Skin and the digestive tract are the largest organs of our body. These are also some of the oldest structures developed in the evolutionary process to provide the organism with essential information about the outside world, largely by delivering nutrients from the outside world. In plant and animal kingdoms skin delineates and establishes identity of the organism, and effectively works as an intercom between the individual organism and the outside environment by selectively delivering, or regulating, the traffic of information, as well as variety of nutrients to the body. The digestive tract has a similar and parallel role to that of the skin in providing nutrients to the body.

Nutrients, whether delivered through the digestive tract or the skin, can be seen as a source of information literally transforming the body. In addition to food derived nutrients like minerals, vitamins, essential fatty acids, amino acids or carbohydrates information can also be provided in the form of ingestible and topical drugs and non-conventional nutrients e.g. daily light, temperature of the environment or humidity for the skin. This myriad of nutrient derived information, from inside and outside the body, is then analyzed and processed in steps comparable to that commonly associated with gastrointestinal digestion. Therefore skin and the digestive tract, although anatomically set apart, are closely allied and mutually supportive in providing nourishment to the organism.

RATIONALE FOR SIMULTANEOUS NUTRIENT DELIVERY THROUGH THE DIGESTIVE TRACT AND SKIN

The mechanisms linking skin and the digestive tract are found in physiological and pathological events occurring daily in the organism. For example, throughout life the nourishing daylight interacting with skin regulates many biological functions including the production of the active form of vitamin D, which may be diminished in daylight deprivation since skin contained 7-dehydrocholesterol needs to be cleaved by daylight to form cholecalciferol or pre-vitamin D, also known as vitamin D3. Vitamin D is also delivered to the body with food (including egg yolk, fish oil and a number of plants; the plant form of vitamin D is called vitamin D2 or ergosterol). Interestingly, northern Europeans (Scandinavian countries) with less exposure to sun have been known to have vitamin D deficiency relating to a higher rate of decreased bone mineral density or osteoporosis, a higher rate of skin cancer and an increased susceptibility to seasonal affective disorders (depression) or SAD. The significance of body status vitamin D has also been recognized because depression in women is associated with osteoporosis. In addition to daylight therapy the concomitant oral vitamin D supplementation is considered to be an important treatment for SAD. The efficient delivery of vitamin D to support physiological functions and prevent pathology is one of many examples where skin and the digestive tract exert synergy in nutrient uptake and utilization by the body.

The advantage of combined nutrient delivery through the skin and the digestive tract should be considered at any age. However, the process of aging gradually diminishes both the ability of skin and the digestive tract to nourish the body. That is why synergistic delivery of nutrients in daily
food and through the skin should be especially stressed in middle-aged and elderly individuals.

**NUTRITIONAL SUPPLEMENTS WITH PROMISING SYNERGY**

This article will discuss the following prominent examples of plant derived nutritional supplements which ingested and applied topically result in synergistic or additive interactions: i) alkaloids piperine (1-4) and tetrahydropiperine or THP (5), both found in fruits of black pepper, *Piper nigrum*, Linn.; ii) phenolic curcuminoids (6) and tetrahydrocurcuminoids or THC (7), both found in rhizomes of turmeric, *Curcuma longa*, Linn.; iii) CoQ10 and CoQ0, naturally occurring biochemical compounds; iv) diterpene forskolin (8), found in roots of *Coleus forskohlii*, Briq.

**THP, Piperine and Nutrient Absorption and Bioavailability**

The important aspect of effective use of an ingested or skin-applied nutrient is its absorption (permeation of epidermal barrier or crossing gastrointestinal barrier by the compound) and ultimately bioavailability of the compound to the target tissues and/or receptors. Natural cosmetics (cosmeceuticals) or ingestible supplements (nutraceuticals) e.g. vitamins, minerals and botanicals may have different rates of absorption and bioavailability, depending on their chemical and biochemical forms. For example, free isoflavones, like genistein, are considered more absorbable/bioavailable than their organic forms of minerals, such as selenium in complex with the amino acid methionine—selenomethionine—is shown to be better absorbed/bioavailable than inorganic sodium selenite. In addition to a more absorbable/bioavailable form of a compound, recent research shows that there are specialized biochemicals that may facilitate nutrient crossing through the biological barriers.

For example, alkaloids responsible for the pungent taste of fruits from black pepper (*Piper nigrum*, Linn. fam. Piperaceae), piperine and its derivative tetrahydropiperine (THP), are considered a new class of oral and topical absorption/bioavailability enhancing compounds. THP has a lower melting point (41-42°C) than piperine (126-132°C) and thus is more amenable for use with cosmetic preparations rather than to enhance gastrointestinal nutrient absorption.

Piperine was evaluated in oral administration for its potential to enhance gastrointestinal absorption of drugs and nutrients in animals and humans. Piperine enriched compounds were successfully studied with nutrients such as fat soluble beta carotene, water soluble vitamin B6, vitamin C, Coenzyme Q10, the mineral selenium in the form of L-selenomethionine, a multivitamin preparation, catechins of green tea and phenolics of turmeric rhizomes (curcuminoids).

The topical potential of THP was successfully evaluated in *in vitro* and *in vivo* studies with the antioxidant compounds tetrahydrocurcuminoids (THC) and catechins of green tea, diterpene forskolin and in experiments with the steroidal anti-inflammatory drug Betamethasone dipropionate or BMDP, and anthelmintic drugs, i.e. Fenvalerate and Albendazole.

Both compounds used in the experiments, piperine and THP, were minimum 95% pure by HPLC and relatively small doses of both compounds were required, i.e. 1% of piperine and 0.01-2% of THP. Clinical studies with piperine did not show subjective or objective side effects, and a THP patch test performed with human volunteers determined that there was no skin irritation with 0.001-0.1% concentrations of THP tested. This study was conducted by the US FDA accredited BioScreen Testing Inc. laboratory.

**Synergy of Curcuminoids and Tetrahydrocurcuminoids**

With advances in science of aging and degenerative diseases, including cancer, the detrimental role of pro-inflammatory mechanisms and biomarkers is increasingly recognized in origin of these conditions. Recently it has been found that receptors for the inflammatory enzyme cyclooxygenase 2 (COX-2) are increased in aged skin fibroblasts. As a result, the activity of COX-2 enzyme increases and fuels production of inflammatory prostaglandins, which corresponds to diseases such as arthritis, cardiovascular disease, cancer, but also to the process of skin aging. Aging skin fibroblasts (cells responsible for manufacturing skin matrix including collagen), in addition to increased expression of inflammation related receptors, undergo significant degenerative changes as compared to young and highly functional cells. Specifically, aged fibroblasts have a decreased ability to multiply, decreased expression of proteins involved in cell repair and regeneration, increased expression of inflammatory enzymes destroying skin collagen, decreased levels of tissue inhibitors of those enzymes and less collagen production by the aging fibroblasts. Interestingly, the experimental use of drugs inhibiting COX-2 activity resulted in the slow down of the above described age-related deterioration of cells and tissues.

With recent controversy surrounding the safety of pharmaceutical COX-2 inhibitors it is reassuring to note that nature has created a class of safe and effective COX-2 inhibitors found, for example, in green tea, rosemary and in turmeric. These plant derived components, used for millennia in Oriental culture as food (turmeric root in preparation of curry), are technically known as phenolic compounds, useful in the prevention and intervention of inflammatory conditions. The phenolic compounds of turmeric (*Curcuma longa*, Linn. fam. Zingiberaceae) are known as curcuminoids and tetrahydrocurcuminoids (THC) and have well recognized inhibitory effects on COX-2. Curcuminoids and THC have also been found to inhibit the activity of tyrosinase, an enzyme that participates in skin pigment formation or melanogenesis, thereby preventing melanin formation that often increases with aging and may predispose to skin cancer.

The differences between curcuminoids and tetrahydrocurcuminoids (THC) advocate synergistic and additive application of both compounds. Unlike its intensely yellow parent curcuminoids, tetrahydrocurcuminoids are color-free compounds and therefore applicable in topical and cosmetic formulations. THC, one of the major metabolites of curcuminoids, inhibits many biochemical and morphological changes in the skin which are associated with inflammation and skin tumor promotion. For example, topical application of a class of known chemical skin irritants and carcinogens (1,1-diphenyl-2-picrylhydrazyl radical or TPA) rapidly induces skin inflammation manifested by an increase in epidermal enzyme ornithine decarboxylase activity (this enzyme stimulates rapid and often uncontrollable cell multiplication). Based on experimental data, THC may inhibit the TPA induced inflammatory process by at least 80%. THC is also effective in the inhibition of UV-induced damage to the exposed skin by a decrease in the extent of sunburn lesions, and a decrease in the number of skin cells with UV-damaged genetic material. Therefore tetrahydrocurcuminoids have sound practical and scientific rationale for their topical use.
On the other hand, the extensive pre-clinical and clinical research done with curcuminoids orally advocate their use in ingestible form as more effective over orally administered THC. In the last 3 years alone there have been several pioneering IND (Investigational New Drug) studies granted by the US FDA and other NIH (US National Institutes of Health) funded studies for the investigation of curcuminoids in treatment of patients with degenerative and inflammatory conditions, including precancerous, cancerous and inflammatory skin conditions. Some of the leading cancer research centers in the US, including MD Anderson Hospital, in Houston, Texas, are involved in pre-clinical and clinical research of the anti-cancer mechanism and application of curcuminoids including such conditions as multiple myeloma and colon cancer; breast, prostate, head and neck and respiratory tract cancers and skin cancer (melanoma) are all in the process of systematic evaluation with curcuminoids therapy.

Curcuminoids inhibit several processes that contribute to the survival, proliferation, invasion and metastasis of tumor cells. These processes with which curcuminoids interfere include signaling mechanisms (critical for tumor growth), regulation of apoptosis (cell death), and tumor angiogenesis (new blood vessel formation which feeds tumors). As previously mentioned, curcuminoids have significant immunomodulating and anti-inflammatory effects, in part due to their inhibition of the cyclooxygenase-2 enzyme (COX-2) along with arachidonic acid metabolism. Like several other immunomodulators, curcuminoids inhibit the activation of the nuclear factor kappa-Β (NF-κΒ) family of transcription factors, which are known to be activated in a wide variety of cancer and inflammatory diseases.

The above mentioned topical application of THC to slow down skin aging and its related preventative skin pathology, can naturally be combined with oral curcuminoids for the additive and synergistic actions on the organism.

Synergistic Action of CoQ with Other Antioxidants

Ubiquinones and ubiquinols or coenzymes Q (CoQ) are components of many cell membranes where they safeguard the integrity of a cell. Besides their role in electron-transfer reactions they may also act as free radical scavengers. The antioxidant efficiency of various coenzymes Q apparently depends on their isoprenoid chain length, from Q0 to Q10. The shorter chain corresponds with higher antioxidant activity. In addition ubiquinols, the reduced forms of CoQ, possess much greater antioxidant activity than the oxidized ubiquinone forms.

The most researched coenzyme Q is coenzyme Q10 (CoQ10). CoQ10 was isolated from the heart muscle of cattle in the late 1950’s, and was found since then to be an important component in the energy production process in the cell mitochondria. Since the early 1970’s CoQ10 has been clinically used to improve the condition of patients with congestive heart failure. This compound is currently one of the most popular nutritional supplements for oral and topical applications in disease prevention and treatment. Because of the apparent biological importance of CoQ10 the issue of its bioavailability has been recently studied. The bioavailability of CoQ10 in humans is complex. CoQ10 is a large molecule that is poorly soluble in water, and shows great variability in its absorption. CoQ10 administered orally to human volunteers in conjunction with the previously discussed botanical compound piperine (120 mg CoQ10 administered with 5 mg of piperine for 21 days) resulted in a 30% increase in blood levels of CoQ10 compared to CoQ10 administered alone.

The topical use of coenzyme Q10 continues to gain popularity because this molecule participates in the outermost skin layer protection. The protective mechanism involves a very complex mixture of skin surface lipids (SSL), which primarily guard the skin against environmental oxidative assault. The skin content of protective lipids, which include monounsaturated and polyunsaturated fatty acids of triglycerides, is higher in young adults than in childhood or old age. The protective composition of SSL is stabilized by the natural presence of squalene, vitamin E and coenzyme Q10, which compounds increase from childhood to maturity, and decrease again in old age. Vitamin E and CoQ10 are the only known lipophilic antioxidants present in SSL. These two fat-soluble compounds synergistically inhibit the UV induced depletion of squalene, cholesterol and unsaturated fatty acids from the protective lipid layer. When the skin is exposed to UV oxidation the antioxidant role of vitamin E and CoQ10 spares squalene and other components of SSL. The importance of these compounds for healthy skin can be appreciated since experimental exposure to UV in the absence of vitamin E and CoQ10 resulted in a 90% depletion of squalene in the SSL.

The complementary oral administration of coenzyme Q10 should be combined with a broad range of botanical and vitamin antioxidants for a sound biological effect. Research data suggest that increasing the diversity and quantity of antioxidants in the diet provides significantly more protection for a tissue and organ than use of an antioxidant individually. In one experiment, animals on diets containing larger quantities of both fat soluble (vitamin E, beta-carotene, coenzyme Q10, ascorbic acid 6-palmitate) and water soluble (selenium, trolol C, acetylcysteine, coenzyme Q0, plant phenolics) antioxidants showed significantly higher protection against oxidative damage to the kidneys, heart, lungs and spleen than afforded by the individual antioxidants.

The oral and topical administration of coenzyme Q10 (and other CoQ compounds) may further benefit by a combined delivery with α-Lipoic acid. One of the most important systemic and topical compounds emerging in skin care is α-Lipoic acid, which helps maintain fat soluble and water soluble antioxidants present in the skin. α-Lipoic acid, also known as thiotic acid, functions as a co-factor for a number of key enzymes that help in the conversion of glucose, fatty acids and other energy sources into ATP. α-Lipoic acid helps to recycle vitamins C and E in the body and increases the levels of CoQ10, which recycles vitamin E. By virtue of its high absorption and bioavailability, it rapidly reaches effective concentrations in the tissues, both in the aqueous and lipid regions of the body.

The versatility and omnipresence in the body of coenzymes Q make these compounds especially important targets for efficient delivery by topical and oral routes.

Synergism of Oral and Topical Administration of Forskolin

Caleus forskohlii, Briq. is a member of the mint family (Labiatae). As a long-standing tradition in India, C. forskohlii roots have been used as a marinated food, or pickle, that is commonly eaten as part of a vegetarian meal. The roots of C. forskohlii contain forskolin, a compound that belongs to a chemical class known as diterpenes. It is the only plant derived compound presently known to directly stimulate
the enzyme adenylate cyclase, and subsequently cyclic AMP (3’5’-adenosine monophosphate). Cyclic AMP is also nicknamed the “second messenger” (the “first messenger” being a hormone or biologically active substance in the body), referring to its ability to facilitate a broad range of activity in the body’s life sustaining reactions.

The novel clinical application for C. forskohlii is for oral and topical delivery to help maintain and regain lean body mass at the expense of body fat. Lean body mass consists of muscles, vital organs, bone, bone marrow, connective tissue collagen and body water. Lean body mass can simply be described as total body weight minus fat. The proportion of lean body mass to fat not only determines the body’s aesthetic look, but more importantly determines a person’s physical fitness, health status and risk for morbidity (disease) and mortality. A person can approximate his/her lean body mass by calculating their body mass index (BMI), attained by taking body weight in kilograms divided by the square of height in meters. Normal BMI is between 18 and 25 kg/m². A value over 25 puts a person in the overweight category.

A patented standardized extract of C. forskohlii known as ForsLean® has been evaluated in an oral dosage form in five 8-12 week clinical studies (250 mg of an extract containing 10% diterpene forskolin taken twice a day). ForsLean® was shown to elicit favorable changes in body composition by significantly increasing lean body mass and decreasing body fat as determined from dual X-ray absorptiometry (DEXA) when compared to the placebo group. Serum free testosterone levels were significantly increased in the young men receiving ForsLean® as compared to the placebo group. Oral supplements of ForsLean® in the marketplace are either a stand alone or part of multi-ingredient, nutraceutical formulations. Plausible combinations in such formulations would include other botanical, mineral or chemical compounds to provide synergistic or additional, potentially helpful actions. Such existing formulations may, for example, include a combination of extracts from green tea, guarana seed or coffee beans.

The health promoting and skin toning value of increasing lean body mass can be directly appreciated due to the known benefits derived from physical exercise in building lean body mass. The healthy, glowing appearance of skin is more than a proverbial “skin-deep” appearance, it reflects internal health as represented by well developed lean body mass. The aging process on the other hand, results in sagging, wrinkled and dimpled (Cellulite) skin which is symptomatic of loss of lean body mass. Topical application of forskolin can help rebuild the skin collagen matrix and restore, to some degree, a youthful appearance to the skin. However, topical forskolin should be considered as an adjunct to an oral delivery, which has clinically proven effects in promoting lean body mass.

The action of forskolin appears to be a predominant result of its systemic action. It has been postulated that by stimulating cyclic AMP, forskolin may increase the circulation of anabolic hormones, e.g. testosterone and enhance their utilization which would theoretically lead to increased lean body mass. Studies have shown that selective inhibitors of phosphodiesterase (PD) enzymes (a group of enzymes inactivating cyclic AMP) and forskolin stimulate the hypothalamic-pituitary-adrenal (HPA) axis when given orally to rodents. The content of cyclic AMP in hypothalamic tissue increases in response to forskolin and anabolic hormones are synthesized. Forskolin also has a stimulatory effect on the cyclic AMP of testicular Leydig cells. This effect is similar to that of the LH (luteinizing hormone) hormone that controls Leydig cell steroidogenesis by stimulation of the androgen pathways, mainly through adenylyl cyclase and cyclic AMP mediated mechanisms. Cyclic AMP-dependent kinase activation and phosphorylation of steroidogenic proteins presumably causes an increase in testosterone production.

Topical administration of ForsLean® requires a high purity extract standardized for minimum 95% diterpene forskolin which can be supported with the 10% extract, as previously mentioned, in oral dosage form. The additive action of both routes of administration can help optimize the biological effect on lean body mass. Maintaining or improving lean body mass as advocated by the US Centers for Disease Control is a particularly important health mission for everyone since lean body mass is an independent, positive predictor of one’s overall health.

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