BioPerine

Influence of Piperine on the Pharmacokinetics of Curcumin in Animals and Human Volunteers.

Planta Med. (1998) 64(4):353-356 G. Shoba, D. Joy, T. Joseph, M. Majeed, R. Rajendran and P. S. Srinivas

Abstract:

The medicinal properties of curcumin obtained from *Curcuma longa* L. cannot be utilized because of poor bioavailability due to its rapid metabolism in the liver and intestinal wall. In this study, the effect of combining piperine, a known inhibitor of hepatic and intestinal glucuronidation, was evaluated on the bioavailability of curcumin in rats and healthy human volunteers . When curcumin was given alone, in the dose 2 g/kg to rats, moderate serum concentrations were achieved over a period of 4 h. Concomitant administration of piperine 20 mg/kg increased the serum concentration of curcumin for a short period of 1-2h post drug. Time to maximum was significantly increased ($P < 0.02$) while elimination half life and clearance significantly decreased ($P< 0.02$), and the bioavailability was increased by 154%. On the other hand in humans after a dose of 2g curcumin alone, serum levels were either undetectable or very low. Concomitant administration of piperine 20 mg produced much higher concentration from 0.25 to 1 h post drug ($P< 0.01$ at 0.25 and 0.5 h; $P< 0.001$ at 1 h), the increase in bioavailability was 2000%. The study shows that in the dosges used, piperine enchances the serum concentration, extent of absorption and bioavailability of curcumin in both rats and humans with no adverse effects.

Piperine Enhances the Bioavailability of the Tea Polyphenol (-)-Epigallocatechin-3-gallate in Mice

Joshua D. Lambert, Jungil Hong, Dou Hwan Kim, Vladimir M. Mishin, and Chung S. Yang J. Nutr. 134: 1948–1952, 2004.

ABSTRACT (-)-Epigallocatechin-3-gallate (EGCG), from green tea (*Camellia sinensis*), has demonstrated chemopreventive activity in

animal models of carcinogenesis. Previously, we reported the bioavailability of EGCG in rats (1.6%) and mice (26.5%). Here, we report that cotreatment with a second dietary component, piperine (from black pepper), enhanced the bioavailability of EGCG in mice. Intragastric coadministration of 163.8 μmol/kg EGCG and 70.2 μmol/kg piperine to male CF-1 mice increased the plasma C_{max} and area under the curve (AUC) by 1.3-fold compared to mice treated with EGCG only. Piperine appeared to increase EGCG bioavailability by inhibiting glucuronidation and gastrointestinal transit. Piperine (100 μmol/L) inhibited EGCG glucuronidation in mouse small intestine (by 40%) but not in hepatic microsomes. Piperine (20 μmol/L) also inhibited production of EGCG-3"-glucuronide in human HT-29 colon adenocarcinoma cells. Small intestinal EGCG levels in CF-1 mice following treatment with EGCG alone had a C_{max} = 37.50 ± 22.50 nmol/g at 60 min that then decreased to 5.14 ±1.65 nmol/g at 90 min; however, cotreatment with piperine resulted in a C_{max} = 31.60 ± 15.08 nmol/g at 90 min, and levels were maintained above 20 nmol/g until 180 min. This resulted in a significant increase in the small intestine EGCG AUC (4621.80 ± 1958.72 vs. 1686.50 ± 757.07 (nmol/g-min)). EGCG appearance in the colon and the feces of piperine-cotreated mice was slower than in mice treated with EGCG alone. **The present study demonstrates the modulation of the EGCG bioavailability by a second dietary component and illustrates a mechanism for interactions between dietary chemicals.**

Piperine, an Alkaloid derived from Black pepper increases serum response of Beta- Carotene during 14-Days of Oral Beta-Carotene Supplementation.

Nutrition Research, Vol 19. No 3, pp 381-388 Vladimir Badmaev MD, PhD, Muhammed Majeed PhD, Edward P. Norkus PhD

The effectiveness of an extract from the fruit of black pepper, consisting of a minimum of 98.0% pure alkaloid piperine, was evaluated for its ability to improve serum response of beta-carotene during oral supplementation using a double- blind, crossover study design. Subjects were randomly selected to ingest a daily beta-carotene dose (15 mg) either with 5 mg of piperine or placebo during each of two 14-day supplementation periods. Inter-subject variability in pre-supplementation serum beta-carotene levels was minimized by

limiting the selection of volunteers to healthy, adult males with fasting serum beta-carotene values <20 µg/dL. The results indicate that significantly greater increases (P<0.0001) in serum beta- carotene occurred during supplementation with beta- carotene plus piperine (49.8± 9.6 µg/dL vs 30.9± 5.4 µg/dL) compared to beta- carotene plus placebo. Supplementation with beta- carotene plus piperine for 14 days produced a 60% greater increase in area under the serum beta - carotene curve (AUC) than was observed during supplementation with beta- carotene plus placebo. **We suggest that the serum response during oral beta-carotene supplementation is improved through the non-specific, thermogenic property(s) of piperine described in this paper as thermonutrient in action**.

Piperine derived from black pepper increases the plasma levels of coenzyme Q10 following oral supplementation.

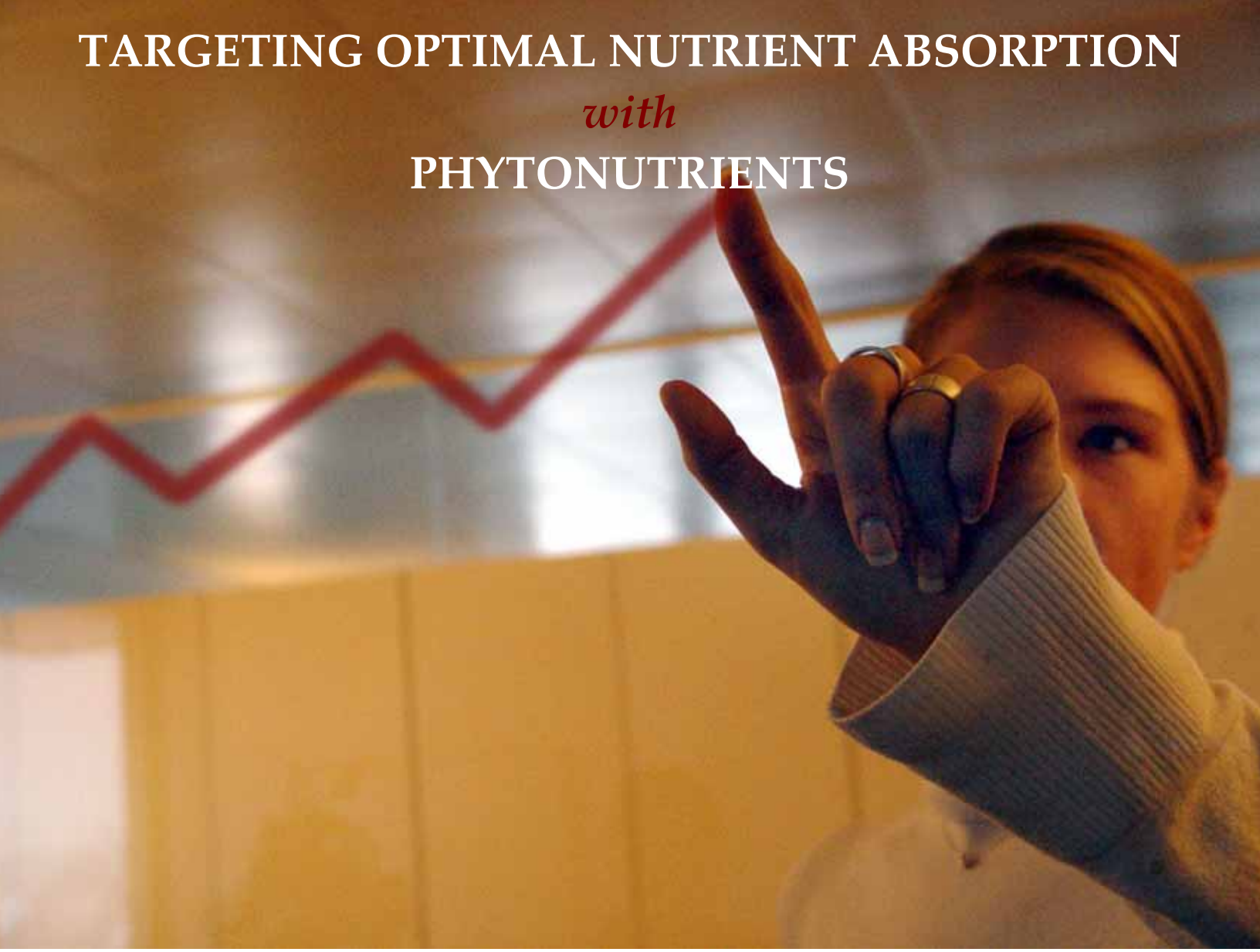
Vladimir Badmaev, Muhammed Majeed, and Lakshmi Prakash
J. Nutr. Biochem. 11:109 –113, 2000

An extract from the fruits of black pepper consisting of a minimum of 98% pure piperine was evaluated in a clinical study using a double-blind design. The relative bioavailability of 90 mg and 120 mg of coenzyme Q10 administered in a single-dose experiment or in separate experiments for 14 and 21 days with placebo or with 5 mg of piperine was determined by comparing measured changes in plasma concentration. The inter-subject variability was minimized by limiting the selection of individuals to healthy adult male volunteers with (presupplementation) fasting coenzyme Q10 values between 0.30 and 0.60 mg/L. The results of the single-dose study and the 14-day study indicate smaller, but not significant, increases in plasma concentrations of coenzyme Q10 in the control group compared with the group receiving coenzyme Q10 with a supplement of piperine. Supplementation of 120 mg coenzyme Q10 with piperine for 21 days produced a statistically significant (p5 0.0348), approximately 30% greater, area under the plasma curve than was observed during supplementation with coenzyme Q10 plus placebo. **It is postulated that the bioenhancing mechanism of piperine to increase plasma levels of supplemental coenzyme Q10 is nonspecific and possibly based on its description in the literature as a thermonutrient.**

TARGETING OPTIMAL NUTRIENT ABSORPTION

with

PHYTONUTRIENTS



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SABINSA CORPORATION

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INTRODUCTION

Do all nutritional supplements consumed, or all topically applied products provide optimal health benefits? A lot depends upon how well they are absorbed along their delivery route. Bioavailability encompasses availability, absorption, retention and utilization of nutrients. Absorption in the body is a key factor for the nutrient to be biologically effective.

NUTRIENT DELIVERY THROUGH THE SKIN AND THE GASTROINTESTINAL TRACT

The skin is the largest organ in the body. It has far-reaching effects such as being a barrier to the environment, an interface with the outside world, and the capability to accentuate aesthetic appeal and beauty. The skin also participates in nourishing and healing the body. It contains actively metabolizing cells that constantly imbibe nutrients and facilitate their transport to the underlying tissues and organs in the body. Simultaneously with the "intake" processes, metabolic wastes are excreted through perspiration.

Conventional nourishment is conveyed through the skin from environmental sources such as light, moisture, and sensory stimuli. These inputs affect neurohormones. Noxious substances in the environment trigger the immune response. Deliberately applied substances and stimuli that can potentially heal, renew and revitalize the body can be similarly conveyed through the skin. It is not surprising therefore, that pharmacologists and cosmetologists alike, look to the skin as a potential delivery pipeline for nutrients and drugs. By analogy, the skin functions quite like the gastrointestinal tract.

ENHANCING NUTRIENT DELIVERY THROUGH THE GASTROINTESTINAL TRACT WITH A UNIQUE PHYTONUTRIENT

The spicy or "hot" taste of pepper when sprinkled on food is well known. The perception of heat is stronger when fresh pepper is used. This heat is in fact a manifestation of the biological activity of some of the active compounds found in pepper, the most notable of these being piperine. Black and long peppers stimulate the skin as well as the tongue. They have therefore also found wide use in topical applications.

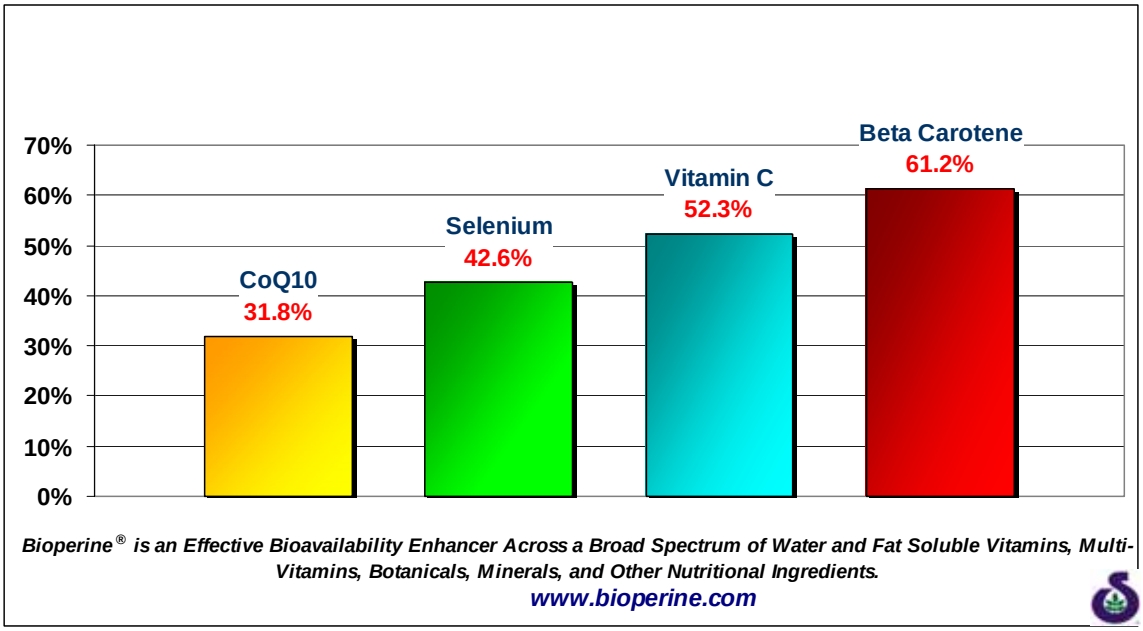
BioPerine®[1] is a standardized extract from the fruits of *Piper nigrum* L. (black pepper) or *Piper longum* L. (long pepper). It contains a minimum piperine content of 95% compared to the 3-9% and 3-5% found in raw forms of *Piper nigrum* and *Piper longum*, respectively. BioPerine may be co-administered with various nutrients for both human and animal health.

Nutritional materials that are benefited by co-administration with BioPerine, include the following groups:

- Herbal extracts: for example, Curcuminoids, *Boswellia serrata* extract, Ashwagandha, Ginkgo biloba extract, Capsaicin, Bioflavonoids and others.
- Water-soluble vitamins: including Vitamin B_1, Vitamin B_2, Niacinamide, Vitamin B_6, Vitamin B_{12}, Folic acid and Vitamin C.
- Fat-soluble vitamins: including Vitamin A, Vitamin D, Vitamin E, and Vitamin K.
- Antioxidants: including 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: such as lysine, isoleucine, leucine, threonine, valine, tryptophan, phenylalanine, and methionine.
- Minerals: such as iron, zinc, vanadium, selenium, chromium, iodine, potassium, manganese, copper, calcium and magnesium.

[1] Trademark of Sabinsa Corporation, U.S. Patent #s. 6,054,585 (2000), 5,972,382 (1999), 5,744,161 (1998) and 5,536,506 (1996), and International patents CA2247467 (2007), JP3953513 (2007), EP0810868 (2001).

In general, BioPerine was found to enhance absorption of nutrients by at least 30%



EFFICACY AND SAFETY

Due to its ability to increase the absorption of nutrients comprising nutritional supplement formulations as shown in Figures 1-4, BioPerine has been termed a natural Thermonutrient® and bioavailability enhancer (Majeed, M. et al; 1999).

A small amount of BioPerine (5 mg) combined with a formula containing 15 mg of beta-carotene, given as a food supplement once a day, increased almost twofold the blood levels of beta carotene in human volunteers (Badmaev, V et al.; 1999). Coenzyme Q10, (Badmaev, V et al., 2000), L(+)-Selenomethionine, Vitamin B_6, Vitamin C (with propranolol hydrochloride) and herbal extracts such as Curcumin (Shoba,G et al., 1998) showed enhanced bioavailability when co-administered with BioPerine. When 5 mg BioPerine was added to a mixture of vitamin C with propranolol hydrochloride, the bioavailability of the nutrient was enhanced, while the bioavailability of the drug remained unchanged.

Based on these properties, a derivative of piperine viz. Tetrahydropiperine was tested to determine if it had better topical bioavailability enhancement properties. Excellent results were obtained. This data provided a basis for a novel bioavailability enhancing natural compound for topical applications on skin in personal care applications.

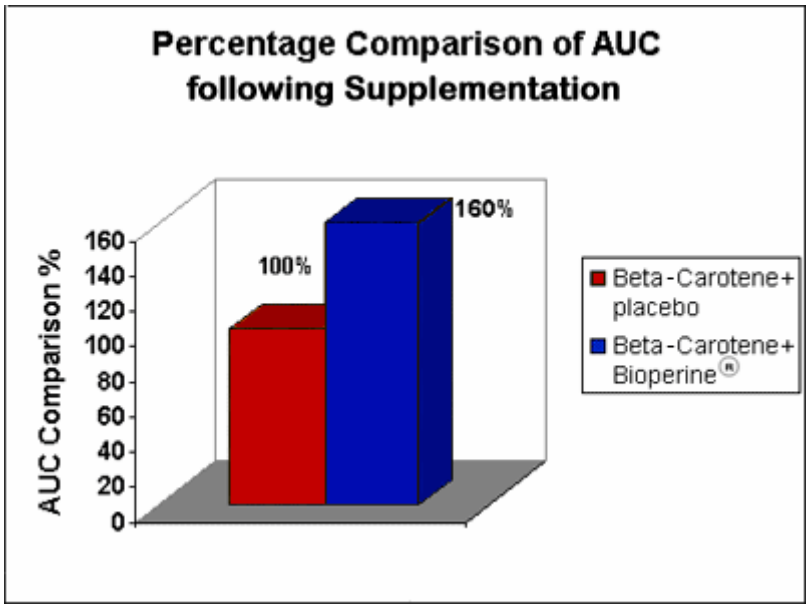


Figure 1. Effect of BioPerine® on the mean serum ß-Carotene levels during a 14 day supplementation trial in human volunteers

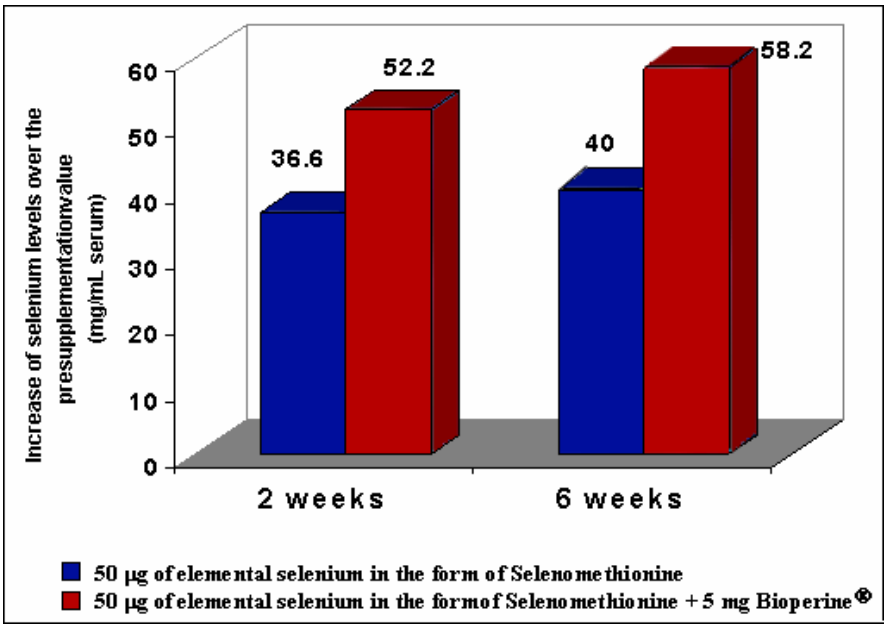


Figure 2. Effect of BioPerine® on serum selenium levels during a 6 week supplementation trial in human volunteers

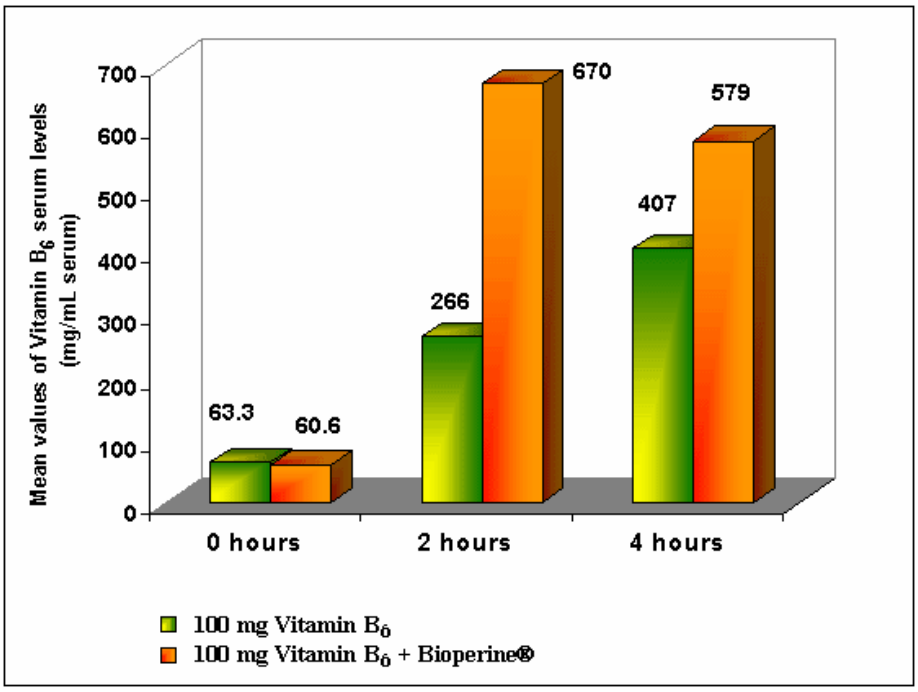


Figure 3. Efficacy of BioPerine® on the bioavailability of vitamin B_6 absorption in human volunteers

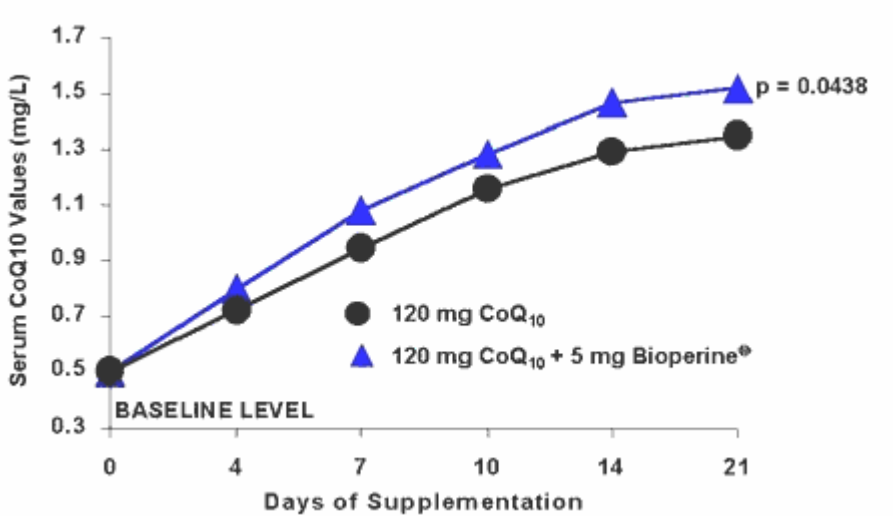


Figure 4. Effect of BioPerine® on serum CoQ10 levels during a 21 day supplementation trial in human volunteers

BioPerine also significantly improved the uptake of Curcumin, the healthful extract from turmeric roots, with clinically validated efficacy in inflammatory conditions including several forms of cancer. It is recognized that the therapeutic effectiveness of curcumin is limited due to its poor absorption from the GI tract, so the use of a natural agent to enhance its uptake is particularly beneficial.

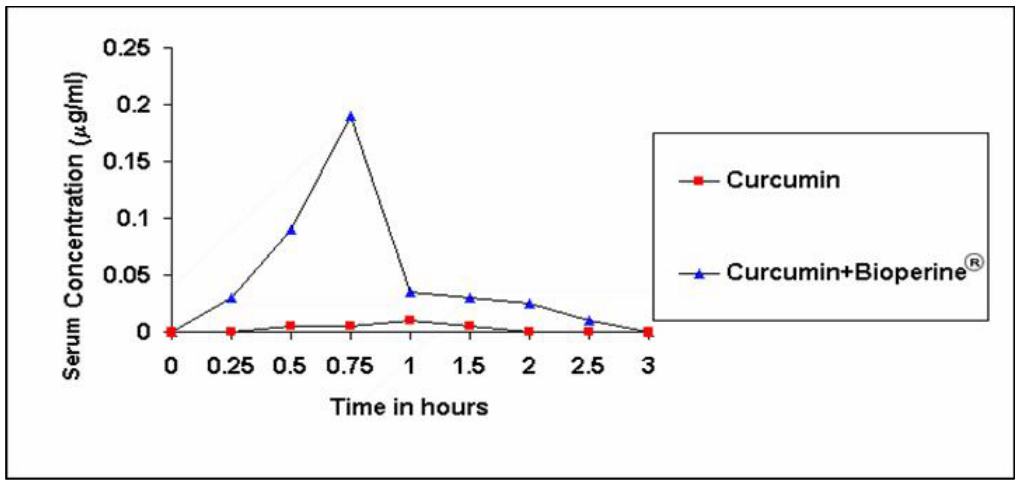


Figure 5: Effect of BioPerine® on Serum Concentrations of Curcumin in Human Volunteers

Acute, subacute and chronic toxicity studies of piperine in laboratory animals indicate that piperine used even in a broad range of doses does not cause abnormalities in the general growth pattern, body to organ weight ratio, clinical symptomatology, or blood chemistry. The dose of piperine considered to be bioenhancing for absorption of nutrients is calculated as 0.04 to 0.08 mg piperine/kg body weight. That dose is 4,000 times less than the LD_{50} dose (dose toxic to 50% animals tested) of piperine established in mice and rats.

Incidentally, the dose of piperine, which increased the bioavailability of the actives studied, was several times lower than the estimated amount of piperine consumed daily in the diet by an average individual in the USA (Majeed, M. et al.; 1999).

PROPOSED MECHANISMS OF ACTION

A thermonutrient such as BioPerine would potentially improve the process of nutrient absorption by enhancing thermogenesis. The leading theory of food-induced thermogenesis relates to the autonomous nervous system. The autonomous nervous system is represented by two main receptors in the gastrointestinal tract, the alpha and beta adrenergic receptors.

Most of the food or thermonutrient-induced thermogenesis is facilitated by beta receptors, which include a compound known as cyclic adenosine 3', 5' monophosphate (cAMP). The role of cAMP as a

"second messenger" to the hormonal and enzymatic actions in the body is well recognized. When thermogenesis occurs, the demand for fresh nutrients to sustain the metabolic processes rapidly increases.

Piperine has been found in independent studies to stimulate the release of catecholamines, thermogenic hormones whose action is made possible by the presence of cAMP. However, the nature of the thermogenic response mediated by catecholamines is relatively short-lived. Therefore the window of opportunity for piperine-induced thermogenesis and enhanced nutrient absorption is narrow.

These thermogenic properties may explain how a small amount of BioPerine (5 mg) can afford such a profound effect on serum nutrient levels (as shown in our studies on water soluble, fat soluble and botanical ingredients). It is possible that when piperine is ingested, it has a localized thermogenic effect on epithelial cells which increase the uptake of nutrients.

Other mechanisms by which piperine stimulates nutrient absorption have also been discussed in literature. These include increased micelle formation, stimulation of active transport of amino acids (gamma-glutamyl transpeptidase), and epithelial cell wall modification due to the affinity of piperine towards fats and fatty substances.

In view of these findings it is proposed that piperine ingested in relatively small amounts would act as a thermonutrient. Localized thermogenic action on the epithelial cells would in turn increase the rate of absorption of supplemented nutrient(s).

ENHANCING NUTRIENT ABSORPTION IN THE SKIN WITH AN INNOVATIVE PHYTONUTRIENT

Cosmoperine® (INCI: Tetrahydropiperine) a patented[2] topical bioenhancer for use in cosmetics, is prepared from piperine using a proprietary process. Its use in improving the skin permeation of active compounds is validated in vitro and clinically. Both piperine and THP occur naturally in black pepper and long pepper.

[2] Trademark of Sabinsa Corporation, US Patent 6,849,645 and International patents - Method Of Increased Bioavailability of Nutrients and Pharmaceutical Preparations with Tetrahydropiperine and its Analogues and Derivatives;
Winner of the 2005 Thomas Alva Edison Award, R & D Council, NJ – USA

EFFICACY AND SAFETY

Cosmoperine is able to enhance natural abilities of the skin to absorb nutrients (Badmaev, V et al., 2001; Majeed, M et al., 2005). Although Cosmoperine is based on a pungent principle, it is non-irritant and it interacts with the skin quantitatively and qualitatively in a different way than a pungent principle like, for example, capsaicin from cayenne pepper. Capsaicin is recognized by the US FDA as an OTC topical pain reliever in a dose of 0.025%. However, besides the pain relieving action this dose provides, it often causes skin reddening due to vascular engorgement as well as a slight skin tingling sensation. This reaction to capsaicin can occur within minutes, or a few hours after topical application, and usually lasts from half an hour to several hours from the moment it occurs. Interestingly this reaction tends to subside with regular, sustained use of topical capsaicin in a pain relieving dose.

A study was conducted to determine whether Cosmoperine, at a level of 0.01% and 0.1%, which is considered an effective dose range for the compound, would produce symptoms of topical irritation. A skin patch test using Cosmoperine in a petrolatum vehicle was conducted on 50 healthy volunteers for 48 hr with reading of the results after 48 hr and 72 hr. Neither dose caused skin irritation at the time of clinical evaluation of the study subjects. The irritation score was reported by the supervising physician, a practicing dermatologist, as 0. This study was conducted by the US FDA accredited BioScreen Testing Inc. laboratory. These results indicate that Cosmoperine does not act as a skin irritant at a dose range considered effective for topical nutrient delivery. (Research report, Midwest Clinical trials, Panel 42-2000, January 2000).

Cosmoperine was tested for efficacy in improving the absorption of a number of natural compounds, *in vitro*. A few examples are presented here.

The bioenhancing potential of Cosmoperine on the free-radical scavenging properties of topically applied Tetrahydrocurcuminoids (THC) a metabolite of the yellow curcuminoids derived from turmeric root, was evaluated. In this *in vitro* study that used the “DPPH radical scavenging method”, the ability of an anti-oxidant to bind and inactivate the 1,1 diphenyl-2-picrylhydrazyl radical, or DPPH, was measured. DPPH is considered an example of a very stable free radical. The control sample contained 0.01% of THC while active samples contained 0.01% of THC with Cosmoperine concentrations ranging from 0.1% - 0.0001%. Additionally, controls containing various concentrations of Cosmoperine alone were also tested for DPPH binding. While Cosmoperine by itself did not show

any significant antioxidant properties, together with THC it was shown to enhance the anti-oxidant properties of THC by up to 30% as compared to when THC was used alone. Even in its highest dilution of 0.0001% Cosmoperine still displayed some beneficial THC bioenhancing activity.

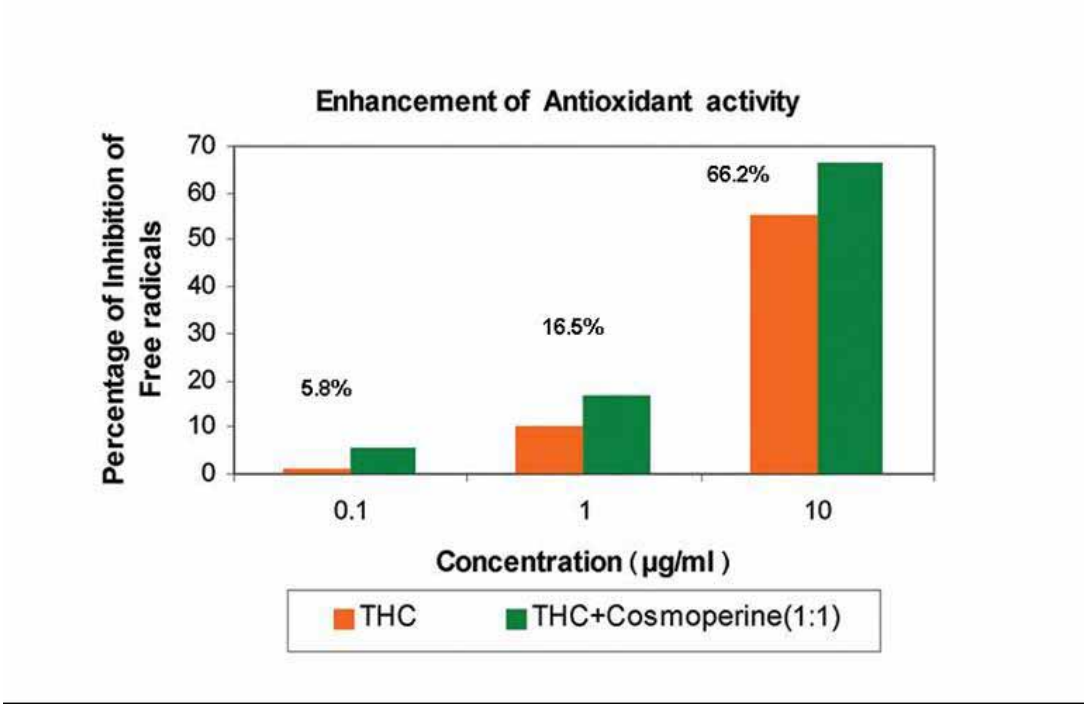


Figure 6: THP enhances the permeation and antioxidant efficacy of THC

Significant improvement in the absorption of forskolin, a diterpene extracted from *Coleus forskohlii* roots, was also observed.

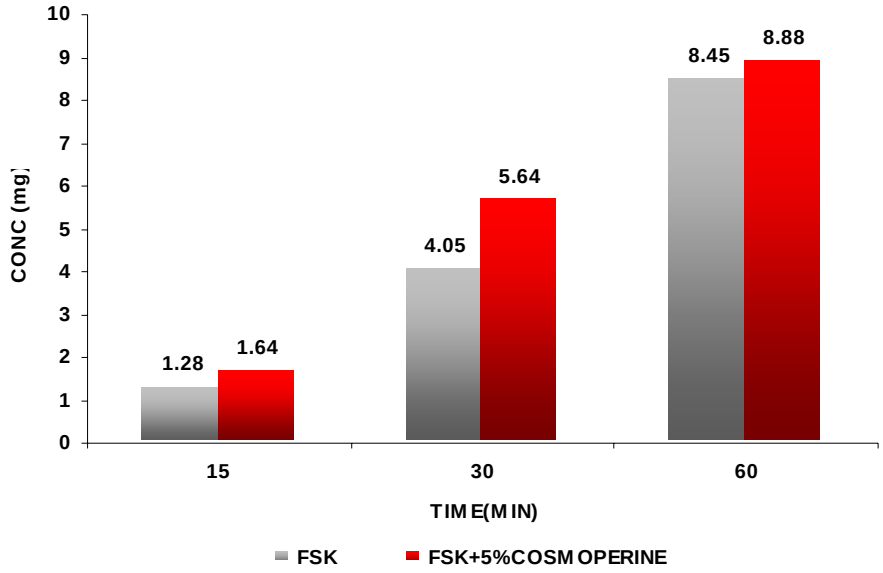


Figure 7: THP enhances the permeation of Forskolin (FSK)

POSTULATED MECHANISMS OF ACTION

At present more experimental data is needed to postulate the bioenhancing mechanism of Cosmoperine. However, there are experiments done both *in vitro* and *in vivo* with the parent compound piperine which indicate that Cosmoperine may operate by increasing either membrane fluidity, and affinity of nutrient/drug to the cell membrane, or on account of its lipophilic nature, increase solubilization of the intracellular lipid moiety in the skin, making it more permeable to the applied nutrient/drug.

Interestingly, Cosmoperine may *per se* be a skin nutrient theoretically able to improve skin health by furthering its ability to receive and selectively absorb various nutrients. This hypothesis is based on the experimental data with its parent compound piperine which was shown to be involved in the regulation of several neuropeptides**.** Neuropeptides, include proteins functioning as neurotransmitters, neuromodulators and neurohormones which participate in nutrient delivery through the skin to the body.

CONCLUSIONS

Based on research data, BioPerine® and Cosmoperine®, derived from black pepper or long pepper, effectively enhance the delivery of actives through the gastrointestinal tract and skin, respectively.

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