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BIOACTIVES AMERICAN CORPORATION

Empowering Nature

Natural Curcumin of Turmeric Origin – The Untold Story

Distinguishing natural curcumin from synthetic and why it's important

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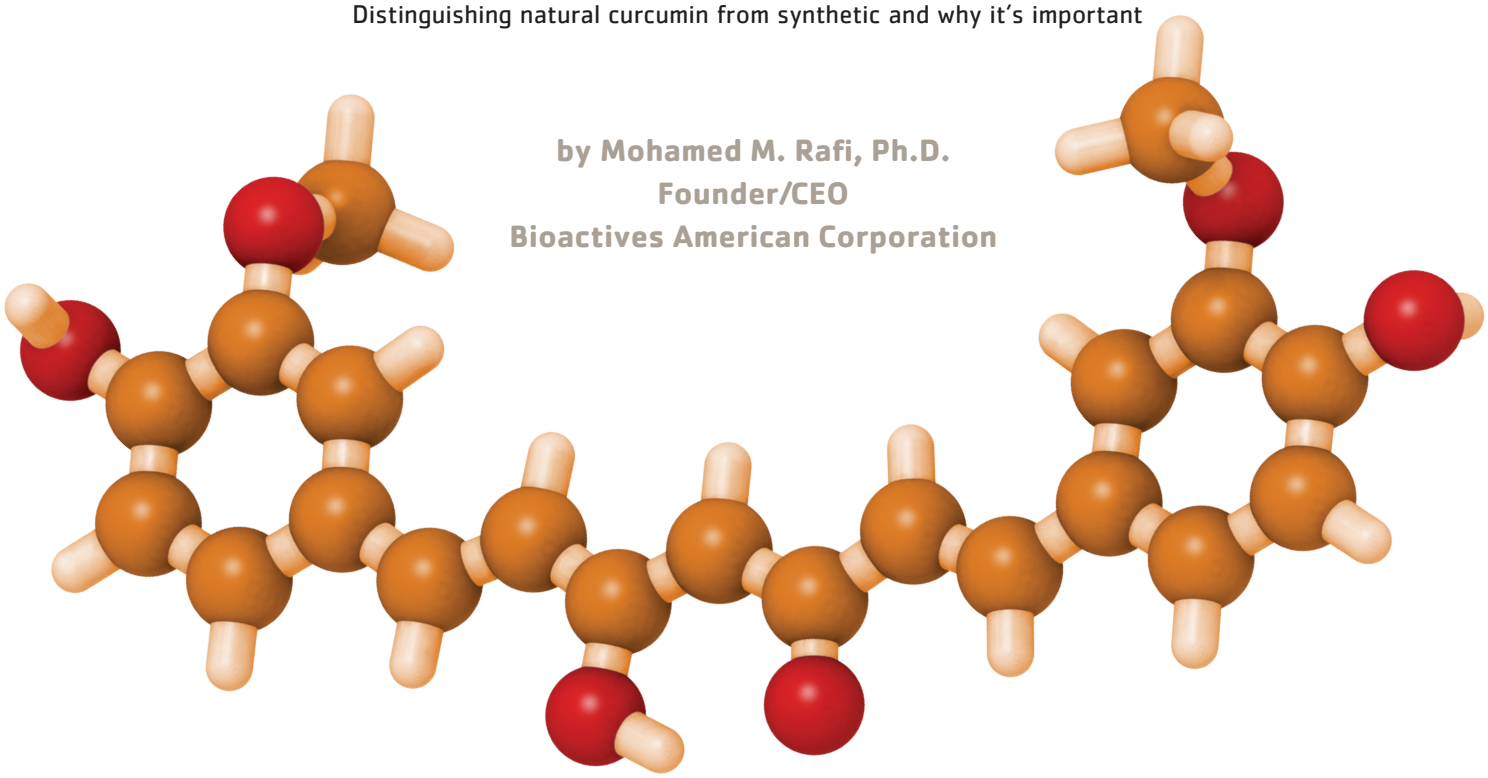

FIGURE 1. 3-D structure of Curcumin. Two ferulic acid molecules connected by a central methylene carbon give the curcumin molecule its unique structure.

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INTRODUCTION

Curcumin with characteristic bright golden color is one of the most successful ingredients in the modern nutritional marketplace. Turmeric (*Curcuma longa*), the plant from which natural curcumin is derived, has become the top selling herbal item since 2013 in the U.S. natural and health food channel (according to American Botanical Council's annual report, U.S. Dietary Supplement Sales in *Herbalgram*). The future continues to be promising as new research heralds its health benefits. Beyond its well-known antioxidant and anti-inflammatory effects, curcumin is generating strong interest from scientists for its potential to support heart, brain and cognitive health, improve digestive and liver function, and enhance physical performance and mood, as well as promote overall healthy aging.[1]

Increased demand for this ancient Ayurvedic herb has led to adulteration of raw material with synthetic curcuminoid ingredients to mimic natural curcumin. These ingredients have not been tested for safety and pharmacological activity. Product developers must start to forge strong relationships with reputable suppliers of high quality, verified 95% curcumin to produce superior, bioavailable products to ensure their proven health benefits.

This white paper provides an overview of the curcumin market, the growing adulteration issues and the new ^{14}C data tests to identify natural versus synthetic material. It also provides information on traditional usage, bioavailability, biological effects, supporting scientific findings, as well as structure and reactivity of curcumin.

THE CURCUMIN MARKET

Growing consumer awareness of the health benefits of curcumin is putting the herb on the radar for a variety of product applications, ranging from nutritional supplements and pharmaceuticals to cosmetics and skin care products. The body of science regarding curcumin's health benefits continues to expand on its antimicrobial, antioxidant and anti-inflammatory properties, and the emerging science supports its benefits for the digestive system, joint pain, the nervous system and cognitive function.† With as many as one in two Americans expected to develop some sort of osteoarthritis in their lifetime (CDC statistics[2]) the growing market for curcumin products is expected to see exponential growth in the near future.

> "The global market for curcumin is predicted to reach $94.3 million by 2022."

According to a recent report by Radiant Insights, the global market for curcumin is predicted to reach $94.3 million by 2022.[3] North America is currently the largest market for curcumin having exceeded $20 million in 2014. Use of the herb in pharmaceuticals and cosmetic applications is expected to be a key market driver for this growth. Europe is currently predicted to be the fastest growing region for curcumin products, the report noted, with an estimated compound

annual growth rate of 17 percent between 2015 and 2022. A positive regulatory environment, along with growing consumer recognition of curcumin's health benefits, is likely to propel this market expansion.

Commercial production remains centered in India, while product demand remains strongest in Europe and North America. As such, supply can be somewhat uneven, with some shortages of available ingredient impacted not only by demand but by occasional poor harvests and variable quality. These supply issues have led to the growing problem of adulteration of the available curcumin supply. Most notably, less expensive synthetic curcumin is being either sold as natural curcumin or mixed with natural curcumin to provide a product that is less expensive to produce.

The issue goes back to about 2011, when suppliers of natural curcumin first began to notice the possibility of commercially available curcumin supplements made with the cheaper synthetic version.[4] The two ingredients, however, are not interchangeable for pharmacological activities. Synthetic curcumin is distinguishable because it is created from petroleum-based toxic chemicals and residual impurities and does not have the synergistic compounds or the characteristic smell of the natural ingredient derived from the turmeric plant. The less expensive synthetic curcumin also has not been studied for its safety or whether it provides any of the same health benefits reported for natural curcumin.[4] While it is unclear whether or not companies are knowingly spiking the natural ingredient with the synthetic version, the continued demand for curcumin is keeping the price of natural curcumin on the rise. It is roughly double the cost of synthetic curcumin. Ingredient spiked with synthetic curcumin cannot be easily detected because adulterators have mastered a technique to make spiked curcumin provide a similar signature in an HPLC test graph (see text on page 7).

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Since this issue first surfaced, various suppliers have been working to develop strategies to identify adulterated products. Notably, the University of Georgia, Center for Applied Isotope Studies has developed a radiocarbon dating test to detect the presence of synthetic curcumin. The ^{14}C-dating method can flag the presence of synthetic curcumin by identifying carbon isotopes that would be obtained from petrochemical-derived raw material used in the synthetic ingredient.[4]

HISTORY & TRADITIONAL USE

Curcumin is extracted from turmeric (*Curcuma longa*) and has long been used in Ayurvedic Medicine for its anti-inflammatory and antioxidant properties. Turmeric constituents include three curcuminoids: curcumin (diferuloylmethane—the primary constituent that is responsible for the vibrant yellow color); demethoxycurcumin;

and bis-demethoxycurcumin, along with volatile oils (tumerone, atlantone, and zingiberone), sugars, proteins and resins.[5] Turmeric, also known as haldi in Hindi and manjal in Malayalam, is a perennial member of the Zingiberaceae (Ginger) family and is cultivated primarily in India and parts of Southeast Asia.[5] The stems (rhizomes) of the plant grow underground and store many of its nutrients and protective phytochemicals. Its golden yellow fine powder turns to a bright red color upon being treating with alkaline alum or slaked lime.

The powder is most widely used as a spice to color and flavor food, such as curry powders, mustard, cheese and butter, and is consumed along with many foods. Turmeric also has many topical and commercial uses. Its red alkaline form is traditionally applied to the face and feet by women in South Asia as socio-religious "markings." It brightens the complexion and protects the skin from infection, and is used to treat pain, burns, inflammation and open wounds in skin and soreness in the mouth. Essential oil extracted from turmeric is used in perfumes, and it has long been utilized as a yellow vegetable dye for cloth.

Turmeric contains a range of chemicals that are bioactive. Like other plants, it carries a variety of terpenoid and phenolic compounds. The distinctive phenolate is curcumin along with minor components tumerone, zingerene, atlantone, zingiberene, phellendrene and cineole. Turmeric has some monoterpene (sabinene and borneol) and commonly occurring carotenoids and tocopherol, but curcumin is the main bioactive ingredient.

In general, turmeric is believed to promote overall wellness. It is used in Ayurvedic Medicine for a variety of ailments to decrease swelling, heal wounds, protect the skin, and provide relief from issues such as headaches, fever, colds, appetite loss, indigestion, nausea and vomiting, and stomach bloating, along with joint pain and gas elimination.†

EVIDENCE OF MEDICINAL PROPERTIES

There is also now a growing body of evidence that turmeric does indeed provide numerous medicinal health properties.[6] Curcumin has been most studied for its antioxidant and anti-inflammatory mechanisms. Research now indicates that curcumin is a highly pleiotropic molecule that interacts with numerous molecular targets involved with inflammation. A 2009 review of human and animal research notes that curcumin may have potential as a therapeutic agent in conditions related to digestion, joint and eye health as well as problems linked to inflammatory response.[1]†

Curcumin's role as an antioxidant and in inflammation is generating strong interest among researchers given that these are implicated in nearly all chronic health issues.[8] Free radicals cause oxidative damage in the human body, and curcumin, with it phenolic structure, is a potent antioxidant that neutralizes the free radicals.[9] Scientists are now finding that the compound fights the complex inflammatory response at a molecular level.[10,11,12] The effect is most likely mediated through curcumin's ability to inhibit cyclooxygenase-2 (COX-2), lipoxygenase (LOX) and inducible nitric oxide synthase (iNOS), all important enzymes that help regulate the inflammatory process.[13] What's more, several studies have noted that it compared favorably to anti-inflammatory drugs, without their corresponding side effects.[1, 14]

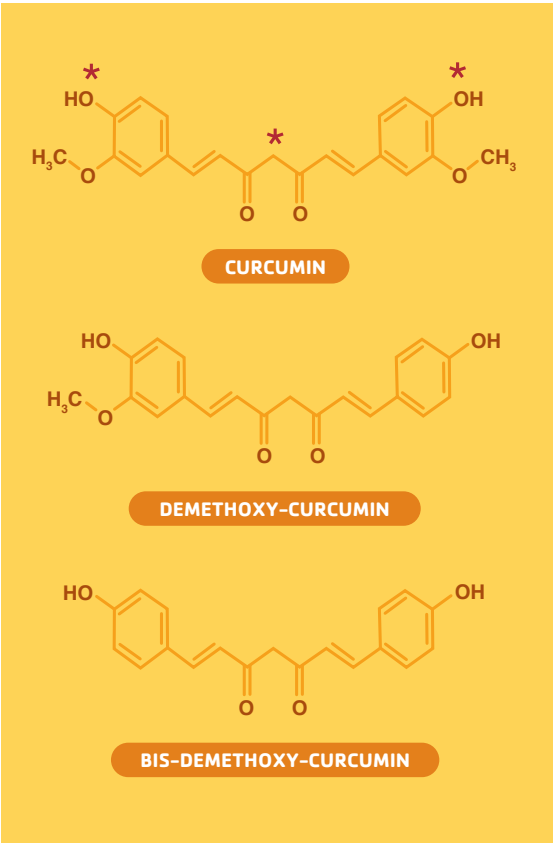

FIGURE 2. Structures of curcumin and its demethoxy derivatives present in the natural product from turmeric. The star indicates the atoms that lose an electron to become radicals.

More recently, research has linked curcumin to brain health, and it may even be effective in support of optimal brain function.† A 2006 study noted that curcumin can increase the levels of the brain-derived neurotrophic factor (BDNF), a growth hormone functioning in the brain, which can decrease as a result of stress and age.[15] In addition, a 2012 study suggests that this interaction with genes related to growth and plasticity, after prolonged use of curcumin in aged rats, provided enhanced non-spatial and spatial memory as well as dentate cell proliferation, and thus may also offer neuro-support qualities in humans.[16]

WHAT MAKES CURCUMIN DISTINCTIVE?

Curcumin, as noted earlier, is a phenolic compound. Its chemical name is diferuloylmethane. It appears to be derived biosynthetically by bridging two ferulic acid molecules by a methane unit. Related phenolic acid without methoxy group, p-coumaric acid, also abundant in plants, substitutes ferulic acid, albeit poorly. Thus, demethoxy-curcumin (one less methoxy group), and bis-demethoxy-curcumin (both methoxy groups missing, also called di-demethoxy-) (Fig. 2) accompany curcumin up to 20 percent in natural turmeric samples.

The two ferulic acid molecules are connected by the central methylene carbon to give the curcumin molecule its unique structure (Figure 1). Enabled by enolization

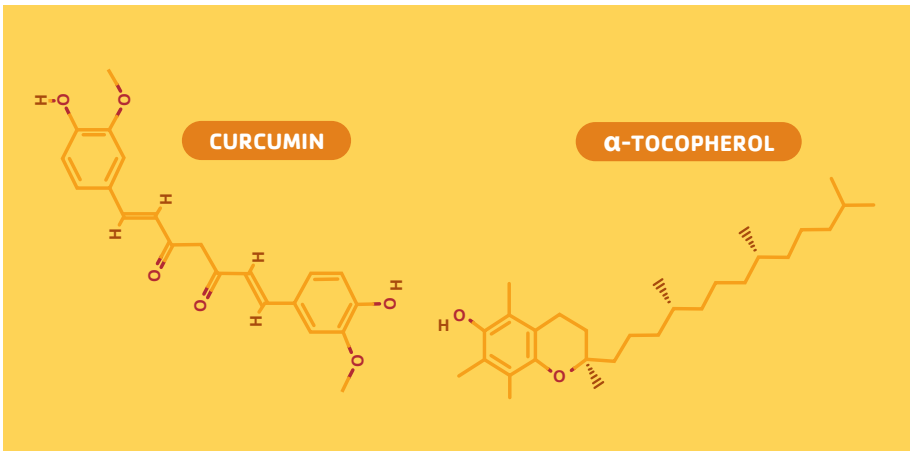

FIGURE 3. Structures of curcumin and α-tocopherol. The oxygen atoms are shown in red. Note substitution with methoxy (curcumin) or methyl (tocopherol) group adjacent to the phenol group.

of a central C=O group, the stretch of conjugated double bonds (-C=C-C=C-) in the middle can support electron exchange between the end phenolic-O radical and the central methylene-C radical (shown by * in Fig. 2). Such a distinctive structure endows the molecule potential for quenching radicals, itself becoming a radical. The antioxidant and other biological activities of curcumin are derived from such structural features.

Curcumin bears a structural relationship to the well-known compound vitamin E, the lipid-antioxidant ubiquitously occurring in animal tissues. Both have an exposed phenol substituted with a methoxy (curcumin) or a methyl (tocopherol) group. This is also true of their parent compound, the water-soluble ferulic acid. Curcumin, in contrast, is hydrophobic despite its multiple oxygen atoms (Fig. 3) and can fit into the membrane bilayer like tocopherol. It is this quality, combined with the substitutions, that makes curcumin unique.

LIMITED UPTAKE OF CURCUMIN

Curcumin is absorbed through the intestines to a limited extent, conjugated in the liver and intestines as glucuronide, and transferred to the blood for excretion through urine. Various studies [17,18,19] have attempted to increase the circulating level of curcumin in blood after oral ingestion in humans and experimental animals. This is based on the presumption that the higher the curcumin concentration in the blood, the higher its "bioavailability" in the body, subsuming that it improves its bioefficacy. This has no experimental support with any of the curcumin actions. Scrutiny of the published data indicates that conjugated form curcumin, mostly as glucuronide (99%), is the form present in blood[20], and not the free phenolic. A compound will stay longer in the blood when excretion is decreased.

The concern about the limited bioavailability of curcumin has led to a variety of opinions and numerous studies on the topic. A new theory is emerging based on traditional usage. It is well known that many plant-derived secondary metabolites are rejected and some are poorly absorbed through the intestines in humans. The efficacy of turmeric powder for treating a number of health conditions is based on knowledge acquired over centuries and was recorded in native medical systems of the East. Some scientists now surmise that what was naturally absorbed of the active principles of turmeric must have been sufficient.

CURCUMIN 95%--THE UNTOLD STORY OF NATURAL CURCUMIN VERSUS SYNTHETIC

Curcuminoids are isolated from turmeric root (*Curcuma longa*) using a variety of different solvents, including hexane, ethyl acetate, acetone and isopropyl alcohol. Notwithstanding yields, ethylene dichloride, methanol or benzene should not be used or found in the samples as they are potentially toxic. The natural turmeric-derived samples usually contain a mixture of curcumin (about 75-80 percent), demethoxy-curcumin (about 15-20 percent) and di-demethoxy-curcumin–also known as bis-demethoxy curcumin–(below 5 percent), as estimated after separation by HPLC (Fig. 4). The mixture is known as curcuminoids 95 percent, consists of generally unbound phenolates, and is referred to as "Curcumin 95%".

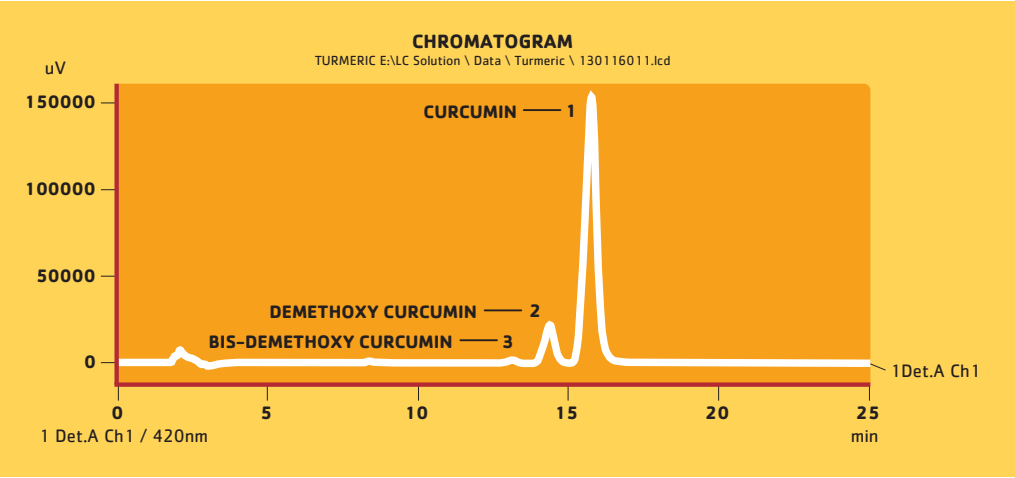

FIGURE 4. High pressure liquid chromatogram (HPLC) of natural Curcuminoids in CURCUZEN™.

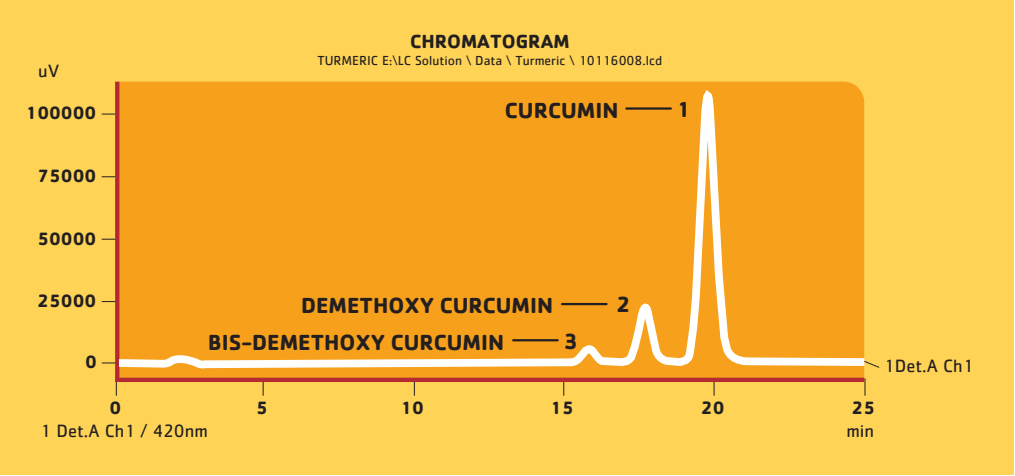

FIGURE 5. High pressure liquid chromatogram (HPLC) of Synthetic Curcuminoids.

The HPLC signature of Natural curcumin (Fig.4) and Synthetic curcumin (Fig.5) is similar and difficult to distinguish one from the other making the ^{14}C carbon dating test method important for identifying adulterated raw material. Some samples on the market are synthetic compounds mixed in the same proportions to imitate the natural version. These are distinguished by carbon dating methods with little ^{14}C (0.06 dpm/g carbon, compared to 14.0 dpm/g carbon for reference standard) indicating that the material originated from fossil fuel derived compounds. Traces of disallowed benzene and methanol are also detected in some of these (in *in-house testing*) revealing their synthetic history.

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Curcumin is becoming one of the most promising and exciting ingredients for use in nutritional products. A growing body of research now points to a wide range of health benefits, including support of the heart, brain and cognitive function, digestive and liver health, as well as sports performance and mood enhancement.† But, as the demand for raw material increases, some curcumin quality issues have begun to surface, including the substitution of cheaper synthetic curcumin for the well-studied and more efficacious natural curcumin derived from turmeric root. Those who are adulterating the raw material have mastered a technique to mix in the synthetic version in a way that it cannot be detected by the standard HPLC testing method. Raw material buyers should be wary of curcumin ingredients that are well below market price. They should endeavor to work only with reputable ingredient suppliers who can control their supply chain from field to packaging. It is also important to use material that has a validated Certificate of Analysis and has been verified with appropriate testing, in particular the ^{14}C dating method. Manufacturers offering quality product at a fair price have a strong and ongoing opportunity to capitalize on continued market growth as studies further support the health benefits of natural curcumin.

CURCUZEN™, THE NATURAL CURCUMIN PRODUCT FROM BIOACTIVES AMERICAN

Bioactives American, a reputed manufacturer utilizing advanced technology, is dedicated to providing high quality products at a reasonable price. Bioactives American follows the guidelines suggested in the product review of curcumin supplements (Consumerlab.com). Its branded curcumin ingredient, Curcuzen™ is a dependable, natural product without any cheap synthetic curcumin blended in. It includes no unnecessary additives or risky excipients and contains 95% curcuminoids, with the three curcuminoids drawn from the raw turmeric source.

MORE INFORMATION ABOUT CURCUZEN™:

- Curcuzen is a trademarked product of Bioactives American Corporation. Curcumin content is 95% (*HPLC method, Health Level One, Hauppauge, NY, USA*)
- It is prepared with top-to-bottom control, from extraction of the root and purification of curcumin to final packing in our facility.
- Curcuzen is natural curcumin authenticated by the radio-carbon dating method (*^{14}C as 13.91 dpm/g carbon, compared to 14.0 dpm/g carbon calculates to 99% natural; analyzed at the Center for Isotope Studies, University of Georgia, Athens, GA, USA*).
- Curcuzen is micronized into small particle size of 20 microns, in contrast to 200 microns of other products and relies on more surface area of the small particle for its absorption.
- Curcuzen is extracted with no excipients and relies on the dictum “what is naturally taken is sufficient.”

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PRODUCT SPECIFIC STUDIES

- Curcuzen preserves and enhances cellular antioxidant capacity of the body. Curcuzen™ (curcumin, 20 micrograms per ml) increased reduced form of glutathione (GSH) from 11 to 19 micromoles per mg protein in HepG2 cells (*In-house testing-unpublished data*).
- Curcuzen is superior in showing an anti-inflammatory effect than other curcumin products. Curcuze^{nTM} (curcumin, 20 mcg per ml} decreased LPS-induced production of the tumor necrosis factor alpha [TNF-α] and of nitric oxide [NO], both markers of inflammation, inhibited with IC_{50} of 5 micrograms/mg protein in HepG2 cells(*In-house testing-unpublished data*).

CURCUZEN™ IS AVAILABLE IN THREE DIFFERENT FORMS:

- Curcuzen 95% (for capsules)
- Micronized Curcuzen 95% (for soft gels)
- Granulated Curcuzen 95% (for tablets)

ABOUT BIOACTIVES AMERICAN:

Bioactives American Corporation is a science-based specialty ingredient company whose mission is to support the health and wellness industry, with a wide range of services, including contract manufacturing and specialized ingredients with proven efficacy. Bioactives American offers a full portfolio of highly specialized and standalone botanical ingredients with superior nutritional value and bioavailability.

† These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure or prevent any disease.

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