AMERICAN BOTANICAL COUNCIL

PROPRIETARY BOTANICAL INGREDIENT SCIENTIFIC and CLINICAL MONOGRAPH for

BCM-95® / CURCUGREEN™

TURMERIC RHIZOME / CURCUMIN EXTRACT PREPARATION

By Marilyn L. Barrett, PhD

Turmeric *Curcuma longa*
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Clinical Research Overview
BCM-95® / CURCUGREEN™
TURMERIC RHIZOME / CURCUMIN EXTRACT PREPARATION

Curcuma longa L. syn. *C. domestica* Valeton
[Fam. Zingiberaceae]

OVERVIEW

This Clinical Research Overview is based on the full monograph covering the published scientific and clinical research on BCM-95® (also known as Curcugreen™), a proprietary preparation made from turmeric rhizomes (underground stems, sometimes referred to as roots) formulated by Arjuna Natural Extracts Ltd. of Alwaye, Kerala, India. BCM-95 contains an extract characterized as a 95% curcuminoid complex (composed of curcumin, demethoxycurcumin, and bisdemethoxycurcumin in their natural ratios), to which turmeric essential oil is added. The final BCM-95/Curcugreen blend contains no less than 86% total curcuminoids and 65% curcumin, and the essential oil in the blend contains approximately 45% ar-turmerone.

In 2017, dietary supplements with turmeric as the primary ingredient were the top-selling supplements natural retail outlets (e.g., natural food stores) in the United States. Turmeric-containing dietary supplements also ranked 6th in sales in mainstream retail stores (e.g., drugstores, grocery stores) in 2017, with a 46.7% increase in sales in this channel from the previous year.

USES

Clinical research conducted with various curcumin preparations indicate therapeutic benefits for a multitude of inflammatory-based disorders (e.g., arthritis), wound healing, diabetes, Alzheimer's disease, cardiovascular disease, and cancer. This monograph covers only those clinical studies conducted on BCM-95, an ingredient which was developed with the goal of improving the bioavailability of curcumin. BCM-95 has been clinically evaluated for the following conditions: major depressive disorder, cognitive health, Alzheimer's disease, osteoarthritis, rheumatoid arthritis, oral submucous fibrosis, oral leukoplakia, and to mitigate adverse effects from radiation therapy in patients with prostate cancer.

PHARMACOLOGICAL ACTIONS

Pharmacological studies employing in vitro and in vivo models have found that BCM-95 has antioxidant, anti-inflammatory, antibacterial, and cytotoxic/antitumor actions. Animal studies investigating BCM-95's potential antidepressant, antiepileptic, and hepatoprotective properties have also been conducted.

DOSAGE & DURATION OF ADMINISTRATION

The following doses were used in the clinical trials reported in the table in the full monograph. [Note: Most of the doses were used in a single study.]

Major depressive disorder: 500 mg/day and 1,000 mg/day

Cognitive health: 1,500 mg/day

Alzheimer's disease: 1,000 mg/day and 4,000 mg/day

Osteoarthritis: 1,000 mg/day

Rheumatoid arthritis: 1,000 mg/day

Oral submucous fibrosis: 1,000 mg/day

Oral leukoplakia: 3,600 mg/day

Mitigation of adverse effects in patients undergoing radiation treatment for prostate cancer: 3,000 mg/day

BCM-95 has been administered daily in clinical studies for periods of six weeks to one year. The most common duration of use was 12 weeks; however, long-term use may be acceptable. Experience with the use of turmeric and/or curcumin as a traditional food or medicine does not indicate any limitation on the duration of use.

MANUFACTURER DOSE RECOMMENDATIONS

The manufacturer's website does not list a specific recommended dose of BCM-95. The most common dosage used in human clinical trials was 500 mg twice daily.

CONTRAINDICATIONS & PRECAUTIONS

There are no known contraindications for BCM-95.

The American Herbal Products Association's *Botanical Safety Handbook*, 2nd ed., lists turmeric as Class 1 (herbs that can be safely consumed when used appropriately) and Interaction Class A (herbs for which no clinically relevant interactions are expected). Mills and Bone, in their book *The Essential Guide to Herbal Safety*, list turmeric as Pregnancy Category A (no proven increase in frequency or malformation or other harmful effects on the fetus despite consumption by a large number of women) and Lactation Category C (compatible with breastfeeding). They contraindicate turmeric preparations in cases of obstruction of the biliary tract and advise to consult a health care professional if someone has gallstones. Adverse reactions associated with oral intake are listed as frequent bowel movements and mild gastric discomfort. The authors advise against combining amounts greater than 15 g turmeric powder per day with antiplatelet or anticoagulant medications.

ADVERSE EFFECTS

There is strong evidence of the overall safety of BCM-95. The US Food and Drug Administration accepted the notification of the self-determination of BCM-95 as Generally Recognized as Safe (GRAS) in a no objection letter from the U.S. FDA, dated July 11, 2017.

Clinical studies that used a dose of 500 mg twice daily for eight weeks to three months reported that BCM-95 was administered safely. In one study, BCM-95 was administered in a dose of 4 g daily for six months without significant adverse effects (AEs). The AEs in this study were considered mild; the most common were gastrointestinal complaints, followed by respiratory tract infections and falls or dizziness.

Phase I human clinical studies indicate that curcumin is not toxic even at a very high dose of 12 g per day. The reported adverse events were mild including diarrhea, headache, rash, and yellow stools. (The maximum tolerated dose could not be determined in this study because amounts more than 12 g could not be consumed comfortably.)

DRUG INTERACTIONS

Some preclinical data indicate that co-administration of curcumin with nonsteroidal anti-inflammatory drugs (NSAIDs) or anticoagulant drugs might result in an increased risk of bleeding. In a human clinical study, BCM-95 was co-administered with the NSAID diclofenac sodium without producing any significant adverse effects. However, any potential effects of the combination therapy on the risk of bleeding was not part of the evaluation. Curcumin may also interfere with drugs metabolized by the CYP enzyme system, according to data from in vitro experiments using enzymes and human cell lines. Only two clinical studies have explored the effects of standard curcumin on enzymes involved in drug metabolism, and further studies are needed to determine the clinical significance of these reports.

CLINICAL REVIEW

As of November 2017, there were a total of 10 published human clinical trials on BCM-95 as a monopreparation or as an ingredient in a combination formula. They evaluated the following: major depressive disorder (three studies), cognitive health (one study), Alzheimer's disease (one study), osteoarthritis (one study), rheumatoid arthritis (one study), oral submucous fibrosis (one study), oral leukoplakia (one study), and radiation therapy for prostate cancer (one study).

Depression

Three randomized, placebo-controlled clinical studies conducted on the effect of BCM-95 on major depression reported favorable results. A single-blind study (N = 45) indicated that BCM-95 (1 g/day) was equal to the pharmaceutical antidepressant fluoxetine (20 mg/day) as measured using HAM-D17 scores. A double-blind study (N = 52) found that BCM-95 (1 g/day) was superior to placebo for subjects with major depression (particularly for a subgroup with atypical depression) as measured using IDS-SR_{30} and STAI scores beginning after four weeks of supplementation. Another double-blind study (N = 111) explored treatment with half the usual dose of BCM-95 (0.5 g/day) and found it to be just as effective against depression (measured using IDS-SR30 and STAI scores) as the full dose.

Cognition

Two placebo-controlled studies that examined the potential benefits of BCM-95 on cognition did not show benefits. A 12-month, randomized, double-blind, placebo-controlled study (N = 96), in which elderly, cognitively healthy subjects received BCM-95 (1.5 g/day) or placebo, failed to demonstrate an effect on cognition, mood, or general quality of life. An obstacle was that the placebo group did not experience a decline in cognitive function as was expected. A second study (N = 27) conducted with patients with probable or possible Alzheimer's disease was complicated by the fact that both treatment and control groups received a standardized ginkgo (*Ginkgo biloba*, Ginkgoaceae) leaf extract, which, depending on the specific extract, has been reported to have a positive effect on cognition. The six-month study failed to show benefit from additional daily treatment with BCM-95 or another curcumin product at daily doses of 1 or 4 g.

Joint Health

Two controlled studies compared the effects of treatment with BCM-95 to standard treatment (no placebo control group) in subjects with osteoarthritis or rheumatoid arthritis. A 12-week randomized, two-arm, open-label study (N = 28) in which subjects with osteoarthritis of the knee were administered either 1 g/day Rhulief® (a combination product containing BCM-95 and an extract of boswellia [*Boswellia serrata*, Burseraceae]) or 200 mg/day celecoxib found similar benefits resulting from both treatments. A separate 8-week, randomized, two-arm, open-label study (N = 45) of patients with rheumatoid arthritis who received BCM-95 (1 g/day), diclofenac sodium (100 mg/day), or both therapies found that all three treatments were equally effective in reducing disease scores, with a significantly better safety profile for BCM-95 compared to diclofenac sodium.

Cancer Chemopreventive Effects

Oral submucous fibrosis (OSMF) is a chronic precancerous condition associated with the chewing of betel quid, which is a combination of areca palm (*Areca catechu*, Arecaceae) nuts wrapped in betel (*Piper betle*, Piperaceae) leaves with slaked lime, often in addition to tobacco (*Nicotiana tabacum*, Solanaceae) or spices. An open-label study (N = 32) explored the potential benefits of BCM-95 (1 g/day)or turmeric oil (24 drops/day) compared to a control of spirulina (*Arthrospira maxima*, Oscillatoriaceae) tablets. After three months, there was a measured improvement in clinical symptoms and in histopathology following treatment with BCM-95 and with turmeric oil compared to the control.

Oral leukoplakia is a potentially malignant white lesion of the oral cavity mucosa. A 6-month, randomized, double-blind placebo-controlled trial (N = 223) compared BCM-95 (3.6 g/day) to placebo (cellulose) in subjects with lesions more than 15 mm^2 in size. The BCM-95 group experienced a significant reduction in the size of lesion compared to the placebo group. There was no change in histopathology for either group.

Radiation therapy

A 20-week, randomized, double-blind placebo-controlled study (N = 40) examined the effects of BCM-95 (3 g/day) on patients with prostate cancer undergoing radiotherapy in combination with hormone ablation. Treatment with BCM-95 was associated with significant improvements in urinary symptoms compared to placebo, but there were no differences between groups in bowel symptoms or sexual activity. The urinary benefits correlated with increases in plasma antioxidant levels.

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By Marilyn L. Barrett, PhD

Editor's note: *Although most of the information contained in this monograph is based on research conducted directly on the proprietary BCM-95® (aka Curcugreen™) curcumin turmeric extract preparation, for the sake of background and appropriate context, a limited number of citations of traditional historical culinary and medicinal uses of turmeric rhizome, as well as limited pharmacological research on generic turmeric and curcumin preparations, have been included. In October 2018, the producer of this proprietary preparation introduced it with another trade name, Curcugreen; all studies cited in this monograph on the proprietary preparation were conducted and published when the ingredient was marketed under its primary name BCM-95. The two names refer to the identical preparation.*

INTRODUCTION/BACKGROUND

This monograph covers the preclinical and clinical studies conducted on BCM-95® (Curcugreen™), a proprietary extract of the rhizome (an underground stem sometimes referred to as root) of *Curcuma longa* L. (syn. *C. domestica* Valeton), a plant belonging to the ginger family (Zingiberaceae), native to India and Southeast Asia.[1] Turmeric rhizome is a popular food, spice, dietary supplement, and traditional medicine in many parts of the world. Turmeric rhizome powder is yellow in color and supplies the characteristic color to yellow curries.[2] Turmeric is also used to color "American mustard," mayonnaise, and margarines. Turmeric is designated by the European Food Safety Authority as an international food additive (E100).[3] In addition to supplying color, turmeric also adds flavoring to numerous condiments and foods. Besides being a common food ingredient and spice, turmeric is also used in the traditional medicines of India, China, and Arabia.[1,2,4]

Prompted by traditional medicinal use, preclinical and clinical research on turmeric, especially on its principal chemical constituent curcumin, has greatly increased in the last two decades. Preclinical studies with curcumin have found multiple biological targets and cellular effects that indicate anti-inflammatory, antioxidant, and immunomodulatory activities.[2,3,5] Curcumin has also been extensively investigated as an anticancer agent due to its documented antioxidant and anti-inflammatory activities.[4,5] Clinical studies have suggested numerous health benefits in inflammatory conditions such as rheumatoid arthritis (RA), inflammatory bowel disease, psoriasis, and others.[2,3]

The list of potential health benefits of curcumin is growing. Researchers are also looking into ways to improve the bioavailability of curcumin, since it has been established that curcuminoids are not easily absorbed by the human gut.[6] Accordingly, BCM-95, the proprietary turmeric/curcumin preparation that is the topic of this monograph, was formulated to enhance absorption.

Due to continued reports of their health benefits, turmeric and turmeric-based dietary supplements have become increasingly popular in the United States and other industrialized nations in recent years. Retail sales of turmeric-based dietary supplements (containing powdered turmeric rhizome and/or more concentrated turmeric extracts standardized to curcumin content) in the United States increased every year from 2012 to 2017.[7-10c] In 2012, turmeric and curcumin-based dietary supplements ranked third in the natural food store channel, with approximately US $17 million in sales, a 40% increase from the previous year.[7] In 2013, turmeric supplements rose to the rank of the top-selling single herbal dietary supplement, with total sales increasing by more than 26% to over $21 million (not including sales in Whole Foods Markets)[8]; sales increased 31% in 2014 in this channel, to over $26 million.[9] In 2015, natural channel sales of turmeric totaled more than $37 million, a 32% increase from the previous year,[10] and in 2016, turmeric sales increased by 32%, totaling more than $47 million.[10b] Natural channel sales of turmeric totaled more than $50 million in 2017, a 12% increase from the previous year.[10c] In contrast, turmeric did not rank in the top 40 single herb supplements in the mass market channel (grocery stores, drug stores, and mass-market retailers, exclusive of Walmart) in 2012.[7] However, in 2013, turmeric rose to the rank of 30th single herb supplement in this market,[8] with a 60% sales increase to a ranking of 26th in 2014,[9] rising to a ranking of 19th in 2015.[10] In 2016, mainstream sales of turmeric increased by 85%, making it the 10th top-selling herbal supplement ingredient in this channel.[10b] Turmeric ranked ninth in mainstream multi-outlet sales in 2017 with a 47% increase in sales from the previous year.[10c]

In summary, this monograph provides a description of the chemical composition of BCM-95 and the scientific and clinical support for its potential uses. Studies on the bioavailability of curcumin that have been conducted in rats, dogs, and humans are detailed below. Pharmacological studies demonstrating antioxidant and anti-inflammatory activities have been conducted in vitro and in several animal studies (e.g., with rats, cats, and racehorses). The potential for antitumor benefits has been explored in cell culture and rodent studies. Both rodent studies and human clinical trials indicate

Table 1. Abbreviations & Symbols Used in this Monograph

Abbreviation/Symbol	Full Name
<	less than
Δ	delta (change)
AUC	area under the curve
C	Celsius
cm	centimeter
COX-2	cyclooxygenase-2
CYP	cytochrome P450
g	gram
h	hour
HPLC	high-performance liquid chromatography
ICH	International Council on Harmonisation
IFN-γ	interferon-gamma
IL	interleukin
kg	kilogram
L	liter
m	meter
M	molar (concentration)
µM	micromolar
µmol	micromole
mA	milliampere
MDD	major depressive disorder
mg	milligram
mL	milliliter
MLD	minimum lethal dose
mm	millimeter
MS/MS	tandem mass spectrometry
MTD	maximum tolerated dose
NAT2	N-acetyltransferase 2
NF-κB	nuclear factor-kappa B
ng	nanogram
nm	nanometer
nmol/L	nanomoles per liter
NSAIDs	nonsteroidal anti-inflammatory drugs
OA	osteoarthritis
OECD	Organisation for Economic Co-operation and Development
ORAC	oxygen radical absorbance capacity
P-gp	P-glycoprotein
pg	picogram
pH	measurement unit of the alkalinity or acidity of a solution
PPAR-γ	peroxisome proliferator-activated receptor gamma
RA	rheumatoid arthritis
TE	Trolox equivalent
THC	tetrahydrocurcumin (not to be confused with THC referring to delta-9-tetrahydrocannabinol, a psychoactive substance in cannabis [Cannabis sativa, Cannabaceae])
TNF-α	tumor necrosis factor-alpha
UV	ultraviolet
VAS	visual analog scale
XO	xanthine oxidase

a potential antidepressant action. Two clinical studies failed to find a definite benefit in cognition for elderly subjects or those with possible Alzheimer's disease. BCM-95 was reported in two studies to have a positive effect on joint health (osteoarthritis [OA] and RA). A rodent study indicates a protective effect against toxin-induced liver injury. This protective effect was duplicated in human clinical trials in which participants had been exposed to toxicities due to chewing betel (areca palm; *Areca catechu*, Arecaceae) quid preparations and to radiation therapy. The potential for a clinical cancer chemopreventative effect was observed in two different precancerous conditions. The safety of BCM-95 has been confirmed in acute, sub-acute, and chronic toxicity studies. Safe use has also been reported in human clinical studies, which are detailed below.

DESCRIPTION OF BCM-95 (CURCUGREEN)

BCM-95 (Curcugreen), originally named Biocurcumax™ (hence, the acronym "BCM"), is a unique preparation of standardized curcuminoids that is blended with the essential oil of turmeric. BCM-95 is formulated by Arjuna Natural Extracts Ltd. of Alwaye, Kerala, India (see Patents section below).

BCM-95 is prepared from turmeric rhizomes, using a proprietary standardized process. The turmeric is grown without herbicides or pesticides in the traditional manner in Assam, a remote area of northeast India. The rhizomes are dried in sunlight, powdered, and treated with a food-grade extraction solvent* (ethyl acetate and ethanol) to concentrate the curcuminoids. Following extraction, the solvent is removed according to procedures and standards set by the *United States Pharmacopeia* (USP).† The raw material and finished goods are analyzed for any level of contamination with class 1, 2a, and 2b solvents, even though none of these is used in the extraction process. The resultant concentrate is cooled, resulting in the formation of crystals of curcuminoids. The volatile oil (essential oil) of turmeric is isolated from dried turmeric rhizomes by steam distillation. The curcuminoids and the volatile oil are blended together into a slurry using filtered and distilled water. The water is removed under low heat and high vacuum to form a uniform blend. The final herb-to-extract ratio is 25:1. The powder

has an orange-red color. The shelf-life of the extract is 36 months when stored in a cool and dry environment. Stability studies conducted at 30°C and 65% humidity for 36 months according to ICH (International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use) guidelines Q1A(R2)[11] did not show any deterioration of physical, chemical, or microbial parameters.‡

BCM-95 contains a 95% curcuminoid complex composed of curcumin, demethoxycurcumin, and bisdemethoxycurcumin, in their natural ratios, along with turmeric essential oil. After the addition of the essential oil, BCM-95 contains no less than 86% total curcuminoids and 65% curcumin. The essential oil contains approximately 45% ar-turmerone.

USE

In the last decade, preclinical studies conducted on various generic and proprietary curcumin preparations (including BCM-95 and other preparations) have reported that curcumin acts on multiple biological targets and has cellular effects that suggest anti-inflammatory, antioxidant, and immunomodulatory activities.[2,3,5] Numerous reviews in the past several years have detailed the potential mechanisms by which curcumin and curcuminoid mixtures might benefit human health. Researchers have examined potential health benefits related to oral hygiene[12] and oral cancer,[13] eye health,[14] vascular health,[15,16] metabolic syndrome,[17] diabetes,[18] inflammatory bowel disease,[19] ulcerative colitis,[20] neurodegenerative diseases such as Alzheimer's disease,[21] and depression.[22] In addition, the results of preliminary clinical studies of curcumin or curcuminoid formulations as adjunct treatments for certain cancers are promising.[4,23]

DOSAGE AND DURATION OF ADMINISTRATION

Various curcumin preparations have been shown to be well-tolerated in humans at doses of up to 12 g per day.[3,24] The dose of BCM-95 used in three clinical studies was 500 mg twice daily for a total of 1 g per day.[25-28] Other clinical studies with BCM-95 used daily doses up to 4 g.[29-34]

BCM-95 is available in softgel capsules supplying either 250 mg or 500 mg curcuminoids. BCM-95 is also available in preparations in which it is combined with other ingredients (Table 2).

There are no data that suggest a limitation on the duration of use for turmeric or its primary constituent curcumin in varying amounts, based on use of turmeric as a traditional food and medicine. BCM-95 has been administered daily in clinical studies for periods of eight weeks to six months without any serious adverse events (see Human Clinical Trials and Safety sections below).

CHEMISTRY

Turmeric chemical constituents

Curcuminoids are naturally present in the rhizomes (underground stems) of turmeric. Turmeric rhizomes are used as a spice in Indian cooking, being one of the principal ingredients in curry powder. Turmeric is known for its bright yellow color, imparting that color to curries and American-style prepared mustard. The chemical constituents responsible for that color are curcuminoids, present in 3-5% of the rhizome.[35] The turmeric rhizome also contains starch (45-55%, including the arabinogalactan ukonane A), essential oil (2.5-6%, with ar-turmerone as the main component), and small amounts of sugars, protein, vitamins (mostly vitamin C), and a resin.[36]

Curcumin

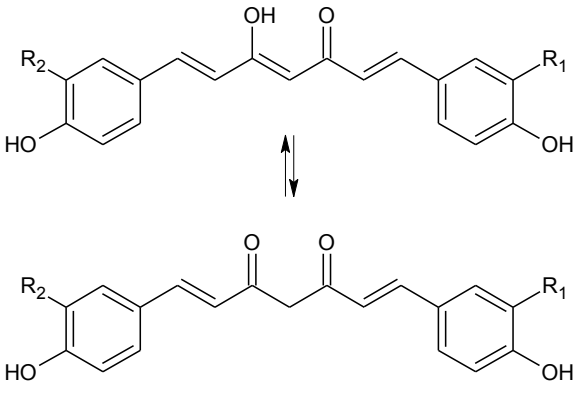
The term *curcumin* can be confusing because it can be used to describe a single compound or a family of compounds known as curcuminoids, of which the single compound curcumin is the most abundant. Curcumin is present at approximately 77% of the curcuminoid mixture. Curcumin is chemically known as a bis-alpha-beta-unsaturated beta-diketone [(1*E*,6*E*)-1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione], a linear diarylheptanoid compound with two oxy-substituted aryl moieties linked together through a seven-carbon chain. The second and third most abundant curcuminoid analogs are demethoxycurcumin at roughly 17% of the total, and bisdemethoxycurcumin, which is present at about 3%.[3] The chemical structures of key curcuminoids are shown in Figure 1.

Curcuminoids

When possible, the terms *curcumin* and *curcuminoid mixture* are used in this publication to differentiate the pure compound from the mixture. However, due to the ambiguity of the use of the terms in the literature, this distinction is not always clear.

Pure curcumin (supplied by Sigma-Aldrich Co. LLC; St. Louis, Missouri) is insoluble in water and ether, but is soluble in ethanol, methanol, dimethyl sulfoxide (DMSO), and acetone. Experiments into the degradation of curcumin revealed that, when placed in a phosphate buffer (0.1 M, pH 7.2 at 37°C), it decomposed by approximately 90% within

Figure 1. Chemical Structures of Curcuminoids



Curcumin: R1 = R2 = OCH3
Demethoxycurcumin: R1 = H, R2 = OCH3
Bisdemethoxycurcumin: R1 = R2 = H

30 minutes. Curcumin was found to be much more stable in human blood, in which less than 20% decomposed after one hour, and roughly 50% decomposed after eight hours. The major (nonenzymatic) degradation product of curcumin is a bicyclopentadione derivative, trans-6-(4'-hydroxy-3'-methoxyphenyl)-2,4-dioxo-5-hexenal.[37,38] Minor degradation products have been identified as vanillin, ferulic acid, and feruloyl methane.

In humans, curcumin is metabolized to glucuronide and sulfate conjugates, which can be measured in plasma samples.[39] Reduction of curcumin to dihydrocurcumin and ultimately to tetrahydrocurcumin (THC; not to be confused with the "THC" that refers to tetrahydrocannabinol, found in *Cannabis sativa*, Cannabaceae) by microorganisms in the human gut also has been reported.[40]

Essential Oil

Essential oil is present in turmeric rhizomes at 2-7%.[41] The concentration of ar-turmerone depends on the turmeric cultivar. Analysis of an oil obtained from Kancor Ingredients Ltd. (Angamaly, Kerala, India) revealed it was composed of ar-turmerone (62%), curlone (12%), and ar-curcumene (6%), in addition to other monoterpenes and sesquiterpenes.[41] Another study reported that alpha- and ar-turmerones were present in turmeric rhizome in yields of 0.03% and 0.027% (by weight), respectively.[42] [Note: As noted above in the Description section, while there is no essential oil in the curcuminoid fraction of turmeric rhizome, and thus no essential oil in most turmeric extracts standardized to a relatively high level of curcuminoids, the BCM-95 extract is blended with turmeric essential oil specifically to enhance absorption and to provide the separate and claimed synergistic activity of the ar-turmerone in the essential oil, according to the US marketer of BCM-95 (C. Myers [EuroPharma] personal communication to M. Blumenthal, February 16, 2016).]

PHARMACOKINETICS

Pharmacokinetic (PK) studies are presented below. Those conducted with generic curcumin preparations are presented first, followed by studies conducted with BCM-95.

Curcumin

Initial experiments conducted with rats on the uptake distribution and excretion of curcumin indicated that the compound was poorly absorbed. Curcumin administered orally to Sprague Dawley® rats at 1 g/kg resulted in 75% being excreted in the feces and only negligible amounts excreted in the urine. Metabolites of curcumin were identified in studies in which the test material was administered intravenously or intraperitoneally. The major metabolites, observed in bile, were glucuronides of THC and hexahydrocurcumin (HHC), while a lesser metabolite was dihydroferulic acid, followed by traces of ferulic acid. Experiments with mice found the major metabolites to be curcumin-glucuronide, dihydrocurcumin-glucuronide, THC-glucuronide, and THC. In another study, rat liver tissue contained the metabolites THC, HHC, and octahydrocurcumin (OHC). These studies have been reviewed by Goel and colleagues.[2]

PK studies in humans showed a similar low degree of absorption following oral administration. A study in which 2 g curcumin powder (four capsules of 500 mg each; Sami Chemicals and Extracts; Bangalore, India) was given to 10 healthy male volunteers found that serum levels of curcumin were either very low or undetectable with a C_{max} of 6 ± 5 ng/mL at one hour. The mean $AUC_{(0\text{-}tn)}$, which was calculated using a trapezoidal method, was found to be 4 ng/h/mL.[43]

In another PK study with men and women with various cancers (N = 25; median age: 60 years; range: 36-77 years), curcumin was observed in the plasma of those who consumed oral doses of 4, 6, and 8 g, but not in the plasma of those who consumed lower doses of 0.5 or 2 g. (The test material was 99.3% curcumin [diferuloylmethane], provided by Yung-Shin Pharmaceutical Co.; Taichung, Taiwan.) The presence of curcumin in plasma peaked between 1.5 and 2 hours and gradually declined over 12 hours. The C_{max} increased along with the dose of curcumin, from 0.51 ± 0.11 µM following the 4-g dose to 1.77 ± 1.87 µM following the 8-g dose. The $AUC_{(0\text{-}24h)}$, which was calculated using the linear trapezoidal technique, was also enhanced with the increase in dose, from 2.55 ± 1.76 nmol/h/mL following administration of 4 g to 13.74 ± 5.63 nmol/h/mL following 8 g. A repetition of this protocol with two patients who had been taking curcumin for more than a month resulted in similar results, indicating that repeat dosing did not change the absorption profile.[44]

A dose-escalation study examined the pharmacokinetics of curcuminoids using 500-mg capsules containing 450 mg curcumin, 40 mg demethoxycurcumin, and 10 mg bisdemethoxycurcumin (Curcumin C3 Complex® provided by Sabinsa Corporation; East Windsor, New Jersey).[45] The study included 15 patients (men and women, ages 50-74) with advanced colorectal cancer who were administered doses of 0.45 g to 3.6 g curcumin (one to eight capsules) daily for up to four months. The levels of curcuminoids were determined in plasma, urine, and feces. Metabolic conjugates of curcuminoids were analyzed by incubating the samples with glucuronidase and sulfatase enzymes, which removed the glucuronide and sulfate groups from the curcuminoids revealing the native compounds. The study found that curcumin was not detected in the plasma of patients that received doses lower than 3.6 g curcuminoids. Following ingestion of a single dose of 3.6 g curcuminoids, unconjugated curcumin was detected in plasma samples of half of the patients. In those patients, curcuminoids were measured in serum samples taken 30 minutes and one hour after consumption, with a mean concentration of 11.1 ± 0.6 nmol/L. When the plasma samples were subjected to enzymatic treatment, curcuminoids were found in measurable amounts in all patients who took the 3.6-g dose. The mean amounts of curcumin sulfate and curcumin glucuronide in pooled plasma samples were 8.9 ± 0.7 nmol/L and 15.8 ± 0.9 nmol/L, respectively. There were no obvious differences in the levels of the conjugates in patients for which the parent curcumin was detected, compared to those for which it was not detected.

BCM-95 (Curcugreen)

A series of experiments have been conducted exploring the bioavailability of BCM-95 comparing it to that of standard curcumin. These studies are described in the following sections.

Ex vivo Pharmacokinetics

The bioavailability of isolated curcumin, curcumin in turmeric powder, and curcumin in BCM-95 were compared in water and traditional food-based vehicles using a non-everted rat intestinal sac model.[46] As an initial step, the solubility of curcumin and BCM-95 in solutions of water, clarified butter (called *ghee* in traditional Ayurvedic medicine in India), and corn (*Zea mays*, Poaceae) oil were compared. BCM-95 was significantly more soluble in water than curcumin (5.4 times, $P < 0.005$). Both curcumin and BCM-95 were more soluble in clarified butter and corn oil compared to water, without any significant differences between them.

The degree of permeability of curcumin through the intestine was in agreement with the solubility findings. Maximum permeability was obtained from the addition of corn oil (13.4%), followed by clarified butter (9.82%), milk (4.24%), and the least was with water (1.66%). The permeability of the curcumin present in turmeric powder and in BCM-95 was significantly greater than the permeability of curcumin alone. There were no significant differences in total permeability between curcumin in turmeric and BCM-95. The authors of the study stated that this result suggested the presence of volatile oil components in both turmeric powder and in BCM-95 was responsible for the enhanced permeability. The rate of permeability (flux) through the membrane was greater for curcumin in turmeric powder compared to curcumin in BCM-95 ($P < 0.05$). Because of this finding, the authors suggested that there may be components such as sugars in turmeric powder, in addition to the essential oil, that assist with the speed of the flow through the membrane.

Animal Pharmacokinetics

Rats

Feeding experiments conducted with rats explored the effect of the addition of the essential oil on the absorption of curcuminoids. Curcuminoids with and without the essential oil were administered orally to the animals in their food in doses of 0.5, 1.5, and 3.0 mg/kg body weight. Animals administered their normal diet were included as controls. The study used albino rats (male and female; 100 to 120 g body weight), divided into seven groups with six animals per group. After 24 hours, the fecal matter from the animals was collected, dried, and weighed. The presence and quantity of curcumin in the fecal matter was detected using a spectrophotometric method from the *Food Chemicals Codex* (FCC). The percentage of absorbed curcumin was determined as the amount fed minus the amount in fecal matter. The amount of standard curcumin that was absorbed was approximately 58%, regardless of the dose. The amount of curcumin absorbed from the curcumin/essential oil mixture was approximately 96%. In summary, this study showed that mixing curcumin with the essential oil from turmeric enhanced the absorption and thus the bioavailability of curcumin.[47]

Dogs

The oral bioavailability of BCM-95 (designated as NMXCC-95) in dogs[§] was assessed using a crossover study design with a one-week washout between tests. The study included six healthy male and female adult dogs (12-15 kg body weight; three to four years old). The animals were divided into two groups of three dogs each and administered BCM-95 or curcuminoids (2 g) following a 12-hour fast. Blood samples were taken before administration (time 0) and at 1, 2, 3, 4, 5, 6, and 8 hours post-dose. Plasma samples were weighed, extracted with ethyl acetate, evaporated, then reconstituted in methanol and analyzed by high-performance liquid chromatography (HPLC) with detection at 420 nm. The resulting C_{max} was significantly (3x) greater with BCM-95; approximately 300 ng/g compared to 99 ng/g for curcumin ($P < 0.5$).** The $AUC_{(0\text{-}8h)}$ also was significantly greater, roughly 1400 ng/h/g compared to 200 ng/h/g. The

Turmeric *Curcuma longa*
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bioavailability of BCM-95 was thus approximately seven times greater than curcumin when measured as AUC.[48]

Human Pharmacokinetics

A pilot PK study was conducted with 15 healthy human volunteers, men and women ages 25 to 45, divided into two groups: curcumin (n = 8) and BCM-95 (n = 7).[49] The subjects were instructed to avoid turmeric-containing foods 24 hours before and during the study. Curcumin (Sigma-Aldrich Co. LLC) and BCM-95 were each administered in a single dose of eight 500-mg capsules, each containing 450 mg total curcuminoids, taken with a glass of water. Blood samples (5 mL each) were taken before (zero hour) and 1, 2, 3, 4, 6, 8, 10, and 12 hours post-dose. The blood samples were extracted with ethyl acetate, concentrated, dissolved in the methanol, and analyzed for the presence of curcuminoids using an HPLC system (column: C18, solvent: isocratic methanol, detection: UV 420 nm). Curcumin was observed in the plasma samples of volunteers after consumption of the Sigma preparation, with a peak plasma concentration of approximately 300 ng/g, a C_{max} at four hours post-dose, and complete elimination by six hours post-dose. BCM-95 produced a peak concentration of 1600 ng/g, a C_{max} in plasma samples at five hours, and a return to baseline after eight hours. The authors of the study calculated that the bioavailability of curcumin was improved five- to sevenfold with BCM-95; presumably this comparison came from measurements of the AUC.

Another PK study compared the profiles of curcumin (Sigma-Aldrich Co. LLC) to BCM-95 and a mixture of curcumin with lecithin and piperine†† (Life Extension; Fort Lauderdale, Florida).[50] The crossover study included 11 healthy adult subjects aged 28-50 years, who refrained from taking aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs) and all foods containing turmeric for two days prior to the study. After an overnight fast, group 1 (n = 4) received four 500-mg capsules of BCM-95 (2 g), group 2 (n = 4) received the same amount of curcumin, and group 3 (n = 3) received the curcumin-lecithin-piperine formula. Blood was drawn immediately prior to dosing and hourly up to six hours and then eight hours post-dose. After a washout period of two weeks, the subjects repeated the protocol taking a different test agent. Group 1 took the standard curcumin and groups 2 and 3 took the BCM-95 product. Blood was tested for the presence of curcuminoids following extraction by ethyl acetate and analyzed via HPLC-UV (column: C18, solvent: isocratic methanol, detection: 420 nm). Peaks were assigned in comparison with a standard reference curcumin preparation from Sigma. Absorption of curcumin from BCM-95 was faster than from standard curcumin, peaking at one hour to give a mean of 316 ng/g, dropping at the second hour to 275 ng/g, and then reaching its highest level of 457 ng/g at 4.5 hours post-dose. Thereafter, plasma levels declined but were still measurable eight hours post-dose. In contrast, standard curcumin produced a peak plasma concentration of approximately 150 ng/g at two hours post-dose and was eliminated by 4.5 hours post-dose. The half-life for BCM-95 was approximately five hours compared to 2.5 hours for standard curcumin. The $AUC_{(0\text{-infinity})}$ was approximately seven times greater for BCM-95 (3200 ng/g/h vs. 460 ng/g/h). In summary, the absorption of BCM-95 was more rapid and resulted in higher plasma levels for a longer period of time compared to standard curcumin.

The mean plasma concentration of curcumin from the curcumin-lecithin-piperine mixture reached a peak plasma level of 344 ng/g at 3.5 hours post-dose. The comparative values for BCM-95 were a peak plasma level of 689 ng/g at 4.7 hours post-dose. The elimination rate constant for curcumin-lecithin-piperine was 0.34/h compared to 0.14/h for BCM-95. The $AUC_{(0\text{-infinity})}$ for BCM-95 was six times higher than that for the curcumin-lecithin-piperine mixture (3975 ng/g/h vs. 624 ng/g/h). Thus, the bioavailability measurements for BCM-95 were also greater than that for the curcumin-lecithin-piperine mixture. The above paper gave separate comparisons for BCM-95 vs. standard curcumin and BCM-95 vs. the curcumin-lecithin-piperine complex, but lacked a direct comparison between standard curcumin and the curcumin-lecithin-piperine complex. The difference between the peak plasma levels of BCM-95 in the two studies (689 ng/g vs. 457 ng/g) suggests differences in the extent of the absorption of BCM-95 or in analyzing of the samples.

A randomized, double-blind, crossover study with 12 healthy volunteers (11 men and one woman) compared the absorption of curcuminoids from four different preparations.[51] Absorption from BCM-95 was compared to a phytosome formulation (CP); a combination product containing a hydrophilic carrier, cellulose derivatives, and natural antioxidants (CHC); and standard curcumin (CS). Subjects consumed six optically identical hard gel capsules of each of the products. According to the paper, the amounts of each product were calculated to provide 376 mg of total curcuminoids, with the exception of CS, which provided 1,800 mg total curcuminoids. The exact amounts of each product given in the study and the means of calculating the 376 mg and 1,800 mg were not provided. Each volunteer completed four trials, with blood being collected over 12 hours following intake of each product. The blood samples were centrifuged and frozen before analysis. Before analysis, the samples were treated with a mixture of beta-glucuronidase and sulfatase to hydrolyze the metabolic conjugates to their aglycone forms. The samples were analyzed using HPLC/MS/MS and compared to an internal standard "salbutamol." Results were obtained individually for curcumin, demethoxycurcumin, bisdemethoxycurcumin, and the metabolite THC. The absorption of total curcuminoids from BCM-95 was only slightly higher than CS (relative absorption 1.3). The relative absorption for CP was 7.9-fold higher than CS, and CHC was 45.9-fold higher than CS. The difference in results for BCM-95 is likely due to differences in methodologies. This method included a hydrolysis step in order to measure both free and conjugated forms in the blood. There is also some ambiguity as to the exact amounts of product administered in the study. Also, there were some differences in the curcuminoid profiles of the products, which were not discussed.

PHARMACOLOGICAL ACTIONS/ MECHANISM OF ACTION

A brief background on activities reported for curcumin and turmeric essential oil is provided as an introduction for pharmacological studies conducted on BCM-95. The pharmacological properties reported for standard curcumin, which include antioxidant, anti-inflammatory, antibacterial, and anticancer activities, have been recently reviewed.[1,3] In vitro reports of enhanced peroxisome proliferator-activated receptor gamma (PPAR-γ) expression along with modulation of nitric oxide synthase (NOS) and glutathione are indicative of antioxidant activity. The anti-inflammatory mechanisms identified for curcumin include reduction of nuclear factor-kappa B (NF-κB) activation, cyclooxygenase-2 (COX-2) expression, as well as pro-inflammatory cytokines interleukin (IL)-1, IL-6, and tumor necrosis factor-alpha (TNF-α) production. Interactions (inhibition, inhibition of protein expression, or other types of activities) with the above targets have shown to provide clinically measurable benefits. These targets translate into clinical improvements in RA, psoriasis, and other inflammatory states.[4] There is strong evidence from preclinical studies that curcumin has antitumor actions, including pro-apoptotic and anti-angiogenic effects, as well as modulation of the cell cycle, growth factor expression, and signal transduction pathways.[4,23] Another area of promising preliminary research is the use of curcumin to treat age-related cognitive impairment and Alzheimer's disease.[21,52,53]

Activity-guided fractionation of a turmeric extract revealed anti-inflammatory activity due to the essential oil of turmeric as well as the curcuminoids. Both components of turmeric inhibited production of the inflammatory mediator prostaglandin E_2 in cultured cells exposed to lipopolysaccharide, but only the curcuminoids inhibited expression of the COX-2 enzyme.[54] Further studies on the essential oil found that it had antioxidant and anti-inflammatory activities when administered orally to mice at a dose of 100 mg/kg body weight.[41] Calculations based upon body surface area suggest that a similar amount of oil might be administered following consumption of about 8 g of turmeric by a 60-kg human.[55] This is a relatively large dose. However, the data suggest that turmeric essential oil might contribute to the pharmacological effects of turmeric, in addition to enhancing the bioavailability of the curcuminoids.

Turmeric *Curcuma longa*
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BCM-95 (Curcugreen)

Antioxidant/Anti-inflammatory Activities

ORAC assay

The ORAC (oxygen radical absorbance capacity) assay provides a measure of the scavenging capacity of antioxidants against the peroxyl radical, one of the most common reactive oxygen species in the human body. The activity is measured against Trolox, a water-soluble vitamin E analog, which serves as a calibration standard. Results of the ORAC assay are reported as micromole (µmol) Trolox equivalent (TE) per gram. Two lots of BCM-95 were tested in the ORAC assays and reported to have a total of 13,115[56] and 15,504[57] µmol TE/g. The water-soluble fraction of the two lots displayed antioxidant capacities of 7,613[56] and 12,617[57] µmol TE/g, which was calculated to be 58% and 81% of the total activity. The remainder of the activity was due to lipid-soluble compo-

nents. In essence, BCM-95 exhibited significant antioxidant activity in this in vitro assay.

Anti-inflammatory

BCM-95 has demonstrated anti-inflammatory activity in animal models using the carrageenan rat paw assay and obesity-associated low-grade inflammation in a study of obese cats.[58,59] BCM-95, as part of a multi-ingredient supplement, reduced exercise-induced increases in inflammatory markers in racehorses.[60]

Rats

The anti-inflammatory effects of BCM-95, compared to a "regular turmeric extract" (an ethyl acetate extract containing 95% curcuminoids as determined using spectrophotometry) and diclofenac sodium (an NSAID), were assessed using the carrageenan rat paw model.[58] Wistar albino rats (sex not given) were divided into 17 groups of six animals each. Vehicle control, BCM-95, turmeric extract (each individually at 10, 20, 40, 60, 80, 150, and 200 mg/kg), or diclofenac sodium (5 and 10 mg/kg) were orally administered to the animals. Thirty minutes after administration of the test agents, carrageenan (0.1 mL of 1% suspension) was injected into the animals' hind paw. The paw volumes were measured before dosing, three hours, and six hours after administration of the carrageenan using a digital plethysmometer. The percent inhibition of paw volume compared to control was calculated for each test agent. As expected, the diclofenac control significantly inhibited the swelling of the rat paws at both doses. The regular turmeric extract did not significantly inhibit swelling at any of the doses tested. BCM-95 appeared to have a bell-shaped response curve, with significant effects with doses of 20, 40, and 60 mg/kg. There was no significant effect with the lower dose of 10 mg/kg or the higher doses of 80, 150, and 200 mg/kg. The authors of the study concluded that the addition of the essential oil to the curcumin extract, as formulated in BCM-95, substantially increased the anti-inflammatory effect in this model. The effective doses of BCM-95 were as effective as diclofenac sodium in reducing the swelling of the rat paws.

Cats

The effect of BCM-95 on obesity-associated low-grade inflammation was examined in obese cats using an eight-week crossover study design with a four-week washout period between treatments.[59] European domestic shorthair neutered cats (N = 8; 3 males, 5 females) classified as obese were divided into two groups. Their diets were supplemented with BCM-95 or citrus polyphenols. BCM-95 was given as 0.09% of the diet. The citrus polyphenols, hesperidin (Natural Orange Extract; Exquim SA; Barcelona, Spain) and naringin (Citroflavonoids Soluble; Exquim SA), were given together at a concentration of 0.05% and 0.1% of the diet, respectively. The levels of the polyphenols in the cats' diet were intended to reflect levels of polyphenols recommended for human consumption. At baseline and at the end of the treatment period, blood was collected from the animals. The concentrations of plasma acute-phase proteins amyloid A, haptoglobin, and alpha-1-acid glycoprotein were determined. In addition, peripheral blood mononuclear cells (PBMCs) were isolated from the blood samples and the levels of cytokine messenger RNA (mRNA) expression were determined. The addition of BCM-95 to the diet caused a significant decrease in the level of haptoglobin in blood compared to baseline ($P < 0.02$), but had no significant effect on the other acute-phase proteins. The citrus polyphenols caused significant decreases in both haptoglobin and alpha-1-acid glycoprotein, but had no effect on amyloid A. Of the panel of 10 cytokine mRNA levels analyzed, only IL-2 mRNA levels were decreased by BCM-95, and interferon-gamma (IFN-γ) mRNA levels were reduced by the citrus flavonoids, both in comparison to baseline levels. The authors suggested that a greater effect on PBMC cytokine levels might be observed with a higher dose of BCM-95. This study indicated that BCM-95, at low levels in the diet, might reduce levels of acute-phase plasma proteins, which are associated with chronic inflammation sometimes related to obesity.

Horses

A controlled, parallel-group, randomized study with thoroughbred racehorses measured the effect of training with and without a multi-ingredient supplement on inflammatory markers in the blood.[60] The study included 25 thoroughbred racehorses (18-21 months old) monitored over an eight-week training period on a grass track. Half of the animals received a supplement twice daily with meals. The supplement (Double Diamond®; Equine Nutriceuticals, LLC; Franklin Lakes, New Jersey) contained 1.6 g curcumin (BCM-95), 1.6 g boswellia (*Boswellia serrata*, Burseraceae) extract (BosPure®; 75% boswellic acids and 10% 3-*O*-acetyl-11-keto-β-boswellic acid; DolCas Biotech, LLC; Landing, New Jersey), 400 mg coenzyme Q10 (Hydro Q Sorb®; Tishcon Corp.; Westbury, New York), 4 g GlycoCarn® glycine propionyl-L-carnitine HCl (Sigma-Tau HealthScience USA, Inc.; Gaithersburg, Maryland), and 10 g D-ribose. The study included four tests of increasing exercise intensity (from 8.0 to 14 m/second) over the 10-week testing period. Peripheral blood samples were collected before each exercise test, as well as immediately afterwards and two hours afterwards. The samples were analyzed for the presence of lactic acid, oxidative stress (lipid peroxidation measured via malondialdehyde), and inflammatory cytokine gene expression (IL-1, IL-6, TNF-α, IFN-γ, and granzyme B). There was a positive correlation between the intensity of the exercise and the levels of lactate, malondialdehyde, and pro-inflammatory cytokine gene expression. The supplement group showed a decrease in PBMC gene expression for cytokine IL-1β levels over time, reaching significance in the fourth test. This effect was observed in blood samples taken before, immediately after, and two hours after the exercise. No change was observed in the control group. There were no significant differences in the other variables measured. The authors concluded that the supplement enhanced adaptation to exercise by reducing the expression of the gene for the pro-inflammatory cytokine IL-1β.

Cytotoxicity and Antitumor Effects

A series of in vitro and in vivo studies by one research group documents the potential use of BCM-95 in the prevention and treatment of colon cancer.[61-65] Another group of researchers used a mouse model to evaluate the effectiveness of curcumin (BCM-95) to prevent the progression of cancer caused by a chemical agent.[66]

A series of in vitro 2D and 3D models were used to examine the effects of BCM-95 and/or 5-fluorouracil (5-FU) on the malignancy of colorectal cancer cells. 5-FU is widely used as a chemotherapeutic agent for the treatment of many types of cancers. It has a chemical structure similar to the nucleotides uracil and thymine, and acts by inhibiting cellular proliferation and inducing apoptosis. However, high rates of metastasis and recurrence of colorectal cancer is common, primarily thought to be the result of a progressive resistance to the drug. Boosting the effectiveness of 5-FU is important as it has been estimated that more than 15% of patients with colorectal cancer are resistant to the drug.[61]

One paper examined the ability of curcumin to enhance the effectiveness of 5-FU in an in vitro model of colorectal cancer.[61] In vitro experiments were conducted with cancerous colorectal cell lines with and without resistance to 5-FU. The studies reported that pretreatment of cancer cells with BCM-95 curcumin (0-20 µM) significantly ($P < 0.05$) enhanced the effectiveness of 5-FU (0-20 µM). The combination of curcumin plus 5-FU increased disintegration of cancerous colonies, enhanced cell death (apoptosis), and inhibited cell growth. The effects of curcumin in enhancing chemosensitivity to 5-FU were further supported by its ability to effectively suppress development of cancer stem cells. Cancer stem cells are a subset of cells that exhibit the stem cell characteristics of self-renewal and pluripotency (capable of differentiating into one of many cell types). Cancer stem cells are thought to be involved in the spread of cancer by forming distant metastasis.

Another paper explored the effects of BCM-95 and 5-FU on the interactions between tumor cells and stromal fibroblasts in an in vitro co-culture model.[62] Stromal fibroblasts play a dynamic role in initiating and enhancing carcinogenesis through upregulation of several chemical mediators. The studies showed that mediator "crosstalk" was increased in the presence of 5-FU (0-10 µM), but dramatically decreased in the presence of curcumin (0-10 µM), inducing biochemical changes that sensitized cancer stem cells to 5-FU treatment. The authors suggested that modulation of this synergistic crosstalk by curcumin might suppress metastasis.

Another experiment used a sophisticated 3D in vitro culture model (an alginate-based 3D scaffold) that mimicked the tumor microenvironment in vivo.[63] In this model, the colon cancer cells encapsulated in alginate proliferated in 3D-colonospheres. During cultivation of cells in alginate, 3 stages of cells were observed: proliferating, invasive, and adherent cells. Tumor-promoting factors were significantly increased in the proliferating and invasive cells compared to the adherent cells.

Studies conducted with this model revealed that the addition of BCM-95 (dose given as 5 µM curcumin) enhanced the ability of 5-FU to decrease proliferation and invasion. The studies indicated that these actions occurred through the transcription factor, NF-κB. NF-κB plays an important role in cell survival, proliferation, invasion, angiogenesis, metastasis, and chemoresistance. NF-κB is constituently activated in human colorectal cancer cells and is associated with disease progression. It is theorized that agents that suppress NF-κB activation might reduce chemoresistance and thus improve clinical outcomes for colorectal cancer. In these experiments, curcumin caused a downregulation of NF-κB activation and NF-κB-regulated gene products.

Chemosensitizing effects of BCM-95 were validated in a xenograft mouse model.[64] Tumors resistant to 5-FU were established by subcutaneous injection of resistant cancer cells into athymic nude mice. Once the average tumor reached 50 mm^2, the animals were divided into four groups of 10 animals each. Treatments were administered via intraperitoneal (IP) injection for 40 days. Treatment with 5-FU (20 mg/kg, IP, every two days) did not significantly reduce tumor growth (measured as tumor volume), demonstrating the resistant nature of the cells. In contrast, treatment with BCM-95 (dose given as curcumin 50 mg/kg, IP, daily) significantly reduced tumor volume compared to controls. The combination of BCM-95 plus 5-FU had an additive effect in reducing tumor volume. Mathematical models indicated that the fraction of the tumor cells resistant to 5-FU was 67%. The addition of BCM-95 reduced the degree of resistance by 30%.

Further experiments using the xenograft mouse model explored the combination of BCM-95 with BosPure, a preparation made from *B. serrata* gum resin containing three boswellic acids (acetyl-α-boswellic acid, acetyl-β-boswellic acid, and acetyl-11-keto-β-boswellic acid [AKBA]; provided by DolCas Biotech, LLC).[65] *Boswellia serrata* gum resin is a traditional remedy for inflammatory conditions. As in the previous study, xenograft tumors were established in mice by subcutaneous injection of colorectal cancer cells. The animals were divided into four groups with 10 animals in each group. Treatments or vehicle controls were injected intraperitoneally daily for three weeks, starting seven days after the injection of cancer cells. BCM-95 was administered in a dose of 25 mg/kg, with and without AKBA in a dose of 75 mg/kg. Administration of either BCM-95 or the boswellic acid suppressed tumor growth at a similar rate and the combination of the two had a synergistic effect (ratio of expected:observed tumor volume > 1). On day 20, the size of tumor in the curcumin group was 58% compared to controls; in the AKBA group, the tumor was 63% compared to controls; and both agents together resulted in a tumor size of 33% of the controls. Gene-expression arrays revealed that curcumin and AKBA regulated distinct cancer-signaling pathways including key cell-cycle regulatory genes. Combined bioinformatics and *in silico* analysis identified apoptosis, proliferation, and cell-cycle regulatory signaling pathways as key modulators of curcumin and AKBA-induced anticancer effects. Micro RNAs (miRNAs) are a class of small non-coding RNA molecules that play critical roles in the regulation of gene expression. Curcumin and AKBA induced upregulation of tumor-suppressive miR-34a and down-regulation of oncogenic‡‡ miR-27a in colorectal cancer cells.

Other researchers used a mouse model to evaluate the effectiveness of BCM-95 and metformin (a medication for type 2 diabetes) either alone or in combination to prevent the progression of tumors caused by 4-nitroquinoline-oxide (4NQO).[66] The study used C57BL/6 mice (N = 60; four to six weeks old), which were initially divided into two groups — a control arm (n = 10) administered with plain drinking water and a treatment arm (n = 50) administered with 4NQO in drinking water (50 ppm) for a period of 17 weeks. Administration of the carcinogen was then stopped and the "treatment" mice (n = 45) were divided into four arms, with treatments administered in their drinking water as follows: arm 1 (n = 15) with plain water, arm 2 (n = 15) with BCM-95 (64 µg/mL), arm 3 (n = 15) with metformin (5 mg/mL), and arm 4 (n = 15) given both BCM-95 and metformin. The average tumor volume in the 4NQO control was 6.65 ± 2.37 mm^3. Tumor volume was reduced by BCM-95 (to 2.54 mm^3) and metformin (to 1.45 mm^3) individually and even more so when the agents were administered together (0.693 ± 0.034 mm^3) (no statistics given). The average number of lesions in the 4NQO control (0.6 ± 0.22) was reduced by BCM-95 and metformin individually and even more so when the agents were administered in combination (0.375 ± 0.17) (again, no statistics given). The overall probability of survival for the combination arm was calculated as improved compared to the individual treatments (P = 0.0006). Further details were not available.[§§]

Antidepressant Activities

Rodent models were used to assess the potential antidepressant activity of BCM-95 when given acutely (in the last 24 hours before evaluation) and when administered for two weeks ("chronic studies").[67] In the acute studies, BCM-95 and the standard antidepressant drugs fluoxetine and imipramine were given to Swiss albino mice in three oral doses 24 hours, five hours, and one hour before evaluating the animals in a forced swimming test, tail suspension test, and measurement of locomotor activity. The chronic study evaluated the mice after 14 days of administration of test agents in a forced swimming test that included an activity wheel. The chronic administration study was repeated using Wistar albino rats. Each experiment was conducted with seven groups of animals with at least six animals in each group. The groups for the studies conducted with mice were the following: group 1, vehicle control (5% gum acacia); group 2, BCM-95 low dose (50 mg/kg); group 3, BCM-95 higher dose (100 mg/kg); group 4, fluoxetine (20 mg/kg); group 5, imipramine (15 mg/kg); group 6, BCM-95 (100 mg/kg) plus fluoxetine; and group 7, BCM-95 (100 mg/kg) plus imipramine. The doses of BCM-95 used in rats were 35 and 70 mg/kg. In the acute forced swimming test with mice, all test groups with the exception of BCM-95 at 50 mg/kg showed a significant decrease in time spent immobile compared to the vehicle control (P < 0.05). The effect of 100 mg/kg BCM-95 was similar to that of fluoxetine and imipramine. The addition of BCM-95 to the antidepressants did not lead to a greater effect. In this assay, swimming time, in comparison to control, was significantly increased by fluoxetine and imipramine but not by either dose of BCM-95. Conversely, climbing time increased significantly, but only for the higher-dose BCM-95 group and not for the groups on standard antidepressants. Immobility time in the tail suspension assay was decreased by all test agents. The chronic study conducted with rats showed an increase in the number of rotations of the activity wheel with all test agents compared to the control group. In summary, BCM-95 demonstrated antidepressant activity similar to that of fluoxetine and imipramine in rodent models. When BCM-95 was added to fluoxetine or imipramine, there were no additive effects.

Antiepileptic Effects

Studies with Swiss albino mice assessed the antiepileptic and memory retention activity of BCM-95, alone and in combination with the two most commonly prescribed antiepileptic drugs, phenytoin and sodium valproate.[68] Antiepileptic activity was evaluated using models of maximal electroshock (MES)- or pentylenetetrazole (PTZ)-induced seizures after oral dosing of the mice for 14 days with the test agents.

For the MES test, animals were divided into six groups, each group having six animals. Group 1 received 5% gum acacia and served as vehicle control. Groups 2 and 3 received BCM-95 in doses of 50 mg/kg and 100 mg/kg, respectively. Group 4 received 50 mg/kg phenytoin. Groups 5 and 6 received phenytoin in therapeutic (50 mg/kg) and sub-therapeutic (25 mg/kg) doses, respectively, in combination with BCM-95 (100 mg/kg). An electroconvulsiometer was used with ear electrodes to deliver the shock at an intensity of 36 mA for 0.2 s. BCM-95 in doses of 50 mg/kg and 100 mg/kg did not produce any significant effects (P = 0.33) on tonic flexion or hind limb extension as compared to the vehicle control group. Phenytoin in a dose of 50 mg/kg abolished the tonic extension phase completely, but did not show any significant difference (P > 0.05) on clonic convulsion as compared to vehicle control. BCM-95, at a dose of 100 mg/kg (but not at 50 mg/kg), produced significant (P < 0.01) reduction in duration of the clonic phase as compared to vehicle control and the phenytoin group. There were no additive effects due to combining curcumin (BCM-95) and phenytoin.

PTZ-induced seizures were caused by intraperitoneal injection in a dose of 95 mg/kg. Animals were divided into six groups each having six animals. Group 1 received 5% gum acacia and served as vehicle control. Groups 2 and 3 received BCM-95 in doses of 50 mg/kg and 100 mg/kg, respectively. Group 4 received 800 mg/kg of sodium valproate. Groups 5 and 6 received sodium valproate in therapeutic (800 mg/kg) and sub-therapeutic (400 mg/kg) doses, respectively, in combination with BCM-95 (100 mg/kg). In the vehicle-treated group, myoclonic jerks followed by tonic-clonic seizure and death were observed. BCM-95 in a dose of 100 mg/kg increased latency for onset of myoclonic jerks and seizures as well as decreased incidence, total duration of seizure, and mortality compared to the vehicle control group (P < 0.001). Sodium valproate completely prevented incidence of tonic-clonic convulsions and mortality as compared to vehicle control. BCM-95 showed no significant additive effect when combined with sodium valproate.

An elevated plus-maze test was used to study the effect of drugs and/or seizures on memory retention in the MES and

PTZ groups. The maze test was performed on days 13 and 14, after recovery from seizure. Neither BCM-95 nor the antiepileptic drugs had any significant effect on memory retention compared to vehicle control.

Hepatoprotective Effects

The ability of BCM-95 to prevent liver injury caused by carbon tetrachloride (CCl_4) was tested in male albino Sprague Dawley rats.[69] In rats administered a low dose of CCl_4 (5 mL/kg body weight via gavage) for three months, liver injury was observed, determined by effects on serum and liver biochemistry. BCM-95 was administered at a daily dose of 300 mg/kg body weight orally via gavage for the same period of time. The experiment included a control group, for a total of three groups, and all groups contained six animals. By week 12, the animals given CCl_4 weighed less than the control group, but those given CCl_4 plus BCM-95 had a body weight comparable to the controls. Liver injury in the CCl_4 group was observed as an increase in clotting time (the liver is responsible for the production of coagulation factors), increases in liver transaminases (alanine aminotransferase/glutamic-pyruvic transaminase [ALT/GPT] and aspartate aminotransferase/glutamic-oxaloacetic transaminase [AST/GOT]), and an increase in lactate dehydrogenase (LDH) in both the serum and the liver. BCM-95 was able to ameliorate the increases in clotting time, liver transaminases, and LDH, but not restore them to the levels in the control animals. CCl_4 reduced the ratio of albumin to globulin in the blood serum (A/G ratio) and this was also partially ameliorated by BCM-95. Cholesterol levels were increased in both the serum and the liver following treatment with CCl_4. This change was also partially reversed by BCM-95. In addition, BCM-95 partly reduced the increase in serum bilirubin and collagen in the liver. In summary, BCM-95 at a dose of 300 mg/kg body weight partially prevented liver injury in rats to which a low dose of CCl_4 was administered.

The same protocol was used to examine the effect of BCM-95 on alcoholic hepatitis induced in rats administered alcohol diluted to 10% in water and fed via intragastric tube daily for three months.[70] In this study, alcoholic hepatitis was observed by altered liver function tests and increased accumulation of lipids (cholesterol and triglycerides) as well as collagen in the liver. As in the CCl_4 model, alcohol caused increases in clotting time, liver transaminases (ALT/GPT and AST/GOT), and LDH levels, in both the serum and the liver. BCM-95 was again able to reduce clotting time, liver transaminases, and LDH concentrations, but not restore them to the levels observed in the control animals. BCM-95 partly normalized the reduced A/G ratio, as well as the increases in serum cholesterol and bilirubin. BCM-95 also reduced elevated cholesterol or triglyceride levels, and decreased amounts of soluble protein and collagen in the liver caused by the administration of alcohol. In summary, BCM-95 at a dose of 300 mg/kg body weight partially prevented liver injury induced by alcohol in rats.


Turmeric *Curcuma longa*
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HUMAN CLINICAL TRIALS

A total of ten human clinical trials have been conducted on BCM-95 and reported in thirteen publications. Six publications involve the category of mental and cognitive health: Three clinical studies explored the benefits for major depression, and an additional publication explored the potential mechanism of action. A fourth trial investigated whether BCM-95 might prevent cognitive decline associated with old age, and a fifth trial investigated the potential benefit to patients with Alzheimer's disease. The study with patients with dementia also investigated the effect of BCM-95 on serum lipid levels. Two additional human studies with BCM-95 are in the category of joint health — one on osteoarthritis (OA) and the other on rheumatoid arthritis (RA).

Two trials explored chemopreventive benefits, evaluating the effects of BCM-95 in patients with oral submucous fibrosis, and oral leukoplakia, chronic precancerous condition of the mouth.

Finally, the last study investigated urinary, sexual, and bowel function, and antioxidant status in patients undergoing radiation therapy for prostate cancer.

Mental & Cognitive Health

Sanmukhani et al., 2014 — Major Depression

A randomized, observer-masked (single-blind), three-arm, parallel study was conducted comparing BCM (500 mg twice daily) to fluoxetine (20 mg/day) and the combination of the two treatments given to patients with major depressive disorder (MDD) for six weeks.[27] The patients were men and women with a mean age of approximately 37 years,

diagnosed with MDD according to criteria in the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. The primary variable was the Hamilton Depression Rating Scale, 17-item version (HAM-D17), measured before and after two, four, and six weeks of treatment. There was no placebo control for ethical reasons. The study began with 60 patients, 20 in each of the three groups. Overall, 45 patients completed the study with no significant difference in the dropout rate for each group. The "intention-to-treat" proportion of responders was highest in the group taking both BCM-95 and fluoxetine (77.8%), compared to the fluoxetine group (64.7%) and the BCM-95 group (62.5%). However, there were no statistically significant differences among groups. The secondary outcome measures — mean change in HAM-D17 scores and remission rate according to the HAM-D17 — also were similar for the three groups. There were also no significant differences among the three groups in global efficacy as assessed by the investigators (P = 0.66). The percentage of patients with 'excellent' or 'good' response to the study medication were 70.5% [46.8 – 86.7] in the fluoxetine group, 75% [50.5 – 89.8] in the curcumin group, and 83.3% [60.7–94.1] in the fluoxetine and curcumin group.

All treatments were administered without effects on vital signs, laboratory tests, or electrocardiograms. The reported adverse effects were mild, with the most common being gastritis in all three groups.

Lopresti et al., 2014 & 2015 — Major Depression

In an eight-week, randomized, double-blind, placebo-controlled study, 52 men and women (18 to 65 years old) with MDD were treated with BCM-95 (500 mg twice daily) or placebo.[28] BCM-95 and placebo were provided by Arjuna Natural Extracts Ltd. The primary measure was the Inventory of Depressive Symptomatology self-rated version (IDS-SR_{30}). Secondary outcomes included the IDS-SR_{30} factor scores and the Spielberger State-Trait Anxiety Inventory (STAI) score.

From baseline to week four, both BCM-95 and placebo were associated with improvements in the IDS-SR_{30} total score and most secondary outcome measures. From weeks four to eight, BCM-95 was significantly more effective than placebo in improving several mood-related symptoms, demonstrated by a significant group × time interaction for IDS-SR_{30} total score (P = 0.045) and IDS-SR_{30} mood score (P = 0.014), but none for IDS-SR_{30} arousal score. Both BCM-95 and placebo groups showed a reduction in STAI scores (state and trait anxiety). There were no significant "group × time" interactions across the full eight weeks of treatment for either STAI score. However, there was a trend towards a reduction in the STAI trait score from week four to week eight (P = 0.097). The authors indicated that the data suggested that depression in both groups improved for the first four weeks and after that, improvement continued in the curcumin group, while the placebo group remained static. Items in the IDS-SR_{30} have been used to categorize patients into categories of atypical or melancholic depression. Greater efficacy from curcumin treatment was identified in a subgroup of individuals with atypical depression.

The same research group published a secondary, exploratory analysis of salivary, urinary, and blood biomarkers collected during the above study in order to identify potential antidepressant mechanisms of action for curcumin.[71] Pre- and post-intervention samples were provided by 50 patients. Compared to placebo, eight weeks of BCM-95 supplementation was associated with elevations in urinary thromboxane B2 (P < 0.05) and substance P (P < 0.001). In the placebo group, there were reductions in aldosterone (P < 0.05) and cortisol (P < 0.05). There were no significant changes to biomarkers in plasma or saliva. Further examination of the data for correlations between the IDS-SR_{30} total score and levels of biomarkers indicated an apparent relationship between high levels of plasma endothelin-1 at baseline (> 1.47 pg/mL) and greater reductions in the IDS-SR_{30} score after eight weeks of curcumin compared to placebo. However, the change in the IDS-SR_{30} score was not accompanied by a decrease in the level of this marker. No changes in urinary biomarkers were related to treatment outcome. The authors of the study commented that these findings should be interpreted cautiously as multiple statistical analyses were completed, increasing the risk of type I errors (detecting an effect that is not present).

Lopresti and Drummond, 2017 — Major Depression

The clinical trial on MDD reported by Lopresti and colleagues, described above, was followed by another study that explored whether half the usual dose of BCM-95 would be as effective against MDD, and whether combining the lower dose of BCM-95 with a saffron extract would have an additive effect in treating depression and anxiety.[32] The study was randomized, double-blind, and placebo-controlled, and had a 12-week treatment period and one-week placebo "run-in" phase. The participants were 111 men and women (18 to 65 years old) with MDD who were divided into four groups: (1) 500 mg BCM-95 twice daily, (2) 250 mg BCM-95 twice daily, (3) 250 mg BCM-95 plus 15 mg saffron extract twice daily, or (4) placebo. The saffron extract was prepared from the stigmas of *Crocus sativus* (Iridaceae) and characterized as containing a minimum of 3.5% lepticrosalides including safranal and crocin. All interventions were provided by Dolcas-Biotech LLT of Landing, New Jersey. As in the previous study, the primary measure was the IDS-SR_{30}, and the secondary outcome measure was the STAI score. Over 12 weeks, the IDS scores were significantly reduced in all groups, although in the placebo group that decrease was limited to the first four weeks of treatment. Results from all of the active groups combined, compared to results from the placebo group, produced a significant "time x group" interaction from baseline to week 12 (P = 0.031). There were no significant differences in "time x group" analysis between the three active treatments. The IDS response rate for the combined active treatments was 28%, which was twice the 13% response rate for the placebo group, but the difference did not reach statistical significance (P = 0.074). The combined active treatment groups also showed significantly greater improvements in STAI-state (STAI-S) and STAI-trait (STAI-T) scores over 12 weeks, compared to the placebo group.Again, comparisons between the active groups did not show any significant differences. As in the previous clinical trial, the active treatments

were more effective for participants diagnosed with atypical depression compared to the other depressed participants (IDS, P = 0.007; STAI-S, P < 0.001; STAI-T, P = 0.009). The response rate for a subgroup with atypical depression (65%) was significantly greater than the overall response rate (35%; P = 0.012). The authors concluded that the results of the present study provide additional support for the use of BCM-95 for anxiety and depression (particularly atypical depression), with no significant differences in efficacy between the doses of 500 mg and 1000 mg per day. The addition of the saffron extract did not enhance efficacy. This study also supported the idea that BCM-95 might help those with atypical depression more often than those with other categories of depression.

Rainey-Smith et al., 2016 — Cognitive Health in Older Adults

A 12-month randomized, double-blind, placebo-controlled study examined the ability of BCM-95 to prevent cognitive decline in a population of healthy older adults [33] Participants were randomly assigned to take either 500 mg three times daily of BCM-95 or matching placebo capsules containing roasted rice powder. The Montreal Cognitive Assessment (MoCA), the Rey Auditory Verbal Learning Test, the Controlled Oral Word Association Test, the Wechsler Digit Symbol Scale from the Wechsler Adult Intelligence Scale, and the CogState battery were administered to patients at baseline, six months, and 12 months. Initially, 160 community-dwelling adults (40 to 90 years old) without significant cognitive impairment were enrolled into the study (80 in each group). The final analysis included 57 patients in the placebo group and 39 patients in the treatment group. There were no differences between groups in cognitive performance from baseline to 12 months. At baseline, the placebo group performed significantly better than the treatment group in the MoCA; at six-months the comparison was reversed, and at 12-months there was no difference between the groups. A significant "time ×treatment" group interaction for MoCA was produced for baseline, six-month, and 12-month data but not when the six-month data was excluded. The authors concluded that the 12-month study did not show a significant effect for BCM-95 on cognitive function, mood, or general quality of life. The participants In the study were cognitively healthy and did not show much decline over the year. The authors speculated that there might not have been sufficient magnitude of change to detect an improvement due to BCM-95. Further studies with larger numbers of participants over longer periods of time may be required to measure the ability of BCM-95 to slow cognitive decline.

Baum et al., 2008 — Alzheimer's Disease

A six-month, randomized, double-blind, placebo-controlled, pilot clinical study explored the effects of two doses of curcumin compared to placebo in patients with probable or possible Alzheimer's disease according to NINCDS-ADRDA.[30***] The study included 31 male and female patients over 50 years old with a progressive decline in memory and cognitive function over the previous six months. Patients were randomly assigned to receive 1 g curcumin, 4 g curcumin, or placebo. As the volume of curcumin was large and thought to be inconvenient, the patients were allowed to choose between taking 10 capsules containing BCM-95 after a meal or packets of curcumin powder (not BCM-95) to be mixed with food. The packets of powder (n = 12) were provided by Kancor Ingredients Ltd. (The forms of curcumin were not the same.) The placebo was yellow starch. All patients received a capsule containing 120 mg standardized ginkgo (*Ginkgo biloba*, Ginkgoaceae) leaf extract (Shanghai Charoma; Shanghai, China; no further description of the ginkgo extract was provided). Patients were also allowed any additional treatment deemed appropriate by their physicians. Plasma samples were obtained at baseline, one month, and six months and assayed for isoprostanes, antioxidants, and amyloid beta-40. Cognition was assessed using the Mini-Mental State Examination (MMSE) at baseline and six months.

Thirty-four male and female patients began the study, and 27 completed it (dropout rate: 20%). The seven dropouts were due to gastrointestinal complaints (n = 3), complications due to falls (n = 3), and respiratory tract infection (n = 1). The final compositions of the groups were as follows: 1-g group (n = 8; one man and seven women), 4-g group (n = 11; three men and eight women), and placebo group (n = 8; three men and five women).

There was no change in cognition due to curcumin at either dose compared to the control group, as measured using the MMSE scores. Serum levels of amyloid beta-40 did not differ significantly among groups. There was a tendency towards an increase in the 4-g group but this did not reach significance. There were no significant changes in plasma levels of isoprostanes. Serum levels of vitamin E increased for those taking the curcumin capsules (BCM-95) but decreased for those taking powdered curcumin and for those in the placebo group. The change in vitamin E levels correlated with the level of total curcuminoids in plasma.

In summary, this study did not demonstrate an improvement in cognitive abilities due to either form of curcumin. The patients in the placebo group did not have a decline in their cognitive abilities and this may have precluded observing any benefit due to curcumin. A weakness of the study design was that all patients were taking a standardized ginkgo extract; a proprietary ginkgo extract from Germany has demonstrated the ability to improve cognition for patients with early stages of Alzheimer's disease in several clinical studies (although, as noted above, the Chinese ginkgo extract used in this study was not adequately described to be able to determine if it was chemically similar to the German extract). Suggested mechanisms for benefits to patients with Alzheimer's disease include disaggregation of amyloid-beta plaques, and anti-inflammatory and antioxidant activity. Ginkgo extracts have demonstrated antioxidant and anti-inflammatory properties, so any changes in these parameters due to curcumin would have to be beyond that due to ginkgo. Another complication of the study was the difference in the form, and perhaps content, of the two curcumin preparations. In summary, no difference was observed among the groups in the Alzheimer's parameters tested.

Cardiovascular Health

Baum et al., 2007 — Blood Lipids

In a report of additional measurements conducted during the 2008 Baum et al. study described above, plasma lipids were measured.[31] Plasma samples were obtained at baseline, one month, and six months and assayed for cholesterol (total, high-density lipoprotein [HDL], and low-density lipoprotein [LDL]) and triacylglycerol. There were no significant between-group differences in these parameters at any of the time points. A complication of this study, as discussed above, was that the patients all took an undefined ginkgo extract and other undisclosed treatments for Alzheimer's disease. In addition, it might have been more likely to observe an effect on cholesterol levels if the study patients had a pre-existing condition of hypercholesterolemia or were fed a high-fat diet.

Joint Health

Antony et al., 2011 — Osteoarthritis

A randomized, two-arm, open, 12-week study[†††]compared the effects of Rhulief® (500 mg twice daily) to celecoxib (100 mg twice daily) for treatment of OA of the knee.[72] Rhulief 500-mg capsules (produced by Arjuna Natural Extracts, Ltd.) contained BCM-95 (350 mg) and BosPure (150 mg *B. serrata* extract standardized to 10% 3-*O*-acetyl-11-keto-β-boswellic acid). The patients were 18 to 65 years old, with moderate OA of the knee characterized as narrowing of the medial joint space with swelling. Patients with more severe OA with gross radiological damage to joints and restricted mobility were excluded. Fifty-four patients were screened, 30 enrolled, and 28 completed the study. Both groups showed improvement in joint pain, which decreased for most patients from moderate pain to mild pain. While there was a trend towards a greater reduction in the Rhulief group, there was no significant difference between groups. Both groups exhibited a significant increase in the number of patients able to walk 1,000 m without limiting pain. Significant improvements were also observed in crepitus and range of motion in both groups. Measurements of joint swelling, warmth of joint, gait, and thigh were not changed by either test agent. There were no safety issues, as monitored using vital signs (blood pressure, pulse, and respiration), hematological parameters, liver enzymes, and renal function parameters. In summary, treatment with Rhulief (500 mg twice daily) resulted in similar benefits to patients with OA as celecoxib (100 mg twice daily) for treatment of OA of the knee.

Chandran and Goel, 2012 — Rheumatoid Arthritis

A randomized, single-blinded, three-arm, eight-week, pilot study explored the effectiveness of BCM-95 (500 mg twice daily), diclofenac sodium (50 mg twice daily), and both therapies in combination for treatment of RA.[25] The study included 45 patients (38 women and 7 men; mean age, 48 years) diagnosed with active RA (American College of Rheumatology [ACR] functional class I or II and Disease Activity Score 28 [DAS28] > 5). Patients taking NSAIDs or other anti-RA therapy within four weeks of entry into the study were excluded. The primary endpoint was the DAS28 and secondary endpoints were ACR scores. All three treatments caused significant reductions in the DAS28 and ACR scores. Although there were trends towards the greatest improvement in the BCM-95 group in measurements including pain (visual analog scale [VAS]), these differences were not significant. The degree of inflammation was assessed using two different blood measurements: erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). There were no significant differences among groups in the ESR measurements. The BCM-95 group was the only one to demonstrate a reduction in CRP. CRP is a protein produced by the liver during an inflammatory reaction and considered to be a more specific measure of inflammation than ESR. In summary, this study found BCM-95 (500 mg twice daily), diclofenac sodium (50 mg twice daily), and both therapies in combination equally effective in reducing disease scores, with a significantly better safety profile for BCM-95 (14% of the diclofenac group withdrew from the trial due to adverse effects; none withdrew from the BCM-95 group). Curcumin treatment was unique in that it also reduced levels of CRP, demonstrating a potential mechanism for an additional anti-inflammatory effect. This study had the weakness of being open-labeled and thus the evaluations were not blinded.

Cancer Chemopreventive Effects

Das et al., 2010 — Oral Submucous Fibrosis

Oral submucous fibrosis (OSMF) is a chronic precancerous condition characterized by epithelial inflammation and progressive fibrosis of the submucosal tissues.[26] As the disease progresses, the jaws become rigid to the point that the sufferer is unable to open his or her mouth. The condition is associated with the chewing of betel quid (areca palm nuts wrapped in betel [*Piper betle*, Piperaceae] leaves with slaked lime [calcium hydroxide], often in addition to tobacco [*Nicotiana tabacum*, Solanaceae] or spices). Betel-quid chewing is a habit, similar to tobacco chewing, that is practiced predominantly in Southeast Asia and India.

An open-label, three-arm study explored the potential benefits of BCM-95 or turmeric oil compared to a control for patients who were clinically and histopathologically confirmed as having OSMF. The patients (N = 48) were randomly divided (method not given) into three groups of 16 patients each. They were treated for three months and then followed for an additional six months. Group 1 was given 500-mg capsules of BCM-95 twice daily for a total daily dose of 1 g. Group 2 was administered turmeric oil (supplied by Kancor Ingredients Ltd.); 12 drops of oil were held in the mouth for a period of time before swallowing, twice daily, for a total of 600 mg per day. Group 3 was the control provided as Multinal® tablets (New Ambadi Estates Pvt. Ltd.; Madras, India) containing spirulina (*Arthrospira* spp., Microcoleaceae), one 500-mg tablet taken twice a day for a total daily dose of 1 g. Upon clinical assessment, the patients were categorized as having mild, moderate, or severe symptoms. Biopsies were conducted ahead of treatment and after three months. Following biopsy, the patients were separated into three grades of disease — early, moderately advanced, and advanced. After three months of treatment,

groups 1 (BCM-95) and 2 (turmeric oil) had significant reductions (P values not given) in burning sensations in their mouths and their tolerance for spicy food also had improved in comparison to the control group. Complete relief from mouth pain was reported for those in the BCM-95 and turmeric oil groups within one month of treatment whereas the pain persisted in five patients in the control group. There were significant increases in the ability of patients in groups the BCM-95 and turmeric oil to open their mouths after one month and three months of treatment. These groups both demonstrated an increase of 0.87 cm in mouth opening compared to 0.18 cm in the control group. Those in the turmeric oil group had the greatest improvement in tongue protrusion. Subjects in this group had a change in color of patients' mucosa, from blanched to erythematous, indicating an increase in vascularity. In addition, three patients in this group had their leukoplakic lesions disappear. The clinical scores were reduced in the BCM-95 and tumeic oil groups after 15 days of treatment. After three and six months, these groups had statistically significant downgrading of clinical scores compared to the control group. After the six-month follow-up period, the turmeric oil group had a better clinical score than those in the BCM-95 group. The histopathology reports from the biopsies taken at baseline and three months indicated that seven patients in the BCM-95 group and nine patients in the turmeric oil group had improved to a better stage, while three patients in the control group deteriorated into the advanced stage. Histopathology reports showed that none of the patients in the BCM-95 or turmeric oil groups had a progression to malignancy. However, the control group showed an increase in mitotic figures, indicating a progression towards cancer. No adverse reactions were reported. All treatment regimens were well tolerated. There were no signs of allergic or adverse reactions. In summary, there was a measured improvement in OSMF following treatment with BCM-95 and with turmeric oil when compared to tablets containing spirulina. A weakness of the study write-up was that the statistical analyses were not included.

Kuriakose et al., 2016 — Oral Leukoplakia

Oral leukoplakia is a white lesion of the mucosa of the oral cavity that is potentially malignant. A multicenter, double-blind, randomized, placebo-controlled trial compared BCM-95 to placebo in subjects with oral leukoplakia that was confirmed both clinically and histologically (via biopsy), more than 15 mm^2 in size, and not previously treated. The subjects received either 3.6 g/day of BCM-95 (n = 111) or a placebo of cellulose (n = 112), for six months. At the end of that time, the lesion was measured and another biopsy performed. Those demonstrating a complete response were observed for six months without further intervention. Those with a partial response (50% or greater decrease in size) were continued on their treatment (BCM-95 or placebo) for an additional six months. The primary endpoint was a change in size of the lesion at six months compared to baseline. A reduction in size of at least 50% was observed in 75 subjects in the curcumin and 62 subjects in placebo arm, with a significant difference between groups (P = 0.03). The histological assessments showed no significant differences between groups. Partial responders who received an additional six months of treatment did not display additional benefits. The authors concluded that treatment of oral leukoplakia with curcumin (3.6 g for six months) was well tolerated and produced a significant reduction in the size of lesions compared to baseline and placebo.

Effects in Patients Undergoing Radiotherapy

Hejazi et al., 2013 & 2016 — Radioprotective Effects

In a randomized, double-blind placebo-controlled study, 40 patients with prostate cancer undergoing treatment with external beam radiotherapy in combination with hormone ablation were randomly assigned to receive BCM-95 (500 mg capsules six times daily, totaling 3 g per day) or placebo (roasted rice [*Oryza sativa*, Poaceae] flour in capsules).[29] The patients all had a life expectancy greater than five years and no detectable metastatic disease. Treatment with BCM-95 or placebo started one week before onset of radiotherapy and continued throughout the radiotherapy. The radiotherapy was given as fractions of 2 Gy, five times a week for roughly eight weeks, with a total dose of 74 Gy. Quality of life specific to prostate cancer was evaluated using a questionnaire (European Organisation for Research and Treatment of Cancer) that assessed urinary, sexual, and bowel function. The questionnaire was completed during face-to-face interviews at baseline (one week prior to radiotherapy) and three months after completion of radiotherapy. At baseline, there were no differences between the groups in urinary symptoms, bowel symptoms, or sexual activity. Comparison of change in urinary symptoms over the 20-week period demonstrated a reduction in urinary symptoms in the BCM-95 group compared to placebo (P < 0.01). Among the urinary symptoms, the greatest improvements were reductions in urination frequency during the day, sleep disturbance due to urination at night, and limitation of daily activity due to urinary problems. There were no comparative differences between groups in bowel symptoms or sexual activity. The authors of the study suggested that BCM-95 might confer protective effects against treatment-related urinary symptoms in patients with prostate cancer that undergo radiation therapy. The authors also suggested the need for additional studies with larger sample sizes and larger doses of curcumin.

In a follow-up publication on this clinical trial, plasma antioxidant levels for participants in the study were reported.[34] Blood was drawn one week before the initiation of radiotherapy and three months after completion, and analyzed for total antioxidant capacity (TAC), glutathione peroxide (GPX) activity, superoxide dismutase (SOD) activity, and catalase activity. Intake of antioxidant and pro-oxidant nutrients (vitamin E, vitamin C, zinc, selenium, iron, and copper) and foods containing phenolic compounds was recorded. There were no significant differences in dietary consumption between the two groups. At baseline, the biochemical variables were similar for the two groups, with the exception of TAC which was higher in the curcumin group.In the BCM-95 group, the levels of TAC were significantly higher post-radiotherapy than at baseline (P < 0.001), and the SOD activity decreased

significantly from baseline (P = 0.018). No other changes over time were observed for either group. The increase in TAC and decrease in SOD for the BCM-95 group were significant compared to the placebo group after adjusting for baseline differences (P = 0.014 and P = 0.018, respectively). The authors of the study recognized that the use of antioxidants in combination with radiotherapy is controversial. In this study, there was no negative effect due to BCM-95 on the outcome of treatment as measured via prostate-specific antigen (PSA) levels and MRI/MRS images. The authors concluded that BCM-95 improved antioxidant status without compromising the efficacy of radiotherapy.

SAFETY OF TURMERIC AND BCM-95 (Curcugreen)

This section begins with evaluations of the safety of turmeric as a common spice, food additive, and as an ingredient used for centuries in traditional, historical medicine. It continues with preclinical toxicological studies and clinical trials conducted on curcumin. More detailed information is given on studies specific to BCM-95.

Turmeric

Turmeric, its essential oil, oleoresin, and/or natural extractives are designated as GRAS (Generally Recognized as Safe) for use as food ingredients and food additives by the United States Food and Drug Administration (US FDA; per 21 CFR 182.10, 182.20).

The American Herbal Products Association's *Botanical Safety Handbook*, 2nd ed. lists turmeric as Class 1 (herbs that can be safely consumed when used appropriately) and Interaction Class A (herbs for which no clinically relevant interactions are expected).[73] Mills and Bone, in their book *The Essential Guide to Herbal Safety*,[74] list turmeric as Pregnancy Category A (no proven increase in frequency or malformation or other harmful effects on the fetus despite consumption by a large number of women) and Lactation Category C (compatible with breastfeeding). They contraindicate turmeric preparations in cases of obstruction of the biliary tract and advise to consult a health care professional if someone has gallstones. Adverse reactions associated with oral intake are listed as frequent bowel movements and mild gastric discomfort. The authors advise against combining amounts greater than 15 g turmeric powder per day with antiplatelet or anticoagulant medications.

Curcumin

Curcumin Preclinical Toxicity Studies

In systematic studies conducted in rats, dogs, and monkeys at oral doses up to 3.5 g standard curcumin/kg body weight for up to 90 days, no adverse effects were observed.[75] No toxicity was observed in 14-day preclinical studies with administration of 2% dietary curcumin (approximately 1.2 g/kg body weight) to rats and approximately 300 mg/kg body weight administered to mice.[76,77]

Curcumin Reproductive Toxicity Studies

A reproductive study in which curcumin was administered orally to rats in doses up to 1 g/kg body weight daily for two successive generations did not report any toxicity.[78]

Curcumin Clinical Safety

Phase I clinical studies indicate that curcumin (Curcumin C3 Complex provided by Sabinsa Corporation) is not toxic even at a very high dose of 12 g/day. A dose-escalation study, which aimed to determine the maximum tolerated dose (MTD), administered single doses ranging from 500 mg to 12,000 mg to 24 healthy volunteers. Seven of the subjects reported mild adverse events, including diarrhea, headache, rash, and yellow stools. All symptoms were Grade I toxicity and not related to dose. The MTD could not be determined in this study because amounts more than 12 g were considered to be too large to be consumed comfortably.[24]

In another dose-escalation clinical study, patients with advanced colorectal cancer received curcumin (Curcumin C3 Complex provided by Sabinsa Corporation) in doses up to 3.6 g daily for up to four months. The reported side effects were minor, with nausea and diarrhea being the most commonly reported complaints.[45]

Potential Drug Interactions with Curcumin

Anticoagulants

Some preclinical data indicate that co-administration of curcumin with NSAIDs or anticoagulant drugs might result in an increased risk of bleeding.[79] Anticoagulant agents include aspirin, clopidogrel (Plavix®), dalteparin (Fragmin®), enoxaparin (Lovenox®, Xaparin®, Clexane®, Oksapar®), heparin, ticlopidine (Ticlid®), and warfarin (Coumadin®, Jantoven®, Marevan®). Curcumin has been shown to have mild anticoagulant properties in assays using human plasma and to prolong bleeding time in a rat-tail transaction assay. Bisdemethoxycurcumin also had anticoagulant activity in these assays, but less so when compared to curcumin.[80]

Drug Metabolism

Curcumin may interfere with drugs metabolized by the cytochrome P450 (CYP) enzyme system.[79] In vitro experiments using recombinant human CYP enzymes, human liver fractions, and human intestinal cell lines indicated that curcumin might affect enzymes involved in drug metabolism. In these experiments, curcumin inhibited sulfotransferase (SULT) enzymes, uridine 5'-diphospho (UDP)-glucuronosyltransferase (UGT), and several CYP enzymes with IC_{50} (half maximal inhibitory concentration) values ranging from 0.99 to 25 µM.[81]

To date, only two human clinical studies have explored the effects of standard curcumin on enzymes involved in drug metabolism.[‡‡‡] The potential effect of standard curcumin on metabolic enzymes was investigated in healthy Chinese men using caffeine as a probe drug. Sixteen volunteers were recruited for this two-phase study. Initially, 100 mg of caffeine was administered to establish baseline PK measurements. Thereafter, the volunteers received 1,000 mg curcumin

Table 2. Human Clinical Studies Conducted on BCM-95® (Curcugreen™)

Reference	Indication	Study Design & Details	Treatment & Dose	Results	Conclusions
	MENTAL HEALTH				
Sanmukhani et al., 2014[27]	Major depressive disorder (MDD)	R, CM; 6 weeks; N = 45 patients with MDD	3 groups: [1] BCM-95 (500 mg b.i.d.); [2] fluoxetine (20 mg/day); [3] both treatments combined	All groups ↓ HAM-D17; NSD among groups.	BCM-95 ↓ MDD symptoms = fluoxetine; no ↑ effect with combo.
Lopresti et al., 2014[28]	MDD	R, DB, PC; 8 weeks; N = 52 patients with MDD (18-65 years)	BCM-95 (500 mg b.i.d.) or placebo	BCM-95 ↓ IDS-SR_{30} score 4-8 weeks. No Δ 0-8 weeks or in STAI trait.	BCM-95 ↓ MDD compared to placebo (4-8 weeks only).
Lopresti et al., 2015[71]		Secondary analysis of salivary, urinary, and blood biomarkers from Lopresti et al., 2014		Δ in urinary markers; no significant Δ in blood or salivary biomarkers	Δ in urinary biomarkers not related to measurements of depression
Lopresti & Drummond, 2017[32]	MDD	R, DB, PC; 12 weeks; N = 123 patients with MDD (18-65 years)	4 groups: [1] BCM-95 (500 mg b.i.d.); [2] BCM-95 (250 mg b.i.d.); [3] BCM-95 (250 mg b.i.d.) + saffron (15 mg b.i.d.); or [4] placebo	All BCM-95 groups combined ↓ IDS-SR_{30} & STAI scores 0-12 weeks. No dose effect.	BCM-95 ↓ MDD compared to placebo (0-12 weeks). No Δ in response with half dose. Best response for those with atypical depression.
Rainey-Smith et al., 2016[33]	Cognitive health in older adults	R, DB, PC; 1 year; N = 96 healthy adults (40-90 years)	BCM-95 (500 mg t.i.d.) or placebo	No Δ in cognition after 1 year. Decline in placebo group at 6 months.	BCM-95 had no effect on cognition after 1 year but may have prevented decline observed in placebo group at 6 months.
Baum et al., 2008[30]	Alzheimer's disease	R, DB, PC, dose study; 6 months; N = 27 patients with dementia (>50 years)	3 groups: [1] 1 g/day BCM-95; [2] 4 g/day BCM-95; or [3] placebo. All groups 120 mg/day ginkgo leaf extract.	All groups no Δ in cognition.	BCM-95 had no effect on cognition. Study design flawed as all patients also received ginkgo.
	CARDIOVASCULAR HEALTH				
Baum et al., 2007[31]	Lipid levels	Secondary analysis of salivary, urinary, and blood biomarkers from Baum et al., 2008		All groups no Δ in lipid levels.	BCM-95 had no effect on lipids. Weak study design as subjects did not have hypercholesterolemia, nor were they fed a high-fat diet.
	JOINT HEALTH				
Antony et al., 2011[72]	Osteoarthritis (OA)	R, CM; 12 weeks; N = 28 patients with OA of knee (18-65 years)	Rhulief (BCM-95 + BosPure; 500 mg b.i.d.) or celecoxib (100 mg b.i.d.)	Both groups ↓ pain, ↑ distance walked, & range of motion.	Rhulief ↓ OA symptoms = celecoxib.
Chandran & Goel, 2012[25]	Rheumatoid arthritis (RA)	R, SB, CM; 8 weeks; N = 45 patients with RA	3 groups: [1] BCM-95 (500 mg b.i.d.); [2] diclofenac sodium (50 mg b.i.d.); or [3] both treatments combined	All groups ↓ DAS and ACR scores. Only BCM-95 ↓ C-reactive protein.	BCM-95 ↓RA symptoms = diclofenac. Only BCM-95 ↓ inflammation (C-reactive protein levels).
	CANCER CHEMOPROVENTIVE EFFECTS				
Das et al., 2010[26]	Oral submucous fibrosis	R, OL; 3 months; N = 48 patients with premalignant lesions	3 groups: [1] BCM-95 (500 mg b.i.d.); [2] turmeric oil (12 drops b.i.d.); or [3] Multinal tabs (spirulina, 500 mg b.i.d.)	BCM-95 & turmeric oil ↓ oral pain & ↑ ability to open mouth & eat spicy foods.	BCM-95 & turmeric oil ↓ clinical scores.
Kuriakose et al., 2016	Oral leukoplakia	R, DB, PC; 6 months; N = 223 patients with lesions > 15 mm^2 in size	BCM-95 (1800 mg b.i.d) or placebo (cellulose)	BCM-95 ↓ size of lesions	BCM-95 ↓ clinical scores.
Hejazi et al., 2013[29]	Radiotherapy side effects	R, DB, PC; 20 weeks; N = 40 men with prostate cancer undergoing radiation therapy	BCM-95 (500 mg 6x/day) or placebo (roasted rice flour)	BCM-95 ↓ urinary symptoms; no Δ in effects on bowel or sexual activity.	BCM-95 ↓ urinary symptoms due to radiation therapy in men with prostate cancer.
Hejazi et al., 2016[34]		Secondary analysis of plasma antioxidant levels from Hejazi et al., 2013		BCM-95 ↑ total antioxidant capacity and superoxide dismutase.	BCM-95 improved antioxidant status without compromising efficacy of radiotherapy.

CM = comparative
DB = double-blind
OL = open-label
PC = placebo-controlled
R = randomized
SB = single-blind

ACR = American College of Rheumatology criteria
DAS = Disease Activity Score
HAM-D17 = Hamilton Rating Scale for Depression
IDS-SR_{30} = Inventory of Depressive Symptomatology
STAI = State-Trait Anxiety Inventory

b.i.d. = 2 times daily
t.i.d. = 3 times daily

NSD = no significant differences
Δ = change
↓ = decreased
↑ = increased

(supplied by General Nutrition Centers, Inc. [GNC]; Greenville, South Carolina) once daily for 14 days. On day 15, caffeine was again administered and PK measurements were taken once more. Urinary caffeine metabolite ratios were used to indicate the activities of CYP1A2, CYP2A6, N-acetyltransferase 2 (NAT2), and xanthine oxidase (XO). Curcumin caused an increase of 49% in CYP2A6 activity and an inhibition of 29% in CYP1A2 activity. There was no significant effect on NAT2 or XO activity.[82]

Another clinical study examined the effect of standard curcumin on the pharmacokinetics of talinolol, a β-adrenoceptor antagonist (beta blocker) that is used to manage cardiac arrhythmias and hypertension. Talinolol was used as a probe for effects on the P-glycoprotein (P-gp)-related drug transport systems. Curcumin (supplied by Shenwei Pharmaceutical Co.; Shijiazhuang, China) was administered to 12 healthy volunteers for six days. A single dose of 50 mg talinolol was administered one week before the curcumin and on the seventh day following curcumin administration. Concentrations of talinolol were measured in plasma samples. Co-administration of curcumin significantly reduced the plasma levels of talinolol (AUC by 33% and C_{max} by 28%) but did not affect the kinetics of absorption (t_{max} and $t_{½}$). The authors suggested that curcumin modified P-gp activity in the intestine by occupying receptor sites.[83]

BCM-95 (Curcugreen)

BCM-95 Preclinical Toxicology

Acute Oral Toxicity — Mice

In an acute oral toxicity study conducted according to international Organisation for Economic Co-operation and Development (OECD) Guideline No. 420, male and female Swiss albino mice (eight to 12 weeks old; 20 to 25 g body weight; five animals per group) were given via gavage 5,000 mg/kg body weight BCM-95 or corn oil as a vehicle control. The animals were fasted for three to four hours prior to oral dosing and one to two hours post-dosing. The animals were observed over 14 days for clinical signs before necropsy. No signs of toxicity were observed at the highest dose tested. Thus, the MTD, minimum lethal dose (MLD), and median lethal dose (LD_{50}) for BCM-95 were all declared to be > 5,000 mg/kg body weight.[84]

Acute Oral Toxicity — Rats

In an acute oral toxicity study conducted under OECD Guideline No. 420, male and female Wistar rats (eight to 12 weeks old; 160 to 200 g body weight; five animals per group) were given via gavage 5,000 mg/kg body weight BCM-95 or corn oil as a vehicle control. The animals were fasted for three to four hours prior to oral dosing and one to two hours post-dosing. The animals were observed over 14 days for clinical signs before necropsy. No signs of toxicity were observed at the highest dose tested. Thus, the MTD, MLD, and LD_{50} for BCM-95 were all declared to be 5,000 mg/kg body weight.[85]

Rat 45-day Study

A 45-day toxicity study was conducted with female Sprague Dawley rats divided into four groups of five animals each. Three doses of BCM-95 mixed with normal rat chow to deliver 100, 250, or 750 mg/kg body weight daily for 45 days were compared to control animals. Physical changes, pharmacotoxic symptoms, body weight, and food intake were measured. The animals were sacrificed after 45 days and hematological, biochemical, and histological analyses were conducted. Continuous administration of BCM-95 did not produce any deaths or physical changes at all doses tested. The increases in body weight were not different from the control animals. There was no change in blood clotting time with any of the doses. There was a trend towards an increase in total leukocyte count, but the differential cell count remained unchanged. There were no changes in serum total protein, albumin, globulin, or glucose levels. In animals receiving the highest dose, serum alkaline phosphatase activity increased. In animals receiving the lowest dose, blood urea levels decreased. There was a dose-related trend towards a decrease in serum cholesterol but no changes in liver cholesterol or serum triglyceride levels. Histopathological evaluations did not reveal any lesions in liver sections. In conclusion, continuous exposure of BCM-95 to female rats for 45 days at doses up to 750 mg/kg body weight was well tolerated by the animals.[86]

Rat 90-day Study

A 90-day toxicity study (based upon OECD Guideline No. 408) was conducted with Sprague Dawley rats divided into four groups of 20 animals each (10 males and 10 females). Three doses of BCM-95 were mixed with normal rat chow to deliver 100, 500, or 1,000 mg/kg body weight daily for 90 days, administered via gavage. The fourth group of animals were given the vehicle (corn oil) and served as controls. The animals were observed daily for behavior, appearance, and potential signs of toxicity, as well as body weight and food consumption. The animals were sacrificed after 90 days and hematological, biochemical, and histological analyses were conducted. Two additional groups of control and high-dose animals (10 animals in each group) were kept under observation for an additional 28 days. Blood from all study animals was collected and analyzed for hematological and biochemical parameters. Organ tissues also were collected, weighed, and examined using histopathological techniques. There were no treatment-related toxic signs, symptoms, or deaths. There were no differences among groups in mean body weights or food consumption. There were no abnormal hematological findings or biochemical parameters. Organ weights and necropsy results did not show any signs of toxicity. The No Observed Adverse Effect Level (NOAEL) was determined to be > 1,000 mg/kg body weight.[87]

BCM-95 Genotoxicity — Mutagenicity, Teratology

BCM-95 was determined to be non-mutagenic at an oral dose of 2,000 mg/kg body weight in mice and rats according to the Mammalian Bone Marrow Micronucleus Test and the Mammalian Bone Marrow Chromosome Aberration Test, respectively.[88] BCM-95 was also determined to be non-mutagenic in the Ames Test (Bacterial Reverse Mutation Test), when tested in vitro against five strains of *Salmonella typhimurium*, at concentrations of 1 to 5 mg/plate, with or wihout metabolic activation.[89] On the basis of these three tests, BCM-95 can be considered non-mutagenic.

Mammalian Bone Marrow Micronucleus Test

A mammalian erythrocyte micronucleus test (based upon OECD Guideline No. 474) was conducted with mice. This test is designed to detect chromosomal damage caused by a test agent. Visualization of damage to the mitotic apparatus in erythroblasts in bone marrow is facilitated because these calls lack a main nucleus. The frequency of micronucleated polychromatic erythrocytes in animals to which the test agent is given is compared to vehicle controls and a known toxin.

In this experiment, a total of 60 Swiss albino mice were divided into three groups of 20 animals each (10 males and 10 females). The BCM-95 group received one dose of 2,000 mg/kg body weight and the control animals received corn oil, both administrated orally via gavage. The positive control group received cyclophosphamide intraperitoneally at a dose of 40 mg/kg body weight. Half of the animals were sacrificed at 24 hours post-dose and the remainder at 48 hours post-dose. Erythrocytes from the marrow of femur bones were fixed, stained, and examined. There was no observable effect on the micronuclei of the animals that received BCM-95, compared to the negative control. BCM-95 did not show any mutagenic potential, as measured via the micronucleus test.[88]

Mammalian Bone Marrow Chromosome Aberration Test

A mammalian bone marrow chromosomal aberration test (based upon OECD Guideline No. 475) was conducted in rats. The purpose of this test is to detect structural aberrations induced by test agents. In this experiment, a total of 60 Wistar albino rats were divided into three groups of 20 animals each (10 males and 10 females). The BCM-95 group received a single dose of 2,000 mg/kg body weight and the control animals received corn oil, both administrated orally via gavage. The positive control group received cyclophosphamide via intraperitoneal route at a dose of 50 mg/kg body weight. Half of the animals were sacrificed at 16 hours post-dose and the remainder at 40 hours post-dose. Two hours prior to sacrifice of the animals, they were injected intraperitoneally with colchicine (4 mg/kg body weight). Chromosomes were isolated from bone marrow cells, stained, classified, and scored. No evidence of numerical or structural aberrations was observed in samples from animals treated with BCM-95 or vehicle control. BCM-95 was declared to be non-mutagenic at a dose of 2,000 mg/kg body weight in rats.[88]

Ames Test (Bacterial Reverse Mutation Test)

The bacterial reverse mutation test is a common screen for genotoxic activity, particularly point mutation. Mutant strains of *Salmonella typhimurium* that have lost the ability to synthesize histidine are incapable of growing on a histidine-deficient medium, unless a reverse mutation has taken place. Some test agents will exert a mutagenic effect only after they have been metabolized, usually in the liver. For this reason, the test is run with and without metabolic activation.

BCM-95 was tested against five strains of *S. typhimurium* (TA-98, TA-100, TA-102, TA-1535, and TA-1537), with and without metabolic activation (S-9 liver fraction), at concentrations of 1, 2, 3, 4, and 5 mg/plate (according to OECD Guideline No. 471). Several known mutagens were used as positive controls. The results of all studies with BCM-95 were negative; there was no growth at any of the test concentrations, with or without metabolic activation. The sensitivity of the assay was confirmed by growth in the positive control plates. Under the conditions of this study, BCM-95 was found to be non-mutagenic.[89]

BCM-95 Human Safety Data

Clinical studies that used a dose of 500 mg twice daily for eight weeks to three months reported that BCM-95 was administered safely.[25-28] In another clinical study, BCM-95 was administered in a dose of 4 g daily for six months without significant adverse effects.[30] This study explicitly examined biochemical markers for indications of toxicity and is reported in detail below.

Safety parameters were examined in a clinical study with patients with Alzheimer's disease.[30] In this study, patients over 50 years old (N = 27, males and females) with a progressive decline in memory and cognitive function over the previous six months received 1 g or 4 g of BCM-95, powdered curcumin, or placebo, in addition to 120 mg standardized ginkgo leaf extract (no description provided) and any additional treatment deemed appropriate by their physicians.


Turmeric *Curcuma longa*
Photo ©2019 Steven Foster

Liver and kidney function was assessed using blood samples obtained at baseline, one month, and six months. The liver function tests included albumin, bilirubin, and ALT (also known as GPT). The kidney function indicators included plasma levels of sodium, potassium, and urea. There were no significant changes in these serum markers for liver and kidney function. Adverse events were mild and distributed among all groups — the largest number in the placebo group (n = 7), followed by the 1-g dose group (n = 6), and the smallest number in the 4-g dose group (n = 2). The most common adverse events were gastrointestinal complaints, followed by respiratory tract infections and falls or dizziness.

Lack of Interaction with NSAIDs

A three-arm study conducted with a total of 45 patients with RA who received BCM-95 (500 mg twice daily), diclofenac sodium (an NSAID; 50 mg twice daily), or both together did not report any interactions between these two treatments.[25] There were no changes to hematological or chemical parameters as measured in plasma samples, but effects on coagulation were not specifically measured.

Summary of Safety Information

Toxicological studies conducted with curcumin in rats, dogs, and monkeys at oral doses up to 3.5 g curcumin per kg body weight for up to 90 days did not produce any adverse effects.[75] No reproductive toxicity was observed in a study in which curcumin was administered orally to rats in doses up to 1 g/kg body weight daily for two successive generations.[78]

Phase I human clinical studies indicate that curcumin is not toxic even at a very high dose of 12 g per day. The reported adverse events were mild including diarrhea, headache, rash, and yellow stools. The MTD could not be determined in this study because amounts more than 12 g could not be consumed comfortably.[24]

BCM-95 has been tested in toxicological studies in rodents and was found to be safe. A study conducted in rats orally administered 100, 500, or 1,000 mg/kg body weight daily for 90 days determined that the NOAEL was greater than the highest dose administered.[87] BCM-95 was determined to be non-mutagenic at an oral dose of 2,000 mg/kg body weight in mice and rats.[88] BCM-95 did not cause chromosomal aberrations.[88]

A human clinical study designed to examine safety parameters, in which BCM-95 was administered in a dose of 4 g daily for six months, did not find any significant changes in serum markers for liver and kidney function.[30] Adverse side effects were mild and the most common was gastrointestinal discomfort.

The US FDA accepted BCM-95 as Generally Recognized as Safe (GRAS) in a no objection letter dated July 11, 2017 (GRAS Notice No. GRN 000686).[90]

Drug Interactions

Some preclinical data indicate that co-administration of curcumin with NSAIDs or anticoagulant drugs might result in an increased risk of bleeding.[79] In a human clinical study cited above, BCM-95 was co-administered with the NSAID diclofenac sodium without producing any significant adverse effects.[25] However, any potential effects of the combination therapy on the risk of bleeding was not part of the evaluation.

Curcumin may interfere with drugs metabolized by the CYP enzyme system.[79] The data that support this caution come from in vitro experiments using enzymes and human cell lines. Only two clinical studies have explored the effects of standard curcumin on enzymes involved in drug metabolism. In one study, curcumin caused an increase of 49% in CYP2A6 activity and an inhibition of 29% in CYP1A2 activity. There was no significant effect on NAT2 or XO activity.[82] The second study suggested that curcumin modified P-gp activity in the intestine by occupying receptor sites.[83] Further studies are needed to determine the clinical significance of these reports.

REGULATORY STATUS WORLDWIDE

Australia: BCM-95 is a listed ingredient as an Australian Approved Name (AAN) on the Australian Register of Therapeutic Goods.

Belgium: Food Supplement

Canada: Natural Health Product

France: Dietetic Supplement

India: Nutritional Supplement

Japan: Dietary Supplement

South Africa: Complementary and Alternative Medicine

Taiwan: Food Ingredient

United States: Dietary Supplement; GRAS (Generally Recognized As Safe), notification to US Food and Drug Administration October 21, 2016. "No objection letter from FDA, dated July 11, 2017 (GRAS Notice No. GRN 000686).

PATENTS

Patents Granted

[Note: According to information provided by the manufacturer of BCM-95, as of the end of 2018, the company holds 33 patents in the European Union, 13 in the United States, and 2 in Japan, plus multiple patents in India. The following is a comprehensive but not exhaustive listing of these patents.]

European Union: Multiple patents for Application and for Method of Making Composition have been filed in the following countries in the European Union:

European Patent Application No. 11765166, filed November 2, 2012. Formulation of Curcumin with Enhanced Bioavailability of Curcumin and Method of Preparation and Treatment Thereof. Granted. Listed as European Patent (EP) 2555787 for Belgium, Denmark, Finland, France, Germany, Greece, Itay, Netherlands, Norway, Poland, Spain, Sweden, Switzerland, United Kingdom

European Patent Application No. 05750098.5, filed May 30, 2005. A Composition to Enhance the Bioavailability of Curcumin. Granted. Listed as European Patent (EP) 1890546 for Austria, Belgium,Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Switzerland/Liechtenstien, Luxembourg, Netherlands, Poland, Portugal, Slovakia, Spain, Sweden, United Kingdom

India: Multiple patents have been filed in India:

India: Indian Patent Application No. 226/CHE/2013, filed January 17, 2013. Sustained Release Formulations of Curcuminoids and Method of Preparation Thereof. **Pending** (as of January, 2019)

Indian Patent Application No. 4128/CHE/2012, filed October 3, 2012. Formulation of Curcumin with Enhanced Bioavailability of Curcumin and Method of Preparation and Treatment Thereof. Pending (as of January, 2019)
Indian Patent Application No. 2356/CHE/2010, filed August 16, 2010. A Pharmaceutical Composition of Reformulated Turmeric Extract and a Method Thereof. Pending (as of January, 2019)
Indian Patent No. 200430, issued May 2006. Antony B (Arjuna Natural Extracts Ltd.; Alwaye, Kerala, India). A Process and Technique to Enhance the Absorption of Curcuminoids.

Japan: Japanese Patent No. 5039032, issued July 13, 2012. Antony B (Arjuna Natural Extracts Ltd.; Alwaye, Kerala, India). A Composition to Enhance the Bioavailability of Curcumin.

Japanese Patent No. 2012130299, issued April 4, 2014. Antony B (Arjuna Natural Extracts Ltd.; Alwaye, Kerala, India). Composition to Enhance the Bioavailability of Curcumin.

United States: US Patent No. 8,993,013, issued March 31, 2015. Antony B (Arjuna Natural Extracts, Ltd.; Alwaye, Kerala, India). Composition to Enhance the Bioavailability of Curcumin. Also published as the following patents:

Application No.	Filing Date	Patent No.	Issue Date Type of Patent
US 11/635,599	December 8, 2006	7,736,679	June 15, 2010 Composition
US 12/662,740	April 30, 2010	7,879,373	February 1, 2011 Process
US 12/073,864	March 11, 2008	7,883,728	February 8, 2011 Composition
US 12/926,985	December 21, 2010	8,153,172	April 10, 2012 Method of preparation of gelatin capsule
US 13/385,717	March 5, 2012	8,623,431	January 7, 2014 Product by process
US 12/926,980	December 21, 2010	8,197,869	June 12, 2012 Process
US 13/506,572	April 30, 2012	8,329,233	December 11, 2012 Process
US 13/645,031	October 4, 2012	8,859,020	October 14, 2014 Application
US 13/674,249	November 12, 2012	8,993,013	March 31, 2015 Product by process
US 14/094,725	December 2, 2013	8,895,087	November 25, 2014 Composition & process
US 14/206,044	March 12, 2014	9,492,402	November 15, 2016 Product by process & Application
US 14/476,555	September 3, 2014	10,159,654	December 25, 2018 Enhanced Bioactivity

MANUFACTURER INFORMATION

Manufacturer: Arjuna Natural Extracts Ltd.; Alwaye, Kerala, India. Website: www.arjunanatural.com.
Importer into the United States: Arjuna Natural Extracts, 600 E. John Carpenter Fwy., Suite 380, Irving, TX 75062, USA. Email: usa@arjunanatural.com.
Distributor in North America (for Health/Natural Food Stores and Professional Practitioner sales channels): EuroPharma USA; 955 Challenger Dr., Green Bay, Wisconsin 54311. Website: www.EuroPharmaUSA.com.

CONFLICT OF INTEREST DISCLOSURE

The primary preparation of this monograph was by Marilyn L. Barrett, PhD, of Pharmacognosy Consulting in Mill Valley, California, USA. This document was formally edited and peer-reviewed by independent medicinal plant scientists with expertise in the areas of herbs and medicinal plants, particularly turmeric and curcumin, under the auspices of the American Botanical Council (ABC), an independent, tax-exempt [under the US Internal Revenue Service code section 501(c)(3)], non-profit research and education organization in Austin, Texas, USA (www.herbalgram.org). Funding for the research, compiling, writing, editing, peer review, copyediting, layout, and digital and print publication of this monograph was provided by an unrestricted educational grant to ABC by EuroPharma, Inc. of Green Bay, Wisconsin, USA. EuroPharma, Inc. is a Sponsor Member of ABC. Sponsor Members do not influence the policies or editorial content of ABC publications.

DISCLAIMER

This publication is intended and designed to present all relevant published pharmacological, toxicological, and human clinical research studies on BCM-95, a patented proprietary extract of turmeric rhizome. The information presented herein is for educational purposes only and should not be misinterpreted as an endorsement or recommendation by the American Botanical Council (ABC) of the BCM-95 (Curcugreen) ingredient, commercial dietary supplement and/or other finished consumer products containing BCM-95, the Indian manufacturer of BCM-95, the United States importer of BCM-95, or any company marketing commercial consumer products containing BCM-95 in the United States or internationally. Consistent with its nonprofit educational mission, ABC does not endorse or recommend commercial ingredients or consumer products.

ENDNOTES

* A solvent is a substance that dissolves or extracts a chemical entity, resulting in a solution.

† USP 32nd Revision-*National Formulary 27th ed.* (USP 32–NF 27) Method <467>. Rockville, MD: United States Pharmacopeial Convention; 2009.

‡ Arjuna internal report titled "Long Term Stability Data: Bio-Curcumin® (BCM-95CG®)."

§ Correspondence with EuroPharma reveals that the dogs in this veterinary study were not sacrificed, and the only invasive procedure was drawing blood to measure serum curcumin levels in an effort to determine the optimal type of curcumin absorption for use in dogs with inflammatory diseases and cancer.

** A conversion factor of 1.053 (density of dog blood) can be used to obtain the µg/mL value.

†† The ratios of ingredients in the mixture were not given in the paper.

‡‡ A gene that in certain circumstances can transform a cell into a tumor cell.

§§ This study was available only in abstract form representing a poster presentation.

*** National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association diagnostic criteria.

††† Study was published as a meeting abstract representing a poster presentation. The full study has not yet been published.

‡‡‡ Studies conducted with curcumin products with added bioavailability enhancers or enhanced formulations are not included here.

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