

BIOPERINE®

PRODUCT WRITE UP

Black Pepper extract or Bioperine® is a patented standardized extract from the dried fruits of *Piper nigrum* and is standardized for minimum 95% Piperine.



Piper nigrum fruits

Bioperine® is obtained from the black pepper fruit that is cultivated in the damp, nutrient-rich soil regions of southern India. The delicate pepper berries are harvested just prior to ripening and then sun dried to assure optimum maturity and quality. The extract of piperine, called Bioperine® has been clinically tested in the United States. Bioperine® significantly enhances the bioavailability of various supplement nutrients through increased absorption.

History and Traditional Uses:

Black pepper was well known to the ancient world. It first appeared in the Sanskrit literature of India some 3,000 years ago. The first Westerner who is known to have encountered black pepper was Alexander the Great when he marched to the Punjab region in northern India in 326 B.C. He sampled it in some

food under the local name of pippali. This spice was eventually exported to the Persians who had difficulty pronouncing the Indian name for it. A name change came about under King Darius who issued a royal edict for everyone to start calling it pipari instead.

Pepper, one of the oldest known spices, is native to tropical Asia. Black pepper has been used traditionally as a spice since several years. It is considered an important healing spice in Ayurveda. Black pepper is a warming spice and contributes the pungent taste. India is one of the largest producers of pepper in the world.

A recognized feature of the 6000-year-old practice of Ayurveda is its preoccupation with the proper functioning of the digestive tract, specifically the digestion and absorption of nutrients. Nearly two-thirds of all traditional Ayurvedic formulas contain a special blend of ingredients, which includes black pepper, for this purpose.

There are various reasons discussed in scientific literature for the unfavorable nutritional status of a given population, but the focus essentially comes down to one single problem-nutrient bioavailability. By far, the greatest factors that reduce the bioavailability of nutrients are those that diminish the intestine's absorption capacity. Even today, there is a growing consensus among nutritionists that the obstacle to better nutrition clearly lies in the efficient delivery of nutrients to the body.

It is not what you eat that counts, it is what you absorb.

Bioavailability and Mechanism:

Bioperine® is promoted as a “Bioavailability Enhancer” and a natural “Thermonutrient”. It may be co-administered with various nutrients for both human and animal health.

Bioavailability is a term used by several branches of scientific study to describe the way chemicals are absorbed by humans and other animals. Bioavailability is a measurement of the extent of a therapeutically active drug that reaches the systemic circulation and is available at the site of action. It is a measurement of the

degree to which or rate at which a drug or other substance is absorbed or becomes available at the site of physiological activity after administration.

It is also referred to as measure of the amount of drug that is actually absorbed from a given dose.

The metabolic process that generates energy at the cellular level in the human body is called **thermogenesis**. Although thermogenesis has been identified as a key factor in weight management, it has also been identified as playing an integral role in utilizing the daily food and nutrients that the human body consumes. It sets in motion the mechanisms that lead to digestion and subsequent gastrointestinal absorption.

Piperine, in the patented form of **Bioperine**[®] enhances the body's natural thermogenic activity - hence the term **Thermonutrient**[®].

This enhancement may be explained as a means of increasing the thermal energy sufficient to "power up" the mechanism related to thermogenesis. This in turn results in increased metabolic processes that creates a "demand" for "supply" of a broad range of nutrients that contribute to metabolism, i.e. vitamins, minerals, herbals, amino acids, etc.

It is as if Bioperine[®] activates a metabolic paddle wheel, of sorts, that selectively provides a more efficient mode of nutrient transportation into the blood.

This remarkable nutrient enhancement of Bioperine[®] has been attributed to the 3 non-specific mechanisms:

- A. Increases blood supply to the GI tract
- B. Increases emulsifying content of the gut
- C. Increases active nutrient transport

The subtle, yet potent properties of Bioperine[®] have been measured in several clinical studies with healthy volunteers in the U.S. These studies measured the absorption of three distinct categories of products. All studies used Bioperine[®] in the amount of 5 mg per dose.

The categories evaluated with and without Bioperine® were

- a. fat- soluble (beta-carotene),
- b. water-soluble (vitamin B 6)
- c. mineral (selenium, in the form of selenomethionine).

Gastrointestinal absorption of all the studied nutrients, as measured by amounts present in the blood, increased dramatically when administered with Bioperine® as compared to the control group receiving the nutrient alone.

Selenium levels increased by 30%, beta-carotene increased by 60%, and the vitamin B 6 increase was slightly higher than beta-carotene.

Effect of Bioperine® on Beta-Carotene absorption

Bioperine® (5mg) was co-administered with Beta-Carotene (15 mg) as capsules to a group of 12 subjects, on regular self-selected diets. The subjects were divided into 2 groups and the trial performed.

The design and methodology details are summarized:

Double-Blind, Crossover Design *		
Volunteer #'s	Phase I	Phase II
# 1 thru # 6	β -Carotene+ placebo	β -Carotene+ Bioperine®
# 7 thru # 12	β -Carotene+ Bioperine®	β -Carotene+ placebo

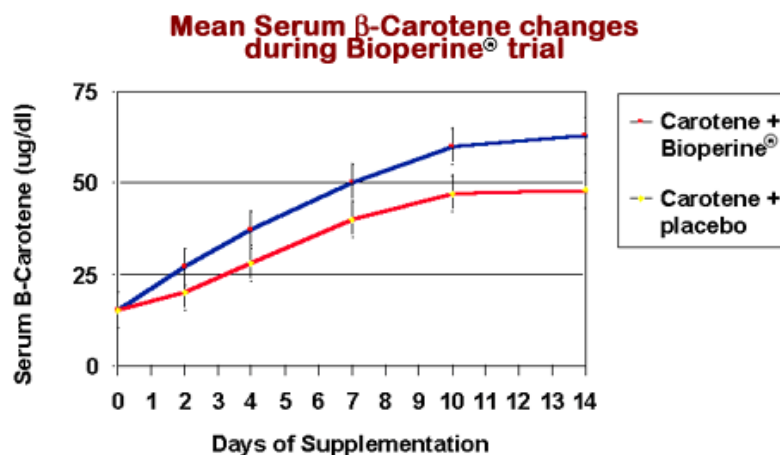
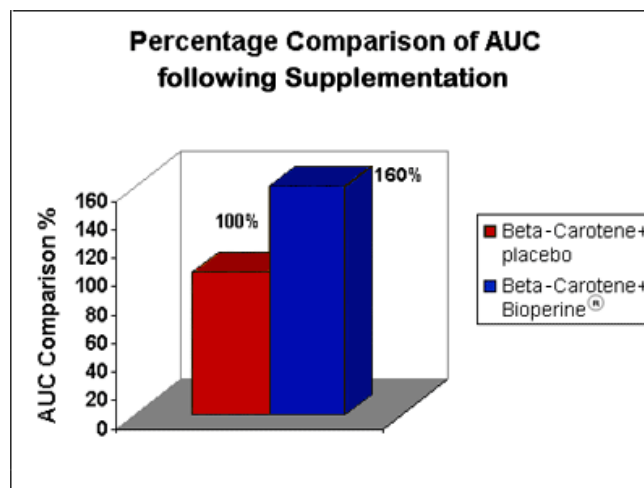
* Phase I & Phase II supplementation periods occurred 12 weeks apart.

Serum β -Carotene AUC Levels at Day 14

Treatment	AUC ug/dl/day	% Difference
β -Carotene+ placebo	272.0 + 47.6	-
β -Carotene+ Bioperine [®]	435.2 + 74.2	160

Comparison of AUC indicated a statistically significant difference ($p < 0.0001$).

Effect of Bioperine[®] on the mean serum β -Carotene levels during a 14 day supplementation trial is represented below.



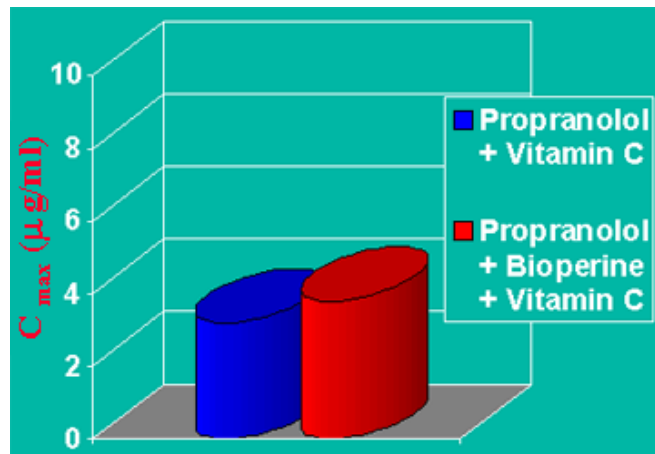
The relative bioavailability of β -Carotene is improved during a 14 day supplementation trail when it is ingested with Bioperine[®].

Effect of Bioperine[®] on Vitamin C absorption

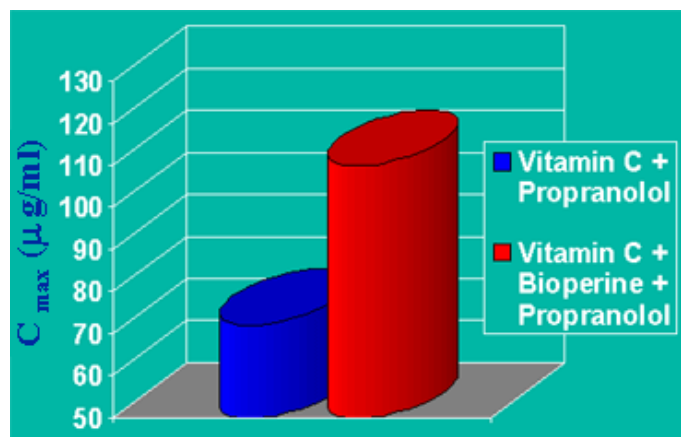
The increased bioavailability of Vitamin C with the co-administration of Bioperine[®] in presence of Drug, Propranolol HCl was studied. This study was conducted on 8 healthy male subjects and divided into two groups of 4 each.

The results are summarized below.

Propranolol HCl plasma levels increased by 9.4% in the Bioperine[®] group.

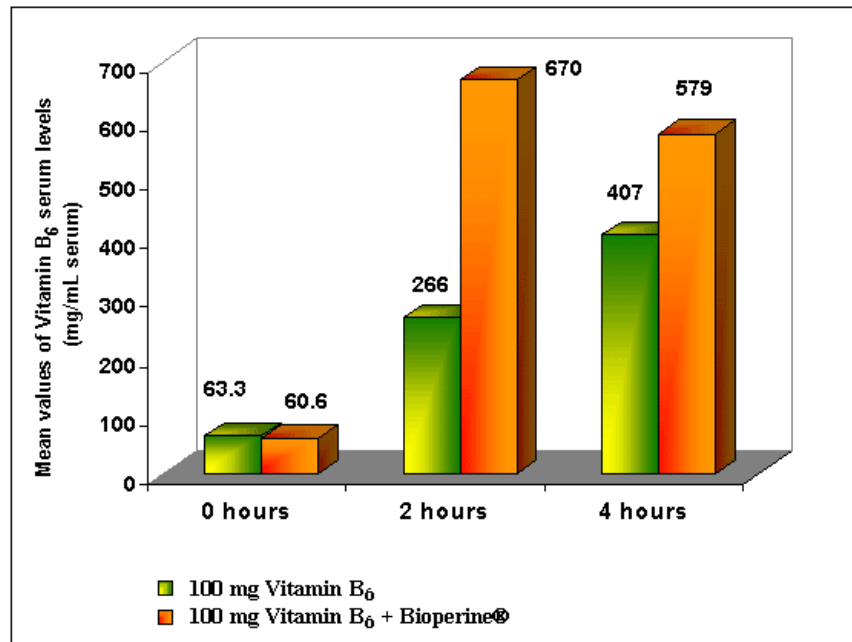


However, the Vitamin C levels in plasma, increased by 39.2% in the Bioperine[®] group.



Effect of Bioperine® on Vitamin B₆ absorption

Six healthy volunteers participated of which 3 received 100mg VitaminB₆ with 5mg Bioperine® and the other 3 received 100mg VitaminB₆ alone. The results are represented below.



Effect of Bioperine® on CoQ10 absorption

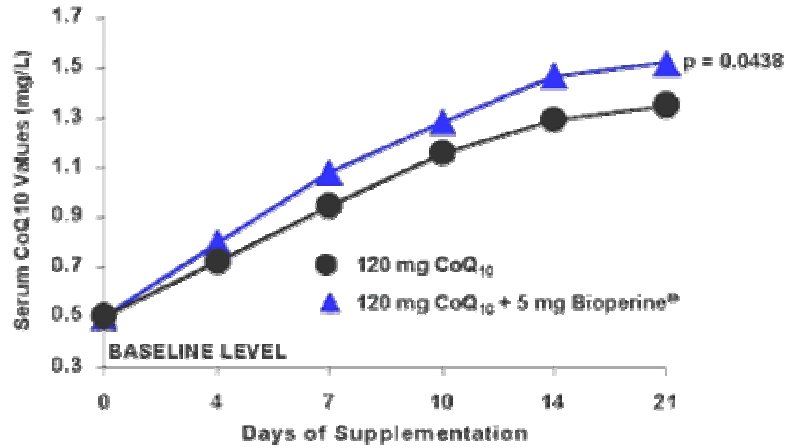
12 healthy volunteers we selected for this study. They were divided into two groups each of 6 each. One group was given 120mg CoQ10 with 5mg of Bioperine while the other group was given 120mg CoQ10 with 5mg of placebo.

The duration of the trial was 21days.

There are inherent unique difficulties in the pharmacokinetic evaluation of CoQ10 due to

- Slow absorption from GI tract
- Enterohepatic recycling
- Endogenous Co Q10 production

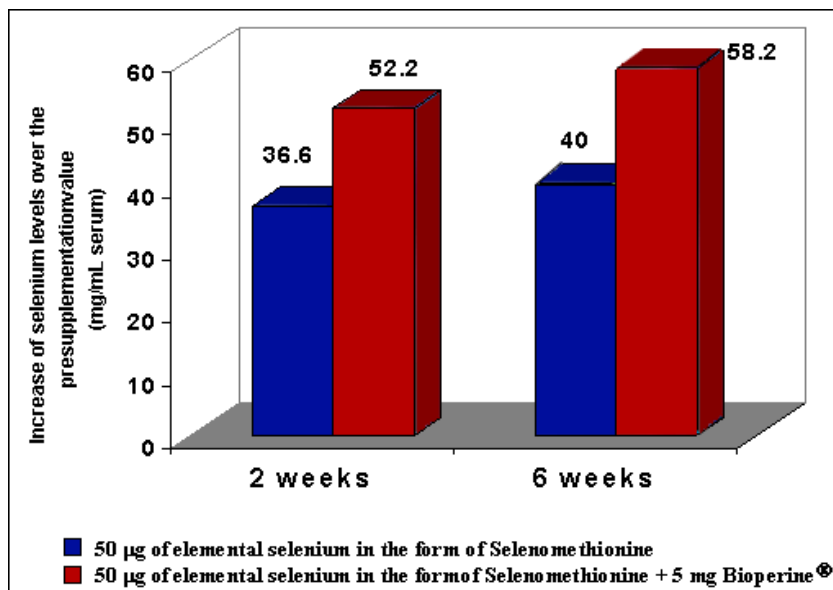
The results of the study, on the effect of Bioperine® on serum CoQ10 levels during a 21 day supplementation trial is as follows.



Effect of Bioperine[®] on co-administration with Mineral supplements like L-Selenomethionine

This study was done on 10 healthy volunteers divided into 2 groups of 5 each. L-Selenomethionine equivalent to 50µg elemental Se was given along with 5mg Bioperine[®] to one group while the other was given only L-Selenomethionine equivalent to 50µg elemental Se

Effect of Bioperine[®] on serum selenium levels during a 6 week supplementation trial is illustrated below.



Effect of Bioperine[®] on the bioavailability of Curcumin

The bioavailability of curcumin co-administered with Bioperine® was evaluated in both animals and human volunteers.

Curcumin, is a phenolic phytochemical obtained from turmeric (*Curcuma longa* L). It has been scientifically researched that Curcumin has a number of effective therapeutic potential.

However, it has been found that the therapeutic effectiveness of curcumin is often limited due to its poor absorption from the GI tract. When taken orally only traces appear in the blood whereas most of the dose is excreted through the feces.

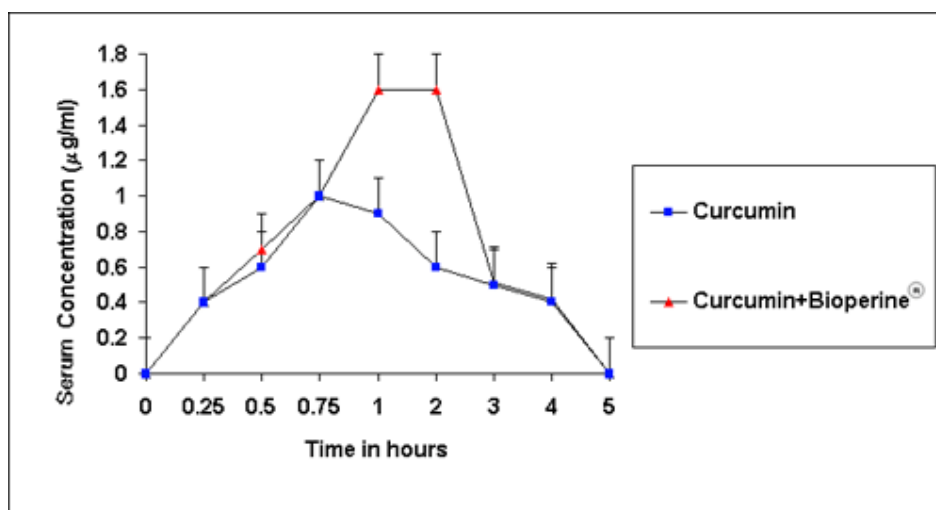
Piperine was found to enhance the bioavailability of Curcumin both in preclinical studies and in studies on human volunteers.

BIOAVAILABILITY STUDIES: CURCUMIN & BIOPERINE®

Pharmacokinetic parameters (mean ± SEM) of oral curcumin 2g/kg alone and in combination with Bioperine® 20 mg/kg in rats (n= 6).

Parameters	Curcumin alone 2 g/kg	Curcumin + Bioperine® 2g/kg + 20mg/kg
C_{max} (mg/ml)	1.35 ± 0.23	1.80 ± 0.16
T_{max} (h)	0.83 ± 0.05	1.29 ± 0.23"
t_{1/2(a)} (h)	0.31 ± 0.07	0.47 ± 0.03
t_{1/2(el)} (h)	1.70 ± 0.58	1.05 ± 0.18"
AUC_(0 - tn) (mg/h/ml)	2.36 ± 0.28	3.64 ± 0.31
V_d (L/kg)	1366.00 ± 248.70	782.90 ± 193.90
Cl(L/h)	713.00 ± 12.00	495.90 ± 37.08"

- "P < 0.02: Statistical significance by Student's "t" test
- C_{max}: Maximum serum concentration
- T_{max}: Time to reach maximal serum concentration
- t_{1/2(a)}: Absorption half-life
- t_{1/2(el)}: Elimination half-life
- AUC(0 - tn): Area under the concentration time curve
- V_d: Volume of distribution
- Cl: Total clearance

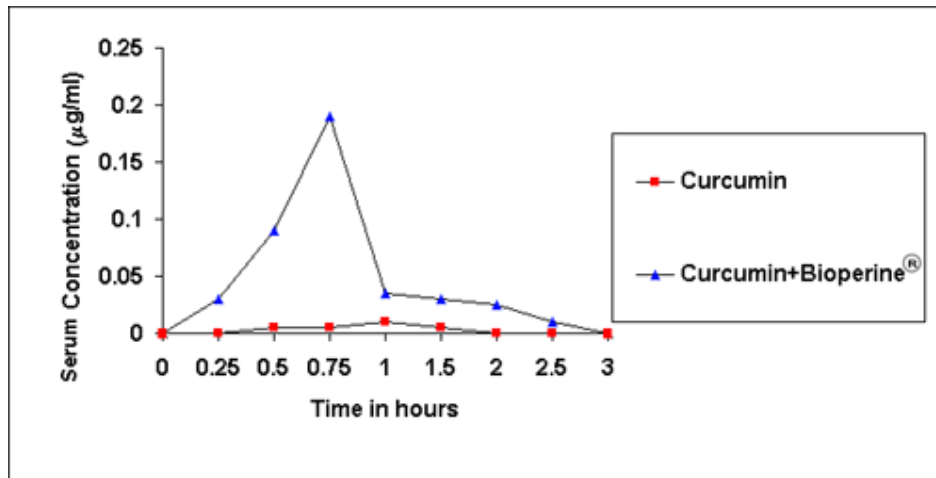


Effect of Bioperine® on serum concentrations of curcumin in rats.

Bioavailability Studies - Curcumin & Bioperine on Healthy Humans

Pharmacokinetic parameters (mean + SEM) of oral curcumin 2 g alone and in combination with Bioperine® 20 mg in normal healthy volunteers (n=8).

Parameters	Curcumin alone 2 g	Curcumin+Bioperine® 2g+20mg
C _{max} (mg/ml)	0.006 ± 0.005	0.18 ± 0.03
T _{max} (h)	1	0.69 ± 0.07
t ¹ / _{2(a)} (h)	-	0.11 ± 0.02
t ¹ / _{2(el)} (h)	-	0.41 ± 0.17
AUC _(0-t_n) (mg/h/ml)	0.004	0.08 ± 0.01
V _d (L/kg)	-	202.60 ± 78.94
Cl(L/h)	-	7.33 ± 1.25
F (Relative bioavailability)	-	2000%



Effect of Bioperine® on Serum Concentrations of Curcumin in Human Volunteers

Nutritional substances with which Bioperine® can be used for increased nutrient absorption:

The following groups of Nutritional materials may be co-administered with Bioperine® for enhance bioavailability.

Herbal extracts :(e.g. Curcumin, Boswellia serrata, Ashwagandha, Capsaicin, Bacopa, Centella, Green tea polyphenols etc.,)

Water-soluble vitamins :(e.g. Vitamin B1, Vitamin B2, Niacinamide, Vitamin B6, Vitamin B12, Folic acid and Vitamin C)

Fat-soluble vitamins :(e.g. Vitamin A, Vitamin D, Vitamin E, and Vitamin K)

Antioxidants :(e.g. Vitamin A, Vitamin C, Vitamin E, alpha-carotene, beta-carotene, beta-cryptoxanthin, lycopene, lutein/zeaxanthin, pine bark bioflavonoids complex, germanium, selenium and zinc).

Amino acids :(e.g. lysine, isoleucine, leucine, threonine, valine, tryptophan, phenylalanine, and methionine)

Minerals :(e.g calcium, iron, zinc, vanadium, selenium, chromium, iodine, potassium, manganese, copper and magnesium).

Bioperine® Vs Black pepper:

According to clinical reports, having Bioperine® in the "right place at the right time" in the digestive tract with supplemented nutrient results in enhanced absorption.

Besides if piperine were to remain captive in the form of raw black pepper, it will take time for its bioavailability enhancing property to be released. Therefore, a purified extract of piperine is necessary to get the increased absorption.

Suggested use level of Bioperine®

The recommended dosage of Bioperine® for increased nutrient absorption is up to 15 mg per day in 3 divided doses of 5 mg each.

This is relatively low when compared to the toxic levels as determined by various studies.

Bioperine® is not toxic at the recommended use level.

Black pepper, which contains approximately 5-9% piperine, is listed by the US FDA as a herb, Generally regarded as Safe (GRAS) for its intended use as spice, seasoning and flavoring (21 CFR 100,01 182,10, 1 82-20).

Based on black pepper imports it is estimated that the average consumption of black pepper in the US is about 359mg per person per day. (Data based on doctoral thesis by Shore Scott Kindell, Drexel University, 1984.)

From this statistical data, **the average consumption of Piperine per person per day is calculated as 17.95 – 32.3 mg.**

Bioperine® standardized for 95% Piperine is given at a maximum dosage of up to 15 mg per day in three divided doses. This is sufficient to deliver enhanced Nutrient absorption.

Hence Bioperine® at the recommended dosage is not toxic and this has been validated.

For more information do visit <http://www.bioperine.com>

Reference:

Shoba, G., Joy, D., Joseph, T., Majeed, M., Rajendran, R., and Srinivas, P.S.S.R. (1998) Influence of Piperine on the pharmacokinetics of curcumin in animals and human volunteers. Planta Med. 64(4); 353-356

Vladimir Badmaev, M.D., Ph.D., Muhammed Majeed, Ph.D. and Edward P. Norkus Ph.D. Piperine, an alkaloid derived from black pepper, increases serum response of beta-carotene during 14-days of oral beta-carotene supplementation. *Nutrition Research* (1999) 19(3) 381-388.

Vladimir Badmaev, M.D., Ph.D., Muhammed Majeed, Ph.D., and Lakshmi Prakash, Ph.D. Piperine Derived From Black Pepper Increases The Plasma Levels Of Coenzyme Q₁₀ Following Oral Supplementation. *J. Nutr. Biochem.* (2000) 11: 109-113.