LOVE™
WELLNESS

# Baby Love Multivitamin White Paper

**Contents:**

**Baby Love Prenatal Multivitamin – White Paper**

## 1. SUPPLEMENT FACTS

# Supplement Facts

Serving Size 3 Vegetable Capsules
Servings Per Container 30

| | Amount Per Serving | % Daily Value for Pregnant & Lactating Women |
|---|---|---|
| Vitamin A (as beta-carotene) | 1300 mcg | 100% |
| Vitamin C (as ascorbic acid) | 500 mg | 417% |
| Vitamin D3 (as cholecalciferol) | 15 mcg (600 IU) | 100% |
| Vitamin E (as d-alpha tocopheryl succinate) | 19 mg | 100% |
| Vitamin K (as menaquinone-7) | 90 mcg | 100% |
| Thiamin (as thiamin mononitrate) | 2.8 mg | 200% |
| Riboflavin (as riboflavin, riboflavin-5-phosphate sodium) | 3.2 mg | 200% |
| Niacin (as niacinamide) | 18 mg | 100% |
| Vitamin B6 (as pyridoxine HCl, pyridoxal-5-phosphate) | 80 mg | 4000% |
| Folate (as L-5 methyltetrahydrofolate calcium) | 800 mcg DFE 480 mcg folic acid) | 133% |
| Vitamin B12 (as methylcobalamin) | 5.6 mcg | 200% |
| Biotin | 70 mcg | 200% |
| Pantothenic acid (as d-calcium pantothenate, pantethine) | 14 mg | 200% |
| Calcium (as calcium carbonate and d-calcium pantothenate) | 100 mg | 8% |
| Iron (as ferrous bisglycinate chelate) (Ferrochel®) | 27 mg | 100% |
| Iodine (as potassium iodide) | 225 mcg | 78% |
| Magnesium (as magnesium oxide) | 25 mg | 6% |
| Zinc (as amino acid chelate) | 13 mg | 100% |
| Selenium (as selenomethionine) | 70 mcg | 100% |
| Copper (as copper gluconate) | 1.3 mg | 100% |

| | | |
|---|---|---|
| Manganese (as manganese aspartate) | 2.6 mg | 100% |
| Chromium (as Crominex® 3+) | 45 mcg | 100% |
| Molybdenum (as amino acid chelate) | 50 mcg | 100% |
| Choline (as choline bitartrate) | 10 mg | 2% |
| Echinacea Purpurea Herb Powder | 200 mg | † |
| Cranberry fruit extract (50% PACs) | 72 mg | † |
| Ginger root extract (rhizome) (5% gingerols) | 40 mg | † |
| † Daily value not established. | | |

## 2. DIRECTIONS

Take 1 capsule, three time daily with meals.

## 3. CLAIMS

| Claim | Substantiation |
|---|---|
| ***Health/wellness & general claims*** | |
| • Contains 100% or more of the daily value for 21 vitamins and minerals for pregnant and lactating women. | Based on the current daily values for pregnant and lactating women. |
| • Promotes intake of key vitamins and minerals more than diet alone.* | Multivitamin study 1 |
| • Contains over 25 vitamins, minerals and nutraceuticals to support health and wellness during pregnancy and lactation.* | The 25+ vitamins, minerals and nutraceuticals are listed in supplement facts box. The other citations in this document show the relationship to supporting health and wellness |
| • Contains B-vitamin coenzymes, the biologically active forms of these nutrients.* | Listed in supplement facts box.<br>Riboflavin study 1<br>Vitamin B6 study 1<br>Vitamin B12 study 1 |
| • Vitamin D helps support healthy bones* | Vitamin D study 1-7 |
| ***Energy claim*** | |
| • Provides B-vitamins to support energy production.* | B vitamins study 2 |
| ***Blood sugar Claims*** | |
| • Chromium helps promote healthy blood glucose metabolism.* | Chromium studies 1-4 |

| | |
|---|---|
| • Chromium promotes healthy insulin levels already within normal ranges.* | Chromium studies 1-2 |
| • Chromium helps promote healthy insulin function.* | Chromium studies 1-2 |
| • Chromium supports healthy insulin-sensitivity.* | Chromium study 1 |
| ***Stress claims*** | |
| • Provides B-vitamins, which are intimately involved in function of nervous system* | B vitamins study 3-4 |
| • Provides B-vitamins, which may help counter some negative effects of stress.* | B vitamins study 5<br>Stress study 1-2 |
| • Provides a generous supply of B-vitamins, some of which can be depleted during stress.* | B vitamins study 6-7 |
| • Provides B-vitamins and other nutrients that may help people handle their stress better.* | B vitamins study 8 |
| ***Immune health-specific claims*** | |
| • Laboratory research demonstrates that Echinacea supports immune function.* | Echinacea study 1 |
| • Supports overall immune health.* | Vitamin C study 1-4<br>Zinc study 1-4<br>Selenium study 1-3 |
| • Supports a healthy immune system.* | |
| • Contains vitamin C, an effective antioxidant which helps support a healthy immune system, including the function of immune cells.* | Vitamin C study 1-3 |
| • Contains 500 mg of vitamin C which helps improve the production of antioxidant compounds from immune cells.* | Vitamin C study 4 |
| • Contains zinc, an essential mineral that supports immune function.*<br>○ Alternative: Zinc is essential for the integrity of the immune system.*<br>○ Alternative: Zinc affects multiple aspects of the immune system, from the barrier of the skin to cellular function.* | Zinc study 1-4 |
| • Contains selenium, an antioxidant mineral that supports a healthy immune system.*<br>○ Alternative: Selenium helps provide antioxidant protection against free radicals and other damaging reactive oxygen species.* | Selenium study 1-3 |
| ***Urinary Tract Claims*** | |
| • Contains 36 mg of PACs, the amount in cranberry shown to promote urinary tract health.* | Cranberry 8 |
| • Traditionally used to support urinary tract health* | Cranberry study 1-4 |

| | |
|---|---|
| • Traditionally used to support healthy urinary tract function.* | Cranberry study 1-4 |
| • Extract standardized for 2-3% PACs, the active compounds in cranberry that support urinary tract health.* | Cranberry study 5-7 |
| ***Morning Sickness Claims*** | |
| • Research suggests that ginger may help reduce common morning sickness associated with pregnancy.* | Ginger study 1-3 |

*These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.

## 4. SUBSTANTIATION STUDIES

Multivitamin study 1

Use of multivitamin-multimineral supplements is widespread and can contribute substantially to total nutrient intakes. In the Hawaii-Los Angeles Multiethnic Cohort (MEC),[1] 48% of men and 56% of women without chronic diseases reported use of multivitamin supplements at least weekly over the past year. We calculated the prevalence of nutrient adequacy for 17 nutrients based on responses to a self-administered quantitative food-frequency questionnaire administered to MEC participants at baseline in 1993-1996. Prevalence of nutrient adequacy from food only was higher for multivitamin supplement users (n = 21,056) than for nonusers (n = 69,715) ($P < 0.0001$).. For multivitamin users, the prevalence of adequacy improved by an average of 8 percentage points for both men and women when intake from supplements was included. Users were also more likely to have potentially excessive intakes, particularly for iron, zinc, vitamin A, and niacin. The 26,735 MEC participants in Hawaii who answered an open-ended question about multivitamin use in 1999-2001 reported using 1246 different products. The nutrient profile of these products varied widely, and the composition of products at the 90th percentile was 10-fold greater than the composition at the median for some nutrients. We conclude that analyses of nutrient adequacy and excess for supplement users should be extended to national samples and that composition data on actual supplements used are preferable to assuming a default nutrient profile for multivitamin supplements. Multivitamin products could be better formulated to reduce the prevalence of inadequacy and also to reduce the risk of excessive intakes.

Multivitamin study 2

To determine whether long-term multivitamin supplementation decreases the risk of total and site-specific cancer events among men, a large-scale, randomized, double-blind, placebo controlled trial[2] was conducted (Physicians" Health Study II) with 14 641 male US physicians initially aged 50 years or older (mean [SD] age, 64.3 [9.2] years), including 1312 men with a history of cancer at randomization, enrolled in a common multivitamin study that began in 1997 with treatment and follow-up through June 1, 2011. The intervention was a daily multivitamin or placebo. The main outcome measures were total cancer (excluding nonmelanoma skin cancer), with prostate, colorectal, and other site-specific cancers among the secondary end points. Results showed that during a median (interquartile range) follow-up of 11.2 (10.7-13.3) years, there were 2669 men with confirmed cancer, including 1373 cases of prostate cancer and 210 cases of colorectal cancer. Compared with placebo, men taking a daily multivitamin had a statistically significant reduction in the incidence of total cancer (multivitamin and placebo groups, 17.0 and 18.3 events, respectively, per 1000 person-years; hazard ratio [HR], 0.92; 95% CI, 0.86-0.998; P=.04). There was no significant effect of a daily multivitamin on prostate cancer (multivitamin and placebo groups, 9.1 and 9.2 events, respectively, per 1000 person-years; HR, 0.98; 95% CI, 0.88-1.09; P=.76), colorectal cancer (multivitamin and placebo groups, 1.2 and 1.4 events, respectively, per 1000 person-years; HR, 0.89; 95% CI, 0.68-1.17; P=.39), or other site-specific cancers. There was no significant difference in the risk of cancer mortality (multivitamin and placebo groups, 4.9 and 5.6 events, respectively, per 1000 person-years; HR, 0.88; 95% CI,

0.77-1.01; P=.07). Daily multivitamin use was associated with a reduction in total cancer among 1312 men with a baseline history of cancer (HR, 0.73; 95% CI, 0.56-0.96; P=.02), but this did not differ significantly from that among 13 329 men initially without cancer (HR, 0.94; 95% CI, 0.87-1.02; P=.15; P for interaction=.07). In conclusion, this large prevention trial of male physicians, daily multivitamin supplementation modestly but significantly reduced the risk of total cancer.

Multivitamin study 3

To evaluate the associations between intakes of vitamins A, C, and E and risk of colon cancer, primary data from 13 cohort studies[3] was used, estimating study- and sex-specific relative risks (RR) with Cox proportional hazards models and subsequently pooled RRs using a random effects model. Results showed that among 676,141 men and women, 5,454 colon cancer cases were identified (7-20 years of follow-up across studies). Vitamin A, C, and E intakes from food only were not associated with colon cancer risk. For intakes from food and supplements (total), the pooled multivariate RRs (95% CI) were 0.88 (0.76-1.02, >4,000 vs. ≤ 1,000 µg/day) for vitamin A, 0.81 (0.71-0.92, >600 vs. ≤ 100 mg/day) for vitamin C, and 0.78 (0.66-0.92, > 200 vs. ≤ 6 mg/day) for vitamin E. Adjustment for total folate intake attenuated these associations, but the inverse associations with vitamins C and E remained significant. Multivitamin use was significantly inversely associated with colon cancer risk (RR = 0.88, 95% CI: 0.81-0.96). In conclusion, modest inverse associations with vitamin C and E intakes may be due to high correlations with folate intake, which had a similar inverse association with colon cancer. An inverse association with multivitamin use, a major source of folate and other vitamins, deserves further study.

Multivitamin study 4

Epidemiologic data relating multivitamin supplement use to the risk of cardiovascular disease are sparse and inconsistent. We examined the association between self-selected use of low dose multivitamin supplements and the risk of myocardial infarction (MI). Our results are based on data from a large population-based, case-control study of subjects aged 45-70 y residing in Sweden, a country in which consumption of fruits and vegetables is relatively low and foods are not fortified with folic acid. The study included 1296 cases (910 men, 386 women) with a first nonfatal MI and 1685 controls (1143 men, 542 women) frequency-matched to the cases by sex, age and hospital catchment area. Odds ratios (OR) and 95% CI were calculated from unconditional logistic regression models. Among controls, 57% of the women and 35% of the men used dietary supplements; corresponding figures for the cases were 42 and 27%, respectively. Of those taking supplements, 80% used multivitamin preparations. After adjustment for major cardiovascular risk factors, the OR of MI comparing regular users of supplements with nonusers were 0.79 (95% CI 0.63-0.98) for men and 0.66 (95% CI 0.48-0.91) for women. This inverse association was not modified by such healthy lifestyle habits as consumption of fruits and vegetables, intake of dietary fiber, smoking habits and level of physical activity, although never smoking appeared to outweigh the association in women. Findings from this study indicate that use of low dose multivitamin supplements may aid in the primary prevention of MI.[4]

Multivitamin study 5

Rates of vitamin-mineral supplement use by US female physicians are unknown but are of particular interest for several epidemiologic and clinical reasons. The objective was to determine rates of and variations in vitamin-mineral supplement use among US female physicians. We used data from the Women Physicians' Health Study, a large (n = 4501) national, randomly sampled mail survey of female physicians aged 30-70 y. Half of the physicians took a multivitamin-mineral supplement; 35.5% of these did so regularly. However, </=33% took any supplement other than calcium and <20% did so regularly. Regular vitamin-mineral supplement use increased with age, and antioxidant intake was higher in those at high risk of heart disease. Those with a history of osteoporosis were nearly 3 times as likely as those with no history to take supplemental calcium regularly. Those who took any supplement regularly also consumed more fruit and vegetables daily than did occasional users or nonusers (P: < 0.0001). Regular users of any supplement also consumed less fat than did occasional users or nonusers (P: < 0.01). Additionally, vegetarians were more likely than were nonvegetarians to regularly consume any supplement (59.9% compared with 46.3%; P: < 0.001) and those who regularly consumed any supplement were more likely to comply with US Preventive Services Task Force guidelines than

were those who were occasional users or nonusers (72.4% compared with 66.5% and 60.2%; P: < 0.0001). In conclusion, female physicians, particularly those who were especially health conscious or at higher risk of heart disease or osteoporosis, used supplements at rates at least equal to those of women in the general population.[5]

Multivitamin study 6

To investigate the effect of supplementation with multivitamin and mineral on blood pressure and C-reactive protein (CRP) in obese women with increased cardiovascular disease risk as having hypertension, hyperglycemia or hyperlipemia. 128 obese Chinese women aged 18-55 years with increased cardiovascular disease risk participated in a 26-week randomized, double-blind, placebo-controlled trial.[6] Subjects were randomized to four groups, and received either one tablet of high-dose multivitamin and mineral supplement (MMS), or one tablet of low-dose MMS (Low MMS), or calcium 162 mg (Calcium) or identical placebo (Placebo) daily during the study. Diastolic blood pressure (DBP), systolic blood pressure (SBP) and serum concentrations of CRP were measured at baseline and end-trial. The results showed that, at baseline, the subjects had an average age of 42.0+/-7.1 years and BMI of 30.9+/-2.8 kg/m2. There were no significant differences between the four groups in baseline characteristics. One hundred and seventeen subjects completed the study. After 26-week supplementation, both SBP and DBP were significantly lower in the MMS group compared to the placebo group ($p < 0.05$). There was also a non-significant trend of lower DBP at 26-week in the MMS and calcium groups compared to baseline ($p < 0.08$). At 26-week, the MMS group also had significantly lower serum concentrations of CRP compared with that of baseline and the placebo group ($p < 0.05$). In conclusion, supplementation with adequate multivitamin and mineral supplement could reduce blood pressure and serum CRP in obese women with increased cardiovascular disease risk.

Multivitamin study 7

The objective of this study[7] was to examine the association between multivitamin use and myocardial infarction (MI) in a prospective, population-based cohort of women.The study included 31,671 women with no history of cardiovascular disease (CVD) and 2262 women with a history of CVD aged 49-83 y from Sweden. Women completed a self-administered questionnaire in 1997 regarding dietary supplement use, diet, and lifestyle factors. Multivitamins were estimated to contain nutrients close to recommended daily allowances: vitamin A (0.9 mg), vitamin C (60 mg), vitamin D (5 μg), vitamin E (9 mg), thiamine (1.2 mg), riboflavin (1.4 mg), vitamin B-6 (1.8 mg), vitamin B-12 (3 μg), and folic acid (400 μg). Results showed that during an average of 10.2 y of follow-up, 932 MI cases were identified in the CVD-free group and 269 cases in the CVD group. In the CVD-free group, use of multivitamins only, compared with no use of supplements, was associated with a multivariable-adjusted hazard ratio (HR) of 0.73 (95% CI: 0.57, 0.93). The HR for multivitamin use together with other supplements was 0.70 (95% CI: 0.57, 0.87). The HR for use of supplements other than multivitamins was 0.93 (95% CI: 0.81, 1.08). The use of multivitamins for ≥5 y was associated with an HR of 0.59 (95% CI: 0.44, 0.80). In the CVD group, use of multivitamins alone or together with other supplements was not associated with MI. In conclusion, the use of multivitamins was inversely associated with MI, especially long-term use among women with no CVD. Further prospective studies with detailed information on the content of preparations and the duration of use are needed to confirm or refute our findings.

B vitamins study 1

The objective of this study[8] was to determine whether oral folic acid (FA) + vitamin B-12 supplementation prevented cognitive decline in a cohort of community-dwelling older adults with elevated psychological distress. This randomized controlled trial (RCT) with a completely crossed 2 · 2 · 2 factorial design comprised daily oral 400 mcg FA + 100 mcg vitamin B-12 supplementation (compared with placebo), physical activity promotion, and depression literacy with comparator control interventions for reducing depressive symptoms was conducted in 900 adults aged 60–74 y with elevated psychological distress (Kessler Distress 10–Scale; scores .15). The 2-y intervention was delivered in 10 modules via mail with concurrent telephone tracking calls. Main outcome measures examined change in cognitive functioning at 12 and 24 mo by using the Telephone Interview for Cognitive Status–Modified (TICS-M) and the Brief Test of Adult Cognition by Telephone (processing speed); the Informant Questionnaire on Cognitive Decline in the Elderly

was administered at 24 mo. The results were that FA + vitamin B-12 improved the TICS-M total (P = 0.032; effect size d = 0.17), TICS-M immediate (P = 0.046; d = 0.15), and TICS-M delayed recall (P = 0.013; effect size d = 0.18) scores at 24 mo in comparison with placebo. Researchers concluded that long-term supplementation of daily oral 400 mcg FA + 100 mcg vitamin B-12 promotes improvement in cognitive functioning after 24 mo, particularly in immediate and delayed memory performance. This trial was registered at linicaltrials.gov as NCT00214682.

B vitamins study 2

Physicians are frequently confronted with patients complaining of fatigue, tiredness and low energy levels. In the absence of underlying disease, these symptoms could be caused by a lack of vitamins, especially B-vitamins, and minerals. Certain risk groups like the elderly and pregnant women are well-recognized. This review[9] describes the inter-relationship between micronutrients, energy metabolism and well-being, especially the role of B-vitamins in energy metabolism, an overview of which follows is shown in Table 1. The review also identifies risk groups for inadequate micronutrient intake. The authors indicated that micronutrient supplementation can alleviate deficiencies, but supplements must be taken for an adequate period of time.

**TABLE 1:**
**Present state of knowledge with regard to the role(s) of individual micronutrients in energy metabolism[7–10]**

| Micronutrient | Function in energy metabolism |
|---|---|
| Vitamins | |
| Thiamine ($B_1$) | • Essential cofactor in the conversion of carbohydrates to energy.<br>• Needed for normal muscle function, including the heart muscle.<br>• Involved in oxidative carboxylation reactions, which also require manganese ions. |
| Riboflavin ($B_2$) | • As a cofactor in the mitochondrial respiratory chain, helps in the release of energy from foods.<br>• Component of the main coenzymes FAD and FMN. |
| Nicotinic acid, niacin ($B_3$) | • As a cofactor in the mitochondrial respiratory chain, helps in the release of energy from foods.<br>• Transformed into NAD and NADP, which play a key role in oxidation – reduction reactions in all cells. |
| Pyridoxine ($B_6$) | • Helps in the release of energy from foods.<br>• Used as a cofactor by nearly 100 enzymatic reactions, mainly in protein and amino acid metabolism. |
| Vitamin $B_{12}$ | • Essential for metabolism of fats and carbohydrates and the synthesis of proteins.<br>• Interacts with folic acid metabolism. |
| Biotin | • As a cofactor, involved in metabolism of fatty acids, amino acids and utilization of B vitamins. |
| Pantothenic acid | • Plays an essential role in the Krebs cycle.<br>• Component of coenzyme A. |
| Vitamin C (ascorbic acid) | • Essential for synthesis of carnitine (transports long-chain fatty acids into mitochondria) and the catecholamines, adrenaline and noradrenaline.<br>• Ascorbic acid facilitates transport and uptake of non-haem iron at the mucosa, the reduction of folic acid intermediates, and the synthesis of cortisol.<br>• Potent antioxidant. |
| Folic acid | • Folates function as a family of cofactors that carry one-carbon (C1) units required for the synthesis of thymidylate, purines and methionine, and required for other methylation reactions.<br>• Folate is essential for metabolic pathways involving cell growth, replication, survival of cells in culture.<br>• Around 30 – 50% of cellular folates are located in the mitochondria. |

B vitamins study 3

B-vitamins function as cofactors in fundamental pathways, such as glycolysis, the Krebs cycle, the respiratory chain and amino acid metabolism. Although all tissues have these vitamin-dependent pathways, they take on increased importance in the brain because of its high metabolic rate and dependence on continuous metabolism. In fact, the discovery of vitamins was closely linked to the sensitivity of the brain to deficiency, specifically that of thiamine. Furthermore, in the brain these pathways are linked to neurotransmitter synthesis.[10]

B vitamins study 4

In the brain, the synthesis of the neurotransmitter, serotonin, from the amino acid, tryptophan, is catalyzed by a pyridoxal 5'-phosphate-dependent enzyme (pyridoxal 5'-phosphate is the metabolized, principle coenzyme form of vitamin B6). Other neurotransmitters, such as dopamine, norepinephrine and gamma-aminobutyric acid (GABA), are also synthesized using PLP-dependent enzymes.[11]

B vitamins study 5

The current study[12] examined the relation of plasma IL-6 to anger, hostility, and severity of depressive symptoms [*which are associated with stress—see following two citations for*

*substantiation*] as a function of multivitamin supplement use (providing a source of B vitamins) in 96 healthy, nonsmoking men (aged 18-46). Plasma IL-6 was independently associated with anger, hostility, and severity of depressive symptoms, as well as with a composite factor score, but only among nonusers. Among users, these associations were not significant. Multivitamin use was associated with lower plasma IL-6 levels, but only among men with high composite factor scores. Statistical adjustments for age, body mass index, resting diastolic blood pressure, fasting total cholesterol, high-density lipoprotein cholesterol, alcohol use, exercise frequency, and educational level did not alter these results. These data suggest that plasma IL-6 is elevated among healthy men characterized by a propensity for anger, a hostile disposition, and greater severity of depressive symptoms and that multivitamin supplements could ameliorate plasma IL-6 levels among these men.

Stress study 1
Stress can come from any event or thought that makes you feel frustrated, angry, or nervous.[13]

Stress study 2
The body responds to each type of stress in similar ways. Different people may feel it in different ways. For example, some people experience mainly digestive symptoms, while others may have headaches, sleeplessness, depressed mood, anger and irritability. People under chronic stress are prone to more frequent and severe viral infections, such as the flu or common cold, and vaccines, such as the flu shot, are less effective for them.[14]

B vitamins study 6
Correlation of actual consumption of vitamins B1, B2 and B6 with biochemical parameters of their utilization has been studied in two groups of workers (one group was engaged in the synthetic leather industry, the second one in the diamond treatment industry). It is shown that the actual utilization of vitamins B1, B2 and B6 correlated well with the stimulation coefficients (SC) of the basal activity of the corresponding erythrocytic enzymes. This correlation can be expressed in an equation of linear regression with a preset SC. Solution of this equation gives the values that can be used in the diagnosis of changes in the vitamins B1, B2 and B6 requirement in certain population groups. The results of the study evidence that vitamin B1 and B6 are especially necessary for workers whose activity is associated with manifest nervous-emotional stress, while the workers engaged in the synthetic leather industry being exposed to dimethyl formamide are in need of vitamin B2.[15]

B vitamins study 7
Previous research has demonstrated that a theoretical model including measures of life stressors, social support, and coping style significantly predicts psychological distress. This study[16] tested plasma pyridoxine (vitamin B6) deficiency status as a predictor of overall psychological distress and specific mood states in this model, controlling for HIV-1 serostatus. Subjects included HIV-1+ (N = 76) and HIV-1- (N = 58) recently bereaved homosexual men. At baseline, subjects completed a battery of psychosocial questionnaires, together with a physical examination and venipuncture. The Profile of Mood States (POMS) provided measures of overall psychological distress as well as specific mood states. Pyridoxine deficiency status (a categorical measure of deficient vs. adequate status) was determined with a bioassay of erythrocyte aspartate aminotransferase activity. Pyridoxine deficiency was a significant predictor of increased overall psychological distress in this model, controlling for life stressors, social support, coping style, and HIV-1 serostatus. In post hoc analyses of specific mood state effects, pyridoxine deficiency status was significantly associated with increases in depressed, fatigued, and confused mood levels, but not with those of anxiety, anger, or vigor. These findings suggest that adequate pyridoxine status may be necessary to avert psychological distress in the setting of bereavement. Inasmuch as pyridoxine is a cofactor for 5-hydroxytryptophan decarboxylase--an enzyme in the biosynthesis pathway of serotonin--serotonin level in the brain is implicated as the mediating factor.

B vitamins study 8

Biochemical processes in the brain affect mood. Minor dietary inadequacies, which are responsible for a small decline in an enzyme's efficiency, could cumulatively influence mood states. When diet does not provide an optimal intake of micronutrients, supplementation is expected to benefit mood. This meta-analysis[17] evaluated the influence of diet supplementation on mood in nonclinical samples. Databases were evaluated and studies were included if they considered aspects of stress, mild psychiatric symptoms, or mood in the general population; were randomized and placebo-controlled; evaluated the influence of multivitamin/mineral supplements for at least 28 days. Eight studies that met the inclusion criteria were integrated using meta-analysis. Supplementation reduced the levels of perceived stress (standard mean difference [SMD]=0.35; 95% confidence interval [CI]=0.47-0.22; p=.001), mild psychiatric symptoms (SMD=0.30; 95% CI=0.43-0.18; p=.001), and anxiety (SMD=0.32; 95% CI=0.48-0.16; p<.001), but not depression (SMD=0.20; 95% CI=0.42-0.030; p<.089). Fatigue (SMD=0.27; 95% CI=0.40-0.146; p<.001) and confusion (SMD=0.225; 95% CI=0.38-0.07; p<.003) were also reduced. Micronutrient supplementation has a beneficial effect on perceived stress, mild psychiatric symptoms, and aspects of everyday mood in apparently healthy individuals. Supplements containing high doses of B vitamins may be more effective in improving mood states. Questions about optimal levels of micronutrient intake, optimal doses, and active ingredients arise.

Riboflavin study 1

Riboflavin is a water-soluble B vitamin, also known as vitamin $B_2$. In the body, riboflavin is primarily found as an integral component of the coenzymes, flavin adenine dinucleotide (FAD) and flavin mononucleotide, also known as or riboflavin-5′-phosphate.[18]

Vitamin B6 study 1

The phosphate ester derivative pyridoxal 5'-phosphate (PLP) is the bioactive coenzyme form of vitamin $B_6$, involved in over 4% of all enzymatic reactions.[19]

Vitamin B12 study 1

Methylcobalamin and 5-deoxyadenosylcobalamin are the coenzyme forms of vitamin $B_{12}$ used in the human body.[20]

Vitamin D study 1

Vitamin D3 is a prohormone produced in skin through ultraviolet irradiation of 7-dehydrocholesterol. The hormonal form of vitamin D3, ie, 1alpha,25-dihydroxyvitamin D3, acts through a nuclear receptor to carry out its many functions, including calcium absorption, phosphate absorption in the intestine, calcium mobilization in bone, and calcium reabsorption in the kidney. It also has several noncalcemic functions in the body. This overview provides a brief description of the physiologic, endocrinologic, and molecular biologic characteristics of vitamin D. It also provides information on new selective analogs of 1alpha,25-dihydroyvitamin D3 for therapy.[21]

Vitamin D study 2

Vitamin D is essential for calcium metabolism as well as for fracture prevention. A multinational study[22] of 18 countries at various latitudes (range 64N-38S) was conducted in 2004 and 2005 to determine the average levels of serum 25(OH)D and the prevalence of vitamin D inadequacy. A total of 2606 postmenopausal women with osteoporosis (low bone mineral density, history of fragility fracture) seeking routine medical care were enrolled and serum 25(OH)D levels were measured at a single laboratory visit. Results showed that mean serum 25(OH)D level was 26.8 ng mL-1 (SE 0.3) and ranged from 7 to 243 ng mL-1. Regional mean values were highest in Latin America (29.6 ng mL-1, SE 0.6) and lowest in the Middle East (20.4 ng mL-1, SE 0.5). Overall, 64% of women had serum levels<30 ng mL-1. Serum parathyroid hormone reached a nadir at serum 25(OH)D levels>35 ng mL-1. In nonequatorial countries, women recruited during the winter months had somewhat lower serum 25(OH)D levels than those recruited during the summer months in some, but not all, countries. In conclusion, low levels of serum 25(OH)D are common amongst women with osteoporosis. The results underscore the value of assuring vitamin D adequacy in these women.

Vitamin D study 3

In a case control study,[23] researchers examined if vitamin K1 and 25(OH)D were associated with an increased risk of hip fracture, and whether the possible synergistic effect of these two micronutrients is mediated through bone turnover markers. Blood was drawn for vitamin K1, 25(OH)D, and the bone turnover marker osteocalcin upon admission for hip fracture and in healthy controls. Results were that vitamin K1 and 25(OH)D were independently associated with a risk of hip fracture. The adjusted odds ratio (95% CI) per ng/ml increase in vitamin K1 was 0.07 (0.02-0.32), and that per nmol/L increase in 25(OH)D was 0.96 (0.95-0.98). There was a significant interaction between 25(OH)D and vitamin K1 ($p < 0.001$), and a significant correlation between total osteocalcin and vitamin K1 and 25(OH)D (rho = 0.18, p = 0.01; rho = 0.20, p = 0.01, respectively). In conclusion, vitamin K1 and 25(OH)D are lower in hip fracture patients compared with controls. Vitamin K1 and 25(OH)D are independently and synergistically associated with the risk of hip fracture when adjusting for confounders. Intervention studies should include both vitamins.

Vitamin D study 4

In an 18-y prospective analysis[24] in 72 337 postmenopausal women, dietary intake and nutritional supplement use were assessed at baseline in 1980 and updated several times during follow-up to assess relations between postmenopausal hip fracture risk and calcium, vitamin D, and milk consumption. We identified 603 incident hip fractures resulting from low or moderate trauma. Relative risks (RRs) from proportional hazards models were controlled for other dietary and nondietary factors. Results were that women consuming ≥ 12.5 microg vitamin D/d (i.e. ≥ 500 IU) from food plus supplements had a 37% lower risk of hip fracture (RR = 0.63; 95% CI: 0.42, 0.94) than did women consuming < 3.5 microg/d (i.e. < 140 IU). Total calcium intake was not associated with hip fracture risk (RR = 0.96; 95% CI: 0.68, 1.34 for > or = 1200 compared with < 600 mg/d). Milk consumption was also not associated with a lower risk of hip fracture (P for trend = 0.21). In conclusion, an adequate vitamin D intake is associated with a lower risk of osteoporotic hip fractures in postmenopausal women. Neither milk nor a high-calcium diet appears to reduce risk. Because women commonly consume less than the recommended intake of vitamin D, supplement use or dark fish consumption may be prudent.

**TABLE 3**
Relative risks of hip fracture by calcium and vitamin D intakes among postmenopausal women ($n$ = 603) in the Nurses' Health Study, 1980–1998[1]

| | | Relative risk (95% CI) | | | | | |
|---|---|---|---|---|---|---|---|
| | Person-years | Age-adjusted[2] | Multivariate 1[3] | Multivariate 1 + protein[4] | Multivariate 1 + retinol[5] | Multivariate 1 + calcium or vitamin D[6] | Multivariate 2[7] |
| Total calcium | | | | | | | |
| <600 mg/d ($n$ = 123) | 180829 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| 600–799 mg/d ($n$ = 168) | 221622 | 1.02 (0.81, 1.29) | 1.15 (0.91, 1.46) | 1.16 (0.92, 1.47) | 1.13 (0.89, 1.44) | 1.19 (0.93, 1.53) | 1.20 (0.93, 1.54) |
| 800–999 mg/d ($n$ = 135) | 189803 | 0.92 (0.72, 1.17) | 1.09 (0.84, 1.40) | 1.10 (0.85, 1.43) | 1.05 (0.81, 1.37) | 1.14 (0.86, 1.50) | 1.16 (0.88, 1.54) |
| 1000–1199 mg/d ($n$ = 96) | 132031 | 0.89 (0.68, 1.17) | 1.12 (0.85, 1.48) | 1.13 (0.85, 1.51) | 1.06 (0.80, 1.42) | 1.16 (0.86, 1.58) | 1.19 (0.88, 1.63) |
| ≥1200 mg/d ($n$ = 81) | 136069 | 0.70 (0.52, 0.92) | 0.90 (0.67, 1.21) | 0.91 (0.67, 1.24) | 0.83 (0.61, 1.14) | 0.93 (0.67, 1.30) | 0.96 (0.68, 1.34) |
| $P$ for trend[8] | | 0.003 | 0.34 | 0.40 | 0.13 | 0.42 | 0.52 |
| Dietary calcium | | | | | | | |
| <500 mg/d ($n$ = 94) | 135799 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| 500–624 mg/d ($n$ = 140) | 190524 | 0.99 (0.76, 1.28) | 1.11 (0.85, 1.45) | 1.19 (0.86, 1.46) | 1.09 (0.84, 1.42) | 1.13 (0.86, 1.48) | 1.13 (0.87, 1.49) |
| 625–749 mg/d ($n$ = 155) | 195028 | 1.02 (0.79, 1.32) | 1.23 (0.95, 1.60) | 1.25 (0.96, 1.63) | 1.19 (0.92, 1.56) | 1.27 (0.96, 1.67) | 1.29 (0.98, 1.71) |
| 750–899 mg/d ($n$ = 103) | 162783 | 0.80 (0.60, 1.05) | 0.97 (0.73, 1.30) | 0.99 (0.73, 1.33) | 0.93 (0.70, 1.25) | 1.00 (0.74, 1.37) | 1.04 (0.76, 1.42) |
| ≥900 mg/d ($n$ = 111) | 176220 | 0.79 (0.60, 1.04) | 0.99 (0.74, 1.31) | 1.00 (0.75, 1.34) | 0.93 (0.69, 1.23) | 1.01 (0.74, 1.38) | 1.08 (0.78, 1.49) |
| $P$ for trend[8] | | 0.006 | 0.21 | 0.25 | 0.08 | 0.27 | 0.51 |
| Total vitamin D | | | | | | | |
| <3.50 μg/d ($n$ = 122) | 175284 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| 3.50–5.99 μg/d ($n$ = 149) | 215342 | 0.87 (0.68, 1.11) | 0.93 (0.73, 1.19) | 0.94 (0.73, 1.20) | 0.86 (0.67, 1.11) | 0.88 (0.68, 1.14) | 0.82 (0.63, 1.07) |
| 6.00–8.99 μg/d ($n$ = 126) | 183322 | 0.81 (0.63, 1.05) | 0.93 (0.72, 1.20) | 0.94 (0.72, 1.21) | 0.80 (0.60, 1.06) | 0.88 (0.67, 1.17) | 0.77 (0.56, 1.04) |
| 9.00–12.49 μg/d ($n$ = 98) | 135209 | 0.83 (0.64, 1.09) | 0.96 (0.73, 1.26) | 0.97 (0.74, 1.28) | 0.77 (0.56, 1.07) | 0.94 (0.70, 1.27) | 0.75 (0.53, 1.07) |
| ≥12.50 μg/d ($n$ = 108) | 151198 | 0.80 (0.61, 1.04) | 0.92 (0.70, 1.20) | 0.93 (0.71, 1.22) | 0.63 (0.43, 0.90) | 0.93 (0.68, 1.25) | 0.63 (0.42, 0.94) |
| $P$ for trend[8] | | 0.25 | 0.91 | 0.97 | 0.03 | 0.25 | 0.09 |
| Dietary vitamin D | | | | | | | |
| <2.50 μg/d ($n$ = 121) | 152427 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| 2.50–3.74 μg/d ($n$ = 134) | 192319 | 0.79 (0.62, 1.01) | 0.87 (0.67, 1.11) | 0.87 (0.68, 1.19) | 0.84 (0.66, 1.09) | 0.81 (0.63, 1.05) | 0.80 (0.62, 1.03) |
| 3.75–4.99 μg/d ($n$ = 146) | 197719 | 0.76 (0.60, 0.97) | 0.85 (0.66, 1.09) | 0.85 (0.66, 1.10) | 0.81 (0.63, 1.05) | 0.76 (0.58, 0.99) | 0.74 (0.56, 0.97) |
| 5.00–6.24 μg/d ($n$ = 95) | 142546 | 0.65 (0.50, 0.86) | 0.77 (0.58, 1.02) | 0.77 (0.58, 1.02) | 0.72 (0.54, 0.96) | 0.70 (0.49, 0.91) | 0.65 (0.48, 0.88) |
| ≥6.25 μg/d ($n$ = 107) | 175345 | 0.58 (0.45, 0.76) | 0.67 (0.51, 0.68) | 0.67 (0.51, 0.89) | 0.62 (0.47, 0.82) | 0.59 (0.43, 0.81) | 0.57 (0.41, 0.78) |
| $P$ for trend[8] | | <0.001 | 0.004 | 0.004 | <0.001 | 0.002 | <0.001 |

[1] Diet was assessed in 1980, 1984, 1986, 1990, and 1994. Nutrient intakes were cumulatively updated over follow-up. Total intakes include multivitamins and supplements. Dietary intakes are from food sources only.
[2] Relative risks were adjusted for age.
[3] Relative risks were adjusted for age, BMI, postmenopausal hormone use, physical activity, smoking, calcium supplement use (dietary calcium model only), multivitamin use (dietary vitamin D model only), and intakes of vitamin K, alcohol, and caffeine.
[4] Relative risks were adjusted for protein intake plus factors in footnote 3.
[5] Relative risks were adjusted for retinol intake plus factors in footnote 3.
[6] Relative risks were adjusted for total vitamin D intake (total and dietary calcium models only) or total calcium intake (total and dietary vitamin D models only) plus factors in footnote 3.
[7] Relative risks were adjusted for intakes of protein, retinol, total vitamin D (total and dietary calcium models only), and total calcium (total and dietary vitamin D models only) plus factors in footnote 3.
[8] $P$ for linear association.

Vitamin D study 5

A meta-analysis[25] was conducted to examine the relationship between vitamin D supplementation and fracture. Participant-level data from 11 double-blind, randomized, controlled trials of oral vitamin D supplementation (daily, weekly, or every 4 months), with or without calcium, as compared with placebo or calcium alone in persons 65 years of age or older were pooled. Primary end points were the incidence of hip and any nonvertebral fractures according to Cox regression analyses, with adjustment for age group, sex, type of dwelling, and study. The primary aim was to compare data from quartiles of actual intake of vitamin D (including each individual participant's adherence to the treatment and supplement use outside the study protocol) in the treatment groups of all trials with data from the control groups. Researchers included 31,022 persons (mean age, 76 years; 91% women) with 1111 incident hip fractures and 3770 nonvertebral fractures. Results showed that participants who were randomly assigned to receive vitamin D, as compared with those assigned to control groups, had a 10% reduction in the risk of hip fracture (hazard ratio, 0.90; 95% confidence interval [CI], 0.80 to 1.01) and a 7% reduction in the risk of nonvertebral fracture (hazard ratio, 0.93; 95% CI, 0.87 to 0.99). By quartiles of actual intake, reduction in the risk of fracture was shown only at the highest intake level (median, 800 IU daily; range, 792 to 2000), with a 30% reduction in the risk of hip fracture (hazard ratio, 0.70; 95% CI, 0.58 to 0.86) and a 14% reduction in the risk of any nonvertebral fracture (hazard ratio, 0.86; 95% CI, 0.76 to 0.96). Benefits at the highest level of vitamin D intake were fairly consistent across subgroups defined by age group, type of dwelling,

baseline 25-hydroxyvitamin D level, and additional calcium intake. In conclusion, high-dose vitamin D supplementation (≥800 IU daily) was somewhat favorable in the prevention of hip fracture and any nonvertebral fracture in persons 65 years of age or older.

**Table 2. Incidence of Fracture among 31,022 Participants, According to Vitamin D Treatment Dose and Actual Intake.***

| Analysis | No. of Participants | Hip Fracture | | | Any Nonvertebral Fracture | | |
|---|---|---|---|---|---|---|---|
| | | No. of Fractures | Relative Risk (95% CI) | P Value | No. of Fractures | Relative Risk (95% CI) | P Value |
| Intention-to-treat analysis | | | | | | | |
| Control | 15,495 | 586 | 1.00 | | 1948 | 1.00 | |
| Treatment | 15,527 | 525 | 0.90 (0.80–1.01) | 0.07 | 1822 | 0.93 (0.87–0.99) | 0.03 |
| Treatment-dose analysis | | | | | | | |
| Control | 15,495 | 586 | 1.00 | | 1948 | 1.00 | |
| ≤400 IU/day | 10,111 | 255 | 0.89 (0.74–1.07) | 0.20 | 1225 | 0.96 (0.89–1.05) | 0.40 |
| >400 IU/day† | 5,416 | 270 | 0.91 (0.78–1.06) | 0.22 | 597 | 0.89 (0.80–0.98) | 0.02 |
| Actual-intake analysis‡ | | | | | | | |
| Control | 15,495 | 586 | 1.00 | | 1948 | 1.00 | |
| 0–360 IU/day | 3,935 | 100 | 1.00 (0.79–1.26) | 0.99 | 425 | 0.96 (0.86–1.07) | 0.44 |
| 361–637 IU/day | 3,836 | 110 | 1.03 (0.83–1.29) | 0.78 | 520 | 1.01 (0.91–1.12) | 0.85 |
| 638–791 IU/day | 3,790 | 164 | 1.01 (0.83–1.23) | 0.92 | 419 | 0.90 (0.80–1.01) | 0.08 |
| 792–2000 IU/day | 3,966 | 151 | 0.70 (0.58–0.86) | <0.001 | 458 | 0.86 (0.76–0.96) | 0.007 |
| Sensitivity analysis | | | | | | | |
| Control | 15,495 | 586 | 1.00 | | 1948 | 1.00 | |
| 0–337 IU/day | 3,353 | 84 | 1.01 (0.79–1.30) | 0.91 | 465 | 1.06 (0.95–1.17) | 0.32 |
| 338–360 IU/day | 5,652 | 114 | 0.83 (0.66–1.05) | 0.11 | 619 | 0.89 (0.80–0.98)§ | 0.02 |
| 361–699 IU/day | 2,640 | 180 | 1.14 (0.93–1.41) | 0.21 | 326 | 1.05 (0.91–1.22) | 0.52 |
| 700–2000 IU/day | 3,882 | 147 | 0.71 (0.58–0.87) | 0.001 | 412 | 0.81 (0.72–0.91) | <0.001 |
| Internal validation | | | | | | | |
| 0–360 IU/day | 18,153 | 639 | 1.00 | | 2193 | 1.00 | |
| 361–637 IU/day | 4,976 | 150 | 1.03 (0.84–1.26) | 0.80 | 681 | 1.04 (0.95–1.15) | 0.37 |
| 638–791 IU/day | 3,865 | 168 | 1.02 (0.84–1.24) | 0.83 | 431 | 0.92 (0.82–1.03) | 0.16 |
| 792–2000 IU/day | 4,028 | 154 | 0.70 (0.58–0.86) | <0.001 | 465 | 0.86 (0.77–0.97) | 0.01 |

* All analyses were adjusted for study, age group, sex, and type of dwelling. To limit false positive results and correct for multiplicity, we used a P value of 0.0125 to indicate significance.
† All trials included doses between 700 and 2000 IU per day.
‡ Among 21,241 participants from the eight trials that used vitamin D combined with any dose of calcium supplementation, a benefit was present only at the highest actual-intake level of vitamin D.
§ In the sensitivity analysis for adherence-adjusted dose without supplements outside the study protocol, 511 participants in the Women's Health Initiative trial[17] shifted from the highest actual-intake level (792 to 2000 IU per day) and 1356 shifted from the second-highest actual-intake level (638 to 791 IU per day) to the second-lowest adherence-adjusted intake level (338 to 360 IU per day). See the Supplementary Appendix for additional information.

<u>Vitamin D study 6</u>

To quantify calcium absorption at two levels of vitamin D repletion, using pharmacokinetic methods and commercially marketed calcium supplements, two experiments[26] were performed in the spring of the year, one year apart. In the first, in which participants were pretreated with 25-hydroxyvitamin D (25OHD, equivalent to 400 IU/day), mean serum 25OHD concentration was 86.5 nmol/L; and in the other, with no pretreatment, mean serum concentration was 50.2 nmol/L. Participants received 500 mg oral calcium loads (which included 200 IU vitamin D/day) as a part of a standard low calcium breakfast. A low calcium lunch was provided at mid-day. Blood was obtained fasting and at frequent intervals for 10 to 12 hours thereafter. Total daily vitamin D intake was 600 IU in the pretreated group and 200 IU in the no pretreatment group. Relative calcium absorption at the two 25OHD concentrations was estimated from the area under the curve (AUC) for the load-induced increment in serum total calcium. Results showed that AUC(9) (+/- SEM), was 3.63 mg hr/dL +/- 0.234 in participants pretreated with 25OHD and 2.20 +/- 0.240 in those not pretreated (P < 0.001). In brief, absorption was 65% higher at

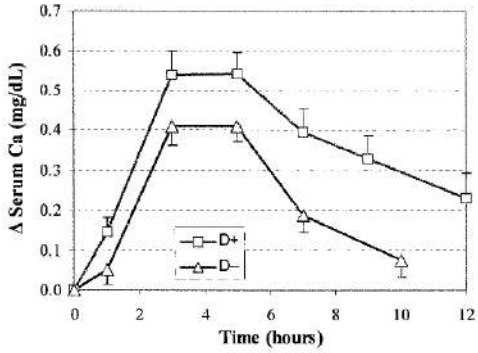


Fig. 2. Time course of the mean increment in serum total calcium in two studies, in one of which vitamin D status was elevated ("D+"), and in the other, it was not ("D−"). Error bars are 1 SEM. (Copyright Robert P. Heaney, 2002. Used with permission.)

serum 25OHD levels averaging 86.5 nmol/L than at levels averaging 50 nmol/L (both values within the nominal reference range for this analyte). In conclusion, despite the fact that the mean serum 25OHD level in the experiment without supplementation was within the current reference ranges, calcium absorptive performance at 50 nmol/L was significantly reduced relative to that at a mean 25OHD level of 86 nmol/L. Thus, individuals with serum 25-hydroxyvitamin D levels at the low end of the current reference ranges may not be getting the full benefit from their calcium intake. We conclude that the lower end of the current reference range is set too low.

Vitamin D study 7

For adults, the 5-µg (200 IU) vitamin D recommended dietary allowance may prevent osteomalacia in the absence of sunlight, but more is needed to help prevent osteoporosis and secondary hyperparathyroidism. Other benefits of vitamin D supplementation are implicated epidemiologically: prevention of some cancers, osteoarthritis progression, multiple sclerosis, and hypertension. Total-body sun exposure easily provides the equivalent of 250 µg (10000 IU) vitamin D/d, suggesting that this is a physiologic limit. Sailors in US submarines are deprived of environmentally acquired vitamin D equivalent to 20–50 µg (800–2000 IU)/d. The assembled data from many vitamin D supplementation studies reveal a curve for vitamin D dose versus serum 25-hydroxyvitamin D [25(OH)D] response that is surprisingly flat up to 250 µg (10000 IU) vitamin D/d. To ensure that serum 25(OH)D concentrations exceed 100 nmol/L, a total vitamin D supply of 100 µg (4000 IU)/d is required. Except in those with conditions causing hypersensitivity, there is no evidence of adverse effects with serum 25(OH)D concentrations <140 nmol/L, which require a total vitamin D supply of 250 µg (10000 IU)/d to attain. Published cases of vitamin D toxicity with hypercalcemia, for which the 25(OH)D concentration and vitamin D dose are known, all involve intake of ≥1000 µg (40000 IU)/d. Because vitamin D is potentially toxic, intake of >25 µg (1000 IU)/d has been avoided even though the weight of evidence shows that the currently accepted, no observed adverse effect limit of 50 µg (2000 IU)/d is too low by at least 5-fold.[27]

*Note*: Crominex® 3+ is an advanced trivalent chromium complex that has been optimized with a standardized extract of Capros® and PrimaVie®. Crominex®3+ has been clinically studied to be one of the most efficacious of all the branded Chromium III supplements on the market and, yet, the most economical. Research has shown it helps support healthy glucose levels, healthy endothelial function and healthy cholesterol levels.

Capros® is a super antioxidant (ORACFN of 47,000 µmoles TE/g) and an excellent cardiovascular support product, which is all natural, derived from the edible fruits of Phyllanthus emblica (Indian Gooseberry), organic and non–GMO. Capros'® efficacy is backed by ten human clinical studies, which demonstrate its efficacy for healthy endothelial function, healthy cholesterol, healthy platelet aggregation and healthy glucose levels.

PrimaVie® is a high quality, clinically studied, Purified Shilajit from the Himalayas, containing dibenzo-α-pyrones (DBPs), DBP-Chromoproteins (DCP), Fulvic Acid and over 40 different minerals. Its' history of use goes back to The Indus Valley Civilization, 3,000 B.C., where British archaeologists have found evidence of use of Shilajit for anti-aging. Research supports its use as a mitochondrial energy booster, to incrase exercise endurance and overall fitness, upregulating genes for collagen synthesis and improving the bioavailability of coenzyme Q10.

Chromium study 1

A biologically active form of chromium participates in glucose metabolism by enhancing the effects of insulin. Insulin is secreted by specialized cells in the pancreas in response to increased blood glucose levels, such as after a meal. Insulin binds to insulin receptors on the surface of cells, which activates the receptors and stimulates glucose uptake by cells. Through its interaction with insulin receptors, insulin provides cells with glucose for energy and prevents blood glucose levels from becoming elevated. In addition to its effects on carbohydrate (glucose) metabolism, insulin also influences the metabolism of fat and protein. A decreased response to insulin or decreased insulin sensitivity may result in impaired glucose tolerance or type 2

diabetes, also known as non-insulin dependent diabetes mellitus (NIDDM). Type 2 diabetes is characterized by elevated blood glucose levels and insulin resistance.[28]

Chromium study 2

The precise structure of the biologically active form of chromium is not known. Recent research suggests that a low-molecular-weight chromium-binding substance (LMWCr) may enhance the response of the insulin receptor to insulin. The following is a proposed model for the effect of chromium on insulin action.

**A proposed model for the enhancing effects of chromium on insulin activity**

First, the inactive form of the insulin receptor is converted to the active form by binding insulin. The binding of insulin by the insulin receptor stimulates the movement of chromium into the cell and results in binding of chromium to apoLMWCr, a form of the LMWCr that lacks chromium. Once it binds chromium, the LMWCr binds to the insulin receptor and enhances its tyrosine kinase activity. The ability of the LMWCr to activate the insulin receptor is dependent on its chromium content. When insulin levels drop due to normalization of blood glucose levels, the LMWCr may be released from the cell in order to terminate its effects.[29]

Crominex study 1

A prospective, randomized, double blind trial[30] was undertaken to evaluate the effect of chromium 200 mcg (group 1), chromium 400 mcg (group 2) and placebo (group 3) on endothelial function in 60 patients with type 2 diabetes mellitus (T2DM) and further study its probable mechanism of action. The chromium was provided in the form of Crominex, a proprietary combination of chromium chloride (CrCl3.6H2O), *Phyllanthus emblica* fruit extract, processed shilajit and microcrystalline cellulose in a proportion of 1:3:3:3. Subjects were reviewed for follow up at 4 weeks, 8 and 12 weeks of therapy. At each visit they were evaluated for efficacy and safety. Pharmacodynamic evaluation for endothelial function was conducted at every visit. Blood samples were collected for evaluation of biomarkers before and at end of treatment. Safety lab investigations for hematological, hepatic and renal biochemical parameters were conducted before and at the end of the study and also as and when required (in case of any adverse drug reaction (ADR)). Subjects were enquired for the presence of ADR and the same was recorded in the case report form. Compliance to therapy was assessed by pill count method. Results demonstrated several statistically significant effects. Treatment with Crominex showed: 1) significant reduction in reflection index (suggesting improvement in endothelial function) with 200 mcg ($p<0.001$ compared to baseline and placebo) and 400 mcg ($p<0.001$ compared to baseline and placebo, and $p<0.001$ compared to 200 mcg); 2) significant increase in nitric oxide (which promotes circulation) with 200 and 400 mcg ($p<0.001$ compared to baseline; 3) significant increases in glutathione (a critical antioxidant) with 200 and 400 mcg ($p<0.001$ compared to baseline); 4) significant reductions in MDA (a marker for oxidative stress) with 200 and 400 mcg ($p<0.001$ compared to baseline); 5) significant reductions in hsCRP (an inflammatory marker) with 200 and 400 mcg ($p<0.001$ compared to baseline); and 6) significant reduction in glycosylated hemoglobin A1C with 200 mcg ($p<0.05$ compared to baseline) and 400 mcg ($p<0.001$ compared to baseline).

**Table No 7: Effect of treatments on Glycosylated Hemoglobin A1c (HbA1c %)**

| Parameter | Crominex 200mcg (n=20) | | Crominex 400mcg(n=20) | | Placebo(n=20) | |
|---|---|---|---|---|---|---|
| | Pretreatment | Post treatment | Pretreatment | Post treatment | Pretreatment | Post treatment |
| HbA1c (%) | 7.14±0.29 | 7.01±0.36 $ | 7.24±0.29 | 6.72±0.36 # | 7.10±0.30 | 7.16±0.32 |

Baseline values between the three treatments were comparable

$=p<0.05 compared to baseline, # = p<0.001 compared to baseline

As seen from table 7, treatment with Crominex 200 mcg and Crominex 400 mcg showed significant reduction in HbA1c levels compared to baseline.

**Table No 7A: Comparison of absolute change between the three treatments on Glycosylated Hemoglobin A1c (HbA1c %)**

| Parameter | Crominex 200mcg (n=20) | Crominex 400mcg (n=20) | Placebo (n=20) |
|---|---|---|---|
| HbA1c (%) | -0.13±0.21# | -0.52±0.20 $ | 0.06±0.18 |

#=p<0.01 Crominex 200 Vs Placebo, $ p<0.001 Crominex 400 Vs Crominex 200 and Crominex 400 Vs Placebo

In addition, there were significant percentage changes in lipid profile after 12 weeks:

| Parameter | Crominex 200mcg (n=20) | Crominex 400mcg (n=20) | Placebo (n=20) |
|---|---|---|---|
| Total Cholesterol (mg/dl) | -9.25±3.48 | -18.05±6.86 | 2.95±4.81 |
| HDL-C(mg/dl) | 12.03±5.90 | 27.34±11.74 | 0.32±6.99 |
| LDL-C(mg/dl) | -16.37±7.47 | -27.70±7.85 | 3.59±4.91 |
| Triglycerides(mg/dl) | -10.07±3.37 | -25.41±8.16 | 0.48±3.60 |
| VLDL-C(mg/dl) | -13.3±5.14 | -22.42±6.02 | 1.04±8.71 |

1. **TC-** p<0.001 Crominex 200mcg Vs Crominex 400mcg, Crominex 200 mcg Vs placebo and Crominex 400mcgVs placebo
2. **HDL-C-** p<0.001 Crominex 200mcg Vs Crominex 400mcg, p<0.001 between Crominex 400 Vs placebo and Crominex 200mcg Vs Placebo
3. **LDL-** p<0.001 Crominex 200mcg Vs Crominex 400mcg, p<0.001 between Crominex 200mcg Vs placebo, p<0.001 TC 400mcg Vs placebo
4. **TG –** p<0.001 Crominex 200mcg Vs Crominex 400mcg, p<0.001 Crominex 200mcg Vs placebo and Crominex 400mcg Vs placebo
5. **VLDL-** p<0.001 Crominex 200mcg Vs Crominex 400mcg, p<0.001 Crominex 200mcg Vs Placebo and Crominex 400mcg Vs placebo

Furthermore, there were no significant changes in safety parameters, including vital, hematological, renal and hepatic functions with all treatments. In conclusion, treatment with Crominex 200mcg and 400mcg produced significant improvement in mean RI index compared to baseline and placebo. Reduction in the levels of markers of oxidative stress were observed suggesting improvement in endothelial function in diabetic patients. Both the active treatments showed significant improvement in the lipid parameters. Treatment with Crominex 200mcg and Crominex 400mcg significantly reduced glycosylated hemoglobin A1c levels compared to baseline and placebo. All the treatments were well tolerated and no patient discontinued the study because of side effects.

Crominex study 2

A prospective, randomized, double blind trial[31] was undertaken to evaluate the effect of chromium 200 mcg (group 1), chromium 400 mcg (group 2) and placebo (group 3) in 61 patients with metabolic syndrome. The chromium was provided in the form of Crominex, described in Crominex study 1 above Subjects were reviewed for follow up at 4 weeks, 8 and 12 weeks of

therapy. At each visit they were evaluated for efficacy and safety. Pharmacodynamic evaluation for endothelial function was conducted at every visit. Blood samples were collected for evaluation of biomarkers before and at end of treatment. Safety lab investigations for hematological, hepatic and renal biochemical parameters were conducted before and at the end of the study and also as and when required (in case of any adverse drug reaction (ADR)). Subjects were enquired for the presence of ADR and the same was recorded in the case report form. Compliance to therapy was assessed by pill count method. Results demonstrated several statistically significant effects. Treatment with Crominex showed: 1) significant reduction in reflection index (suggesting improvement in endothelial function) with 400 mcg ($p<0.001$ compared to baseline and placebo); 2) significant increase in nitric oxide (which promotes circulation) with 400 mcg ($p<0.001$ compared to baseline; 3) significant increase in glutathione (a critical antioxidant) with 400 mcg ($p<0.001$ compared to baseline); 4) significant reduction in MDA (a marker for oxidative stress) with 400 mcg ($p<0.001$ compared to baseline); and 5) significant reduction in hsCRP (an inflammatory marker) with 400 mcg ($p<0.001$ compared to baseline). In addition, there were significant percentage changes in lipid profile after 12 weeks:

| Parameter | Crominex 200mcg (n=20) | Crominex 400mcg (n=21) | Placebo (n=20) |
|---|---|---|---|
| Total Cholesterol (mg/dl) | -1.39±2.71 | -2.75±2.75 | 1.76±3.80 |
| HDL-C(mg/dl) | 0.57±5.63 | 3.41±5.67 | -2.62±6.58 |
| LDL-C(mg/dl) | -1.51±4.43 | -12.86±6.41 | 1.98±3.20 |
| Triglycerides(mg/dl) | -1.05±2.06 | -2.92±4.48 | -0.12±3.44 |

1. **TC-** Nonsignificant Crominex 200mcg Vs Crominex 400mcg,$p<0.01$ Crominex 200 mcg Vs placebo and Crominex 400mcgVs placebo
2. **HDL-C**- Nonsignificant Crominex 200mcg Vs Crominex 400mcg, Nonsignificant Crominex 200 Vs placebo and $p<0.01$ Crominex 400mcg Vs Placebo
3. **LDL-** $p<0.001$ Crominex 200mcg Vs Crominex 400mcg, $p<0.01$ between Crominex 200mcg Vs placebo, $p<0.001$ Crominex 400mcg Vs placebo
4. **TG –** Nonsignificant Crominex 200mcg Vs Crominex 400mcg and Crominex 200mcg Vs placebo, $p<0.05$ Crominex 400mcg Vs placebo

In conclusion, treatment with Crominex 400 mcg produced significant improvement in mean reflection index compared to baseline. Reduction in the levels of markers of oxidative stress was observed suggesting improvement in endothelial function in subjects with metabolic syndrome. Treatment with Crominex 400 mcg showed significant improvement in the lipid parameters compared to baseline and placebo.

*Note*: The following summary discusses two studies, the first of which is "Crominex study 1" described above. The second study in the summary below demonstrates the efficacy of Crominex over other forms of chromium.

Crominex study 3

Crominex 3+ is a proprietary chromium complex, designed to keep chromium in trivalent state under oxidative conditions and to improve bioavailability of chromium. A randomized, placebo-controlled, double-blind clinical study[32] was conducted to evaluate the effect of Crominex 3+ and its individual components in comparison to chromium picolinate, chromium polynicotinate and chromium dinicocysteinate on endothelial function, glycosylated hemoglobin and lipid profile in type 2 diabetics. The study was done in two parts. Part I: 60 type 2 diabetic patients of either sex, who are already stabilized on metformin treatment, have been given either 200 mcg or 400 mcg of the Crominex 3+ per day with the third group receiving a matching placebo capsule for a duration of 12 weeks and patients visited the clinic at 4, 8 and 12 weeks after the first visit. Pharmacodynamic evaluation for endothelial function was conducted at every visit. Blood samples were collected for evaluation of biomarkers before and at the end of the treatment period. Part –II: When the results were highly significant, especially with the 400 mcg dose, more patients were included (n=96) to evaluate the individual components of Crominex 3+ and other branded chromium salts available in the market, at 400 mcg dose level. Results were that Crominex 3+ significantly improved endothelial function and increased the levels of the nitric oxide and glutathione, and significantly decreased the levels of malondialdehyde and highly

sensitive C-reactive protein at both 200 mcg and 400 mcg per day dose levels, with the results being much more significant at the 400 mcg dose level. Similarly, the effect on lipid profile was highly significant with improvement of lipid levels from 18-28% and a decrease of half a point in the glycosylated hemoglobin A1c level with the 400 mcg dose. The results from the Crominex 3+ group were much more significant than the sum of the results from the individual component arms, indicating that the proprietary chromium complex has significant synergistic activity. With respect to efficacy, Crominex 3+ was the best, followed by the combination of Phyllathus emblica and Shilajit extracts (the two other components in Crominex 3+), chromium picolinate, chromium polynicotinate, chromium dinicocysteinate and the placebo, in that order. In conclusion, Crominex 3+ improves endothelial function, nitric oxide, glutathione and hsCRP levels, lipid profile and glycosylated hemoglobin in type 2 diabetics and it appears to have a significant synergistic activity. In addition, Crominex 3+ proved to be the most efficacious in the parameters tested among all the chromium products studied.

Table 8. Effect of Crominex 3+ and placebo on glycosylated hemoglobin (HbA1c)

| Biomarker | 200 mcg (n=20) | | 400 mcg (n=20) | | Placebo (n=20) | |
|---|---|---|---|---|---|---|
| | Baseline | 12 weeks | Baseline | 12 weeks | Baseline | 12 weeks |
| HbA1c, % | 7.14±0.29 | 7.01±0.36 $ | 7.24±0.29 | 6.72±0.36 # | 7.10±0.30 | 7.16±0.32 |

Table 9. Comparison of absolute change between the three treatments on glycosylated hemoglobin (HbA1c)

| Parameter | 200 mcg (n=20) | 400 mcg (n=20) | Placebo (n=20) |
|---|---|---|---|
| HbA1c, % | -0.13±0.21# | -0.52±0.20 $ | 0.06±0.18 |

# p<0.01 200 mcg Vs Placebo,

$ p<0.001 400 mcg Vs 200 mcg and 400 mcg Vs placebo

Crominex study 4

Chromium chelates/complexes are widely used as nutritional supplements to redress complications of type 2 diabetic mellitus (T2DM) patients. However, most of these chelates could be susceptible to oxidation into toxic Cr(VI) state. Complexation of Cr (III) with gallo-ellagi tannoids produces a herbochromium supplement (HCrS) that maintains its Cr3+ oxidation state under oxidizing circumstances in vitro. It was tested with conventional oral hypoglycemic drugs [(oral antidiabetic drugs (OAD)] for its beneficial effects in T2DM patients. A randomized clinical study[33] with three OADs with or without HCrS was carried out in 150 T2DM patients to evaluate the efficacy of the HCrS supplement. The patients were randomized into six treatment groups. After 60 days of treatment, fasting blood glucose and post-prandial blood glucose (FBG and PPBG, respectively), $HbA_{1C}$, HsCRP, oxidized low density lipoprotein (LDL), and urinary microalbumin levels and other diabetic symptoms were evaluated. Findings were compared using one-way analysis of variance (ANOVA) with post hoc pairwise comparisons of groups using the least significant difference method. Results showed better control of FBG and PPBG levels were observed in patients receiving HCrS (-12.4 to -16.6%) compared to placebo groups (-3.4 to -9.4%). There was a 5.5–7.4% decrease in HsCRP and LDL levels in patients receiving HCrS, which is better than placebo treated groups. Significant decrease in urinary microalbumin level was observed in patients receiving HCrS (-20.0 to -22.5%) compared to placebo groups (-7.8 to -11.6%). Significant decreases in diabetic symptoms were observed in patients receiving HCrS (-47.4 to -59.4%) compared to that observed in placebo groups (-18.0 to 34.0%). T2DM patients who took HCrS as an adjunct therapy experienced a better decrease in HbA1c (ranging from -5.2 to -6.7%; mean

-6.1%) levels compared to that of only OAD treated groups (ranging from -2.1 to -6.2%; mean -4.1%). In conclusion, the findings indicate that HCrS with OAD improves overall diabetic complications within 2 months and may be useful in long-term therapy.

Vitamin C study 1

Vitamin C has been shown to affect various components of the human immune response, including antimicrobial and natural killer cell activities, lymphocyte proliferation, chemotaxis, and delayed dermal sensitivity (DDS). Except for the metabolic unit study of Jacob et al. (1991) and the study of patients with furunculosis (Levy et al., 1996), the studies involved apparently healthy free-living populations supplemented with from 200 mg/day to 6 g/day of vitamin C in addition to dietary vitamin intake. Hence, the results relate largely to the pharmacological range of vitamin C intakes rather than the nutritional range of intakes usually provided from food alone.[34]

Vitamin C study 2

As elements of the antioxidant system, cofactors of enzymes, components of transcription factors, and epigenetic modulators, micronutrients, such as vitamins and trace elements, influence various metabolic processes that are directly associated with immune functions. Specifically, the vitamins C and D have been shown to have significance immune function. Therefore, the objective of this review is to elucidate interactions between micronutrients and the immune system. In the initial section of this review, we present a general overview of interactions between the immune system and micronutrients, with a focus on the immunobiologically relevant functions of vitamin C. Immune competent cells accumulate vitamin C against a concentration gradient, with a close relationship between vitamin C supply and immune cell activity, especially phagocytosis activity and T-cell function. Accordingly, one of the consequences of vitamin C deficiency is impaired resistance to various pathogens, while an enhanced supply increases antibody activity and infection resistance.[35]

Vitamin C study 3

To investigate the relationship between the common cold and vitamin C supplementation, a double-blind, 5-year randomized controlled trial[36] was conducted. Participants were recruited from in annual screening programs for circulatory diseases conducted under the National Health and Welfare Services Law for the Aged, and diagnosed as having atrophic gastritis. Of the 439 eligible subjects, 144 and 161 were assigned to receive 50 or 500 mg of vitamin C, respectively, after protocol amendment. During the supplementation phase, 61 dropped out, and 244 completed the trial. Intervention: Daily vitamin C supplementation of 50 mg (low-dose group) or 500 mg (high-dose group). The results were that the total number of common colds (per 1000 person-months) was 21.3 and 17.1 for the low- and high-dose groups, respectively. After adjustment for several factors, the relative risks (95% confidence interval (CI)) of suffering from a common cold three or more times during the survey period was 0.34 (0.12-0.97) for the high-dose group. No apparent reduction was seen for the severity and duration of the common cold. In conclusion this randomized, controlled 5-year trial suggests that that those who took 500 mg/day of supplemental vitamin C had a 66% lower risk for contracting three or more colds in a five-year period compared to those who took 50 mg/day of supplemental vitamin C.

Vitamin C study 4

Oxidative stress induces adaptations in the expression of protective enzymes and heat shock proteins (HSPs) in a variety of tissues. We have examined the possibility that supplementation of subjects with the nutritional antioxidant, vitamin C, influences the ability of lymphocytes to express protective enzymes and HSPs following exposure to an exogenous oxidant and the response of skeletal muscle to the physiological oxidative stress that occurs during exercise in vivo. Our hypothesis was that an elevation of tissue vitamin C content would reduce oxidant-induced expression of protective enzymes and HSP content. Lymphocytes from non-supplemented subjects responded to hydrogen peroxide with increased activity of superoxide dismutase (SOD) and catalase, and HSP60 and HSP70 content over 48 h. Vitamin C supplementation at a dose of 500 mg day-1 for 8 weeks was found to increase the serum vitamin C concentration by ~50 %. Lymphocytes from vitamin C-supplemented subjects had increased baseline SOD and catalase

activities and an elevated HSP60 content. The SOD and catalase activities and the HSP60 and HSP70 content of lymphocytes from supplemented subjects did not increase significantly in response to hydrogen peroxide. In non-supplemented subjects, a single period of cycle ergometry was found to significantly increase the HSP70 content of the vastus lateralis. Following vitamin C supplementation, the HSP70 content of the muscle was increased at baseline with no further increase following exercise. We conclude that, in vitamin C-supplemented subjects, adaptive responses to oxidants are attenuated, but that this may reflect an increased baseline expression of potential protective systems against oxidative stress (SOD, catalase and HSPs).[37]

Zinc study 1

Zinc is essential for the integrity of the immune system, and inadequate zinc intake has many adverse effects. Though the immune system, which is thought to underlie several of the most important sequelae of mild zinc deficiency, is sensitive to even mild zinc deficiency, the effects on functional indexes of zinc status are not specific. At this time, therefore, changes in indexes of immune status with manipulation of dietary zinc can serve only as a limited indicator for dietary zinc requirements.[38]

Zinc study 2

Although the essentiality of zinc for plants and animals has been known for many decades, the essentiality of zinc for humans was recognized only 40 years ago in the Middle East. The zinc-deficient patients had severe immune dysfunctions, inasmuch as they died of intercurrent infections by the time they were 25 years of age. In our studies in an experimental human model of zinc deficiency, we documented decreased serum testosterone level, oligospermia, severe immune dysfunctions mainly affecting T helper cells, hyperammonemia, neurosensory disorders, and decreased lean body mass. It appears that zinc deficiency is prevalent in the developing world and as many as two billion subjects may be growth retarded due to zinc deficiency. Besides growth retardation and immune dysfunctions, cognitive impairment due to zinc deficiency also has been reported recently. Our studies in the cell culture models showed that the activation of many zinc-dependent enzymes and transcription factors were adversely affected due to zinc deficiency. In HUT-78 (T helper 0 [Th(0)] cell line), we showed that a decrease in gene expression of interleukin-2 (IL-2) and IL-2 receptor alpha(IL-2Ralpha) were due to decreased activation of nuclear factor-kappaB (NF-kappaB) in zinc deficient cells. Decreased NF-kappaB activation in HUT-78 due to zinc deficiency was due to decreased binding of NF-kappaB to DNA, decreased level of NF-kappaB p105 (the precursor of NF-kappaB p50) mRNA, decreased kappaB inhibitory protein (IkappaB) phosphorylation, and decreased Ikappa kappa. These effects of zinc were cell specific. Zinc also is an antioxidant and has anti-inflammatory actions. The therapeutic roles of zinc in acute infantile diarrhea, acrodermatitis enteropathica, prevention of blindness in patients with age-related macular degeneration, and treatment of common cold with zinc have been reported. In HL-60 cells (promyelocytic leukemia cell line), zinc enhances the up-regulation of A20 mRNA, which, via TRAF pathway, decreases NF-kappaB activation, leading to decreased gene expression and generation of tumor necrosis factor-alpha (TNF-alpha), IL-1beta, and IL-8. We have reported recently that in both young adults and elderly subjects, zinc supplementation decreased oxidative stress markers and generation of inflammatory cytokines.[39]

Zinc study 3

Zinc is known to play a central role in the immune system, and zinc-deficient persons experience increased susceptibility to a variety of pathogens. The immunologic mechanisms whereby zinc modulates increased susceptibility to infection have been studied for several decades. It is clear that zinc affects multiple aspects of the immune system, from the barrier of the skin to gene regulation within lymphocytes. Zinc is crucial for normal development and function of cells mediating nonspecific immunity such as neutrophils and natural killer cells. Zinc deficiency also affects development of acquired immunity by preventing both the outgrowth and certain functions of T lymphocytes such as activation, Th1 cytokine production, and B lymphocyte help. Likewise, B lymphocyte development and antibody production, particularly immunoglobulin G, is compromised. The macrophage, a pivotal cell in many immunologic functions, is adversely affected by zinc deficiency, which can dysregulate intracellular killing, cytokine production, and phagocytosis. The effects of zinc on these key immunologic mediators is rooted in the myriad

roles for zinc in basic cellular functions such as DNA replication, RNA transcription, cell division, and cell activation. Apoptosis is potentiated by zinc deficiency. Zinc also functions as an antioxidant and can stabilize membranes. This review explores these aspects of zinc biology of the immune system and attempts to provide a biological basis for the altered host resistance to infections observed during zinc deficiency and supplementation.[40]

Zinc study 4
Zinc performs a number of unique functions in immunology, which distinguish it from all other trace elements. This special role is based upon its properties as a catalyst of a larger number of enzyme-controlled metabolic processes. Zinc supports, it even enhances, humoral and cell-mediated immunity by facilitating proliferative reactions to stimulus by different mitogens. This is as a result of its acting, above all, on the cell as co-factor for 24 presently known, important enzymes, by exercising a biocatalytic influence and regulatory (in the sense of protective) function. A long-term reduction in food intake, especially extended parenteral feeding, without taking special account of trace elements, leads for all of them, but especially for zinc, to a depletion of body reserves. The latter results in immunological changes that are at first sub-clinical and scarcely recognizable, but which, over the course of time, can lead to life-threatening infections. Cell-mediated immunity, antibody reactions and antibody affinity, complement system and phagocyte activity are perceptibly diminished. The zinc concentration in the blood has an essential influence on the extent and consequences of immunological deficiency.[41]

Selenium study 1
As a trace mineral, selenium is essential in small amounts. Selenium, as selenocysteine, is incorporated into a number of selenium-dependent antioxidant enzymes, also known as selenoproteins. It is these selenoproteins that are responsible for selenium's biological functions. These selenoproteins include Glutathione peroxidases which offer antioxidant protection against free radicals and other damaging reactive oxygen species.[42]

Selenium study 2
Selenium is an essential component of selenocysteine-containing protein is involved in most aspects of cell biochemistry and function. As such, there is much potential for selenium to influence the immune system. For example, the antioxidant glutathione peroxidases are likely to protect neutrophils from oxygen-derived radicals that are produced to kill ingested foreign organisms. When the functions of all selenoproteins are described, only then will it be possible to fully understand their role in maintaining optimal immune function.[43]

Selenium study 3
The uncertainty surrounding dietary requirements for selenium (Se) is partly due to limitations in biomarkers of Se status that are related to health outcomes. In this study we determined the effect of different doses and forms of Se on gene expression of selenoprotein S (SEPS1), selenoprotein W (SEPW1) and selenoprotein R (SEPR), and responses to an immune function challenge, influenza vaccine, were measured in order to identify functional markers of Se status. A 12 week human dietary intervention study[44] was undertaken in 119 volunteers who received placebo, 50, 100 or 200 µg/day Se-enriched yeast (Se-yeast) or meals containing unenriched or Se-enriched onions (50 µg/day). Gene expression was quantified in RNA samples extracted from human peripheral blood mononuclear cells (PBMC's) using quantitative RT-PCR. There was a significant increase in SEPW1 mRNA in the Se-enriched onion group (50 µg/day) compared with the unenriched onion group. SEPR and SEPW1 did not change significantly over the duration of the supplementation period in the control or Se-yeast groups, except at week 10 when SEPW1 mRNA levels were significantly lower in the 200 µg/day Se-yeast group compared to the placebo group. Levels of SEPS1 mRNA increased significantly 7 days after the influenza vaccine challenge, the magnitude of the increase in SEPS1 gene expression was dose-dependent, with a significantly greater response with higher Se supplementation. This novel finding provides preliminary evidence for a role of SEPS1 in the immune response, and further supports the relationship between Se status and immune function.

Echinacea study 1

Stems, leaves, and flowers of Echinacea purpurea. (L.) Moench (Heliantheae: Asteraceae) were fractionated by various solvents and the fractions evaluated for antiviral activity in relation to chemical composition and distribution within the plant. All of the aqueous fractions contained potent activity against herpes simplex virus and influenza virus. However, although some of this activity could be attributed to polysaccharide and cichoric acid components, their individual contributions could not account for the total antiviral activity; other potent antivirals must be present. In addition, the ethanol- and ethyl acetate–soluble fractions from leaves and stem contained an uncharacterized but potent antiviral photosensitizer, which was absent from the flower extract. None of the fractions, however, contained anti-rhinovirus activity. Thus, part of the alleged benefits of Echinacea purpurea. extracts can be attributed to the presence of anti-influenza and anti-HSV compounds, and some of these activities are likely to be present in various commercial tinctures, teas, capsules, and tablets.[45]

*Note: In research, 1 g (1,000 mg) of ginger daily has shown efficacy in reducing nausea of morning sickness. The current formula utilizes a ginger rhizome extract that is ~ 25:1—meaning that 25 g of ginger was used to make 1 gram of ginger extract. Consequently, 40 mg of extract is equivalent to 1 g of ginger.*

Ginger study 1

Nausea and vomiting can pose a significant burden to patients in a variety of clinical settings. Previous evidence suggests that ginger may be an effective treatment for these symptoms; however, current evidence has been mixed. This article[46] discusses recent clinical trials that have investigated ginger as a treatment for multiple types of nausea and vomiting. In addition, the potential mechanisms of action of ginger will be discussed. This article identified nine studies and seven reviews that investigated ginger for morning sickness, postoperative nausea and vomiting, chemotherapy-induced, and antiretroviral-induced nausea and vomiting. All studies reported that ginger provided a significant reduction in nausea and vomiting; however, the clinical relevance of some studies is less certain. Common limitations within the literature include the lack of standardized extracts, poorly controlled or blinded studies, and limited sample size. In addition, recent evidence has provided further support for 5-HT3 receptor antagonism as a mechanism by which ginger may exert its potentially beneficial effect on nausea and vomiting.

Ginger study 2

Nausea and vomiting in early pregnancy (NVEP) is commonly encountered in family medicine. Ginger (Zingiber officinale) is a popular nonpharmacological treatment but consensus of its use is lacking. We conducted a meta-analysis[47] of clinical trials using ginger for NVEP as published in PubMed and EMBASE, CINAHL, Cochrane Library, and all EBM reviews. Studies satisfying 3 criteria were selected: (1) randomized placebo-controlled design; (2) use of ginger or Z. officinale; and (3) extractable data on improvement in NVEP. Data were synthesized into pooled odd ratios based on the random effects model, and results were tabulated with the aid of Forest plots. Results were that we identified 135 potentially relevant records; only 6 studies met the final criteria. Of the total 508 subjects, 256 and 252 subjects were randomly assigned to receive ginger and placebo, respectively. The use of ginger (~1 g daily) for at least 4 days is associated with a 5-fold likelihood of improvement in NVEP. Heterogeneity among the clinical studies were acknowledged in the final interpretation of results. In conclusion, despite the widespread use of ginger in the diet, its clinic value and safety profile in treating NVEP is still unknown. Our meta-analysis suggests that ginger is an effective nonpharmacological treatment for NVEP.

Ginger study 3

A 2013 systematic review[48] investigated four randomized, controlled trials to examine the evidence for the safety and effectiveness of ginger in morning sickness. The results were that all trials found orally administered ginger to be significantly more effective than placebo in reducing the frequency of vomiting and intensity of nausea. The researchers concluded that best available evidence suggests that ginger is a safe and effective treatment for pregnancy-induced nausea and vomiting.

Cranberry study 1

Cranberry, a fruit native to North American, was valued both by indigenous Americans and colonists for its medicinal and nutritional properties. American sailors and colonists used cranberry to prevent scurvy. In addition, they used cranberry for various conditions including blood disorders, stomach ailments and liver problems. Cranberry has also been traditionally used to treat urinary tract infections. Therapeutic Uses: Urinary tract infections (treatment and prevention).[49]

Cranberry study 2
The Indians also employed cranberry medicinally; it was applied as a poultice for cuts and abrasions and arrow wounds, as a cure for indigestion, kidney diseases and lung ailments. Native Americans introduced the cranberry to European colonists, who quickly adopted it as both food and medicine. It became a remedy for digestive problems, gallbladder attacks, blood disorders, and kidney stones. In the late 1800s, cranberry gained popularity to treat urinary tract infections.[50]

Cranberry study 3
Its tradition of use in folk medicine began when German physicians in the mid-1800s noticed that urinary excretion of hippuric acid increased after drinking cranberry juice. Although the mechanism of action is not established, the consensus among regular drinkers of the juice point to its effectiveness in preventing chronic urinary tract infections and in deodorizing the urine. Kidney ailments are commonly treated with cranberry fruit.[51]

Cranberry study 4
Cranberries have been used widely for several decades for the prevention and treatment of urinary tract infections (UTIs). To assess the effectiveness of cranberry products in preventing UTIs in susceptible populations, a review[52] was conducted where authors searched MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL in The Cochrane Library) and the Internet. Authors contacted companies involved with the promotion and distribution of cranberry preparations and checked reference lists of review articles and relevant studies. Date of last search: January 2007, using all randomised controlled trials (RCTs) or quasi-RCTs of cranberry products for the prevention of UTIs in all populations. Two authors independently assessed and extracted information. Information was collected on methods, participants, interventions and outcomes (UTIs - symptomatic and asymptomatic, side effects, adherence to therapy). Relative risk (RR) were calculated where appropriate, otherwise a narrative synthesis was undertaken. Quality was assessed using the Cochrane criteria. MAIN RESULTS: Ten studies (n = 1049, five cross-over, five parallel group) were included. Cranberry/cranberry-lingonberry juice versus placebo, juice or water was evaluated in seven studies, and cranberries tablets versus placebo in four studies (one study evaluated both juice and tablets). Cranberry products significantly reduced the incidence of UTIs at 12 months (RR 0.65, 95% CI 0.46 to 0.90) compared with placebo/control. Cranberry products were more effective reducing the incidence of UTIs in women with recurrent UTIs, than elderly men and women or people requiring catheterisation. Six studies were not included in the meta-analyses due to methodological issues or lack of available data. However, only one reported a significant result for the outcome of symptomatic UTIs. Side effects were common in all studies, and dropouts/withdrawals in several of the studies were high. AUTHORS' CONCLUSIONS: There is some evidence that cranberry juice may decrease the number of symptomatic UTIs over a 12 month period, particularly for women with recurrent UTIs. It's effectiveness for other groups is less certain. The large number of dropouts/withdrawals indicates that cranberry juice may not be acceptable over long periods of time. It is not clear what is the optimum dosage or method of administration (e.g. juice, tablets or capsules). Further properly designed studies with relevant outcomes are needed.

Cranberry study 5
Cranberries contain proanthocyanidins, also known as condensed tannins, and a high-molecular weight compound that has not yet been identified. These constituents seem to interfere with bacterial adherence to the urinary tract epithelial cells. For example, proanthocyanidins seem to be capable of "wrapping" around Escherichia coli (E. coli), which is the cause of most urinary tract

infections (UTIs), and preventing it from adhering to the urinary tract wall. It probably also has this effect against other urinary tract pathogens.[53]

Cranberry study 6

Proanthocyanidin is commonly used for inhibiting urinary tract infection (UTI) of sensitive strains of *Escherichia coli*. The aim of this study was to investigate the effect of proanthocyanidin on adherence of uropathogenic multi-drug resistant *E. coli* to uroepithelial cells, which has not yet been investigated so far. Extracts of the purified proanthocyanidin were prepared from dried cranberry juice. Purity and structural assignment of proanthocyanidin was assessed using high performance liquid chromatography and $^{13}C$ nuclear magnetic resonance spectroscopy, respectively. Subsequently, its affect on multi-drug resistant bacteria as well as quantification of anti-adherence bioactivity on human vaginal and bladder epithelial cells was appraised. Inhibition of adherence to an extent of about 70% with multi-drug resistant *E. coli* strains was observed on uroepithelial cell. The anti-adherence bioactivity of the proanthocyanidin was detected at concentrations of 10–50 µg/ml with significant bacteriuria. Probable proanthocyanidin through A-type linkages either combines to P-fimbriae of bacterial cells or modifies the structural entity of P-fimbriae and inhibits bacterial adherence to uroepithelial cells. The proanthocyanidin exhibited anti-adherence property with multi-drug resistant strains of uropathogenic P-fimbriated *E. coli* with in vitro study. Hence proanthocyanidin may be considered as an inhibitory agent for multi-drug resistant strains of *E. coli* adherence to uroepithelial cells.[54]

Cranberry study 7

Cranberry proanthocyanidins have been identified as possible inhibitors of Escherichia coli adherence to uroepithelial cells. However, little is known about the dose range of this effect. Furthermore, it has not been studied directly in the urogenital system. To address these issues we tested[55] the effect of a cranberry powder and proanthocyanidin extract on adherence of a P-fimbriated uropathogenic E. coli isolate to 2 new urogenital model systems, namely primary cultured bladder epithelial cells and vaginal epithelial cells. MATERIALS AND METHODS: E. coli IA2 was pre-incubated with a commercially available cranberry powder (9 mg proanthocyanidin per gm) or with increasing concentrations of proanthocyanidin extract. Adherence of E. coli IA2 to primary cultured bladder epithelial cells or vaginal epithelial cells was measured before and after exposure to these products. RESULTS: Cranberry powder decreased mean adherence of E. coli IA2 to vaginal epithelial cells from 18.6 to 1.8 bacteria per cell ($p < 0.001$). Mean adherence of E. coli to primary cultured bladder epithelial cells was decreased by exposure to 50 mug/ml proanthocyanidin extract from 6.9 to 1.6 bacteria per cell ($p < 0.001$). Inhibition of adherence of E. coli by proanthocyanidin extract occurred in linear, dose dependent fashion over a proanthocyanidin concentration range of 75 to 5 mug/ml. Cranberry products can inhibit E. coli adherence to biologically relevant model systems of primary cultured bladder and vaginal epithelial cells. This effect occurs in a dose dependent relationship. These findings provide further mechanistic evidence and biological plausibility for the role of cranberry products for preventing urinary tract infection.

Cranberry study 8

This randomized, double-blind, placebo-controlled crossover study[56] investigated the effective dose of cranberry proanthocyanidins (PACs) per day and to determine if the urinary anti-adhesion effect following cranberry is detected within volunteers of different origins. Two separate bioassays (a mannose-resistant hemagglutination assay (MRHA) and an original new human T24 epithelial cell-line assay) have assessed the ex-vivo urinary bacterial anti-adhesion activity on urines samples collected from 32 volunteers from Japan, Hungary, Spain and France. An in vivo *Caenorhabditis elegans* model was used to evaluate the influence of cranberry regimen on the virulence of E. coli strain. The cranberry capsule dosages were standardized to deliver 18 or 36 mg of PAC equivalents in the cranberry powder. The volunteers in Japan and Hungary received 0, 36 or 72 mg PAC equivalents per day and those in France and Spain received 0, 18 or 36 mg PAC equivalents per day. MRHA results indicated significant anti-adhesion activity (AAA) in urines collected from volunteers that consumed cranberry powder compared to placebo ($p < 0.001$) (Table 1). This inhibition was clearly dose-dependent, increasing with the amount of

PAC equivalents consumed in each cranberry powder regimen. A peak of AAA was determined over the time course of the experiment. In urines samples collected at 6 h, there was a significant difference between the cranberry dosages containing 18 mg PAC and those with either 36 or 72 mg PAC (p = 0.002); however, no statistical difference was detected between 36 and 72 mg PAC. In urine samples collected at 24 h, there was a significant difference between the AAA of urines belonging to patients who had consumed cranberry dosages containing 72 mg of PAC (50% AAA) and the AAA of urines belonging to patients who had consumed 18 or 36 mg of PAC (0 and 12% AAA, respectively) (p = 0.002). The ex vivo epithelial cell adhesion assay results indicated a highly significant reduction in bacterial adhesion to T24 cells compared to placebo (p < 0.001) following the consumption of cranberry dosages containing 36 or 72 mg of PAC (Table 1, Figure 1). There was a dose-dependent decrease in bacterial adhesion with cranberry intake. The Adhesion Index (AI) of bacteria grown in urine samples collected after consumption of cranberry with 36 or 72 mg PAC was significantly lower than the AI following the dose with 18 mg PAC (p < 0.001). In conclusion, to achieve a bacterial anti-adhesion effect in urine, 36 mg of cranberry PAC equivalents per day is effective, but 72 mg may offer a nyctohemeral protection.

**Table 1: Urinary bacterial Anti-Adhesion Activity (AAA) detected with Mannose-resistant Hemagglutination (MRHA) assay (A) and urinary bacterial adhesion to T24 cells (B) expressed as Adhesion Index (AI) following consumption of increasing doses of cranberry powder standardized for 18, 36 or 72 mg of proanthocyanidins (PAC) vs placebo by participants in the 4 countries. (Continued)**

| B | AI Median [Range] | | | | P | | | |
|---|---|---|---|---|---|---|---|---|
| Regimen | Placebo | 18 mg PAC | 36 mg PAC | 72 mg PAC | 18 vs 36 | 36 vs 72 | 6 h vs 24 h | Sp-Fr vs Ja-Hu |
| **Spain (n = 8)** | | | | | | | | |
| **1-6 h** | 18.5 [15-22] | 8.5 [5-14] | 5.0 [1-11] | - | <0.001 | ND | <0.001 | <0.001 |
| **24 h** | 20.0 [18-22] | 14.5 [10-18] | 12.5 [5-17] | - | <0.001 | ND | <0.001 | |
| **France (n = 8)** | | | | | | | | |
| **1-6 h** | 17.5 [15-28] | 8.0 [5-16] | 4.0 [2-10] | - | <0.001 | ND | <0.001 | |
| **24 h** | 19.5 [18-25] | 17.5 [12-22] | 5.0 [2-10] | - | <0.001 | ND | <0.001 | |
| **Japan (n = 8)** | | | | | | | | <0.001 |
| **1-6 h** | 21.5 [18-28] | - | 5.0 [1-9] | 3.5 [1-6] | ND | NS | <0.001 | |
| **24 h** | 25.5 [17-29] | - | 13.5 [10-18] | 10.0 [2-15] | ND | 0.01 | <0.001 | |
| **Hungary (n = 8)** | | | | | | | | |
| **1-6 h** | 18.5 [15-22] | - | 2.0 [1-5] | 1.0 [1-5] | ND | NS | <0.001 | |
| **24 h** | 20 [15-25] | - | 9.5 [5-25] | 4.5 [2-10] | ND | <0.001 | <0.001 | |
| **Total (n = 32)** | | | | | | | | |
| **1-6 h** | 21.5 [15-28] | 10.5 [5-16] | 5.9 [1-11] | 2.5 [1-6] | <0.001 | <0.001 | <0.001 | ND |
| **24 h** | 22.3 [15-29] | 16.0 [10-22] | 14.5 [2-25] | 9.9 [2-15] | <0.001 | <0.001 | <0.001 | ND |

The results are representative of at least three independent trials. NS, not significant; ND, not determined. 0 h, pre-cranberry consumption collection

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