RISING TO NEW HEIGHTS

** IN 'FREE-CURCUMINOIDS' BIOAVAILABILITY **

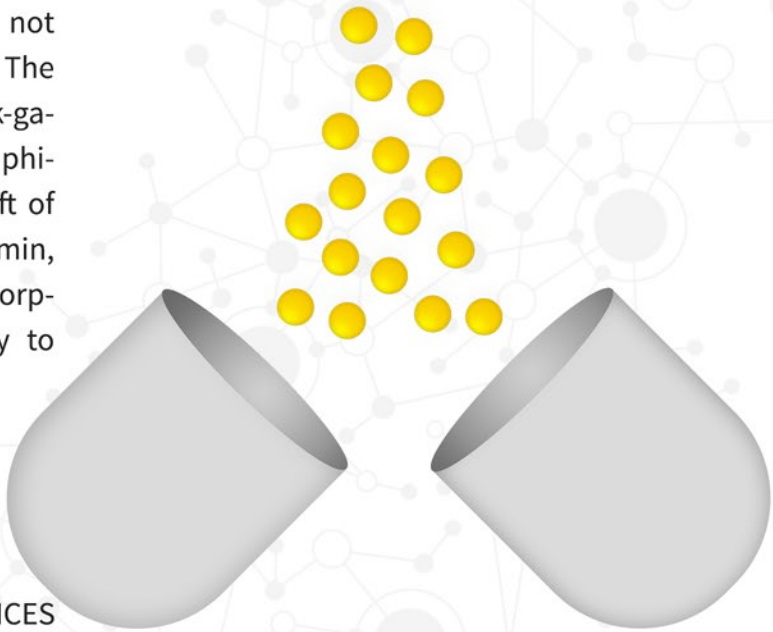
CurQfen®

USA Patented | Self-affirmed GRAS

While bioavailable curcumins are developed to address the problem of poor absorption of curcuminoids, CurQfen® is designed and developed to address the problems or challenges of the bioavailable curcumins - **THE NEXT GENERATION BIOAVAILABLE CURCUMIN!**

A GREEN APPROACH IN PHYTONUTRIENT DELIVERY

CurQfen® is designed on the principles of SELF-EMULSIFYING NANO DRUG DELIVERY, but based on a 100% natural & food grade platform - **FenuMAT**™ – employing a patented composition of Fenugreek (*Trigonella foenum graecum*) derived soluble dietary fibre (de-bitterised and purified galactomannans without containing any phytochemicals such as saponins). **FenuMAT**™ is a water based process and does not contain any synthetic emulsifiers or even silica. The unique physicochemical properties of fenugreek-galactomannans and its structurally specific amphiphilicity has been brilliantly executed in the craft of **FenuMAT**™ – for phytonutrients like curcumin, boswellic acids, gingerol, etc. with enhanced absorption (organic certified option available). Happy to note, **FenuMAT**™ is getting into pharmaceuticals!



SCIENCE BEHIND CURQFEN® AND FENUMAT™

It is the SCIENCE and RESEARCH-BASED EVIDENCES that makes CurQfen® and its delivery technology FenuMAT™ different and unique in the over crowded bioavailable curcumin market place. Being a health ingredient having therapeutic end points, any formulation of curcumin should be scientifically explainable with facts & figures and should be able to address the most modern scientific understandings on the subject. That is where CurQfen® has significance. The strength of CurQfen® lies in the fact that it meets the most stringent benchmarks for a BIO-EFFICIENT curcumin, rather than BIOAVAILABLE curcumin - very often misused and confused in recent times.

- 'Free' curcuminoids bioavailability (45–270 X)
- Peer-reviewed publications in academic journals of high impact factor
- Preferential absorption of 'free' curcuminoids over 'conjugated' metabolites (FCR >1)
- Blood-brain-barrier permeability & brain pharmacokinetics study
- Patented & unique mechanism of delivery
- 100% natural, food grade & clean label
- Cellular absorption
- Low dosage

45.5X

FREE CURCUMINOIDS BIOAVAILABILITY

CURCUMIN AND

CurQfen®

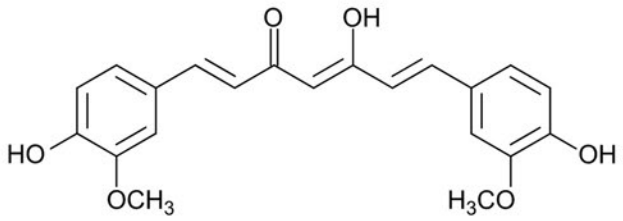
Have you ever thought of the reason for the emergence and popularity of curcumin globally? It is the science (safety, mechanism of action and efficacy) that made curcumin - the most accepted natural molecule and turmeric - the global herbal leader!

Though curcumin was isolated and chemical structure was elucidated in 1910, the therapeutic significance of curcumin was realised with the very first reports on its anticancer property and human clinical trial on hypolipidemic effect by Dr. Ramadassan Kuttan, a pioneer in curcumin biology (*Milobedzka et al., 1910; Kuttan et al, 1985; Sony and Kuttan, 1992*). Further post-genomic research employing the tools of molecular biology and pharmacokinetics established the immense therapeutic possibilities hidden in curcumin; *but its poor absorption and oral bioavailability (pharmacokinetics) was the challenge.* Knowledge on poor bioavailability has led to the developments of various formulations with enhanced bioavailability as calculated by the plasma concentration of conjugated curcumin metabolites, glucuronides & sulfates. But, recently curcumin glucuronides have been shown to possess weak or no antioxidant, anti-inflammatory and antiproliferative effect due to its big molecular size and lack of cellular permeability (*Pal et al, 2014; Shoji et al; 2014; Choudhari et al, 2015*). So, the current understanding on curcumin biology demands for technologies capable of **'FREE' curcuminoids delivery and pharmacokinetics**.

CurQfen® assumes significance in the context of **FREE** curcuminoids delivery, cellular uptake and pharmacokinetics. In a collaborative research with Dr. Ramadassan Kuttan, Amala Cancer Research Center, India, CurQfen® established its **FREE** curcuminoids bioavailability (45 X), total curcuminoids (free + conjugated) bioavailability (270 X), and ratio of the plasma concentration of 'free' curcuminoids over conjugated curcuminoids in human subjects (n=50) using UPLC-ESI-MS/MS and published in the reputed '*Journal of Functional Foods, 2016'*.

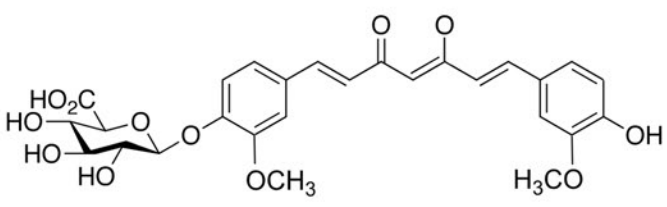
FREE CURCUMINOIDS & ITS SIGNIFICANCE

There exist a tremendous difference among the bioavailability of various formulations, since most of the reports follow the total plasma curcumin glucuronides as curcumin concentration. So, the claimed number of folds of bioavailability is only that of curcumin glucuronides and not the curcumin bioavailability.



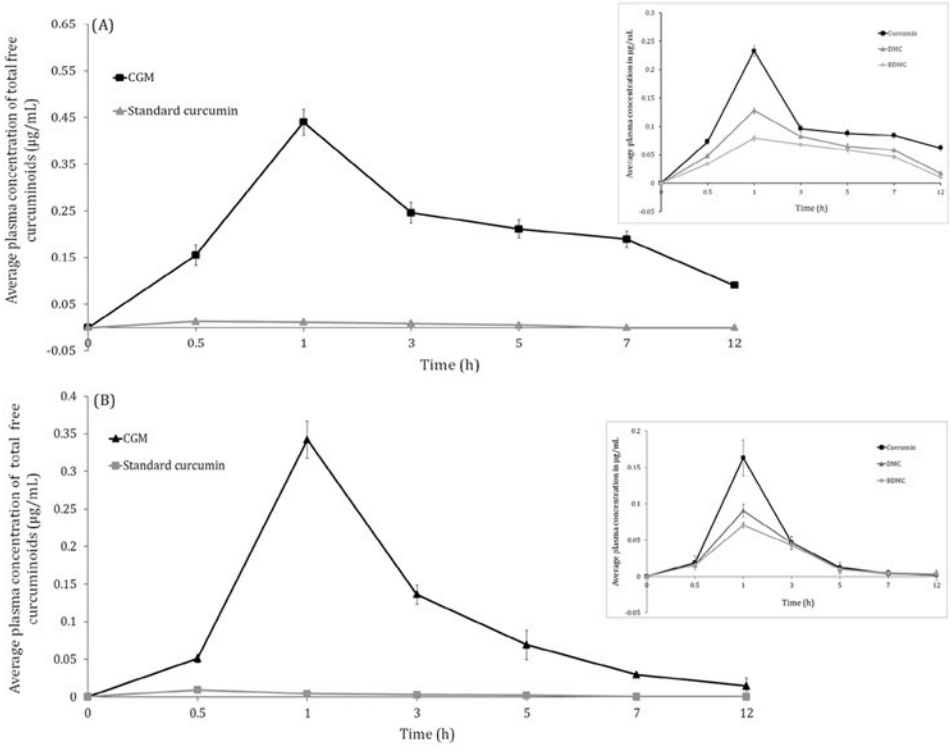
FREE

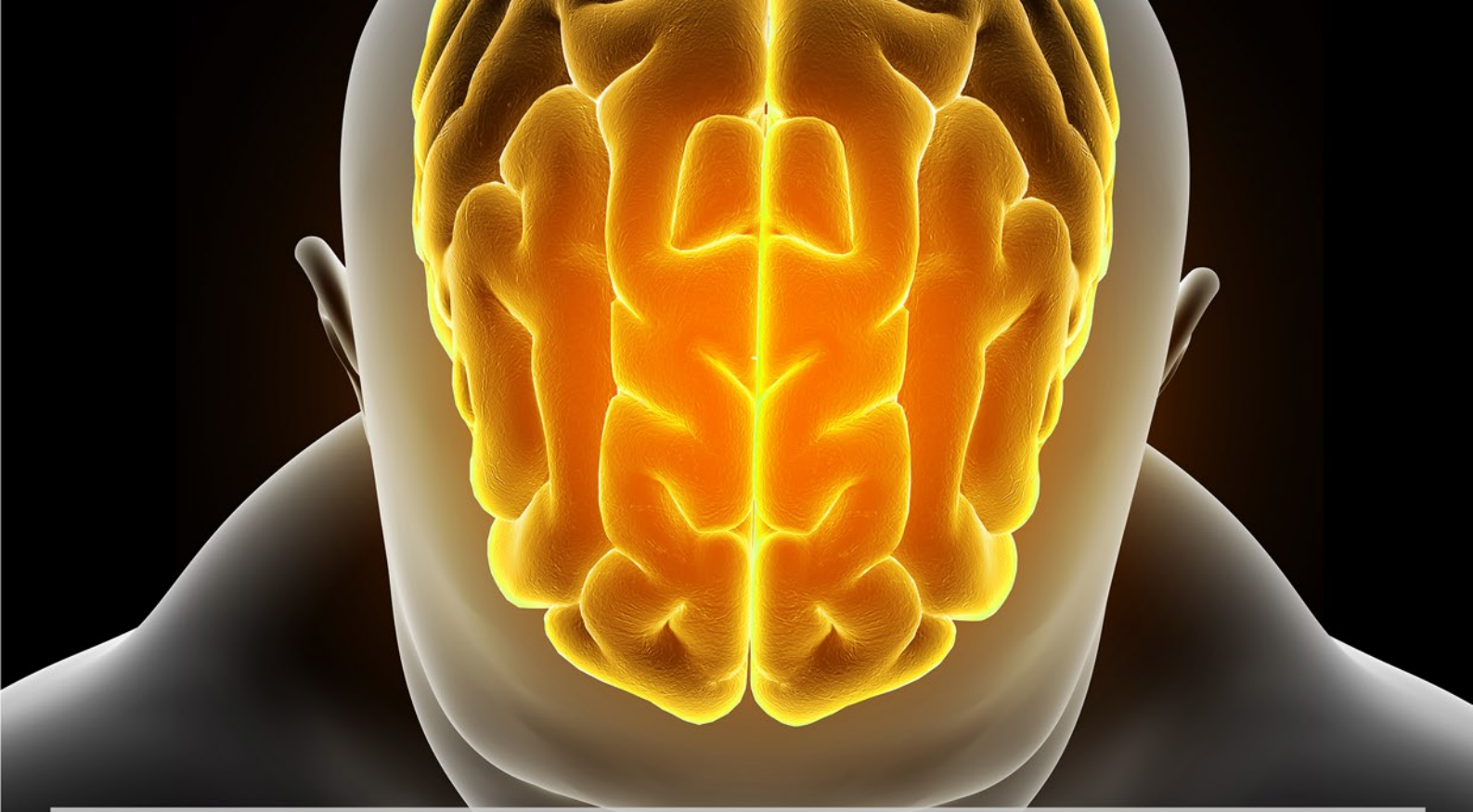
The significance of free (unconjugated) curcuminoids came out from the recent studies from USA and Japan that the major metabolite (curcumin glucuronides) possess no anti-proliferative, anti-inflammatory and antioxidant activities (*Pal et al, 2014; Shoji et al, 2014; Choudhari et al, 2015*). Curcumin glucuronides were also demonstrated to have low membrane permeability with no ability to cross the blood-brain-barrier (BBB) (*Begum et al., 2008*). Only the native form of free curcumin (not the glucuronides) possess the anti-amyloidic property and binds with tau proteins to exhibit benefits in alzheimer's or other neurodegenerative diseases. Free curcuminoids have shown to stimulate neurogenesis, synaptogenesis and migration in brain derived adult neural stem cells, indicating its possible efficacy in hippocampus dysfunction states mediated by conditions of stroke, trauma, radiation and neurodegenerative diseases (*Kim et al., 2008; Lim et al., 2001*). Thus, the real challenge in the craft of bioavailable curcumin formulation turned out to be the ability to provide significant levels of free-form of curcuminoids, rather than the conjugated curcumin glucuronides (Fig. 1).



Curcumin Glucuronide
(Conjugated)

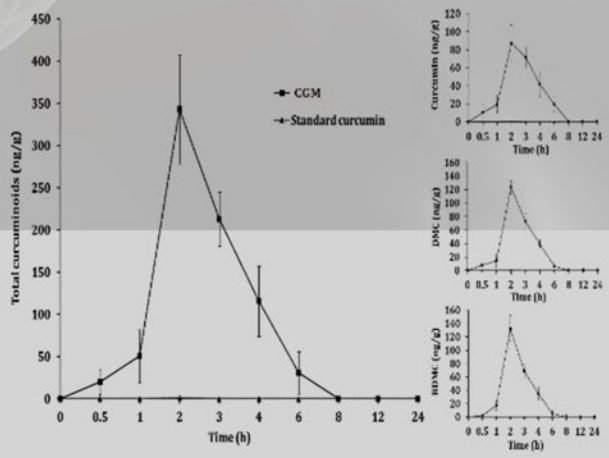
CurQfen® is the only formulation with clinical study (n=50) to establish the pharmacokinetics of 'free' curcuminoids absorption and distribution. The title of the publication itself has claimed **'FREE'** curcuminoids bioavailability, while no other curcumin formulation has this credibility (*Kumar et al., 2016*).





BLOOD-BRAIN-BARRIER PERMEABILITY & TISSUE DISTRIBUTION

Absorption and organ tissue distribution of the bioactive form of any substance is very crucial for the functional benefits/therapeutic efficacy at the target site. Thus, the important difference among the various curcumin formulations lies in their inherent ability to deliver the 'free' bioactive curcuminoids into the target sites. Studies on CurQfen® have demonstrated significant *in vivo* stability and permeability to overcome the metabolic turnover to deliver significantly high levels of free curcuminoids for blood-brain-barrier (BBB) permeability.



CurQfen® is the only bioavailable curcumin with complete brain PK study. Brain tissue distribution and brain regional distribution of all the three curcuminoids (curcumin, DMC & BDMC) upon CurQfen® oral administration have been established (*Krishnakumar et al., 2015*).

Improved BBB permeability and cell uptake of CurQfen® has significant implications on optimum brain health. CurQfen® has proved its enhanced neuroprotective effects and enhanced anti-neuroinflammatory effects with significant behavioural changes and modulation of neurotransmitters, and brain mitochondrial enzymes in various animal models (*Sunny et al., 2019; Sindhu et al., 2018*). CurQfen® has shown to deposit free curcuminoids, (including curcumin, DMC & BDMC) at >100 ng/g in brain tissues, with extended elimination half-life of 4 hours. Standard unformulated curcumin, on the other hand, detected only 1.4 ± 0.8 ng/g of curcumin in the brain tissues, indicating the improved BBB permeability. The depositions at the other organ tissues at (ng/g), heart (391.7 ± 102.5), liver (445.52 ± 83), kidney (240.1 ±47.2), and spleen (229.72 ± 42.2) also conforms the cell uptake of bioactive curcuminoids, which is an essential feature for extending the efficacy of any drugs (*Krishnakumar et al., 2015*).

BEYOND
BIOAVAILABILITY

RATIO OF PLASMA CONCENTRATION OF FREE CURCUMINOIDS TO CONJUGATED CURCUMINOIDS (FCR)

Prof. Liu at the University of Illinois states that 'the current methodology of bioavailability determinations is misleading and creates a lot of confusion among the users since it does not specify the detected levels of curcuminoids as whether 'free-form' or 'conjugated forms' (*Szymusiak et al., 2016*). Since most of these formulations are not capable of providing the free-form of curcuminoids, the observed number of folds of curcumin bioavailability is the bioavailability of curcumin glucuronides, not the bioavailability of curcumin only. Here comes the requirement of new measure of bioavailability - Ratio OF Plasma Concentration of FREE curcuminoids to conjugated curcuminoids (FCR).

FCR – A NEW DIMENSION IN BIOAVAILABILITY

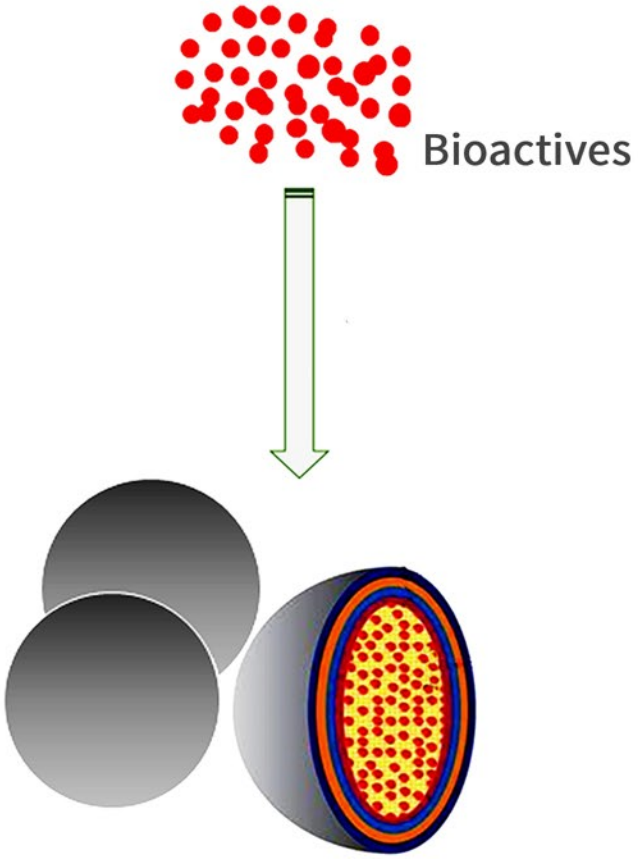
The measurement of the relative percentage of 'free verses conjugated' curcuminoids in circulation is the new dimension in curcumin bioavailability. Employing a standardized method, Kumar et al., measured the 'free' curcuminoids ratio (FCR) as a measure of the effectiveness of a curcumin formulation for the first time (*Kumar et al., 2016*). FCR represents a direct measure of the free curcuminoids in circulation verses the glucuronide conjugates. Higher the FCR, greater is the 'free' curcuminoids delivery and hence the efficacy, especially the brain health, since only free-form is BBB-permeable. Thus, checking the FCR can be a new benchmark to distinguish a particular formulation from other formulations based on their capacity to deliver bioactive 'free-form' curcuminoids - something more than the mere 'number of folds' of bioavailability! CurQfen® has a FCR of 1.3.

FenuMAT™

Enhance bioavailability - naturally...

AN INNOVATIVE GREEN APPROACH IN ORAL DELIVERY

FenuMAT™ is an innovative technology (backed by two patents) comprising a 'green approach' for the oral delivery of phytonutrients with enhanced bioavailability and better pharmacokinetic profile. The technology employs a unique composition and process of soluble dietary fibre (galactomannans) from fenugreek seeds. Gel-phase dispersion technology allows the formation of molecular solutions of phytonutrients in the amorphous and water soluble fibre matrix, by a 'water only' process. Resulting **'FENUBEADS'** provides a novel muco-adhesive micro gels for the safe sustained oral delivery of soluble actives.



Bioactive Microgel Beadlets
- **FenuBEADS**

- Food-grade & 100% Natural
- Patented water based process
- No synthetic emulsifiers/excipients
- Functional prebiotic mediated delivery

STUDIES THAT MAKE THE DIFFERENCE OF CURQFEN®

CurQfen® is the only commercially available Curcumin formulation investigated and published for FREE curcuminoids bioavailability & pharmacokinetics (UPLC-ESI-MS/MS) (*JFF 2016*), plasma concentration of free curcuminoids over conjugated metabolites

(FCR) & its half-life (*JFF 2016*), Brain pharmacokinetics and brain regional tissue distribution (*JFF 2015*), and BBB-permeability as shown by brain waves in humans (Communicated). CurQfen® has been clinically investigated for its efficacy on stress, anxiety and fatigue in comparison with unformulated curcumin and hence the role of bioavailability on efficacy (*Journal of Clinical psychopharmacology 2016*). It has also been studied for its influence on cognitive improvements among dementia subjects, and effect on joint mobility and pain score among osteoarthritis (*communicated*). CurQfen® has been found to offer significant reduction in arterial stiffness and homocystein levels of young obese subjects with significant elevation in HDL levels when supplemented at just 500 mg/day, without exercise (*JFF, 2017; Nutrition, 2019*). Supplementation of CurQfen® at 250 mg ×2/day has been found to reduce hepatic inflammation and modulates the elevation in liver function markers among chronic alcoholics (*BioMed Res Int, 2018*). Also a number of in vivo studies employing post-genomic techniques of molecular biology have also been conducted to investigate the unique mechanism of delivery and action of CurQfen®.

FREQUENTLY ASKED QUESTIONS

1. How CurQfen® is standardised?

CurQfen® contains not less than 35% of curcuminoids, as the sum of curcumin, demethoxycurcumin (DMC) and bisdemethoxycurcumin (BDMC), which means that each lot will have not less than 28% curcumin, 6.13% DMC and 0.88 % BDMC. 500 mg of a single 0 size capsule will have approximately 140mg Curcumin, 30.65mg DMC and 4.4mg BDMC with a total curcuminoids content of 175 mg.

2. Does CurQfen® contains excipients or additives?

CurQfen® is the one and only formulation which is 100% natural. It is free from any synthetic emulsifiers such as polysorbate (Tween 80), glycerine, silica, microcrystalline cellulose, maltodextrin, polyvinyl alcohol, magnesium sterate, saturated fatty acids like palmitic acid tec..

3. What are the solvents in CurQfen®?

CurQfen® is manufactured by a water-process employing standard unformulated curcumin and fenugreek dietary fibre. The fibre is produced by a proprietary process without using any solvents. So, the only solvents in CurQfen® are the ones used for its isolation from turmeric rhizomes. Either acetone, ethanol or ethyl acetate can be used as desired by the customer. No hexane or chlorinated solvents would be involved in the process.

4. What are the certifications for CurQfen®?

CurQfen® is manufactured in a GMP certified plant with ISO 9001, ISO 14001, BS OHSAS 18001 & FSSC 22000. It is 100% vegan, non-GMO, gluten-free, halal & kosher certified. And it also hold self-affirmed GRAS and USA patent. CurQfen® is a CLEAN-LABEL ingredient.

5. Is CurQfen® food-grade? And what about its solubility?

CurQfen® is food-grade and suitable for powder beverages (sachets, stick packs, Golden milk), protein bars, protein supplements, gummies, yogurt, instant soup powders, chocolates, etc at 100 to 200 mg/serving size without taste issues. CurQfen® is the only bioavailable formulation of CurQfen® that has been used as a functional food ingredient and the bioavailability from the food matrix has been confirmed on humans at 100 mg dosage/serving size (*Food & Function, 2014*). It is water dispersible and can dissolve completely on stirring. However, a significant settling may observe on standing the water solution. But, it is good for liquid shots and liposomes.

6. Does CurQfen® contains phytoestrogens or saponins found in fenugreek?

CurQfen® does not contain any phytochemicals in fenugreek since purified dietary fibre is used for the formulation. It is de-bitterised making it suitable for food applications.

7. Does CurQfen® induce gastrointestinal issues or diarrhoea?

CurQfen® is just a formulation using Fenugreek dietary fiber; - a prebiotic fiber that has been clinically substantiated for a number of health beneficial pharmacological effects, including blood-sugar and cholesterol management effects (Hypoglycemic & Hypolipidemic) and Gastroprotective effects. It has been found to slow down gastric emptying and improves satiety and reduces heart burn. It can hold nearly 25 mL of water/gram and hence increases the bulkiness and helps to manage constipation. It is non-digestible, ferments in the colon to produce short chain fatty acids and is a good colon cleanser. However, 1 to 2% of population have been shown to have diarrhoea-like symptoms even with unformulated curcumin.

8. What are the 'uniqueness' of CurQfen® and how it is distinguished itself in the curcumin marketplace?

The current practice of expressing curcumin bioavailability in the market place is 'the measurement of plasma concentration of curcumin glucuronides/sufates' by hydrolysis with β-glucuronidase enzyme and expressing it as 'curcumin' bioavailability as the NUMBER OF FOLDS of enhancement. So, the declared bioavailability is that of curcumin-glucuronides/sulfates only; NOT the 'curcumin' bioavailability. In the light of the recent studies that curcuminglucuronides have no anti-inflammatory & antiproliferative and anti-amyloidic activities, there exist a great need for a new generation of bioavailable curcumins' capable of delivering **FREE** curcuminoids.

CurQfen® is a new generation bioavailable curcumin in this respect. It is the only bioavailable curcumin in the market place whose **FREE** curcuminoids bioavailability has been confirmed and quantified by Triple quadruple, time-of-flight (TOF), and ion Trap tandem mass spectrometric analysis. CurQfen® is the only formulation which has been shown the relative distribution of free curcuminoids in plasma over the conjugated curcuminoids. That is, how much curcuminoids in plasma is in free form and how much as glucuronides. So, CurQfen® is talking about the latest understanding on curcumin absorption, beyond the "***number of folds***".

Moreover, BBB-permeability, brain-regional distribution pharmacokinetics, organ tissue distribution (cellular uptake), and clinical studies on brain, heart, liver and joint-health at relatively low dosage of 500 mg/day. It is also 100% Natural & CLEAN LABEL with no synthetic excipients, which makes CurQfen® unique and novel.

9. Why CurQfen® is mentioned as new generation bioavailable curcumin - beyond the 'number of folds'? What is FCR?

The current understanding on curcumin pharmacokinetics and pharmacodynamics urge for non-NANO & natural delivery forms (regulatory compliance) capable of providing **FREE** curcuminoids over conjugated metabolites and proof for the same. It has to be noted that even unformulated curcumin has been shown to provide free curcuminoids into plasma and absorbs via lymphatic system, though majority of absorption is via blood. In 2008, *Begum et al* detected and estimated curcuminoids in rat plasma and brain tissues at significantly high levels when chronically fed with 2000 ppm curcumin, indicating that 'unformulated curcumin' can provide free curcuminoids in plasma, further to brain tissues and can lead to amyloid-plaque reduction (*J Pharmacol Exptl Ther, 2008, 321, 196-208*) . But, once it is metabolised to conjugates (glucuronides/sulfates), all these properties are getting lost. So, a new generation bioavailable curcumin should talk about the ratio of plasma concentration of free curcuminoids to conjugated curcuminoids (FCR), more than the number of folds of bioavailability. FCR will reflect how much curcuminoids are absorbed in free form and how much in conjugated form. Higher the FCR, better the formulation (*JFF 2016*).

CurQfen® is the only formulation which has determined FCR of 1.3. Once free curcuminoids are available in the systemic circulation, it gets automatically absorbed into brain and other tissues. So, brain tissue distribution is a litmus test for free curcuminoids bioavailability. CurQfen® has addressed and proved all these check points and published in peer reviewed journals (*JFF 2015, 2016*). It is 100% Natural, food-grade, CLEAN label and free from excipients.

10.What is the bioavailability of CurQfen®, in terms of the number of folds?

As per the clinical study on 50 subjects, CurQfen® has 45-fold free curcuminoids bioavailability as compared to the total absorption of 1000 mg single dose of unformulated curcuminoids 95%, when performed a triple quadruple-electrospray ionisation tandem mass spectrometric study (*Kumar et al., 2016*). When compare the bioavailability of total curcuminoids as the sum of free and conjugated curcuminoids with respect to the respective curcuminoids upon a single dose of 1000 mg unformulated curcuminoids 95%, it is 270-fold bioavailable.

11. How the free curcuminoids in biomatrices confirmed?

Three levels of mass spectrometric evaluations using Triple quadruple, Time of flight and Ion trap tandem mass spectrometry were used to confirm the curcuminoids and their metabolites.

12. What made the formulation of CurQfen® possible?

The identification of unique physicochemical properties of fenugreek galactomannans and the invention of a proprietary water-based mechanical process for the isolation of a unique composition of phytochemicals free and debitterised dietary fibre were the key. It binds with curcuminoids in high affinity and forms amorphous curcumagalactomannosides (curcumin-galactomannan biocomplex or CGM) exhibiting mucoadhesive character. CGM swells extensively in the gastrointestinal tract, binds with the epithelial membranes and leaches the colloidal nano sized soluble curcuminoids (sustained release) from the galactomannan network and absorbs via both circulatory and lymphatic systems.

13. What about the dose escalation and dose response of CurQfen®?

CurQfen® has been studied for its pharmacokinetics at various dosages ranging from 100, 250, 500 and 1000 mg single doses (*Kumar et al., 2016*) and repeated dose studies at 500 mg/day for 30 days (*Sudheeran et al., 2016*).

14. Is CurQfen® organic?

CurQfen® is the first organic bioavailable curcumin in the market place. It contains only two GRAS-listed kitchen spices, namely curcumin from turmeric and dietary fibre from fenugreek. Organic and non-organic grades are available.

15. What are the delivery forms for CurQfen®?

CurQfen® is available in both granular and powder formats for a variety of delivery forms. Granular is also available in non-colour leaching format employing our patented technology to prevent colour explosion in the manufacturing facility, and hence to ease the labour and to bring hygiene. Directly compressible granules with density ranging from 0.6 to 0.8 g/mL are suitable for capsules, tablets and brisk effervescence tablets, even at 600 mg/dose level and also as combinations with other botanicals. Powder is suitable for soft gels, sachets, stick packs, gummies, for liquid formulations such as liposomes, protein bars, chocolates, soups, etc.

16. What about the sustainability and traceability of CurQfen®?

CurQfen® production is based on our 'Nature to Nutraceuticals®' program by which we have adopted sustainability initiatives in terms of our own organic farms, contract farming and global sourcing for turmeric and selected farm level operations for fenugreek. Past 25 years of our journey and innovation in spices have paved the foundation and farm level knowledge on precision farming, pre & post-harvest operations, better yielded continuous extractions for supporting our customers with stable pricing and quality. We manufacture all our ingredients in-house and no trading, which makes us unique among the ingredient suppliers.

17. What is the environmental policy of CurQfen®?

CurQfen® production is now powered by solar energy and water harvest - **a 100% green process and green product** to go along with the slogan **GO GREEN, GO NATURAL!**

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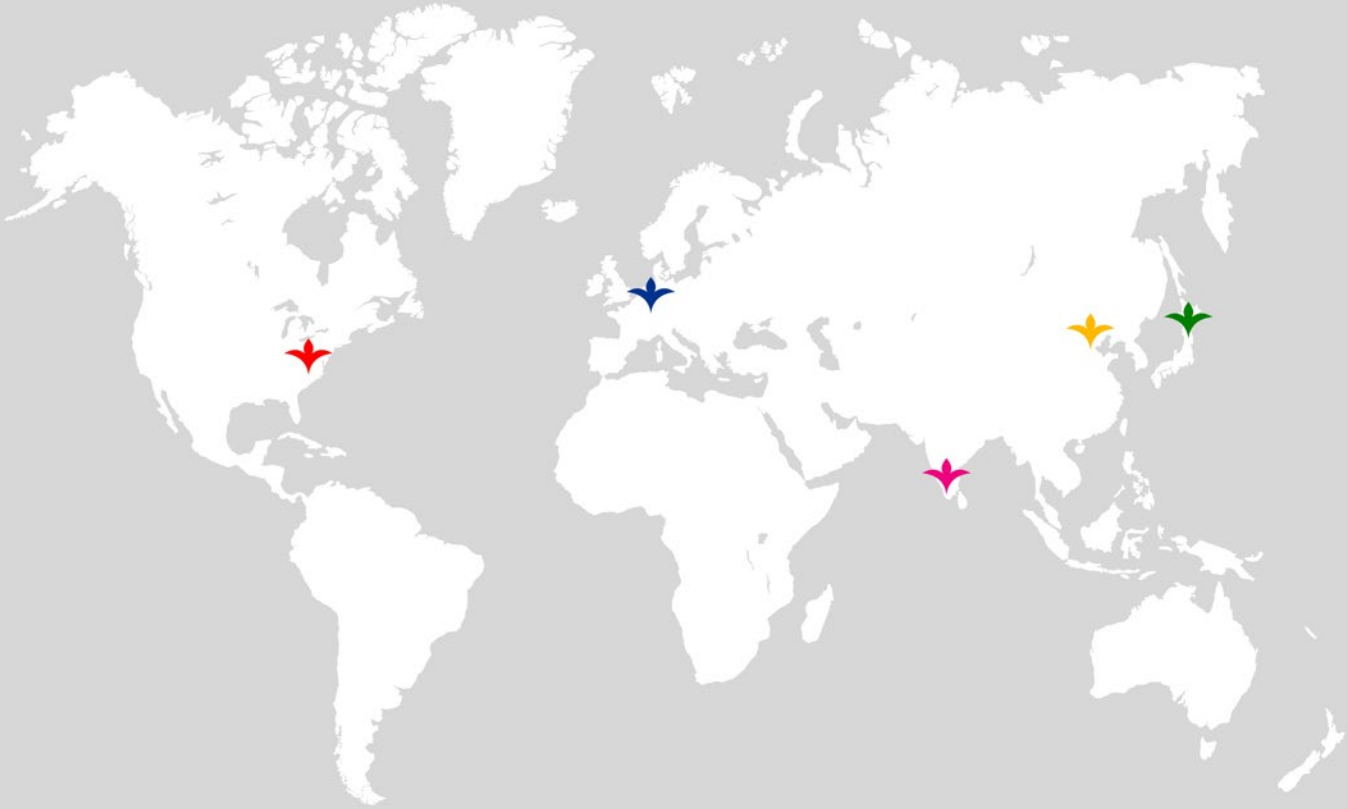

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Spiceuticals®

Unlocking the nutritional secrets of spices

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