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Unlocking the Efficacy of Turmeric Root: Could the Absorption of Curcumin be the Wrong Key?

This paper explores the conundrum between absorption, bioavailability and efficacy, as it pertains to the application of curcumin-related human clinical outcomes. We will show that, for the most part, the large increases in the absorption of curcumin using most "bioavailability-enhanced" curcumin compounds result in extremely small increases in free curcumin, subsequently resulting in only limited increases in bioactivity. Furthermore, we will discuss the evidence that suggests some of curcumin's bioactivities may be achieved at low concentrations and that curcumin's interaction with the human gut microbiome may be a key mechanism driving its bioactivity. Finally, we will propose that the therapeutic potential that resides within turmeric cannot be delivered by curcuminoids alone; and that the pharmaceutical approach of concentrated single entities may have been a wrong-headed approach for leveraging the therapeutic potential of turmeric in the first place.

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The Point Institute
Director: Thomas Guilliams Ph.D.
Website: www.pointinstitute.org
Email: info@pointinstitute.org

Introduction

Clinical research and therapeutic use of botanically derived ingredients continue to grow worldwide. This includes ingredients that are minimally processed (e.g., ginger root powder), as well as those that are highly concentrated compounds (e.g., quercetin). While many botanical preparations have been used for millennia in various medicinal traditions (numerous of which are recorded in ancient pharmacopeias), some have also been evaluated using the latest drug discovery techniques. Turmeric (*Curcuma longa* L. and related species), and several of its phytochemicals (e.g., curcuminoids), is one of the most notable (and popular) botanicals to reach both ends of the spectrum.

The use of turmeric as a culinary and medicinal herb has been recorded for nearly 4000 years. In Ayurveda and Traditional Chinese Medicine, turmeric has been well documented as an anti-inflammatory agent to treat various ailments such as arthritis, jaundice, hepatic disorders, digestive disorders, gynecological problems, skin diseases, cough, cold and dental problems.[1,2] Turmeric powder has also been used ubiquitously as a flavoring, coloring and beautifying agent in Southeast Asia. The root and rhizome of this perennial herb are usually boiled, cleaned, dried and ground, yielding a bright yellow colored powder.[3]

Despite these historical uses, and identification of many bioactive components in turmeric, the research focus over the past few decades has been almost exclusively centered on one group of phytochemical compounds from turmeric, its curcuminoids. Purified and concentrated extracts of one or more curcuminoids (often 95% or greater) are commonly used in dietary supplements, functional foods, and clinical research trials across the globe (over 8,000 citations in PubMed include "curcumin" it their title!). However, despite its popularity and hopeful research, the clinical results using curcumin in humans is often greatly muted compared to the promising results from *in vitro* research and mechanistic studies. The reason for this disparity is almost universally attributed to curcumin's poor absorption/bioavailability, for which the creation of a variety of bioavailability-enhanced delivery forms has been postulated as the logical solution.

Today, at least a dozen different ingredients are commercially available that are specifically designed to increase the oral absorption of curcumin, using a variety of different technologies (e.g., liposomes, nanotechnologies, micelles, etc.). Indeed, most of these complexes have been shown to result in much higher serum levels of curcumin compounds, when compared with unmodified 95% curcumin preparations. However, despite the claims being made about these modified ingredients, their increased absorption has not yet been demonstrated to significantly increase clinical efficacy in human clinical trials.[4]

In this paper we will explore the conundrum between absorption, bioavailability and efficacy, as it pertains to the application of curcumin-related human clinical outcomes. We will show that, for the most part, the large increases in the absorption of curcumin using most "bioavailability-enhanced" curcumin compounds result in extremely small increases in free curcumin, subsequently resulting in only limited increases in bioactivity. This will lead us into a discussion of the ongoing debate about which curcumin metabolites are considered to be the most bioactive when consumed orally. Furthermore, we will discuss the evidence that suggests some of curcumin's bioactivities may be achieved at low concentrations and that curcumin's interaction with the human gut microbiome (a bioactivity which may not even require human

bioavailability) may be a key mechanism driving its bioactivity. Finally, we will propose that the therapeutic potential that resides within turmeric cannot be delivered by curcuminoids alone; and that the pharmaceutical approach of concentrated single entities may have been a wrong-headed approach for leveraging the therapeutic potential of turmeric in the first place.

The Basic Phytochemistry of Turmeric

Turmeric, a perennial native to South Asia, is the common name of *Curcuma longa*, of which the rhizome is the most extensively used part. Other synonyms of *Curcuma longa* include *Curcuma aromatica, Curcuma wenyujin* and *Curcuma domestica.*[5] The most abundant compounds from turmeric include carbohydrates (60-70%), water (6-13%), proteins (6-8%), fatty acids (5-10%), essential oils (3-7%), minerals (3-7%), fiber (2-7%) and curcuminoids (2-6%).[6] However, more than 235 different compounds have been reported in turmeric extracts, mainly phenolic compounds and terpenoids.[3] Turmeric extracts are generally prepared using solvents like ethanol, methanol, water or ethyl acetate. Essential oil preparations, obtained by steam distillation of the rhizome, have been reported to contain 84 different chemical constituents; including sesquiterpenes (53%), zingiberene (25%), α-phellandrene (1%), sabinene (0.6%), cineol (1%), and borneol (0.5%).[7,8] The α- and β- turmerones and ar-turmerones (sesquiterpenes) present in the essential oil of turmeric are primarily responsible for its aroma.[6] In the midst of all these phytochemicals, the pharmacological activity of turmeric has been attributed mostly to polyphenolic curcuminoids; therefore turmeric research has mostly focused on the isolation and use of curcuminoids/curcumin.

Curcuminoids are a mixture of turmeric-derived phenolic compounds that include curcumin (diferuloylmethane), demethoxycurcumin and bisdemethoxycurcumin, which give turmeric their characteristic yellow/orange color. Curcuminoids are typically extracted from the dried rhizome using solvent extraction and column chromatography using consecutive non-polar and polar solvents.[8,9] A typical composition of Indian varieties of curcuminoids consist of 52-63% curcumin, 19-27% demethoxycurcumin and 18-28% bisdemethoxycurcumin.[10] Highly concentrated forms of these turmeric extracts are obtained by further purification and crystallization of the initial extract (initially containing about 40% curcuminoids).[11] Most of the commercially available curcuminoid ingredients used for therapeutic and research purposes are standardized to contain 95% curcuminoids; of which 70-80% is curcumin, 15-25% is demethoxycurcumin and 2.5-6.5%% is bisdemethoxycurcumin.[10,12] The term "curcumin," in both research publications and on product labels, is often confusing and incorrect; since it can refer to a purified curcumin-only ingredient (most often used for research purposes), though it is most often describing (incorrectly) a purified extract containing all 3 major curcuminoids.

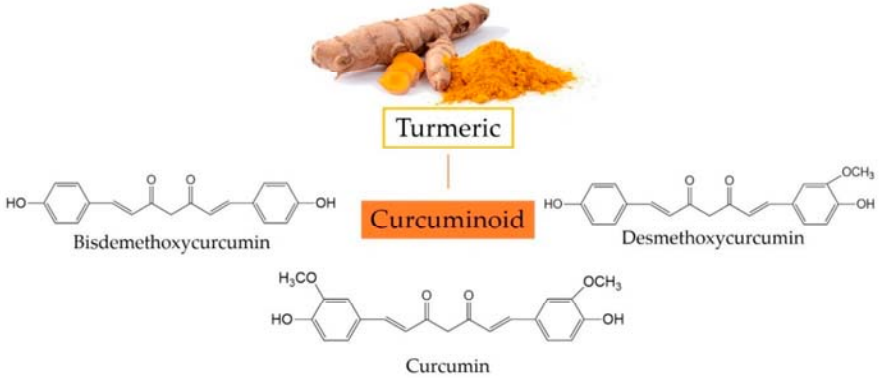

Figure 1: Chemical structure of curcuminoids[13]

Bioactivities of Curcuminoids

As mentioned, most of the clinical research using turmeric-derived compounds is focused exclusively on the activities of curcuminoids (including dozens of synthetic analogs of curcumin). Since the term "curcumin" is not always distinguished from curcuminoids in the materials and methods section of a publication, it can sometimes be difficult to know whether the ingredient used was a pure form of curcumin (i.e., 100% diferuloylmethane) or is a purified extract containing the three typical curcuminoids in commercially-prepared turmeric root extracts. While this distinction may be subtle, there are those that suggest these differences can greatly influence its efficacy.[14] Nonetheless, curcumin/curcuminoids and their synthetic analogs have been tested in nearly every possible *in vitro* assay and drug discovery protocol, attempting to uncover their potential therapeutic mechanisms.

After isolation of curcumin by Vogel and Pelletier, the first scientific biological activity of curcumin was recorded in 1949 as an anti-bacterial agent.[15] Further interest in curcumin's potential as a modern medicine was sparked in the early 1970s when cholesterol-lowering, anti-diabetic, anti-inflammatory, and antioxidant properties were recognized. Extensive biomedical research on curcumin has increased considerably since then, revealing a wide range of potential therapeutic benefits. The pleiotropic effects attributed to curcuminoids have been demonstrated primarily by various cell-based *in vitro* assays and preclinical animal studies.[10] These studies have identified numerous curcumin-related targets and mechanisms at the molecular level including a) transcription factors such as NF-κB, STAT3, Egr-1, PPAR-γ and β-catenin[16] b) modulation of enzyme activity[17,18] such as COX-2, 5-LOX, iNOS, MMPs, caspases, protein kinases[19] (MAPK, JNK, PKA, PKC, src tyrosine kinase, phosphorylase kinase) c) inflammatory cytokines such as IL -1, -2, -6, -8, -12, TNF-α d)growth factors and their receptors and e) adhesion molecules like ICAM-1, VCAM-1, and ELAM-1. More recent research has suggested curcuminoids modulate the expression of non-coding RNA and may affect gene expression through epigenetic pathways.[20-23]

Based on the promising results of these types of studies, it is not surprising that curcumin has become a leading candidate for drug development. However, translating *in vitro* research results into similar clinical outcomes has been met with limited success. Though some have speculated that the *in vitro* results are themselves misleading, most researchers believe that these failures are due to curcumin being poorly absorbed, highly reactive and unstable after consumption.[24] Therefore, despite the historical therapeutic benefits attributed to various turmeric preparations, including many publications of clinical benefit using concentrated curcumin products (discussed in a later section), there has been an emphasis on finding ways to increase the absorption and stability of curcumin preparations, or on synthesizing curcumin-like synthetic compounds that have better clinical outcomes.

Absorption and Metabolism of Curcumin

Pharmacokinetic-type studies of curcumin in humans generally show a very low recovery of curcumin in the serum after oral intake. One study indicated that the amount of free curcumin in human plasma after intake of 3.6-12 g curcumin for a week or longer was below 25 nM[25] (for comparison, concentrations typically used in *in vitro* studies mostly range from 1-80 μM). The reasons for this low recovery are many, and include processes that affect the intestinal absorption

of curcuminoids and several different metabolic steps that occur in the gut lumen, within the enterocytes, in the liver and within target tissues.[26] Curcuminoids undergo extensive metabolism during and after ingestion.[26] Bioreduction of curcuminoids through phase I metabolism forms major products like tetrahydrocurcumin and hexahydrocurcumin. Further, curcumin and its reduced forms are extensively conjugated through phase II glucuronidation and sulfation; leading to formation of conjugated metabolites like curcumin glucuronide, curcumin sulfate, curcumin sulfate-glucuronide, dihydrocurcumin-glucuronide and tetrahydrocurcumin-glucuronide, etc. While some have speculated biological activity for some of these metabolites[27], the *in vitro* assessment of the biological activity of the phase II metabolites of curcumin has demonstrated that predominant serum metabolites, like curcumin glucuronides, do not possess significant bioactivity, compared to free curcumin.[28-30] Additionally, while small curcumin metabolites that have been isolated from *in vitro* studies (such as vanillin and ferulic acid and their derivatives) have been shown to have potential therapeutic effects, little is known about their formation, pharmacokinetics and bioactivity in animals or humans after oral ingestion of curcuminoids.[31,32]

Therefore, while curcumin metabolites and conjugates are an important part of the pharmacokinetic profile when assessing the bioavailability of curcumin (though they are often not reported in these studies), limited information is available on how these compounds affect the potential therapeutic outcomes in human subjects consuming turmeric or curcumin products. Furthermore, recent studies suggest that curcuminoids can be modified by certain bacteria residing in the human gut microbiome. The relationship between these metabolites and curcumin's potential therapeutic benefits (mediated through microbiota, directly on cells of the intestinal tract or by systemic absorption) is an area of current investigation (covered briefly in a later section).

Modifying Curcumin to Enhance Absorption

Although there is ample evidence that oral intake of turmeric extracts and concentrated curcumin ingredients (typically 95% curcuminoids) have measurable clinical effects for a variety of outcomes,[1,33-38] it is generally assumed that the poor bioavailability of curcumin prevents high levels of bioactive compounds from reaching relevant tissues, thereby limiting these effects. This conclusion is especially common when comparing the clinical benefits seen with oral intake of curcuminoids with those from cell culture studies.[†] Equally common is the assumption that technologies designed to improve the bioavailability of curcumin will increase its bioactivity, allowing researchers to realize many of the predicted *in vitro* benefits in animal or human subjects after oral intake of these modified curcumin preparations.[12]

A variety of technologies have been designed to resolve the problem of curcumin's low bioavailability and metabolic inactivation after oral ingestion.[39-43] These technologies include the mixture of agents designed to prevent the efflux and metabolism of curcumin in the enterocyte (piperine) and a range of drug delivery systems such as nanoparticles, liposomes, micelles or phospholipid complexes; a great number of which are commercially available to consumers and researchers. Indeed, both animal and human clinical trials confirm an increase in serum levels of

[†] While it is beyond the scope of our discussion, there are significant potential differences in the curcumin metabolites that form *in vitro*, with those that occur *in vivo* (which are greatly affected by the cell culture medium, light, pH and other factors). It is quite possible that some of the promising *in vitro* results are a consequence of high levels of curcumin metabolites that may not be present after ingestion in mammals, further complicating the translation of these potential bioactivities.

total curcuminoids with most commercially available "enhanced" forms of curcumin, when compared to the unmodified curcumin (i.e., 95% curcuminoid).[10] Published reports have suggested up to 20 times increase in serum levels with curcumin+piperine, 6.93 times increase with Biocurcumax, 8.88 times increase with Meriva[44], 9 times increase with micronized curcumin[42], 27 times increase with Theracurmin[41], 45.9 times increase with CurcuWIn[43], 185 fold increase with Novasol[42] etc. We should note that these increases are almost always measured as the difference of the serum levels (area under the curve, AUC) over a specified time after ingestion, and usually includes all curcumin compounds (i.e., including glucuronide and sulfate conjugates). Free curcumin levels, when reported, are significantly lower in their respective differences compared to the total.[41-45]

As it turns out, this difference is likely to be very important in explaining why the dramatic increases in serum levels of curcumin that result from using these enhanced forms of curcumin have yet to result in efficacy differences that mirror these same increases (if they increase their efficacy at all). In other words, the vast majority of the increase in curcumin levels in the blood after ingestion of these enhanced forms is conjugated (as a glucuronide or sulfide) and, most likely, has little therapeutic benefit. However, what makes this difficult to discover when reading these publications is the fact that these data are typically reported as total curcumin, total curcuminoids or just curcumin. One needs to dig into the materials and methods section of these publications to discover that the serum samples are treated with glucuronidase and sulfatase enzymes, effectively converting all the compounds to "free" curcumin.[‡46] Therefore, while large increases in total curcumin are realized by using a variety of enhanced-forms of curcuminoids, the increase in bioactive curcumin reaching tissues is likely to be very limited since the majority (~95%+) of the absorbed curcumin is in the conjugated forms. Thus, we conclude that these enhanced forms of curcumin increase absorption, but it is misleading to say that these compounds have improved bioavailability (i.e., tissue availability of the bioactive form).

Comparing Bioactivity of Enhanced vs Non-Enhanced Curcumins

As mentioned previously, the past three decades have witnessed a large number of clinical studies, including a multitude of randomized controlled clinical trials, investigating the therapeutic benefits of various turmeric and curcumin preparations, with varying degrees of clinical benefit. Likewise, since the invention of various enhanced forms of curcumin, clinical studies have investigated their potential benefits in many clinical trials. However, while nearly all the enhanced forms of curcumin have been compared (head-to-head) against 95% curcumin in measures of absorption (often incorrectly called bioavailability- see above), there are no published studies which compare these enhanced forms with 95% curcumin using a clinical outcome (i.e., therapeutic effect).[47-52] Instead, like the earlier studies using unenhanced forms of turmeric or curcumin, they have been compared to placebo, or in some cases, to other relevant active ingredients such as a known anti-inflammatory agent. One would imagine that since these enhanced forms were created with a goal to resolve a recognized efficacy gap (the assumption that efficacy was hindered by poor bioavailability), that comparing their therapeutic outcomes with unenhanced curcumin preparations would have been a high priority once absorption enhancement had been established. The lack of interest in this question (or the lack of published

[‡] The detection of free curcumin in the presence of its metabolites and conjugates is not straightforward and has only recently been refined.[46]

data to answer it) is problematic, especially since the primary marketing strategy in the sale of these new ingredients implies greater efficacy at lower doses.

Even without direct head-to-head studies, those who have objectively assessed the clinical effects of both enhanced and unenhanced curcumins conclude that they have similar efficacy in human subjects. In fact, one review article on the subject attempts to tackle this conundrum: "*The collected outcomes raise an open question: why significantly improved bioavailability of curcumin does not produce improved pharmacological efficacy in many studies? Here, we attempt to explain the reason that enhanced bioavailability of curcumin is not associated with improved pharmacological efficacy.*"[4] While they use the term "bioavailability" to mean absorption, they also say that efficacy is not different in *many* studies; implying that efficacy is improved in some studies using enhanced forms of curcumin. Ironically, no human study is cited in their review that shows improved efficacy of the enhanced forms of curcumin over the unenhanced forms.

Regardless, two lines of evidence suggest that the difference in efficacy between the enhanced forms and the unenhanced forms is likely to be limited. The first we have already mentioned, that the majority of the increase in curcumin absorption is almost all found in the conjugated glucuronide and sulfate forms and only small increases in free curcumin (or other potentially active metabolites) are realized. The second is that most of the formulations used to increase the absorption of curcumin are likely to alter the interface between curcuminoids and gut microbes and/or other active sites within the gut lumen. Since emerging research suggests that some of curcumin's local and systemic effects require interaction with gut microbiota, it is possible that these effects are diminished in many of the commercially available enhanced curcumin formulations.

The Emerging Role of Gut Microbiota

The human gut microbiome is now considered to influence nearly every aspect of human metabolism and health; and is also recognized as an important mediator of phytonutrient therapeutic activities.[53,54] In fact, since many bioactive phytonutrients have naturally low bioavailability/absorption, resulting in relatively high intestinal concentrations after oral ingestion, researchers have begun to consider the gut and its microbiota as the primary target of phytonutrients like curcumin.[55-57] Indeed, during the past several years scientific advances have suggested a strong bidirectional interconnection between the human gut microbiome and curcumin; whereby curcumin metabolism is influenced by certain gut microbiota and curcumin metabolites modulate the function and therapeutic activities of certain gut microbes.[58] In addition, neurohormonal signaling from the gut (e.g., gut/brain, etc.) appear to be modulated by curcumin administration. Therefore, despite its low systemic bioavailability, these emerging studies may help to explain some of curcumin's systemic pharmacological activities and mechanisms of action despite its low systemic bioavailability.

- Dose- dependent administration of curcumin has been shown to alter the makeup of gut microbiota in animal models affecting the management of obesity[59], colitis[60], non-alcoholic fatty liver disease; including microbiota changes induced by a high-fat diet.[61]
- Production of the bacterial endotoxin, lipopolysaccharides (LPS), which can be induced with "Western" diet challenge in animals, was significantly lowered with curcumin supplementation.[62] This same model showed curcumin's ability to improve measures of gut barrier function that was deteriorated with the same diet challenge.

- Studies show that specific bacterial species isolated from human gut or stool samples are capable of metabolizing curcuminoids to bioactive metabolites; some of which cannot be produced without microbe biotransformation.[63-69]
- Administration of curcumin significantly ameliorated alterations in neurotransmitters such as 5-HT (serotonin), BDNF (Brain-derived neurotrophic factor) and pCREB (phosphorylation of cAMP response element-binding protein) in the hippocampus and colon of a rat model of IBS-induced anxiety.[70,71]
- Curcumin exhibited anti-arthritic effects by improving the cholinergic anti-inflammatory system, increasing the synthesis of the neurotransmitter, acetylcholine, through the stimulation of the vagus nerve.[72,73]

Beyond Curcumin: The Other Bioactives in Turmeric

For historical reasons, the therapeutic potential of turmeric has been disproportionally focused on curcuminoids, which make up only around 5% of the total weight of turmeric root. However, clinical trials have shown that preparations of whole turmeric or turmeric preparations not designed to concentrate curcuminoids have shown some clinical benefit. These include trials demonstrating biological activities of turmeric when used alone or as an adjuvant therapy in the management and treatment of inflammatory diseases[74], rheumatoid arthritis[75], osteoarthritis[38,76], autoimmune disorders like lupus nephritis[77], cancer[78-80], diabetes[81,82], irritable bowel syndrome[83,84], mutagens[85] and fibrosis.[86] In an *in vitro* antiproliferation study, whole turmeric preparation had stronger growth-inhibitory effects compared to concentrated curcumin alone (both delivered the same level of curcumin) in various cancer cell lines.[87] Another study reported that a turmeric oil-rich extract was more effective than curcumin in inhibiting prostaglandin E2; whereas it had no effect in inhibiting cyclooxygenase-2 (COX-2), like curcumin did.[88] These studies highlight the importance of the multi-component therapeutic potency of turmeric; showing that its therapeutic efficacy may be attributed to non-curcuminoid compounds, as well as the synergy between these compounds and curcuminoids.

In fact, while most researchers have been focusing on the promise of increased curcumin bioavailability, many others have been finding therapeutic activities attributed to many of the non-curcuminoid compounds in turmeric, especially related to anti-inflammatory and anti-cancer outcomes.[5,89] These include compounds such as turmerin[90-93], turmerones[94-96], elemene[97,98], furanodiene[99], curdione[100-102], bisacurone[103], cyclocurcumin[104-106], calebin A[107-109], and germacrone.[110-112]. Preliminary clinical studies even suggest that curcumin-free extracts can reduce markers of pain and inflammation, actions which are usually assumed to require curcumin.[113]

A way forward

As other botanicals have, turmeric root has bridged the gap between an ancient medicinal herb and a modern phytopharmaceutical. However, in that transition a disproportionate focus has been placed upon the therapeutic potential of one set of constituents- its curcuminoids; in the hopes that these compounds would unlock turmeric's medicinal treasures. Though we agree that curcuminoids are indeed an important participant in the therapeutic potential of turmeric root, and we have learned much by using purified and concentrated curcuminoid preparations; it is important to acknowledge the limitations that curcumin-only therapy has produced. While these limitations were assumed to be based on curcumin's poor bioavailability, the fact that enhanced

forms of curcumin designed to greatly increase its absorption and serum levels have not yet been shown to improve therapeutic activities in human subjects suggests there is more to the story. Ironically, human biology appears to limit the accumulation of free curcumin and quickly forms inactive conjugates, which appears to nullify most of the gains achieved in increasing curcumin's absorption using almost every technology implemented so far. Therefore, we believe further attempts to improve absorption are likely to meet the same efficacy-related barriers. Though synthetic curcuminoids or concomitant use of compounds that inhibit the formation of curcumin conjugates may be discovered, the safety parameters of these sorts of solutions must be verified before testing their efficacy in human subjects. These types of phytopharmaceutical solutions may have specific applications in medicine; however, they fall far outside the original use of the turmeric root.

We believe the key to unlock the clinical benefits of turmeric are best accomplished by delivering curcuminoids within the context of other turmeric-derived phytochemicals, rather than by new technologies designed to increase the absorption/bioavailability of curcumin concentrates. Emerging mechanistic data has revealed the activities of many non-curcuminoid, turmeric-derived compounds and preliminary studies using curcumin-free turmeric preparations have shown clinically relevant outcomes. In addition, we believe that since many of the proposed mechanisms for curcumin (and other turmeric-derived compounds) can be facilitated by low doses in the human serum (genomic, epigenetic and hormetic) or by interaction with the human gut microbiota (requiring little or no systemic absorption), that technologies designed to increase curcumin absorption may be unnecessary or even counterproductive for most therapeutic outcomes. Thankfully, researchers are beginning to look beyond curcumin in their attempts to leverage turmeric's therapeutic potential and it is our hope that additional research will establish the best way to deliver curcuminoids, within the context of other turmeric-derived phytonutrients. This will allow us to establish the range of therapeutic potential for the whole turmeric root complex, allowing for synergy with other botanicals and nutrients to allow for safe, effective and predictable therapeutic outcomes.

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