent drug [62]. Large number of cucumin derivatives and curcumin analogues have been synthesized. Some of them have higher activities while others are less active than curcumin at the multiple molecular targets. However, there is no published data available on the specific bioavailability studies in humans for any of the synthetic derivatives of curcumin. Further research needs to focus on human bioavailability studies of the more active curcumin analogues in which the diketone moiety is replaced by isoxazole and pyrazole [34].

Attempts have also been made to use adjuvants, which can block metabolic pathways of curcumin, so as to improve its bioavailability. Nanoparticles, liposomes, micelles, phospholipid complexes and cyclodextrin complexes are other promising novel formulations, designed to sustain desired serum levels,improve tissue permeability and resist metabolic processes.

Adjuvants:

When combined with piperine, the bioavailability of curcumin increased 2000% in humans as compared to only 154% in rats. Piperine is known to inhibit hepatic and intestinal glucuronidation [63]. When combined with piperine, the clearance of curcumin was significantly decreased. Hence the effect of piperine on bioavailability of curcumin is much greater in humans than in rats [64]. Piperine may have an inhibitory effect in metabolism of other drugs that are detoxified by glucuronidation thus increasing their toxicity.

BCM-95 (also called Biocurcumax), a formulation of curcuminoid with essential oil of turmeric enhanced the bioavailability of curcumin and augmented the biological activity of curcumin in humans, where curcumin is the main constituent of curcuminoid and Ar-turmerone is the main constituent, 45% of the essential oil of turmeric[65]. This study stands apart as the enhanced bioavailability of curcumin has been demonstrated in human volunteers.

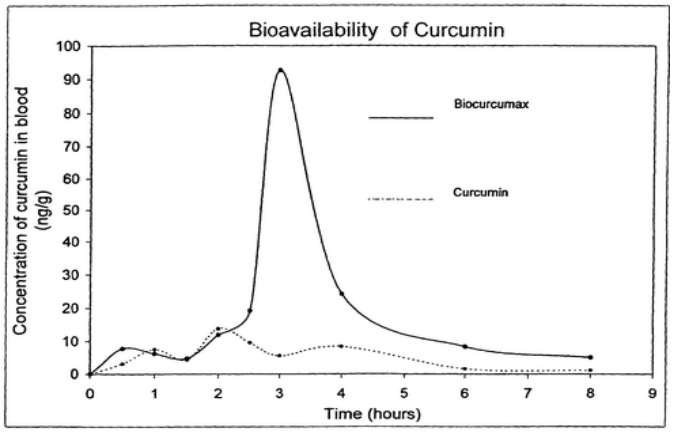


FIG. 8: AUC OF BIOCURCUMAX

Enhancement of bioavailability of the curcumin ranges from about 5-fold to about 16-fold [65].

Biocurcumax has the additional benefit that the essential oil components are themselves bioactive and thus are expected to synergistically enhance the bioactivity of curcumin [66]. AUC was 7–8 times higher when curcumin was combined with turmeric oil. Hence this formulation holds promise for clinical use in humans [67, 68].

A new fenugreek derived polysaccharide (referred to as galactomannans) containing fenugreek proteins was found to enhance the bioavailability of curcumin both in preclinical studies and in studies on human volunteers when formulated as amorphous microgranulate dispersions with proper molecular binding with curcuminoids. Fenugreek polysaccharide used in the present invention is non digestible, but swell extensively in the intestine and form a gel matrix in which curcumin is impregnated and leaches out very slowly. The advantage of the present formulation of micro granulate is that when consumed, it is very stable under physiological conditions and protect curcumin from easy access to enzymes responsible for its rapid degradation [69]. This formulation enhances bioavailability without inhibition of glucuronidation. Whether this promising formulation provides optimum concentration at tissue levels is yet to be studied.

Nanoparticles:

A polymer based nanoparticle of curcumin namely ‘‘nanocurcumin’’ was found to overcome the problem of poor aqueous solubility to some extentas reported recently. Nanocurcumin was found to have *in vitro* activity similar to that of free curcumin in pancreatic cancer cell lines[70].However no *in-vivo* studies are reported with nanocurcumin. An *in vivo* study with healthy volunteers showed improved efficiency of a topical application cream containing curcuminoid loaded solid lipid nanoparticles (SLNs) over that containing free curcuminoids [71]. Further *in-vivo* studies on nanoparticle based formulations is warranted in humans.

Liposomes:

Liposomes are excellent drug delivery systems as they can carry both hydrophilic and hydrophobic molecules. Liposomal curcumin suppressed the pancreatic carcinoma growth in murine xenograft models and inhibited tumor angiogenesis [72]. The efficacy of liposomal curcumin was compared with that of oxaliplatin, a standard chemotherapeutic agent for colorectal cancer. Liposomal curcumin exhibited greater*in-vitro* and *in-vivo* activity than oxaliplatin. Liposomal curcumin is currently being developed for introduction into the clinical setting[73]. Studies have shown that liposomal vehicle is capable of loading more curcumin in to cells than either HSA or aqueous-DMSO, and lymphoma cells showed preferential uptake of curcumin to lymphocytes [74]. However studies are yet to prove enhancement of bioavailability by liposomal curcumin.

Micelles and phospholipid complexes:

Micelles and phospholipid complexes can improve the gastrointestinal absorption of natural drugs, thereby giving higher plasma levels and enhance the bioavailability due to lower kinetic elimination. Further, the *in-vitro* intestinal absorption of curcumin was found to increase from 47% to 56% when the same was present in micelles[75].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 [76].

Curcumin-phospholipid complex formation showed a significant improvement in curcumin bioavailability[77]. Curcumin formulated with phosphatidylcholine (Meriva) was given by oral gavage. Peak plasma levels for parent curcumin after administration of Meriva were 5-fold higher than the equivalent values seen after unformulated curcumin dosing. A 13×10^{5} fold increase in curcumin solubility in a polymeric micellar formulation containingmethoxy poly (ethylene glycol)-block-polycaprolactonediblock copolymers (MePEG-b-PCL) [78]. The enormous increase in solubility of curcumin in the above said micelle is very encouraging to continue further studies on the same.

Cyclodextrin complexes:

Several attempts have been made to design water soluble and stable complexes formed from cyclodextrin and curcumin. Cyclodextrins are cyclic oligosaccharides consisting of α-(1-4)-linked glucopyranose units, which form a lipophilic cavity and a hydrophilic outer surface. Their non polar cavity is able to include hydrophobic molecules by

non-covalent forces and thereby improve their water solubility. These formulations give hope for use in several critical conditions where it is necessary to give curcumin by parenteral routes. A novel cyclodextrin complex of curcumin (CDC) was found to be more active than free curcumin for antiproliferative and anti-inflammatory activities.

Compared with free curcumin, CDC had a greater cellular uptake and longer half-life in the cells. This novel complex is soluble at much higher curcumin concentrations. Only a low molar excess of cyclodextrin is required for the formation of this complex, which reduces the risk of adverse effects of cyclodextrins when administered at high doses[79].

CONCLUSION: Despite the low toxicity and enormous therapeutic potential of curcumin, its effective clinical use still remains a distant dream. The pharmacokinetic parameters of the parent drug remain a significant challenge to widespread clinical use of curcumin for the treatment of many human diseases. Several clinical trials in humans have found that oral and even intravenous administration of free curcumin have been ineffective in achieving significant concentration of curcumin in any tissue due to rapid metabolism in gastrointestinal tract and in circulation. There is urgent need to design delivery systems for use through different routes that would achieve optimum drug concentrations in various tissues to elicit desired pharmacological actions in clinical settings.

Tremendous amount of promising work is being conducted to overcome this problem through the utilization of unique delivery systems and chemical modifications. Some curcumin formulations reviewed here that are particularly promising are Biocurcumax, curcumin-fenugreek galactomannan, and novel cyclodextrin complex (CDC).

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