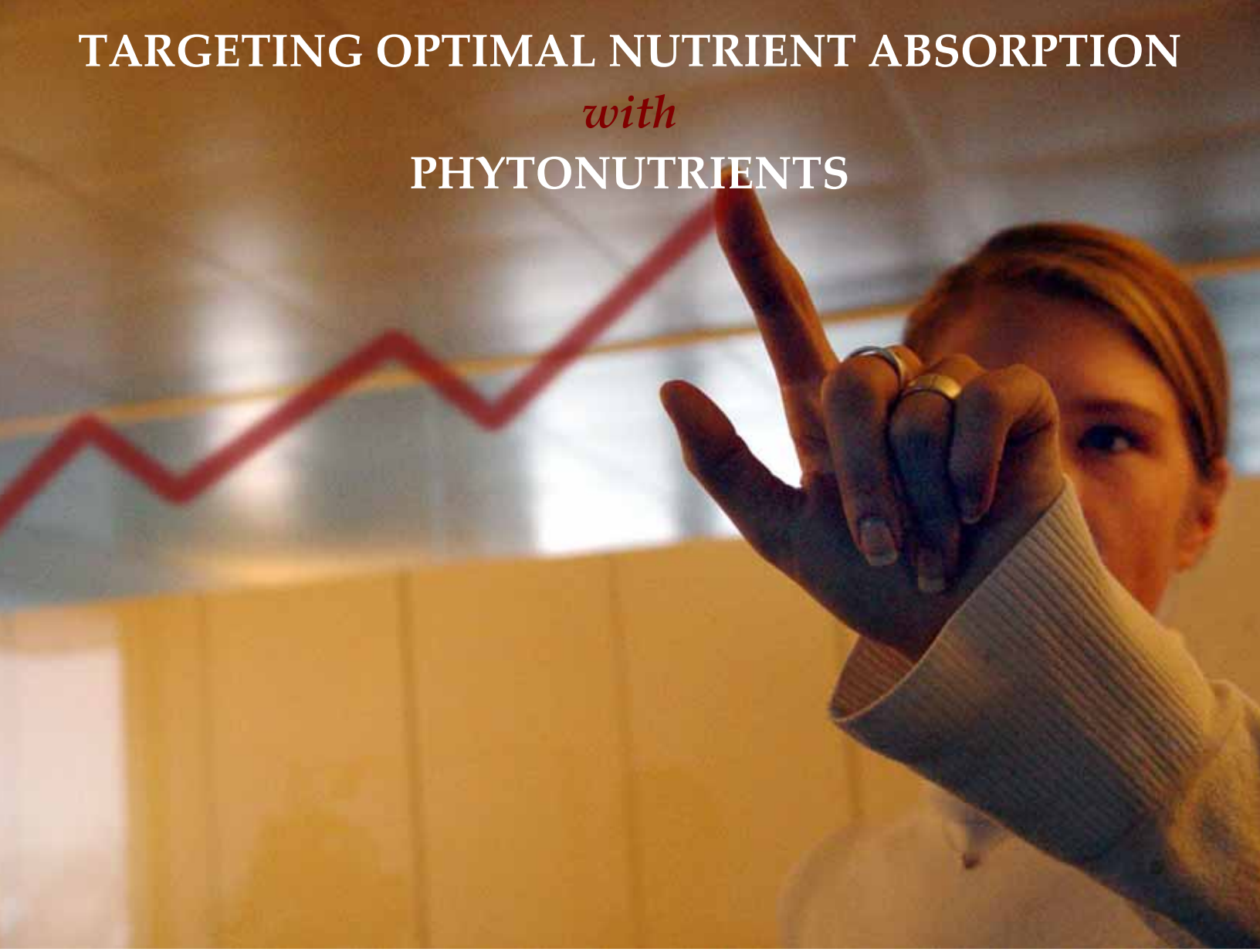
TARGETING OPTIMAL NUTRIENT ABSORPTION

with

PHYTONUTRIENTS



presented by

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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.

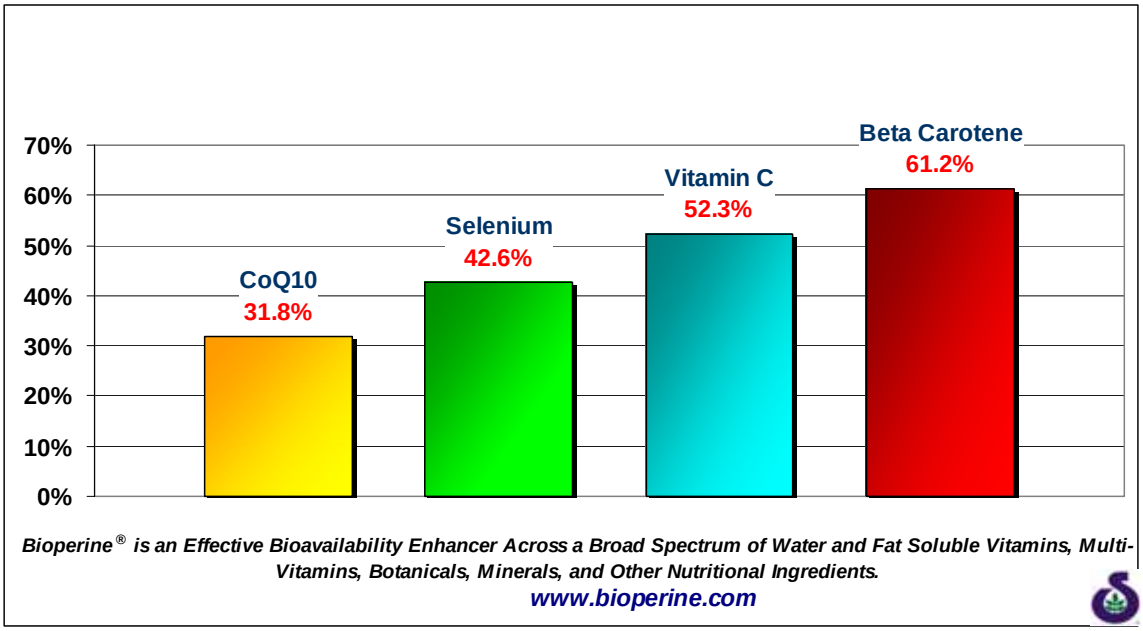
BioPerine®[1] is a standardized extract from the fruits of *Piper nigrum* L. (black pepper) or *Piper longum* L. (long pepper). It contains a minimum piperine content of 95% compared to the 3-9% and 3-5% found in raw forms of *Piper nigrum* and *Piper longum*, respectively. BioPerine may be co-administered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

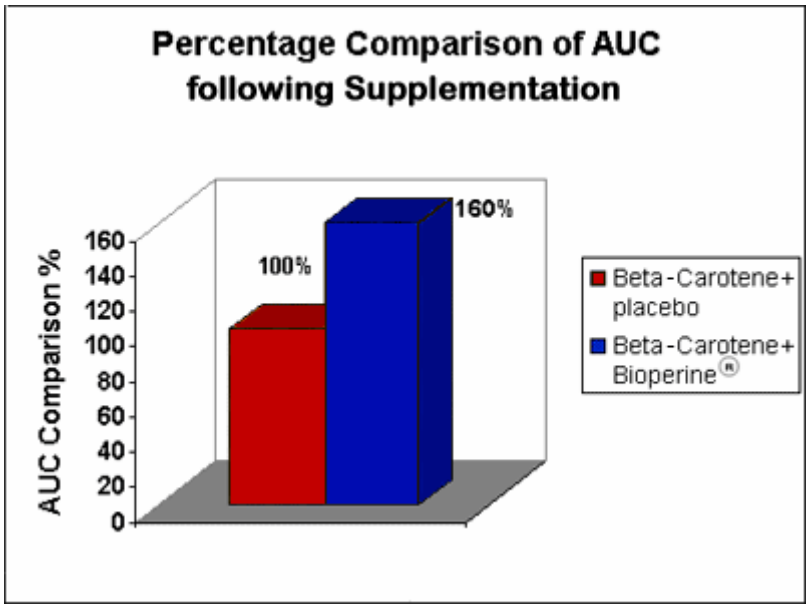


Figure 1. Effect of BioPerine® on the mean serum ß-Carotene levels during a 14 day supplementation trial in human volunteers

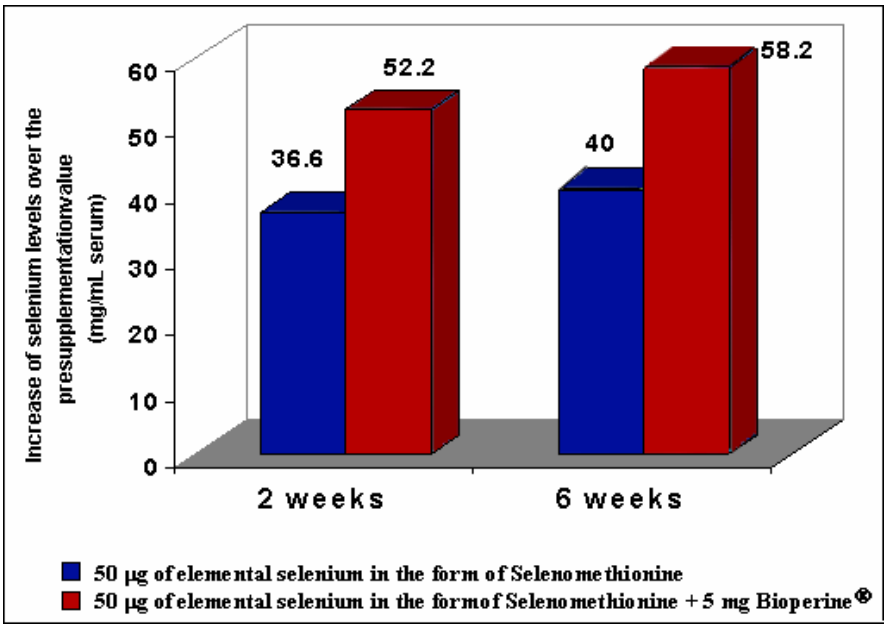


Figure 2. Effect of BioPerine® on serum selenium levels during a 6 week supplementation trial in human volunteers

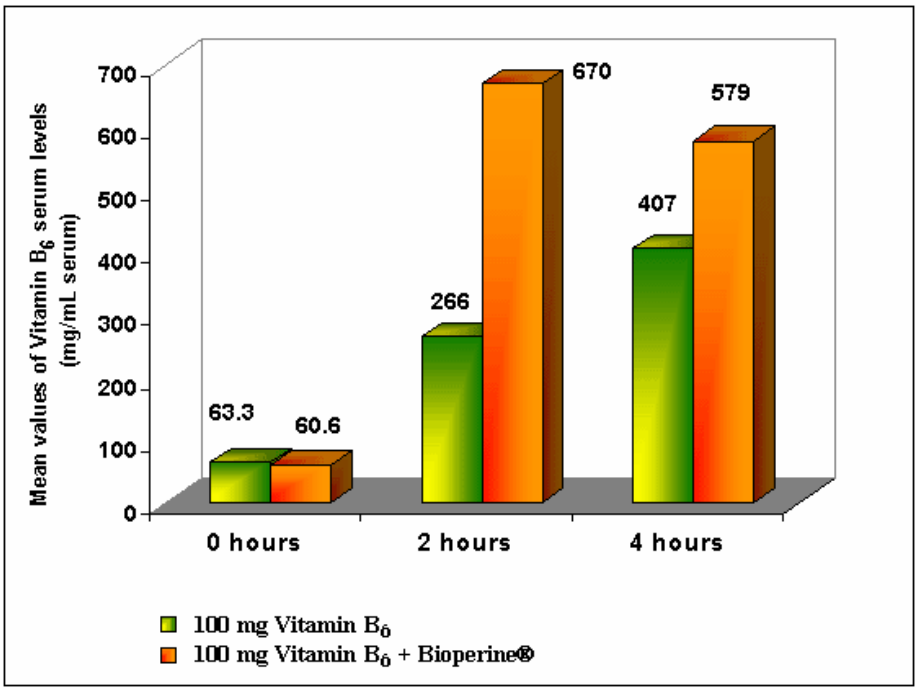


Figure 3. Efficacy of BioPerine® on the bioavailability of vitamin B_6 absorption in human volunteers

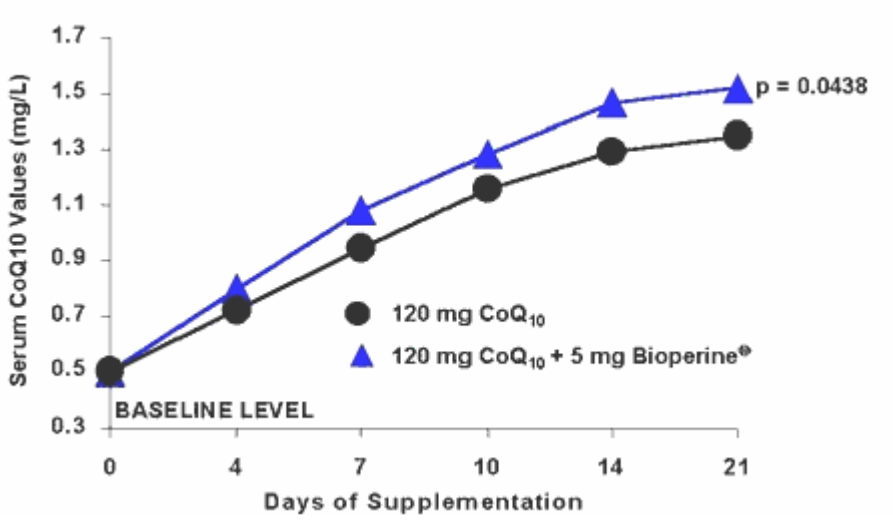


Figure 4. Effect of BioPerine® on serum CoQ10 levels during a 21 day supplementation trial in human volunteers

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.

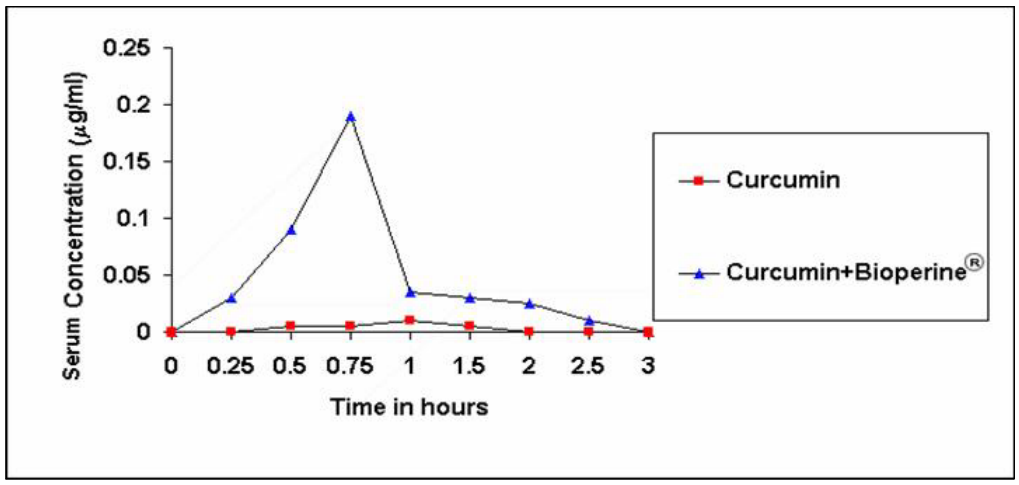


Figure 5: Effect of BioPerine® on Serum Concentrations of Curcumin in Human Volunteers

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.

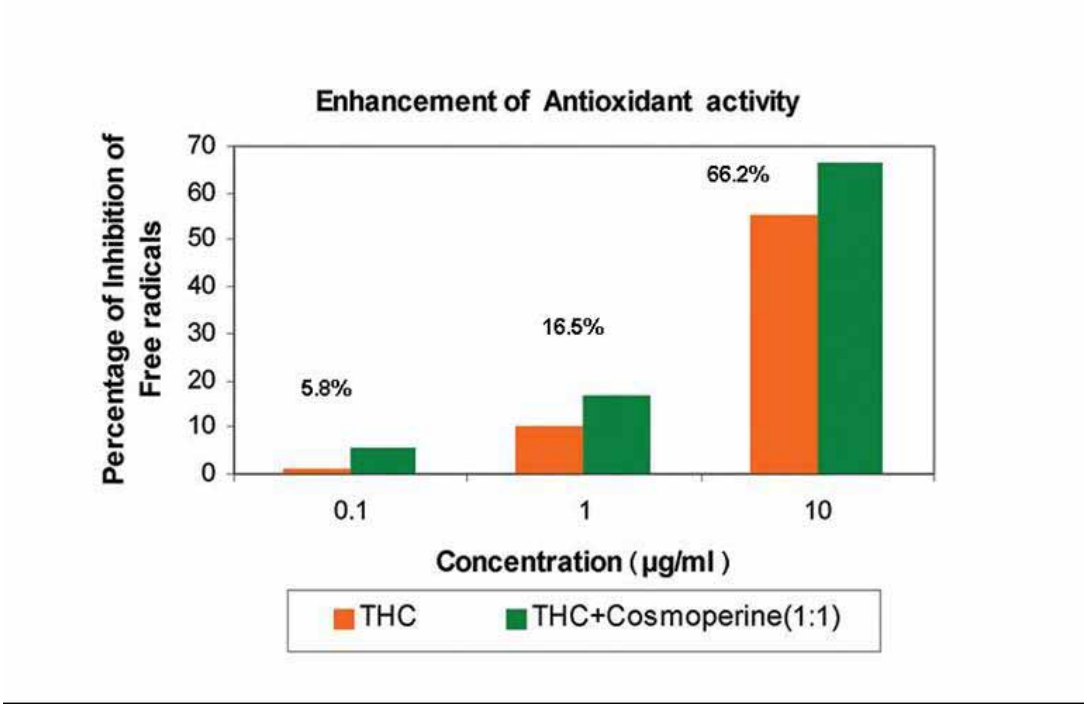


Figure 6: THP enhances the permeation and antioxidant efficacy of THC

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

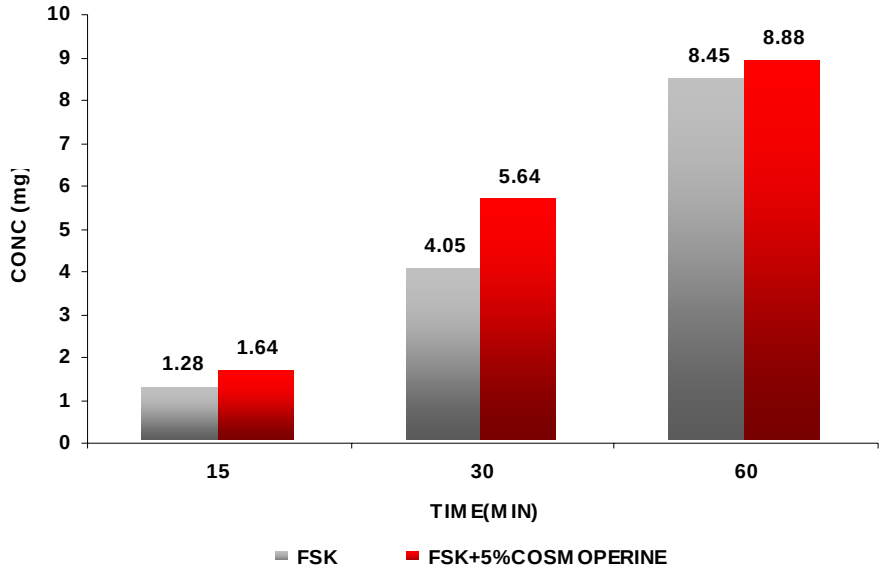


Figure 7: THP enhances the permeation of Forskolin (FSK)

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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