LOVE™
WELLNESS

Daily Love Multivitamin White Paper

Contents:

Love Wellness Daily Love Multivitamin White Paper

At Love Wellness, our mission is to create clean, high-quality products that do more for women than the other junk out there. Equally as important is the education process that comes with creating innovative wellness products, and we work hard to make products in the right way for your body. When we started researching multivitamins, we learned a lot about this product category and discovered that most of the products on the market for women are being sold with questionable amounts of ingredients, types of ingredients, and deceptive marketing messaging.

We made it our goal to make the first truly complete multivitamin for women 18+ that gives you everything to cover your baseline vitamin and mineral needs, plus extra herbs and nutraceuticals to help you feel your best.

Below you will find our Supplement Facts panel, our product claims, and the research behind our claims. Daily Love is the new multivitamin made of more that helps you Love Yourself Well™.

1. SUPPLEMENT FACTS

Supplement Facts

Serving Size 2 Vegetable Capsules
Servings Per Container 30

	Amount Per Serving	% Daily Value
Vitamin A (as beta-carotene)	3,006 mcg	334%
Vitamin C (as ascorbic acid)	90 mg	100%
Vitamin D3 (as cholecalciferol)	25 mcg (1,000 IU)	125%
Vitamin E (as d-alpha tocopheryl succinate)	15 mg	100%
Vitamin K2 (as menaquinone-7)	92 mcg	77%
Vitamin B1 (as thiamin mononitrate)	15 mg	1250%
Vitamin B2 (as riboflavin, riboflavin-5-phosphate)	15 mg	1154%
Niacin (as niacinamide)	15 mg	94%
Vitamin B6 (as pyridoxine HCl, pyridoxal-5-phosphate)	16 mg	941%
Folate (as L-5 methyltetrahydrofolate calcium)	667 mcg DFE (400 mcg folic acid)	167%
Vitamin B12 (as methylcobalamin)	100 mcg	4167%
Biotin	30 mcg	100%
Pantothenic acid (as d-calcium pantothenate)	15 mcg	300%
Calcium (as calcium carbonate)	75 mg	6%
Iron (as Ferrochel® iron bisglycinate)	18 mg	100%
Iodine (as potassium iodide)	150 mcg	100%

Magnesium (as magnesium oxide)	50 mg	12%
Zinc (as amino acid chelate)	11 mg	100%
Selenium (as selenomethionine)	55 mcg	100%
Copper (as copper gluconate)	0.9 mg	100%
Manganese (as manganese aspartate)	2.3 mg	100%
Chromium (as Crominex® 3+)	400 mcg	1143%
Molybdenum (as amino acid chelate)	45 mcg	100%
Choline (as choline bitartrate)	10 mg	2%
Inositol (as myo-inositol)	12 mg	†
Organic Ashwagandha root (KSM-66®, full-spectrum extract)	600 mg	†
Chaste Tree Berry (Vitex agnus castus) standardized 0.5% Agnuside	40 mg	†
† Daily value not established.		

2. DIRECTIONS

Take 2 capsules daily, preferably one with breakfast and one with lunch.

3. CLAIMS

Claim	**Substantiation**
Health/wellness & general claims	
• At least half of all women physicians surveyed use multivitamins. Shouldn't you?	Multivitamin study 5
• Promotes intake of key vitamins and minerals better than diet alone.*	Multivitamin study 1
• Contains over 25 vitamins, minerals and nutraceuticals to support health and wellness.*	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, as do Multivitamin study 2-7.
• Contains B-vitamin coenzymes, the biologically active forms of these nutrients.*	Listed in supplement facts box. Riboflavin study 1 Vitamin B6 study 1 Vitamin B12 study 1
Heart health claims	
• Supports healthy heart function in women.*	Multivitamin study 7

• Vitamin K2 supports a healthy heart*, or ○ Vitamin K2 provides support for cardiovascular health.*	Vitamin K2 study 1
• Folic acid has been clinically tested to help maintain healthy homocysteine levels already within normal ranges.*	Folic acid/homocysteine study 1-7
Memory/cognitive claims	
• Provides key B vitamins which support healthy cognitive function.*	B vitamins study 1
• Provides key B vitamins which support some measures of healthy memory performance.*	B vitamins study 1
Energy claim	
• Provides B-vitamins to support energy production.*	B vitamins study 2
• KSM-66 ashwagandha supports energy and endurance.*	KSM-66 study 4
Nutrient adequacy claim	
• Promotes intake of key vitamins and minerals better than diet alone.*	Multivitamin study 2
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 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
• KSM-66 ashwagandha helps reduce the effects of stress.*	KSM-66 study 5
• KSM-66 ashwagandha may help alleviate the effects of stress and tension.*	KSM-66 study 5, 7
• KSM-66 ashwagandha helps improves mood when stressed.*	KSM-66 study 5, 7
• KSM-66 ashwagandha helps reduce cortisol, the “stress hormone”.*	KSM-66 study 5, 7
• KSM-66 ashwagandha reduces the stress hormone cortisol.*	KSM-66 study 5, 7
• KSM-66 ashwagandha was clinically tested to reduce food cravings and emotional eating related to stress.*	KSM-66 study 7
• KSM-66 ashwagandha helps reduce stress-related food cravings.*	KSM-66 study 7
• KSM-66 ashwagandha helps reduce emotional eating related to stress.*	KSM-66 study 7

• KSM-66 ashwagandha helps support a good night sleep when stressed.*	KSM-66 study 5
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
• Crominex 3+ has been clinically tested to be more effective than chromium picolinate, chromium polynicotinate, and chromium dinicocysteinate.*	Crominex study 3
• Chromium has been clinically tested to help maintain long-term, healthy glucose metabolism.*	Crominex study 3-4
• Crominex 3+ have been clinically tested to help maintain a healthy balance of total and HDL cholesterol already within normal ranges.*	Crominex study 1-2
• Crominex 3+ have been clinically tested to help support healthy triglyceride levels already within normal ranges.*	Crominex study 1-2
• Crominex 3+ has been clinically tested to help support healthy blood vessel function.*	Crominex study 1-2
• Crominex 3+ has been clinically tested to help support healthy circulation.*	Crominex study 1-2
Female-specific health claims	
• KSM-66 ashwagandha was clinically tested to promote sexual function in healthy women	KSM-66 study 1
• KSM-66 ashwagandha was clinically tested to support healthy sexual function in women.	KSM-66 study 1
• Chasteberry helps relieve premenstrual symptoms.*	Vitex study 1-8
• Chasteberry helps relieve premenstrual-related discomfort.*	Vitex study 1-8
• Chasteberry helps relieve premenstrual-related acne.*	Vitex study 9-11
• Chasteberry supports a healthy female cycle.*	Vitex study 14-18
• Chasteberry supports a healthy balance of female hormones.*	Vitex study 12-13, 18
• Chasteberry may help relieve menopausal symptoms.*	Vitex study 19
• May help to reduce UV-induced skin aging.*	Beta-carotene study 1
• Healthful diets with adequate folic acid may reduce a woman's risk of having a child with a brain or spinal cord defect.	Approved health claim Folic acid /birth defects study 1-2

*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. • Needed for normal muscle function, including the heart muscle. • 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. • 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. • 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. • 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. • 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. • 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. • Ascorbic acid facilitates transport and uptake of non-haem iron at the mucosa, the reduction of folic acid intermediates, and the synthesis of cortisol. • 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. • Folate is essential for metabolic pathways involving cell growth, replication, survival of cells in culture. • 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]

Folic acid/homocysteine study 1

Researchers used a prospective case-cohort design to determine whether total homocysteine (tHcy)-related factors are associated with incidence of CHD over an average of 3.3 years of follow-up in a biracial sample of middle-aged men and women. Age-, race-, and field center-adjusted CHD incidence was associated positively (P<0.05) with tHcy in women but not men, and CHD was associated negatively (P<0.05) with plasma folate (women only), plasma pyridoxal 5'-phosphate (both sexes), and vitamin supplementation (women only). However, after accounting for other risk factors, only plasma pyridoxal 5'-phosphate (a vitamin B6 coenzyme) was associated with CHD incidence; the relative risk for the highest versus lowest quintile of pyridoxal 5'-phosphate was 0.28 (95% CI=0.1 to 0.7). There was no association of CHD with the C677T mutation of the methylenetetrahydrofolate reductase gene or with 3 mutations of the cystathionine beta-synthase gene. In conclusion, researchers suggest that vitamin B6 offers independent protection against tHcy-mediated CHD.[21]

Folic acid/homocysteine study 2

In a multicenter case-control study[22] in Europe, 750 patients with documented vascular disease and 800 control subjects frequency-matched for age and sex were compared. Plasma levels of total homocysteine (before and after methionine loading) were determined, as were those of red cell folate, vitamin B12, and vitamin B6. Results showed that lower levels of folate and vitamin B6 confer an increased risk of atherosclerosis.

Folic acid/homocysteine study 3

In a placebo-controlled study,[23] one hundred men with hyperhomocysteinemia were randomly assigned to five groups and treated with a daily dose of placebo, folic acid (0.65 mg), vitamin B12 (0.4 mg), vitamin B6 (10 mg) or a combination of the three vitamins for 6 wk. Folic acid supplementation reduced plasma homocysteine concentrations by 41.7% (P < 0.001), whereas the daily vitamin B12 supplement lowered homocysteine concentrations by 14.8% (P < 0.01). The daily pyridoxine dose did not reduce significantly plasma homocysteine concentrations. The combination of the three vitamins reduced circulating homocysteine concentrations by 49.8%, which was not significantly different (P = 0.48) from the reduction achieved by folate supplementation alone. However, vitamin B6 supplementation was effective in lowering

blood homocysteine levels after an oral dose of methionine (methionine load test) was given, suggesting vitamin B6 may play a role in the metabolism of homocysteine after meals.

Folic acid/homocysteine study 4
Increasing folate intake through folate-rich foods or supplements has been found to lower homocysteine levels. Moreover, blood homocysteine levels have declined since the FDA mandated folic acid fortification of the grain supply.[24]

Folic acid/homocysteine study 5
A meta-analysis[25] of 25 randomized controlled trials involving individual data on 2596 subjects assessed the effect of different doses of folic acid and of the addition of vitamins B12 and B6, on plasma homocysteine concentrations. The proportional reductions in plasma homocysteine concentrations produced by folic acid were greater at higher homocysteine ($P < 0.001$) and lower folate ($P < 0.001$) pretreatment concentrations; they were also greater in women than in men ($P < 0.001$). After standardization for sex and to pretreatment plasma concentrations of 12 micromol homocysteine/L and 12 nmol folate/L, daily doses of 0.2, 0.4, 0.8, 2.0, and 5.0 mg folic acid were associated with reductions in homocysteine of 13% (95% CI: 10%, 16%), 20% (17%, 22%), 23% (21%, 26%), 23% (20%, 26%), and 25% (22%, 28%), respectively. Vitamin B-12 (x: 0.4 mg/d) produced 7% (95% CI: 4%, 9%) further reduction in homocysteine concentrations, but vitamin B-6 had no significant effect. Researchers concluded that daily doses of > or =0.8 mg folic acid are typically required to achieve the maximal reduction in plasma homocysteine concentrations produced by folic acid supplementation. Doses of 0.2 and 0.4 mg are associated with 60% and 90%, respectively, of this maximal effect.

Folic acid/homocysteine study 6
A supplement regimen of 400 mcg of folic acid, 2 mg of vitamin B_6, and 6 mcg of vitamin B_{12} has been advocated by the American Heart Association if an initial trial of a folate-rich diet (is not successful in adequately lowering homocysteine levels.[26]

Folic acid/homocysteine study 7
Meta-analysis[27] of 12 randomised controlled trials that included individual data on 1114 people assessed the effects of folic acid based supplements on blood homocysteine concentrations. Results showed that, typically in Western populations, daily supplementation with both 0.5-5 mg folic acid and about 0.5 mg vitamin B-12 would be expected to reduce blood homocysteine concentrations by about a quarter to a third (for example, from about 12 mumol/l to 8-9 mumol/l). Folic acid supplementation had the greatest lowering effect on blood homocysteine levels (25% decrease); co-supplementation with folic acid and vitamin B_{12} (mean 0.5 mg/day or 500 mcg/day) provided an additional 7% reduction (32% decrease) in blood homocysteine concentrations.

Approved health claim
Guidance for Industry: A Food Labeling Guide (11. Appendix C: Health Claims), (21 CFR 101.79). January 2013

> Model Claim: "Healthful diets with adequate folate (or folic acid) may reduce a woman's risk of having a child with a brain or spinal cord defect."

Folic acid/birth defects study 1
Folic acid plays a critical role in protecting against some serious birth defects, including neural tube defects, when taken by women of childbearing age before and during pregnancy. The Food and Nutrition Board of the Institute of Medicine recognized these findings when it issued new dietary recommendations for the B vitamins in 1998, recommending "that women capable of becoming pregnant should obtain 400 mcg/day of folic acid from dietary supplements and/or fortified foods in addition to the folate present in a varied diet." The Food and Nutrition Board added, "At this time the evidence for a protective effect from folate supplements is much stronger than that for food folate."[28]

Folic acid/birth defects study 2
The Centers for Disease Control and Prevention (CDC) started even earlier by issuing a public health recommendation in 1992 urging all women of childbearing age to get 400 mcg of folic acid daily to help neural tube defects.[29]

Vitamin K2 study 1
In a population-based study[30], 4807 subjects were analyzed for their vitamin K intake as well as its relationship to aortic calcification and coronary heart disease (CHD). The risk of incident CHD, all-cause mortality, and aortic atherosclerosis was studied in tertiles of energy-adjusted vitamin K intake after

adjustment for age, gender, BMI, smoking, diabetes, education, and dietary factors. The relative risk (RR) of CHD mortality was reduced in the mid and upper tertiles of dietary menaquinone (vitamin K2), particularly in those consuming about 45 mcg menaquinone daily, compared to the lower tertile [RR = 0.73 (95% CI: 0.45, 1.17) and 0.43 (0.24, 0.77), respectively]. Intake of menaquinone was also inversely related to all-cause mortality [RR = 0.91 (0.75, 1.09) and 0.74 (0.59, 0.92), respectively] and severe aortic calcification [odds ratio of 0.71 (0.50, 1.00) and 0.48 (0.32, 0.71), respectively]. Phylloquinone (vitamin K1) intake was not related to any of the outcomes.

Vitex study 1

In this randomized, placebo-controlled, double-blind study,[31] the therapeutic effect of Vitex agnus castus on women who had the PMS, in comparison with placebo, were investigated. From 134 selected patients 128 women suffered from PMS were evaluated (active 62, placebo 66). All patients answered to a self-assessment questionnaire about their headache, anger, irritability, depression, breast fullness and bloating and tympani during the premenstrual period before the study. Forty drops (4.5 mg) of Vitex agnus extract or matching placebo, administrated for 6 days before menses for 6 consecutive cycles. Patients answered the self-assessment questionnaires after 6 menstrual cycles, again. Each item rated using a visual analogue scale (VAS). The mean age was 30.77 (SD=4.37) years in the active group and 30.89 (SD=4.02) years in the placebo group. Rank of variables had significantly difference in active and placebo group before and after the study (P<0.0001) also we noticed significant differences on the use of Vitex agnus in comparison with placebo (P<0.0001). Vitex agnus can be considered as an effective and well tolerated treatment for the relief of symptoms of mild and moderate PMS.

Vitex study 2

A randomized, double blind, placebo controlled, parallel group study[32] over three menstrual cycles was conducted to compare the efficacy and tolerability of agnus castus fruit (Vitex agnus castus L extract Ze 440) with placebo for women with the premenstrual syndrome. 178 women were screened and 170 were evaluated (active 86; placebo 84). Mean age was 36 years, mean cycle length was 28 days, mean duration of menses was 4.5 days. Agnus castus (fruit extract ZE 440: 60% ethanol m/m, extract ratio 612:1; standardised for casticin) one 20 mg tablet daily or matching placebo, given for three consecutive cycles. The main efficacy variable: change from baseline to end point (end of third cycle) in women's self-assessment of irritability, mood alteration, anger, headache, breast fullness, and other menstrual symptoms including bloating. Secondary efficacy variables: changes in clinical global impression (severity of condition, global improvement, and risk or benefit) and responder rate (50% reduction in symptoms). Results showed that improvement in the main variable was greater in the active group compared with placebo group (P<0.001). Analysis of the secondary variables showed significant (P<0.001) superiority of active treatment in each of the three global impression items. Responder rates were 52% and 24% for active and placebo, respectively. Seven women reported mild adverse events (four active; three placebo), none of which caused discontinuation of treatment. In conclusion, dry extract of agnus castus fruit is an effective and well tolerated treatment for the relief of symptoms of the premenstrual syndrome.

Vitex study 3

In a multicenter, double-blind, placebo-controlled, parallel-group study,[33] 162 female patients with PMS (18-45 years) were randomized to either placebo or different doses of Ze 440 (8, 20 and 30 mg) over three menstrual cycles. PMS symptoms' severity was assessed by patients using visual analog scales (VAS) for the symptoms irritability, mood alteration, anger, headache, bloating and breast fullness. Results showed that each of the treatments was well tolerated. Improvement in the total symptom score (TSS) in the 20 mg group was significantly higher than in the placebo and 8 mg treatment group. The higher dose of 30 mg, on the other hand, did not significantly decrease symptom severity compared to the 20 mg treatment, providing a rational for the usage of 20 mg. Corresponding results were observed with the single PMS symptom scores. In conclusion, this study demonstrated that the extract Ze 440 was effective in relieving symptoms of PMS, when applied in a dose of 20mg. Therefore, for patients suffering from PMS, 20mg Ze 440 should be the preferred daily dose.

Vitex study 4

A prospective randomised double-blind placebo-controlled study[34 35] was conducted to assess efficacy of the extract of Vitex agnus castus (VAC, BNO 1095 (70% ethanol, 30% H2O extract) 20 mg) in the treatment of Chinese women suffering from moderate to severe premenstrual syndrome (PMS). Eligible patients were randomly assigned into VAC or placebo group. Symptoms were documented with a daily rating scale with four symptom factors (negative affect, water retention, food cravings and pain). Sixty-seven patients were enrolled and randomly assigned to receive one tablet of VAC or placebo once a day. Results showed the premenstrual syndrome diary (PMSD) sum score decreased from 29.38 +/- 7.63 score points at baseline to 4.28 +/- 5.76 at the 3rd cycle in the treatment group, while it decreased from 28.76 +/- 8.23 to 11.79 +/- 11.78 in

the placebo group. All the four symptom factor scores were significantly reduced by the 3rd treatment cycle. There was significant difference in PMSD sum score, score of negative affect and water retention between two groups at cycle 3 (P < 0.05). PMSD sum scores decreased 60% was defined as efficacy, and the efficacy rate in treatment group was significantly higher than that in placebo group at the 3rd treatment cycle. In conclusion, Vitex agnus castus extract BNO 1095 shows effective in treating moderate to severe PMS in Chinese women, especially in symptoms of negative affect and water retention.

Vitex study 5

A prospective, double-blind, placebo controlled, parallel-group, multi-center clinical trial[36] was employed to investigate the efficacy and safety of Vitex agnus castus (VAC, BNO 1095 40 mg) extract in Chinese women suffering from moderate to severe premenstrual syndrome (PMS). After screening and preparation phase lasting three cycles, Eligible patients were randomly assigned into treatment or placebo groups and had treatment with VAC extract or placebo for up to three cycles. Efficacy was assessed using the Chinese version PMS-diary (PMSD) and PMTS. Two hundred and seventeen women were eligible to enter the treatment phase (TP) and were randomly assigned into the treatment group (108) or the placebo group (109), 208 provided the efficacy data (treatment 104, placebo 104), and 202 completed the treatment phase (treatment 101, placebo 101). Results showed that the mean total PMSD score decreased from 29.23 at baseline (0 cycle) to 6.41 at the termination (3rd cycle) for the treatment group and from 28.14 at baseline (0 cycle) to 12.64 at the termination (3rd cycle) for the placebo group. The total PMSD score of 3rd cycle was significantly lower than the baseline in both groups ($p<0.0001$). The difference in the mean scores from the baseline to the 3rd cycle in the treatment group (22.71+/-10.33) was significantly lower than the difference in the placebo group (15.50+/-12.94, $p<0.0001$). Results of PMTS were similar, the total scores for PMTS were significantly lower between the two groups ($p<0.01$) and within each group ($p<0.01$). The score was decreased from 26.17+/-4.79 to 9.92+/-9.01 for the treatment group, and from 27.10+/-4.76 to 14.59+/-10.69 for the placebo group. A placebo effect of 50% was found in the present study. No serious adverse event (SAE) occurred in both groups. In conclusion, Vitex agnus castus (VAC BNO 1095 corresponding to 40mg herbal drug) is a safe, well tolerated and effective drug of the treatment for Chinese women with the moderate to severe PMS.

Vitex study 6

A randomized, controlled trial[37] was conducted to determine the efficacy and tolerability of a new solid formulation (capsules) of Agnolyt® (Ze 440) versus pyridoxine in women with PMTS over a period of three treatment cycles (Vitex agnus castus (VAC): 1 capsule + 1 placebo capsule/day, n = 90; pyridoxine (B6): 2 capsules day, n = 85). The therapeutic response was assessed using the premenstrual tension syndrome scale (PMTS scale), the recording of six characteristic complaints of the syndrome, and the clinical global impression scale (CGI scale). Upon completion of the trial, efficacy of the treatment was assessed by the physician as well as by the patient. On the PMTS scale, treatment with VAC and B6 produced a reduction in score points from 15.2 to 5.1 (−47,4%) and from 11.9 to 5.1 (−48%), respectively. In comparison with pyridoxine, VAC caused a considerably more marked alleviation of typical PMTS complaints, such as breast tenderness, edema, inner tension, headache, constipation, and depression. Analogous results were obtained with the CGI scale. In both treatment groups, efficacy was rated as at least adequate by more than 80% of the investigators; however, VAC treatment was rated as excellent by 24.5% and pyridoxine treatment by 12.1% of the investigators. According to the patients' assessment, 36.1% of the cases in the VAC group and 21.3% in the pyridoxine group were free from complaints. Adverse events (gastrointestinal and lower abdominal complaints, skin manifestations and transitory headache) occurred in 5 patients under B6 and in 12 patients under VAC. Serious adverse events were not observed. The results of the present study confirm the efficacy and safety of Agnolyt® capsules in the treatment of PMTS.

Vitex study 7

A Randomized, double blind, placebo controlled, parallel group study[38] was conducted over two menstrual cycles on students of Tehran Medical University and Tehran University to assess the effects of *Vitex agnus-castus* (4.3-4.8 mg dry extract) on treatment of premenstrual syndrome. Volunteers underwent a preliminary screening interview, completed Daily Symptom Rating (DSR) (contain 18 symptoms) for two cycle, and attended a medical screening visit before being diagnosed with premenstrual syndrome and screening for depression by Beck questionnary. 116 students were screened and 99 were evaluated (active: 49; placebo: 50). Participants took *Vitex agnus-castus* (dry extract tablets) one tablet daily or matching placebo for two cycles. Data were analyzed by descriptive and analytic statistics (chi-square, fisher exact test, willcoxon, mann-whitney u and t test). Results showed that decrease of severity of premenstrual syndrome was significantly greater in the Vitex group compared with placebo group in total symptoms of premenstrual syndrome (60.73% versus 20.79%, $p<0.001$), psychological symptoms (65.62% versus 28.19%, $p<0.001$) and physical symptoms (57.98% versus 16.22%, $p<0.001$). Sixteen of eighteen symptoms of premenstrual syndrome indicate significant superiority for Vitex, other symptoms including (suicide and swelling of

extremities) being unaffected by treatment. There was no statistically significant difference between two groups in regard to adverse events. In conclusion, Vitex is an effective treatment for the relief of symptoms of the premenstrual syndrome.

Vitex study 8

The aim of the first part of this randomised and controlled clinical study[39] was to evaluate the efficacy and tolerability of a fast-acting form of Agnus castus fruit extract (Monoselect Agnus, MA) administered for 90 days, in comparison with a magnesium supplement, for women with the premenstrual syndrome (PMS). The aim of the second part of the study was to establish the efficacy of a treatment scheme where MA was given only 7 days before the menstrual cycle for a further 3 months in comparison with the suspended therapy. 82 women were enrolled and randomised in two groups (MA group: 42; Magnesium group: 40). MA 40 mg/tablet) or matching Magnesium (300 mg/tablet) were given, 1 tablet daily, for first 3 consecutive months. For the following 3 months only MA was administered (1 tablet/day for 7 days/month). Efficacy was evaluated as change from baseline to end point (90th, 120th, 150th and 180th day) as regards to back pain, menstrual pain, breast fullness, headache, asthenia, irritability, appetite modulation and sleep disturbances. As regards to the first part of the study, improvement in the variables was greater in the MA group compared with Magnesium group ($P<0.001$). With regards to the second part of the study, improvement was greater in the MA group versus the non-treated one: results were kept treating patients 7 days/month and a 2-month wash-out cancelled the results obtained in the first 90 days treatment. During the study, 5 women reported very mild adverse events (2 MA; 3 Magnesium), none of which caused drop-out. The results demonstrate that MA is an effective and well-tolerated treatment for the relief of symptoms of PMS. Its action is evident after 90 days of continuative treatment and can be kept with a treatment scheme of 7 days/month.

Vitex study 9-10

These two older, preliminary German studies[40] [41]suggest that Vitext a*gnus castus* may contribute to clearing of premenstrual acne, possibly by regulating hormonal influences on acne. Women in these studies used 40 drops of a concentrated liquid product (Agnolyt) once daily.[13]

Vitex study 11

In a placebo-controlled trial[42] of 161 male and female acne patients, after three months treatment with Vitex agnus castus resulted in a 70% improvement in acne, which was significantly better than placebo.

Vitex study 12

Eight botanical preparations that are commonly used for the treatment of menopausal symptoms were tested for estrogenic activity. Methanol extracts of red clover (Trifolium pratense L.), chasteberry (Vitex agnus-castus L.), and hops (Humulus lupulus L.) showed significant competitive binding to estrogen receptors alpha (ER alpha) and beta (ER beta). With cultured Ishikawa (endometrial) cells, red clover and hops exhibited estrogenic activity as indicated by induction of alkaline phosphatase (AP) activity and up-regulation of progesterone receptor (PR) mRNA. Chasteberry also stimulated PR expression, but no induction of AP activity was observed. In S30 breast cancer cells, pS2 (presenelin-2), another estrogen-inducible gene, was up-regulated in the presence of red clover, hops, and chasteberry. Interestingly, extracts of Asian ginseng (Panax ginseng C.A. Meyer) and North American ginseng (Panax quinquefolius L.) induced pS2 mRNA expression in S30 cells, but no significant ER binding affinity, AP induction, or PR expression was noted in Ishikawa cells. Dong quai [Angelica sinensis (Oliv.) Diels] and licorice (Glycyrrhiza glabra L.) showed only weak ER binding and PR and pS2 mRNA induction. Black cohosh [Cimicifuga racemosa (L.) Nutt.] showed no activity in any of the above in vitro assays. Bioassay-guided isolation utilizing ER competitive binding as a monitor and screening using ultrafiltration LC-MS revealed that genistein was the most active component of red clover. Consistent with this observation, genistein was found to be the most effective of four red clover isoflavones tested in the above in vitro assays. Therefore, estrogenic components of plant extracts can be identified using assays for estrogenic activity along with screening and identification of the active components using ultrafiltration LC-MS. These data suggest a potential use for some dietary supplements, ingested by human beings, in the treatment of menopausal symptoms.[43]

Vitex study 13

Extracts of the fruits of chaste tree (Vitex agnus castus = AC) are widely used to treat premenstrual symptoms. Double-blind placebo-controlled studies indicate that one of the most common premenstrual symptoms, i.e. premenstrual mastodynia (mastalgia) is beneficially influenced by an AC extract. In addition, numerous less rigidly controlled studies indicate that AC extracts have also beneficial effects on other psychic and somatic symptoms of the PMS. Premenstrual mastodynia is most likely due to a latent hyperprolactinemia, i.e. patients release more than physiologic amounts of prolactin in response to stressful situations and during deep sleep phases which appear to stimulate the mammary gland. Premenstrually

this unphysiological prolactin release is so high that the serum prolactin levels often approach heights which are misinterpreted as prolactinomas. Since AC extracts were shown to have beneficial effects on premenstrual mastodynia serum prolactin levels in such patients were also studied in one double-blind, placebo-controlled clinical study. Serum prolactin levels were indeed reduced in the patients treated with the extract. The search for the prolactin-suppressive principle(s) yielded a number of compounds with dopaminergic properties: they bound to recombinant DA2-receptor protein and suppressed prolactin release from cultivated lactotrophs as well as in animal experiments. The search for the chemical identity of the dopaminergic compounds resulted in isolation of a number of diterpenes of which some clerodadienols were most important for the prolactin-suppressive effects. They were almost identical in their prolactin-suppressive properties than dopamine itself. Hence, it is concluded that dopaminergic compounds present in Vitex agnus castus are clinically the important compounds which improve premenstrual mastodynia and possibly also other symptoms of the premenstrual syndrome.[44]

Vitex study 14
The effects of Mastodynon(R), an Agnus castus-containing preparation, were investigated in 96 women with fertility disorders in a prospective, randomized, placebo-controlled, double-blind study.[45] 38 women with secondary amenorrhoea, 31 women with luteal insuffciency and 27 women with idiopathic infertility received 30 drops of Mastodynon or placebo twice a day over a period of 3 months.
The outcome measure, which was pregnancy or spontaneous menstruation in women with amenorrhoea and pregnancy or improved concentrations of luteal hormones in both other groups, was achieved in 31 out of 66 women who were suitable for evaluation. It was achieved more often in the Mastodynon group compared to the placebo group (57.6% versus 36.0%, p = 0.069). 15 women conceived during the observation period (n = 7 with amenorrhoea, n = 4 with idiopathic infertility, n = 4 with luteal insufficiency). In women with amenorrhoea or luteal insufficiency, pregnancy occurred in the Mastodynon group more than twice as often as in the placebo group. Under therapy no hormonal changes were found at a 5% significance level. Only very few undesirable drug effects were observed. In conclusion, in women with sterility due to secondary amenorrhoea and luteal insufficiency, a treatment with Mastodynon can be recommended over a period of 3 to 6 months.

Vitex study 15
In a placebo-controlled, randomized, double-blind study[46] the efficacy of a Vitex agnus castus extract-containing solution (VACS) was investigated in patients suffering from cyclical mastalgia. Patients had mastalgia on at least 5 days in the pre-treatment cycle. During this cycle and during treatment (3 cycles; 2 x 30 drops/day), the intensity of mastalgia was recorded once per cycle using a visual analogue scale (VAS). After one/two treatment cycles, the mean decrease in pain intensity (mm, VAS) was 21.4 mm /33.7 mm in women taking VACS (n=48) and 10.6 mm/20.3 mm with placebo (n=49). The differences of the VAS-values for VACS were significantly greater than those with placebo (p=0.018; p=0.006). After three cycles, the mean VAS-score reduction for women taking VACS was 34.3 mm, a reduction of 'borderline significance' (p=0.064) on statistical testing compared with placebo (25.7 mm). There was no difference in the frequency of adverse events between both groups (VACS: n=5; placebo : n=4). VACS appears effective and was well tolerated and further evaluation of this agent in the treatment of cyclical mastalgia is warranted.

Vitex study 16
In a placebo-controlled, randomized, double-blind study[47] the efficacy of a Vitex agnus castus extract-containing solution (VACS) was investigated in patients suffering from cyclical mastalgia. Patients had mastalgia on at least 5 days in the pre-treatment cycle. During this cycle and during treatment (3 cycles; 2 x 30 drops/day), the intensity of mastalgia was recorded once per cycle using a visual analogue scale (VAS). After one/two treatment cycles, the mean decrease in pain intensity (mm, VAS) was 21.4 mm /33.7 mm in women taking VACS (n=48) and 10.6 mm/20.3 mm with placebo (n=49). The differences of the VAS-values for VACS were significantly greater than those with placebo (p=0.018; p=0.006). After three cycles, the mean VAS-score reduction for women taking VACS was 34.3 mm, a reduction of 'borderline significance' (p=0.064) on statistical testing compared with placebo (25.7 mm). There was no difference in the frequency of adverse events between both groups (VACS: n=5; placebo : n=4). VACS appears effective and was well tolerated and further evaluation of this agent in the treatment of cyclical mastalgia is warranted.

Vitex study 17
The aim of study[48] presented here was to gather the data about the tolerability and efficacy of Vitex agnus castus (VACS) extract. The study was designed as double-blind, placebo controlled in two parallel groups (each 50 patients). Treatment phase lasted 3 consequent menstrual cycles (2 x 30 drops/day = 1.8 ml of VASC) or placebo. Mastalgia during at least 5 days of the cycle before the treatment was the strict inclusion condition. For assessment of the efficacy visual analogue scale was used. Altogether 97 patients were included into the statistical analysis (VACS: n = 48, placebo: n = 49). Intensity of breast pain diminished

quicker with VACS group. The tolerability was satisfactory. We found VACS to be useful in the treatment of cyclical breast pain in women.

Vitex study 18

The therapeutic effect of a long-term Gestagen therapy (lynestrenol) and a phytotherapy (Mastodynon) in comparison to a placebo group is reported[49] in 160 cases of severe mastopathy with cyclic mastalgia. In 82.1 percent of the patients in the gestagen-group and in 74.5 percent of the patients in the Mastodynon-group a good relief of the premenstrual symptoms was achieved. In the placebo group only 36.8 percent of the patients reported a relief of symptoms. The difference is significant. The evaluation and analysis of serum HPRL and serum-progesterone showed a significant rise of the HPRL-level and a significant decrease of the progesterone-level. Because of this severe influence on the endocrine balance the recommendation for an alternative phytotherapy prior to a long term gestagen therapy is justified.

Vitex study 19

A randomized, double-blind, placebo-controlled clinical trial[50] was conducted to compare the efficacy of Vitex agnus-castus (Vitex) with placebo in postmenopausal women with hot flashes. Participants included sixty postmenopausal teachers (45-60 years old) an academic center in Gorgan-Iran. The participants divided in two equal groups randomly and treated with Vitex or placebo, 40 drops per day for 8 weeks. Data collected by using interview, individual characteristics questionnaire and evaluated by Blatt-kapperman's index at four follow-up visits. Statistical analysis was carried out by using descriptive statistics and multivariable analysis. Results were that the difference in frequency of hot flushes between groups was significant at 2nd, 4th, 6th and 8th weeks of intervention (P=0.015, p=0.000, p=0.000 and p=0.000, respectively) and also the decline in the severity of hot flashes in women who received Vitex was more evident on 2nd, 4th, 6th and 8th weeks (p=0.015, p=0.12, p=0.000 and p=0.000, respectively). Furthermore, comparing both study groups the result showed that the difference in Blatt-Kupperman index was not significant on the 2nd week of treatment (p=0.198); however, it was statistically significant between the two groups on the 4th, 6th and 8th week of treatment (p=0.008, p=0.00 and p=0.00, respectively). Some adverse events recoded between groups were statistically significant (p=0.012). In conclusion, despite some unimportant adverse events, this study showed that Vitex as a natural therapeutic agent is an effective treatment for the early vasomotor symptoms of postmenopausal women especially in women who have a contraindication to use of female hormones, but this recommendation requires to more studies with larger samples.

Table 2. Mean changes in the number of hot flushes during 24 hours in both groups

Frequency	Baseline	2nd week of intervention	4th week of intervention	6th week of intervention	8th week of intervention
Vitex	6 ± 2.58	4 ± 2.52	2 ± 2.38	1.28 ± 2.26	0.76 ± 2.16
Placebo	5.94 ± 2.2	6 ± 2.34	5.81 ± 2.40	5.44 ± 2.42	4.75 ± 2.84
Significance	**0.938**	**0.015**	**0.000**	**0.000**	**0.000**

**Values are given as mean ± SD.*

Table 3. Mean changes in the hot flush severity score during 24 hours in both groups

	Baseline				2nd week of intervention				4th week of intervention				6th week of intervention				8th week of intervention			
Severity	0	1	2	3	0	1	2	3	0	1	2	3	0	1	2	3	0	1	2	3
Vitex	0	20	68	12	0	36	60	4	32	24	40	4	48	32	20	0	80	8	12	0
Placebo	0	18.8	75	6.3	0	18.8	75	6.3	0	18.8	7	6.3	0	18.8	75	6.3	12.5	18.8	62.5	6.3
Significance*	**0.815**				**0.015**				**0.012**				**0.000**				**0.000**			

**Manwittny test showed that the differences between two groups were statistically significant in severity on the 2nd, 4th, 6th and 8th weeks of intervention.*
0= None; 1= Mild; 2= Moderate; 3= Sever;

Table 4. Mean changes in the Blatt-Kuppermam Index during 24 hours in both groups

Blatt- Kuppermam Index	Baseline	2nd week of intervention	4th week of intervention	6th week of intervention	8th week of intervention
Vitex*	8.22 ± 19.22	8.33 ± 15.84	8.01 ± 11.72	7.02 ± 8.20	5.35 ± 5.16
Placebo*	6.04 ± 20.19	6.55 ± 19.06	6.26 ± 18.31	5.98 ± 16.88	5.32 ± 16.38
Significance*	**0.922**	**0.198**	**0.008**	**0.000**	**0.000**

**Values are given as mean ± SD.*

Beta-carotene study 1

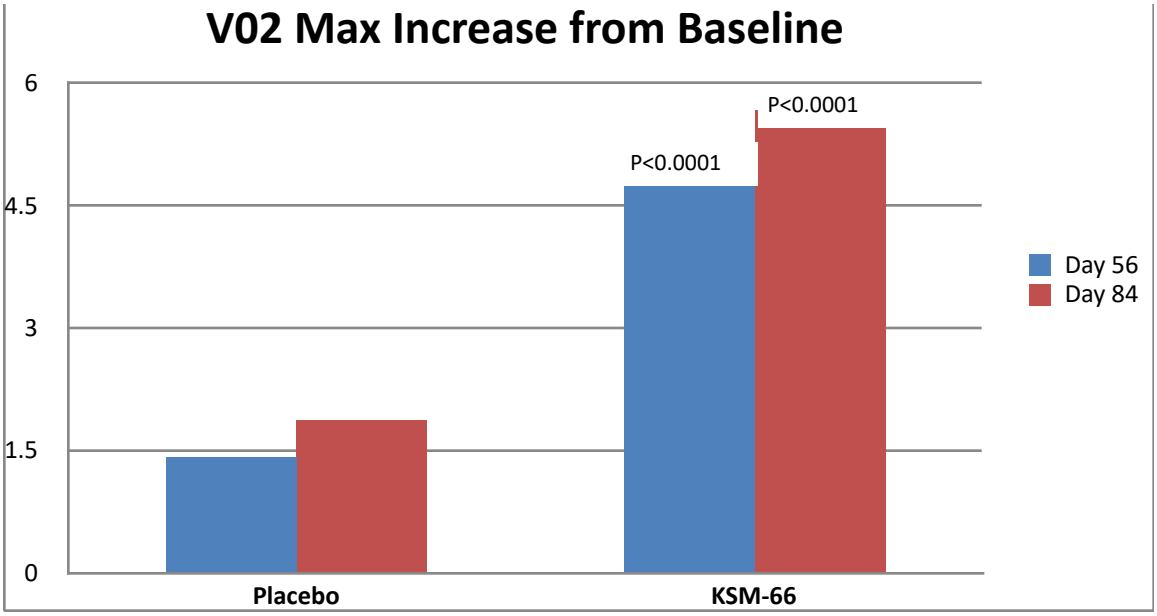
The purpose of this study[51] was to determine the effects of 2 different doses of dietary beta-carotene on wrinkles and elasticity, procollagen gene expression and ultraviolet (UV)-induced DNA damage in human skin. Thirty healthy female subjects over the age of 50 years were randomized and received 2 different doses (30 and 90 mg/day) of beta-carotene for 90 days. The baseline status was used as control. At baseline and completion of the study, facial wrinkles and elasticity were measured objectively. Buttock skin was taken to determine the type I procollagen, matrix metalloproteinase-1 and fibrillin-1 mRNA levels, and UV-induced thymine dimer and 8-hydroxy-2'-deoxyguanosine formation. Results showed that beta-carotene improved facial wrinkles and elasticity significantly only in the low-dose group. The minimal erythema dose decreased significantly only in the high-dose group. Type I procollagen mRNA levels were significantly increased to 4.4 +/- 1.6 times the baseline level only in the low-dose group, and procollagen immunostaining increased accordingly. UV-induced thymine dimer staining was reduced in the low-dose group but tended to increase in the high-dose group. 8-hydroxy-2'-deoxyguanosine staining was significantly reduced in the low-dose group. 30 mg/day of beta-carotene supplementation is demonstrated to prevent and repair photoaging.

KSM-66 study 1

Many women experience sexual dysfunction where there are orgasm disorders and sexual difficulties. Ashwagandha (Withania somnifera) is a herb known to improve the body's physical and psychological condition. The purpose of the study[52] was to determine the efficacy and safety of a high-concentration ashwagandha root extract (HCARE) supplementation for improving sexual function in healthy females. In this pilot study, 50 study subjects were randomized to either (i) HCARE-treated group or (ii) placebo-(starch-) treated group. The subjects consumed either HCARE or placebo capsules of 300mg twice daily for 8 weeks. Sexual function was assessed using two psychometric scales, the Female Sexual Function Index (FSFI) Questionnaire and the Female Sexual Distress Scale (FSDS), and by the number of total and successful sexual encounters. Results were that treatment with HCARE leads to significantly higher improvement, relative to placebo, in the FSFI Total score ($p < 0.001$), FSFI domain score for "arousal" ($p < 0.001$), "lubrication" ($p < 0.001$), "orgasm" ($p = 0.004$), and "satisfaction" ($p < 0.001$), and also FSDS score ($p < 0.001$) and the number of successful sexual encounters ($p < 0.001$) at the end of the treatment. In conclusion, this study demonstrated that oral administration of HCARE may improve sexual function in healthy women.

KSM-66 study 4

This study double-blind, randomized placebo-controlled trial[53] was conducted to evaluate the safety and efficacy of a high-concentration full-spectrum extract of Ashwagandha roots (KSM-66) in enhancing cardiorespiratory endurance and improving the quality of life in 49 healthy athletic adults. The study subjects were randomized to either: (i) Group I- the Placebo treatment Group or (ii) Group II - the Study Drug-treatment Group. The study subjects in Group II were administered one capsule (containing 300 mg of KSM-66) orally, twice daily for a period of 12 weeks; whereas, in Group I one capsule containing matching placebo 300 mg was administered similarly. During the treatment period (12 weeks), the subjects were required to present themselves at the trial center on specified intervals. Visit 1 was at Day 28 ± 3 days, Visit 2 was at Day 56 ± 3 days and Visit 3 was at Day 84 ± 3 days. At Visit 0, Visit 2 and Visit 3, the 20 meter shuttle run test was performed and the results translated to VO_2max measures.[54] The results of Visit 2 and Visit 3 were compared with the results of Visit 0 to evaluate the effect of KSM-66 on cardiorespiratory endurance. Final safety and efficacy assessments were done on Day 84 of the study. Statistical analysis of the data was done using paired and impaired t tests. Values are expressed as mean ± SD. The results were that treatment with KSM-66 significantly ($p < 0.0001$) increased the cardiorespiratory endurance and improved the quality of life of the study subjects. A progressive increment in the enhanced cardiopulmonary fitness and the improved quality of life of the study subjects was observed at Day 56 and Day 84 of the study period. The quality of life was assessed on the basis of their response to the questions of the World Health Organization, Quality of Life (WHO-QOL) Questionnaire. This suggests sustained beneficial effects of Ashwagandha and evidences the safety of the root extract on moderately long-term use. Conclusion: The findings of this study suggest that KSM-66 safely and effectively enhances the cardiorespiratory endurance and improves self-assessed quality of life in healthy athletic adults.



KSM-66 study 5

This double-blind, randomized, placebo-controlled trial[55] was conducted to evaluate the safety and efficacy of a high-concentration full-spectrum extract of Ashwagandha roots (KSM-66) in reducing stress and anxiety and in improving the general well-being of 61 adults who were under stress. Relevant clinical examinations and laboratory tests were performed, including a measurement of serum cortisol, and assessment of scores on standard stress-assessment questionnaires. They were randomized to either the placebo control group or the study drug treatment group, and were asked to take one capsule twice a day for a period of 60 days. In the study drug treatment group, each capsule contained 300 mg of KSM-66. During the treatment period (on Day 15, Day 30 and Day 45), a follow-up telephone call was made to all subjects to check for treatment compliance and to note any adverse reactions. Final safety and efficacy assessments were done on Day 60. Statistical Analysis: t-test, Mann-Whitney test. Results showed that the KSM-66 treatment group exhibited a significant reduction (P<0.0001) in scores on all the stress-assessment scales on Day 60, relative to the placebo group. Specifically, in the KSM-66 group, there was a significant reduction in scores corresponding to all of the item-subsets: 76.1% for the "Somatic" item-subset, 69.7% for the "Anxiety and Insomnia" item-subset, 68.1% for the "Social Dysfunction" item-subset, 79.2% for the "Severe Depression" itemsubset. In contrast, in the placebo control group, the corresponding reductions in scores were much smaller: 4.9%, 11.6%, -3.7% and -10.6%, respectively. The serum cortisol levels were substantially reduced (P=0.0006) in the KSM-66 group, relative to the placebo group. The adverse effects were mild in nature and were comparable in both the groups. No serious adverse events were reported. In conclusion, the findings of this study suggest that KSM-66 safely and effectively improves an individual's resistance towards stress and thereby improves self-assessed quality of life.

KSM-66 study 6

A prospective, randomized, double-blind, placebo-controlled study[56] was conducted to evaluate the efficacy and safety of Ashwagandha (KSM-66) toward improving memory and certain aspects of cognitive functioning in 50 healthy adults. Subjects were treated with either KSM-66 (300 mg capsule) or placebo, twice daily for eight weeks. The primary efficacy parameters were improvements in immediate memory, general memory and working memory as assessed through the Wechsler Memory Scale III (WMS-IIIIND). The secondary efficacy outcomes were improvements in visuo-spatial processing/response, executive function, attention and information processing speed, as assessed through WMS-IIIIND subtest scores for Visual

Table 2: Data analysis for perceived stress score data

	Ashwagandha		Placebo		*P*

Table 4: Data analysis for depression–anxiety stress scale data

	Ashwagandha (*n*=30)		Placebo (*n*=31)		*P*
	Mean	SD	Mean	SD	
DASS depression					
Baseline	17.5	9.3	18.6	11.5	0.697
Day 60	4.0	6.6	17.6	13.8	<0.0001
Change from baseline	−13.5	11.4	−1.0	9.0	<0.0001
% change from baseline	−77.0	–	−5.2	–	–
DASS anxiety					
Baseline	15.9	7.6	13.4	7.8	0.213
Day 60	3.9	5.4	14.0	11.5	<0.0001
Change from baseline	−12.0	8.6	0.6	7.9	<0.0001
% change from baseline	−75.6	–	4.3	–	–
DASS stress					
Baseline	21.4	8.5	22.9	10.7	0.556
Day 60	7.7	7.2	20.5	13.0	<0.0001
Change from baseline	−13.8	12.2	−2.4	10.5	<0.0001
% change from baseline	−64.2	–	10.4	–	–
DASS total					
Baseline	54.8	22.8	54.9	28.2	0.9954
Day 60	15.6	18.0	52.1	37.0	<0.0001
Change from baseline	−39.3	29.9	−2.8	25.4	<0.0001
% change from baseline	−71.6	–	−5.0	–	–

Table 3: Data analysis for GHQ-28 questionnaire data

	Ashwagandha (*n*=30)		Placebo (*n*=31)		*P*
	Mean	SD	Mean	SD	
GHQ-28 somatic					
Baseline	8.5	4.3	7.9	4.1	0.5825
Day 60	2.0	2.4	7.5	5.2	<0.0001
Change from baseline	−6.5	4.3	−0.4	4.3	<0.0001
% change from baseline	−76.1	–	−4.9	–	–
GHQ-28 anxiety and insomnia					
Baseline	9.7	4.6	10.0	5.4	0.7772
Day 60	2.9	3.2	8.9	6.3	<0.0001
Change from baseline	−6.7	4.9	−1.2	5.1	<0.0001
% change from baseline	−69.7	–	−11.6	–	–
GHQ-28 social dysfunction					
Baseline	10.6	3.8	8.7	3.9	0.0611
Day 60	3.4	3.7	9.0	5.2	<0.0001
Change from baseline	−7.2	5.1	0.3	3.9	<0.0001
% change from baseline	−68.1	–	3.7	–	–
GHQ-28 severe depression					
Baseline	5.3	4.4	4.9	4.7	0.7147
Day 60	1.1	1.9	5.4	5.9	0.0002
Change from baseline	4.2	4.0	0.5	4.8	<0.0001
% change from baseline	−79.3	–	10.6	–	–
GHQ-28 total					
Day 0	34.0	14.1	31.5	15.0	0.4977
Day 60	9.4	9.5	30.8	20.5	<0.0001
Change from baseline	−24.6	14.8	−0.7	14.9	<0.0001
% change from baseline	−72.3	–	−2.3	–	–

Reproduction I & II, Shepard's mental rotation task, Erikson Flanker task, Wisconsin Card Sort test, Trail Making Test part A and Mackworth's sustained attention test. Safety was evaluated by recording adverse events. Results: At baseline, no significant difference in cognitive impairment, subjective complaints and vital parameters was seen across the two groups. After 8 weeks, the KSM-66 group showed greater improvement than the placebo group for immediate memory and general memory, evidenced in greater improvement in the subtest scores for Logical Memory I (p = 0.007), Verbal Paired Associates I (p=0.043), Faces I (p=0.020), Family Pictures I (p=0.006) and Logical Memory II (p = 0.006), Verbal Paired Associates II (p=0.031), Faces II (p=0.014), Family Pictures II (p=0.006). However, there was only mixed evidence for improvement in working memory. The KSM-66 group showed greater improvement than the placebo group also
for executive function, attention and information processing speed, through greater improvement on the Erikson Flanker task (p=0.002), Wisconsin Card Sort test (p=0.014), Trail Making Test part A (p=0.006) and Mackworth's sustained attention test (p=0.009). However, no significant improvement was observed for visuo-spatial processing and response. In conclusion, KSM-66 can be effective in improving immediate memory and general memory, and in improving executive function, attention and information processing speed without any side effects.

KSM-66 study 7

A total of 50 subjects under chronic stress received either KSM-66® (300 mg) or placebo twice daily for 8 weeks. The purpose of the study[57] was to evaluate the efficacy of Ashwagandha root extract compared with placebo in reducing markers of stress, and in controlling weight gain and improving general well-being in adults under chronic stress. The primary outcome measures were the Perceived Stress Score (PSS), and the Food Cravings Questionnaire–Trait (FCQ-T). The secondary outcome measures included the Oxford Happiness Questionnaire (OHQ), the Three-Factor Eating Questionnaire (TFEQ), serum cortisol levels, initial and final body weight. The results were as follows with the treatment group compared to the placebo group:

Outcome	Test	Results at 4 weeks	Results at 8 weeks
Stress	PSS score	Significant decreased (22.1%, P = 0.0025)	Significantly decreased (32.7%, P = 0.001).
Food Cravings	FCQ "Planning" score	Significant decreased (P = 0.0269)	Significant decreased (P = 0.0087).
	FCQ "Positive Reinforcement" score	Significant decreased (P = 0.0067)	Significant decreased (P = 0.0001).
	FCQ "Lack of Control" score	Significant decreased (P = 0.0443)	Significant decreased 8 weeks (P = 0.0097).
	FCQ "Emotion" score	Significant decreased (P = 0.0352)	Significant decreased (P = 0.0068).
	FCQ "Environment" Score	n/a	Significant decreased (P = 0.039).

Happiness	OHQ score	Significant increased (P = 0.032)	Significant increased (P = 0.0001), with an overall improvement of 19.18%.
Cortisol	Serum levels	Significant decreased (P = 0.0328	Significant decreased (P = 0.0019)
Body Weight	Scale	n/a	Significant decreased (3.03% vs. 1.46% with placebo, P = 0.0148)
Uncontrolled Eating	The TFEQ ‘‘Uncontrolled Eating’’ score	n/a	Significant decreased (P = 0.0247).
Emotional Eating	TFEQ ‘‘Emotional Eating’’ score	Significant decreased (P = 0.0207	Significant decreased and 8 weeks (P = 0.0135).

In summary, 600 mg/day of KSM-66® reduced food cravings and body weight more effectively than a placebo, while also reducing measures of stress and cortisol.

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