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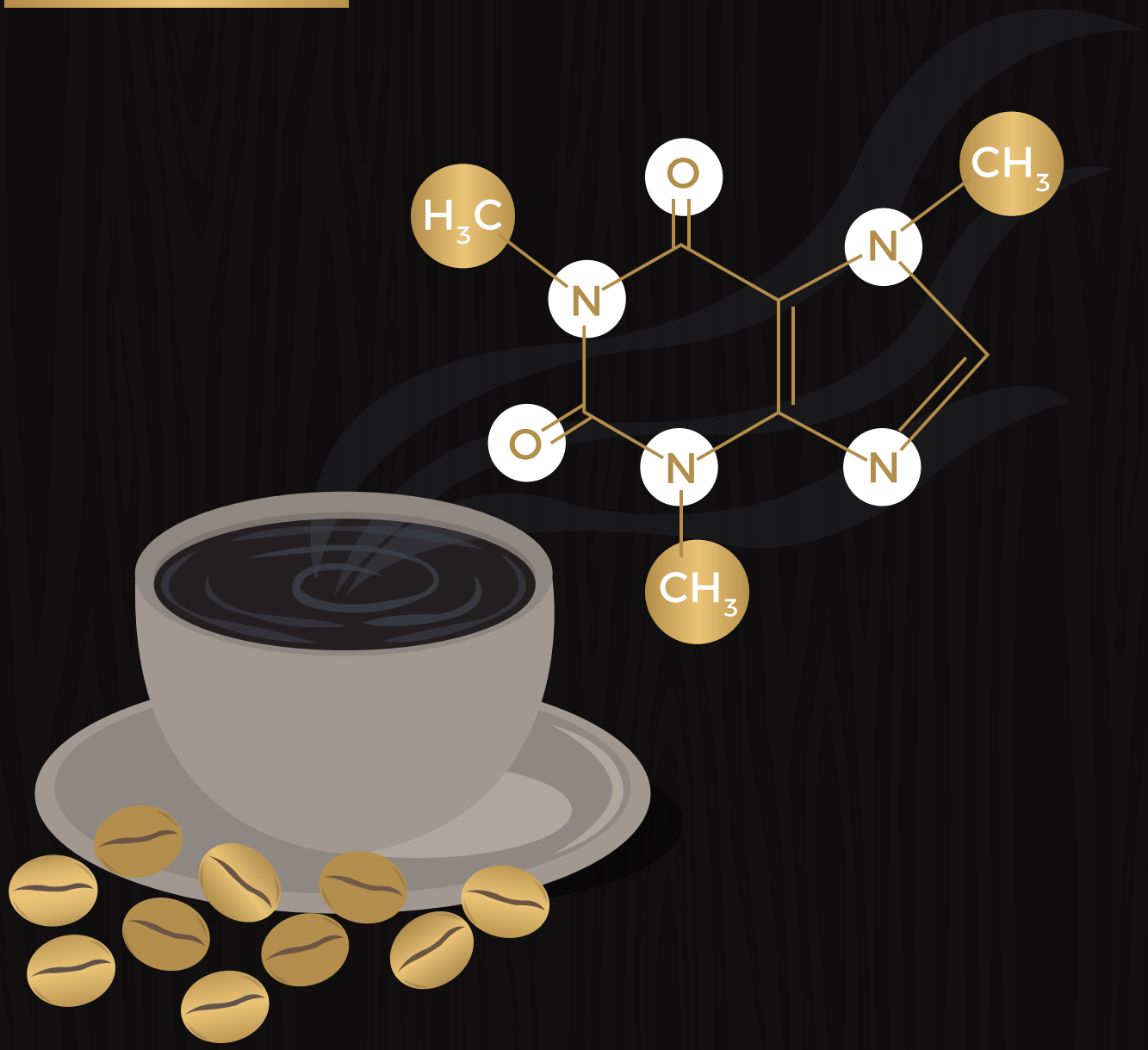
White Paper



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Claim Substantiation

Vitamin D study 1

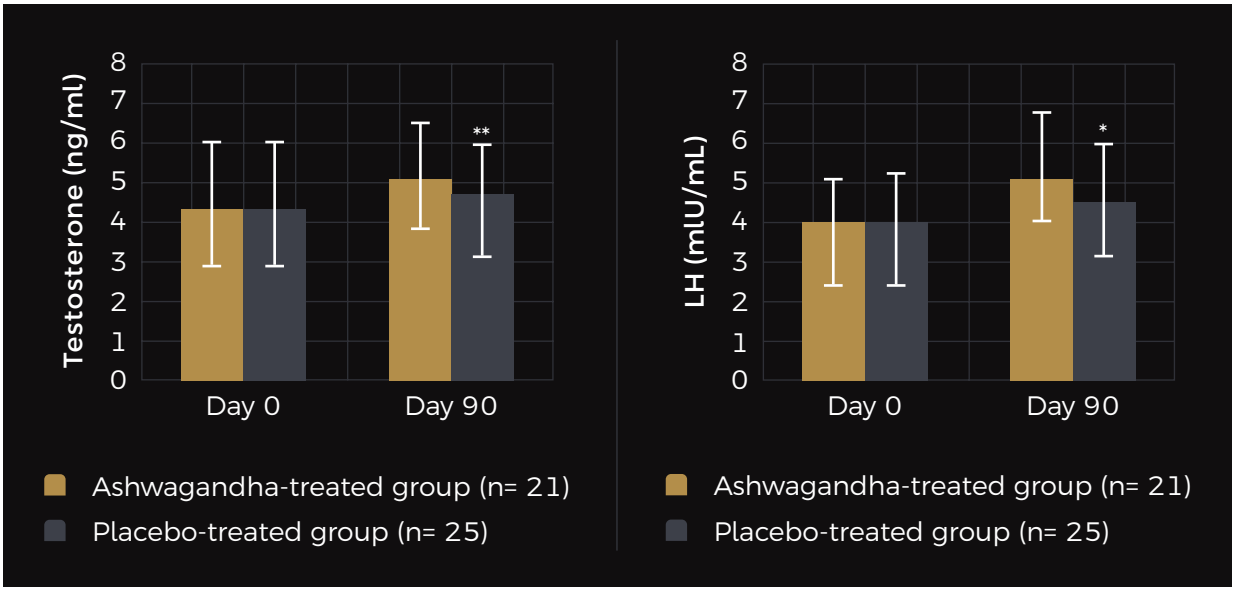
Interrelationships between hormones of the hypothalamic-pituitary-testicular (HPT) axis, hypogonadism, vitamin D and seasonality remain poorly defined. Researchers investigated whether HPT axis hormones and hypogonadism are associated with serum levels of 25-hydroxyvitamin D (25(OH)D) in men. A cross-sectional survey[1] of 3369 community-dwelling men aged 40-79 years in eight European centers was conducted. Testosterone (T), oestradiol (E(2)) and dihydrotestosterone were measured by gas chromatography-mass spectrometry; LH, FSH, sex hormone binding globulin (SHBG), 25(OH) D and parathyroid hormone by immunoassay. Free T was calculated from total T, SHBG and albumin. Gonadal status was categorised as eugonadal (normal T/LH), secondary (low T, low/normal LH), primary (low T, elevated LH) and compensated (normal T, elevated LH) hypogonadism. Associations of HPT axis hormones with 25(OH)D were examined using linear regression and hypogonadism with vitamin D using multinomial logistic regression. The results were that in univariate analyses, free T levels were lower (P=0.02) and E(2) and LH levels were higher (P<0.05) in men with vitamin D deficiency (25(OH)D <50 nmol/l). 25(OH)D was positively associated with total and free T and negatively with E(2) and LH in age- and centre-adjusted linear regressions. After adjusting for health and lifestyle factors, no significant associations were observed between 25(OH)D and individual hormones of the HPT axis. However, vitamin D deficiency was significantly associated with compensated (relative risk ratio (RRR)=1.52, P=0.03) and secondary hypogonadism (RRR=1.16, P=0.05). Seasonal variation was only observed for 25(OH)D (P<0.001). Researchers concluded that secondary and compensated hypogonadism were associated with vitamin D deficiency and the clinical significance of this relationship warrants further investigation.

Vitamin D study 2

Studies in rodents indicate a role of vitamin D in male reproduction, but the relationship between vitamin D and androgen levels in men is largely unexplored. Researchers aimed to investigate the association of 25-hydroxyvitamin D [25(OH)D] levels with testosterone, free androgen index (FAI) and SHBG. Moreover, they examined whether androgen levels show a similar seasonal variation to 25(OH)D. In this cross-sectional study,[2] 25(OH)D, testosterone and SHBG levels were assessed by immunoassay in 2299 men who were routinely referred for coronary angiography (1997-2000). Main outcome measures were associations of 25(OH)D levels with testosterone, SHBG and FAI. FAI was calculated as testosterone (nmol/l)/ SHBG (nmol/l) x 100. The results were that men with sufficient 25(OH)D levels (> or =30 microg/l) had significantly higher levels of testosterone and FAI and significantly lower levels of SHBG when compared to 25(OH)D insufficient (20-29.9 microg/l) and 25(OH) D-deficient (<20 microg/l) men (P < 0.05 for all). In linear regression analyses adjusted for possible confounders, we found significant associations of 25(OH)D levels with testosterone, FAI and SHBG levels (P < 0.05 for all). 25(OH)D, testosterone and FAI levels followed a similar seasonal pattern with a nadir in March (12.2 microg/l, 15.9 nmol/l and 40.8, respectively) and peak levels in August (23.4 microg/l, 18.7 nmol/l and 49.7, respectively) (P < 0.05 for all). Researchers concluded that androgen levels and 25(OH)D levels are associated in men and reveal a concordant seasonal variation. Randomized controlled trials are warranted to evaluate the effect of vitamin D supplementation on androgen levels.

KSM-66 study 1

This two-arm, double-blind, randomized, placebo-controlled, parallel-group study[3] using conducted to evaluate the effects of Ashwagandha root extract (KSM-66 Ashwagandha) or placebo on spermatogenic activity and serum hormone levels in patients with oligospermia (sperm count < 20 million/mL semen). Forty-six male patients were randomized either to treatment (n = 21) with KSM-66 Ashwagandha (675 mg/d in three doses for 90 days) or to placebo (n = 25) in the same protocol. Semen parameters and serum hormone levels were estimated at the end of 90-day treatment.



Results showed that there was a 167% increase in sperm count (P<0.0001), 53% increase in semen volume (P< 0.0001), and 57% increase in sperm motility (P<0.0001) on day 90 from baseline. The improvement in these parameters was minimal in the placebo-treated group. Furthermore, a significantly greater improvement and regulation were observed in serum hormone levels with the Ashwagandha treatment as compared to the placebo. Serum testosterone increased significantly by 17% (from 4.45 ± 1.41 ng/mL to 5.22 ± 1.39 ng/mL; P<0.01) and LH by 34% (from 3.97 ±1.21 IU/mL to 5.31 ± 1.33 mIU/mL; P< 0.02), following treatment with Ashwagandha root extract, as compared to the baseline (Day 0) values of these parameters. See table below for data on statistical significance on the testosterone increase:

Effect of Ashwagandha on Testosterone

	Ashwagandha Mean	Ashwagandha StdDev	Placbo Mean	Placbo StdDev	Pvalue
Day 0	4.45	1.41	4.42	1.50	**= 0.9423**
Day 90	5.22	1.39	4.59	1.48	**= 0.144**
Change at Day90 from Beseline	0.77	0.67	0.17	0.72	**= 0.0057**

Notes:

- The improvement from baseline is significantly higher in ashwagandha group than in the placebo group, (0.77 vs 0.17) based on the following three statistical significance tests.
- The p-value using repeated-measures ANOVA is 0.0057.
- The p-value using repeated-measures ANOVA with Wilcoxon test is 0.0071.
- The p-value using ANCOVA is 0.0047.

KSM-66 study 2

This 8-week randomized, prospective, double-blind, placebo-controlled clinical study[4] was designed to examine the effects of the KSM-66 Ashwagandha root extract (one 300 mg capsule, twice daily) or placebo on muscle strength and endurance, size and recovery, testosterone, and body fat in 50 healthy and physically active males (18-45 years of age, n=25 for each group) with little experience in resistance training. Creatine kinase (CK) was assessed as a biomarker of recovery from muscle injury. Following baseline measurements, subjects underwent resistance training for 8 weeks; thereafter, measurements of the specific parameters were repeated at the end of week 8 (completion of study).

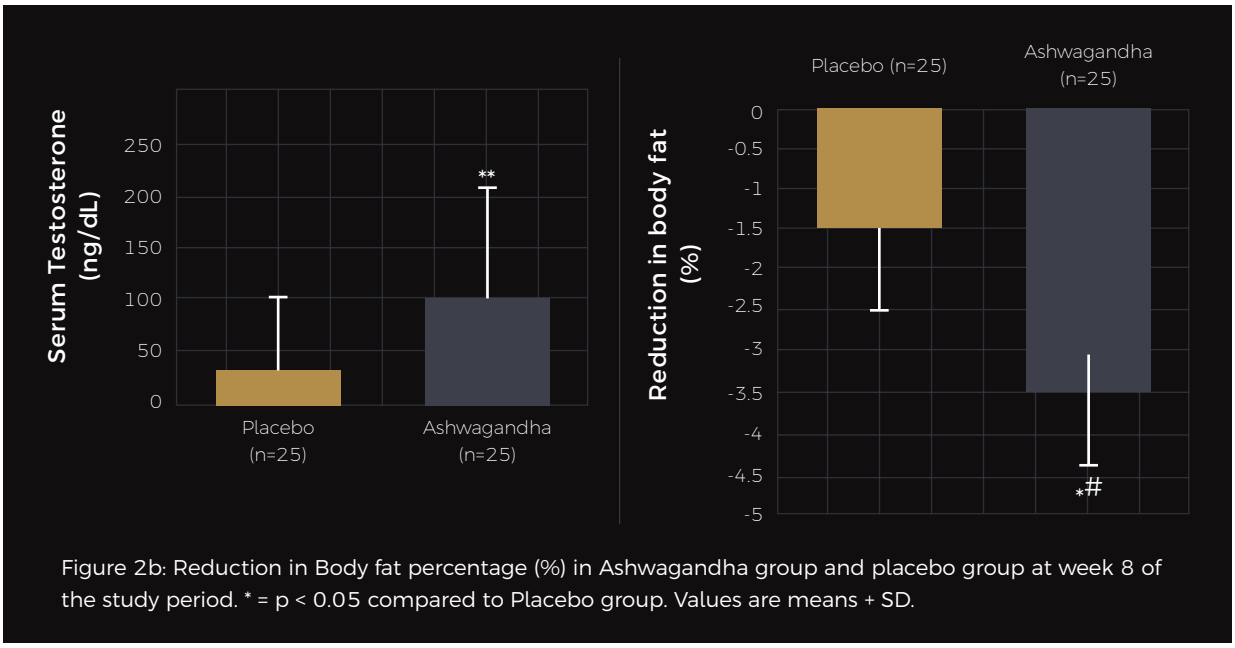


Figure 2b: Reduction in Body fat percentage (%) in Ashwagandha group and placebo group at week 8 of the study period. * = p < 0.05 compared to Placebo group. Values are means + SD.

The results were that both muscle strength (bench press) and muscle size (arm), increased significantly in the Ashwagandha group as compared to the Placebo group (P<0.001 and P<0.05, respectively). There was also a significant increase of 15% in the concentration of total serum testosterone in the Ashwagandha group at week 8 of the study period as compared to the corresponding baseline value (P<0.05). The increase was significant also as compared to the Placebo group (P<0.01). In addition, the expected increase in creatine kinase (CK) between 24 and 48 hours following exercise was significantly lower in the Ashwagandha group compared to placebo (P<0.05), and the reduction in body fat percentage was significantly greater in the Ashwagandha group compared to placebo (P<0.05). The findings of this study clearly demonstrate the beneficial effect of Ashwagandha root extract in attenuating muscle damage, increasing muscle strength and endurance and decreasing body fat percentage in healthy adults undergoing resistance training for eight weeks.

KSM-66 study 3

This 8-week, randomized, prospective, double-blind, placebo-controlled clinical study[5] was conducted to examine the possible effects of ashwagandha root extract consumption (KSM-66) on muscle mass and strength in 57 healthy men (18-50 years old) engaged in resistance training. Subjects with little experience in resistance training were randomized into treatment (29 subjects) and placebo (28 subjects) groups. Subjects in the treatment group consumed 300 mg of KSM-66 twice daily, while the control group consumed starch placebos. Following baseline measurements, both groups of subjects underwent resistance training for 8 weeks and measurements were repeated at the end of week 8. Muscle strength was evaluated using the 1 -RM load for the bench press and leg extension exercises. Both groups of subjects were also evaluated by measuring muscle size, body composition, and testosterone levels. Muscle recovery was evaluated by using serum creatine kinase level as a marker of muscle injury from the effects of exercise. Results: Compared to the placebo subjects, the group treated with KSM-66 had significantly greater increases in muscle strength on the bench-press exercise (p=0.001) and the leg-extension exercise (p=0.037), and significantly greater muscle size increase at the arms (p=0.010) and chest (p<0.001) compared to the placebo subjects, the subjects receiving KSM-66 also had significantly faster recovery (p=0.029) of muscles from exercise-induced muscle damage as indicated by the stabilization of serum creatine kinase, significantly greater increase in testosterone level (p=0.004 1), and a significantly greater decrease in body fat percentage (p=0.032). In conclusion, this study reports that KSM-66 supplementation is associated with significant increases in muscle mass and strength and suggests that ashwagandha supplementation may be useful in conjunction with a resistance training program.

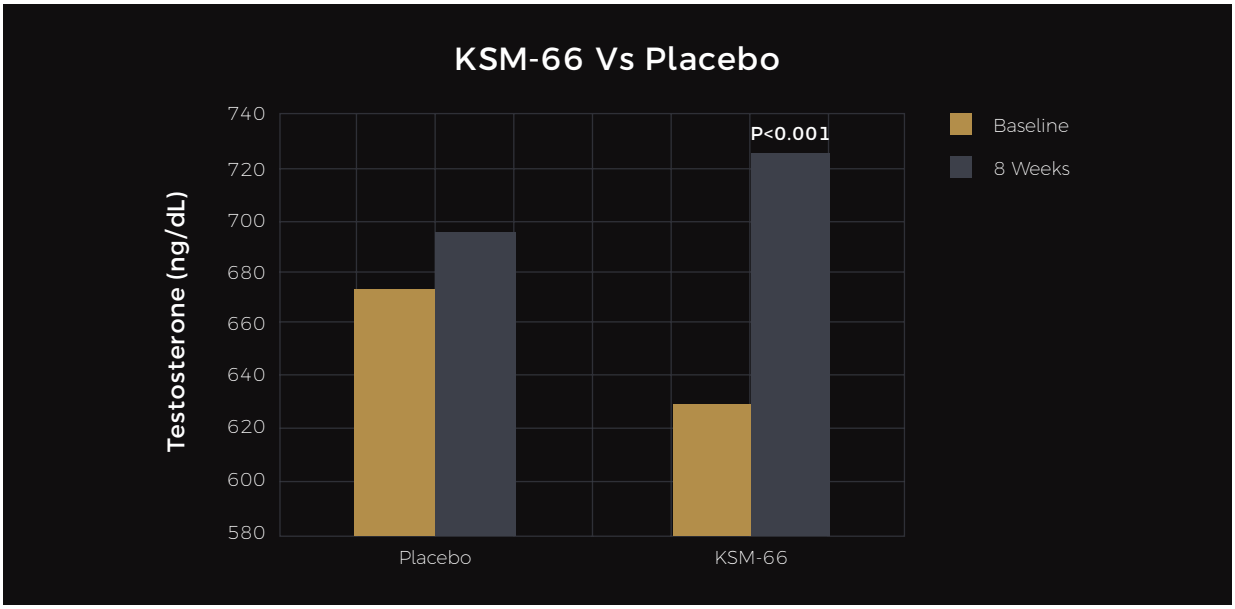


Table 1: Body Composition

Body fat percentage

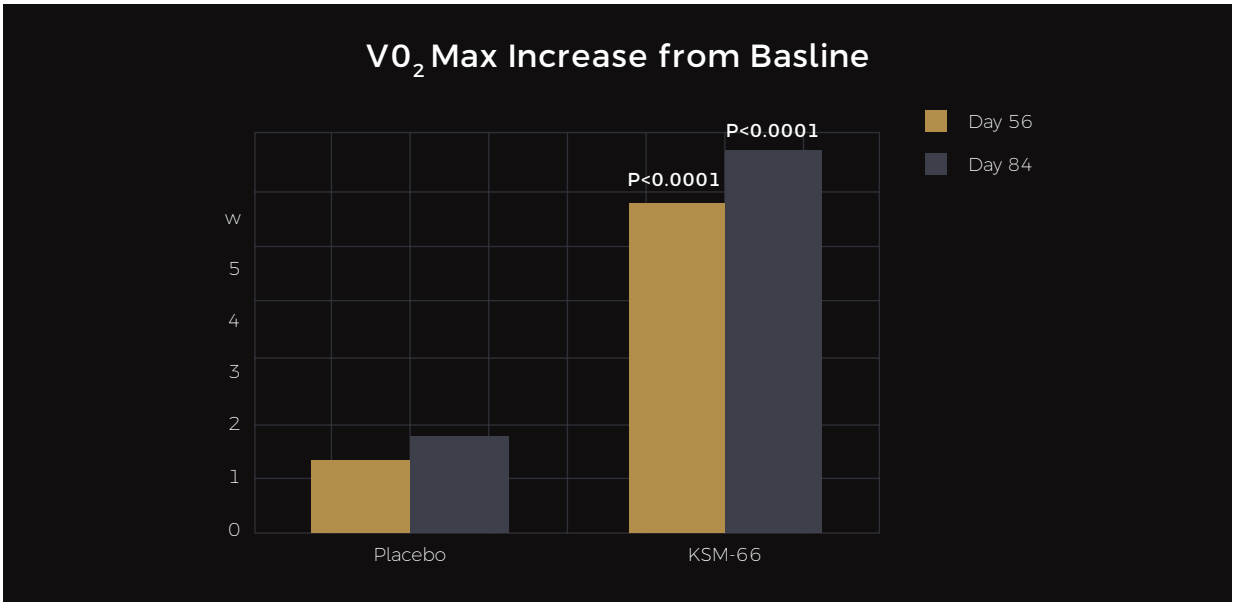
	Treatment Group Mean (SD)	Placebo Group Mean (SD)	p-valuse
Sample size (n)	n=25	n=25	
Pre intervention	21.60 (3.91)	22.01 (3.37)	0.6974
Post intervention	18.13 (3.13)	20.48 (1.85)	0.0025
Decrease from pre to post	3.47 (3.58)	1.52 (2.58)	0.0327

Summary statistics are represemed as mean (SD). The change from the preintervention point to the postintervention point is statistically signifuant in the treatment group (p< 0.001) and in the placebo group (p=0.007).

KSM-66 study 4

This study double-blind, randomized placebo-controlled trial[6] 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 VO2max measures.[a]

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[7] 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.

Table 2: Data analysis for perceived stress score data

	Ashwagandha (n=30)		Placebo (n=31)		p
	Mean	SD	Mean	SD	
Baseline	20.6	4.8	24.6	6.7	0.0094
Day 60	11.5	6.2	23.3	7.2	<0.0001
Change from baseline	-9.1	8.6	-1.4	5.3	<0.0001
% change from baseline	-44.0	-	-5.5	-	-

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	-	-

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	54.0	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	-	-

KSM-66 study 6

A prospective, randomized, double-blind, placebo-controlled study[8] 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 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[9] 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.

KSM-66 study 8

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[10] 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.

Notes:

- The following two studies used 5 g/day of Ashwagandha root powder. Nevertheless, they still lend lend credence to Ashwagandha's general efficacy in promoting increases in testosterone since the amount of KSM-66 Ashwagandha root extract used in the aforementioned studies is roughly equivalent to 5 g of root powder used in the following studies. Here's the rationale:

According to Alternative Medicine Review,[11] "The major biochemical constituents of ashwaganda root are steroidal alkaloids and steroidal lactones in a class of constituents called withanolides."

According to Kumar et al,[12] the amount of withanolides found in commercial Ashwagandha root[b] ranges between 0.38-0.76% based upon whether the plant is harvested during its vegetative, flowering or seed phenostage:

Root phenostage	% Withanolides	Withanolides in 5 g
Vegetative	0.76	38 mg
Flowering	0.58	38 mg
Seed	0.52	26 mg

According to the spec sheet, KSM-66 Ashwagandha root extract provides >5 % total withanolides, so 675 mg would provide at least 33.75 mg of withanolides. On this basis, 675 mg of KSM-66 Ashwagandha root extract is roughly equivalent to 5 g Ashwagandha root powder.

Ashwagandha study 1

A prospective study[13] was conducted to investigate the impact of 5 g/day Withania somnifera root powder on semen profile, oxidative biomarkers, and reproductive hormone levels. Seventy-five normal healthy fertile men (control subjects) and 75 infertile men undergoing infertility screening were the subjects. Measurements of the following were taken before and after the treatment: seminal plasma biochemical parameters, antioxidant vitamins, and serum testosterone (T), luteinizing hormone (LH), follicle stimulating hormone (FSH), and prolactin (PRL) levels. Results showed that Withania somnifera inhibited lipid peroxidation and protein carbonyl content and improved sperm count and motility. Treatment of infertile men recovered the seminal plasma levels of antioxidant enzymes and vitamins A, C, and E and corrected fructose. Moreover, treatment also significantly increased serum T and LH and reduced the levels of FSH and PRL:

Table 5: **Effect of Withania somnifera on hormonal profile inserum of infertile men.**

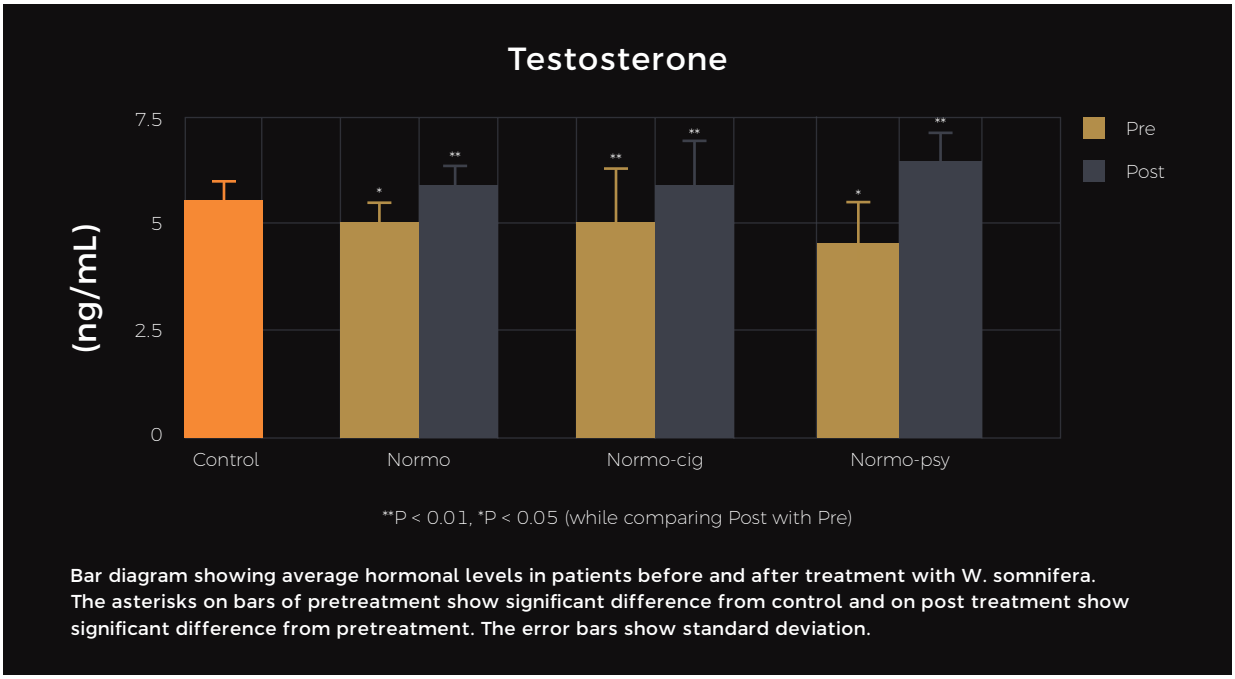
Group	Treatment	LH (mIU/mL)	T (ng/mL)	FSH (mIU/mL)	PRL (ng/mL)
Control (n=75)		7.94 ± 1.00	7.09 ± 0.63	5.67 ± 0.91	7.10 ± 0.67
Normozoospermic (n=25)	Pretreatment	6.87 ± 0.60^{a}	5.80 ± 0.88^{a}	6.07 ± 0.69^{NS}	7.21 ± 0.72^{NS}
	Posttreatment	7.85 ± 0.53^{b}	6.65 ± 0.78^{b}	5.75 ± 0.60**	6.93 ± 0.67^{NS}
Oligozoospermic (n=25)	Pretreatment	4.02 ± 0.57^{a}	3.51 ± 0.56^{a}	7.78 ± 77^{a}	10.57 ± 1.42^{a}
	Posttreatment	5.98 ± 0.80^{b}	4.94 ± 0.54^{b}	6.27 ± 0.76^{b}	8.75 ± 1.28^{b}
Asthenozoospermic (n=25)	Pretreatment	3.82 ± 0.59^{a}	4.32 ± 0.89^{a}	6.49 ± 0.85^{a}	7.78 ± 0.82*
	Posttreatment	5.37 ± 061^{b}	5.23 ± 0.80^{b}	5.95 ±0.96**	7.78 ± 0.82^{b}

- ^{a}**P < .01** compared with control.
- ^{b}**P < .01** compared with pretreatment.
- ***P < .05** compared with control.
- ****P < .05** compared with pretreatment.
- ^{NS}**Not significant.**

Ahmad. Effect of Withania somnifera on infertile males. Fertil Steril 2010.

Ashwagandha study 2

A 3-month, controlled study[14] was conducted to examine the role of stress in male infertility, and to test the effect of ashwagandha root powder (5 g/day) on stress and the treatment of normozoospermic male infertility (n = 60). Subjects included normozoospermic heavy smokers (n = 20), normozoospermics under psychological stress (n = 20) and normozoospermics with infertility of unknown etiology (n = 20). Normozoospermic fertile men (n = 60) were used as controls.



Bar diagram showing average hormonal levels in patients before and after treatment with W. somnifera. The asterisks on bars of pretreatment show significant difference from control and on post treatment show significant difference from pretreatment. The error bars show standard deviation.

Measuring various biochemical and stress parameters before and after treatment, suggested a definite role of stress in male infertility and the ability of ashwagandha to treat stress-related infertility. In normozoospermics with infertility of unknown etiology, normozoospermic cigarette smokers and normozoospermics under psychological stress:

- Sperm concentration was increased by 17, 20 and 36%, respectively
- Sperm concentration was increased by 17, 20 and 36%, respectively
- Semen liquefaction time decreased by 19, 20 and 34%, respectively
- Cortisol levels significantly decreased by 11, 28 and 32%, respectively
- Testosterone level improved by 13, 10 and 22%, respectively
- Luteinizing hormone levels improved by 5, 14 and 22%, respectively

Likewise, treatment resulted in a decrease in stress and improved the level of anti-oxidants in a significant number of individuals. The treatment also resulted in pregnancy in the partners of 14% of the patients.

Ashwagandha study 3

"It [Withania somnifera (asvagandhdá, modern: ashwagandha)] is regarded as tonic, alterative and aphrodisiac and is used in consumption, emaciation of children, debility from old age, rheumatism, etc." [p.211, 1st paragraph][15]

"About half a drachm of asvagandhdá root, taken with milk or clarified butter is said to act as an aphrodisiac and restorative to old men. Asvagandhdá enters into the composition of several medicines intended for use as aphrodisiacs." [p.211, 2nd paragraph]

Ashwagandha study 4

"Ayurveda, the traditional system of medicine practiced in India, can be traced back to 6000 BC. For most of this history, Ashwagandha (Withania somnifera), also known as "Indian ginseng" due to its rejuvenating effects, has been described in folk medicine as an aphrodisiac and geriatric tonic." [Pg 1, 2nd paragraph under "I. Introduction"][16]

Ashwagandha study 5

"In Ayurveda, Withania is widely claimed to have potent aphrodisiac, sedative, rejuvenative and life prolonging properties." [pg 2374, 3rd paragraph, 1st sentence][17]

Ashwagandha study 6

"Asgand consists of the roots of Withania somnifera which has various therapeutic actions such as anti-inflammatory (Muhallil-e-Warm), sedative (Musakkin), alterative (Muaddil) and aphrodisiac (Muqawwi-e-Bah)." [pg 170, under "Abstract", 4th sentence][18]

Ashwagandha study 7

"W. somnifera is a traditional medicine, the roots of which have been used not only as anti-stress agent but also as an aphrodisiac and male sexual stimulant." [pg 2, 2nd paragraph, second sentence][19]

Ashwagandha study 8

"Withania somnifera, also known as Indian ginseng, has been described in folk medicine as an aphrodisiac and geriatric tonic." [pg 990, 2nd paragraph, 2nd sentence][20]

Ashwagandha study 9

"The root of Ashwagandha is regarded as tonic, aphrodisiac, narcotic, diuretic, anthelmintic, astringent, thermogenic and stimulant." [pg 209, 2nd paragraph, 1st sentence][21]

L-theanine study 1

L-theanine significantly increases activity in the alpha frequency band which indicates that it relaxes the mind without inducing drowsiness. However, this effect has only been established at higher doses than that typically found in a cup of black tea (approximately 20mg). The aim of the current research[22] was to establish this effect at more realistic dietary levels. EEG was measured in healthy, young participants at baseline and 45, 60, 75, 90 and 105 minutes after ingestion of 50mg L-theanine (n=16) or placebo (n=19). Participants were resting with their eyes closed during EEG recording. There was a greater increase in alpha activity across time in the L-theanine condition (relative to placebo ($p<0.05$). A second study replicated this effect in participants engaged in passive activity. These data indicate that L-theanine, at realistic dietary levels, has a significant effect on the general state of mental alertness or arousal. Furthermore, alpha activity is known to play an important role in critical aspects of attention, and further research is therefore focused on understanding the effect of L-theanine on attentional processes.

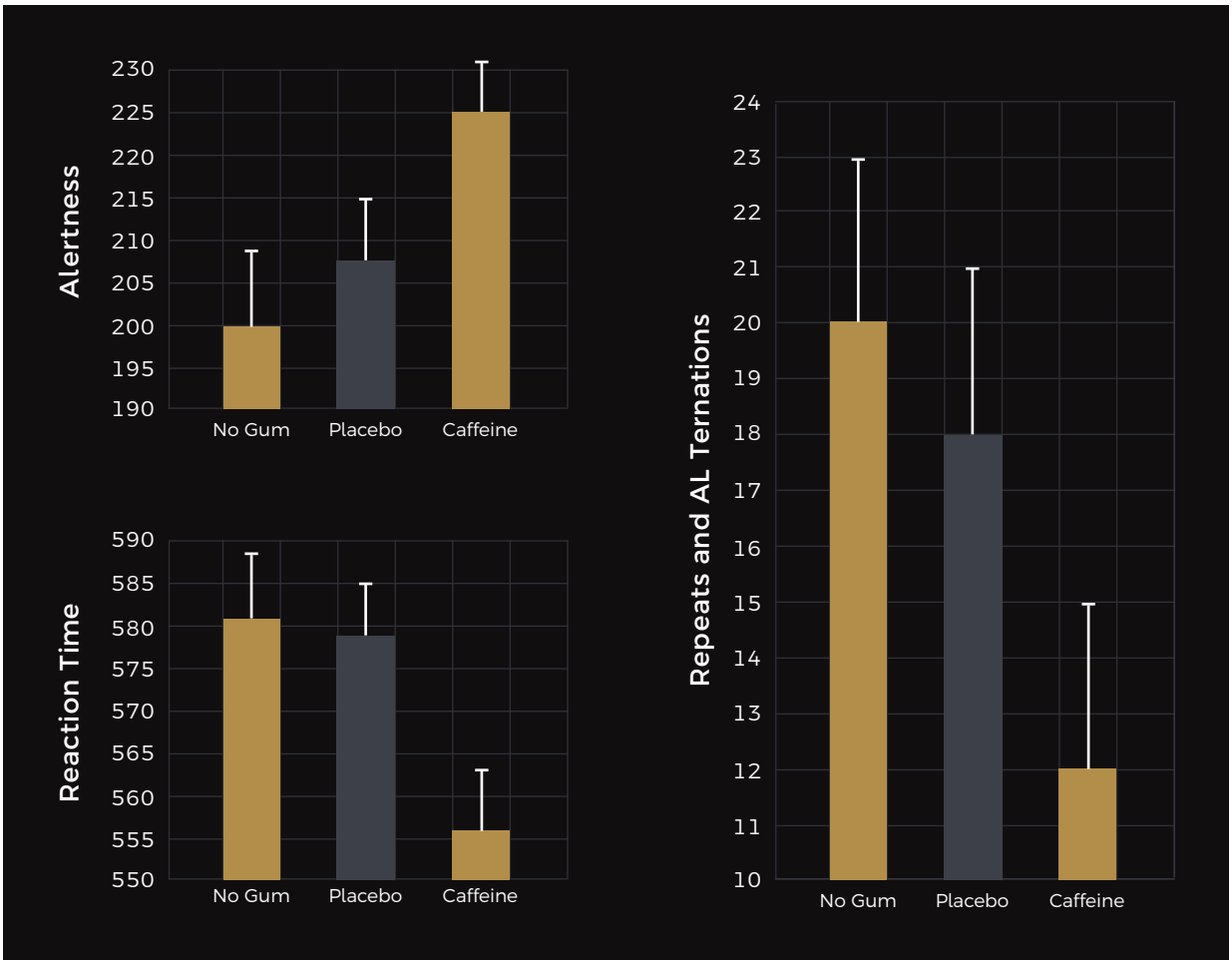
L-theanine study 2 and caffeine study 1

Recent neuropharmacological research has suggested that certain constituents of tea may have modulatory effects on brain state. The bulk of this research has focused on either L-theanine or caffeine ingested alone (mostly the latter) and has been limited to behavioral testing, subjective rating, or neurophysiological assessments during resting. In this study,[23] we investigated the effects of both L-theanine and caffeine, ingested separately or together, on behavioral and electrophysiological indices of tonic (background) and phasic (event-related) visuospatial attentional deployment. Subjects underwent 4 d of testing, ingesting either placebo, 100 mg of L-theanine, 50 mg of caffeine, or these treatments combined. The task involved cued shifts of attention to the left or right visual hemifield in anticipation of an imperative stimulus requiring discrimination. In addition to behavioral measures, we examined overall, tonic attentional focus as well as phasic, cue-dependent anticipatory attentional biasing, as indexed by scalp-recorded alpha-band (8-14 Hz) activity. We found an increase in hit rate and target discriminability (d') for the combined treatment relative to placebo, and an increase in d' but not hit rate for caffeine alone, whereas no effects were detected for L-theanine alone. Electrophysiological results did not show increased differential biasing in phasic alpha across hemifields but showed lower overall tonic alpha power in the combined treatment, similar to previous findings at a larger dosage of L-theanine alone. This may signify a more generalized tonic deployment of attentional resources to the visual modality and may underlie the facilitated behavioral performance on the combined ingestion of these 2 major constituents of tea.

Caffeine study 2

To compare the effects of caffeinated gum (40 mg), placebo gum and no gum conditions on mood and attention, a double blind placebo controlled study[24] was conducted with volunteers (18-30 yrs) being randomly assigned to one of the three conditions. Baseline measures of mood and attention were taken prior to chewing and a test session was then conducted. One hundred and eighteen young adults participated in the study. Those in the gum groups chewed the gum for 20 minutes.

The results were: 1) T-tests showed that the caffeinated gum group gave higher alertness ratings than the other groups; 2) those in the caffeinated gum conditions had faster reaction times than the other two groups; and 3) T-tests revealed that the caffeine condition was better than the other two in repeats and alternations[c] (see charts below). In conclusion, the implications of the present study are that chewing caffeinated gum has been shown to improve performance efficiency and mood by its alerting and energizing effects.



Caffeine study 3

The FDA has indicated that caffeine is a stimulant that "helps restore mental alertness or wakefulness during fatigue or drowsiness," and identifies it for this purpose in its monograph on over-the-counter stimulants. The amount of caffeine identified as effective is a dose of 100 mg.[25]

Caffeine study 4

According to the Institute of Medicine (IOM):[26]

"Although there is considerable variation in both the doses tested and subjects' responses to the effects of caffeine on cognitive function, overall research shows that caffeine in the range of 100 to 600 mg is effective in increasing the speed of reaction time without affecting accuracy and in improving performance on visual and audio vigilance tasks. A number of studies have also reported improved performance on long-term memory recall, but not short-term word recall. These enhancing effects of caffeine on cognitive performance are most pronounced when functions are impaired or suboptimal (e.g., as a result of sleep deprivation)." [pg. 7]

"Caffeine in doses of 100–600 mg may be used to maintain cognitive performance, particularly in situations of sleep deprivation. Specifically it can be used in maintaining speed of reactions and visual and auditory vigilance, which in military operations could be a life or death situation." [pg. 7]

"The effects of caffeine on cognitive behavior vary according to dose, the subject's experience with caffeine, and gender. In general, low to intermediate doses (100–600 mg) of caffeine are associated with increased alertness, energy, and concentration, while higher doses can lead to anxiety, restlessness, insomnia, and tachycardia (Heishman and Henningfield, 1992, 1994)." [pg. 39]

Caffeine study 5

Notes:

This study used 1 mg/kg body weight and 3 mg/kilo body weight on subjects. Using the accepted average body weight of 75 kilos, this would translate to 75 mg and 225 mg caffeine.

In a placebo-controlled, randomized study,[27] the effects of 1 mg/kg caffeine (LOWCAF), 3 mg/kg (MODCAF) or placebo (0 mg/kg) and time of day (TOD) on human performance were studied in 188 male psychology students using a multiple forceband discrimination task (MFDT)[d] and subjective ratings. Results were that a significant main effect of caffeine was found, Wilk's Approx. $F(10, 332) = 2.50$, $p < 0.01$, indicating that caffeine had an overall effect on MFDT performance. Also, caffeine had an effect on response latency, $F(2, 170) = 3.99$, $p < .02$, resulting in an overall increase in time to respond. Interestingly, the 1 mg/kg dose slowed responding to a greater extent than did the 3 mg/kg dose.

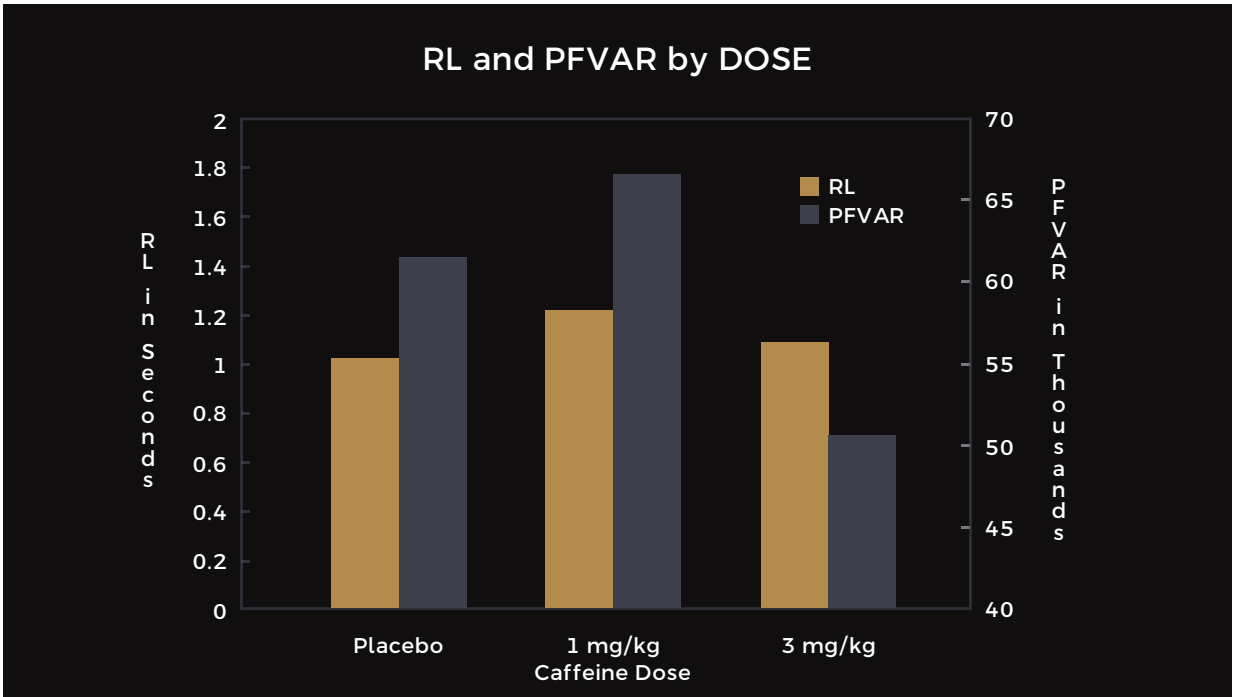
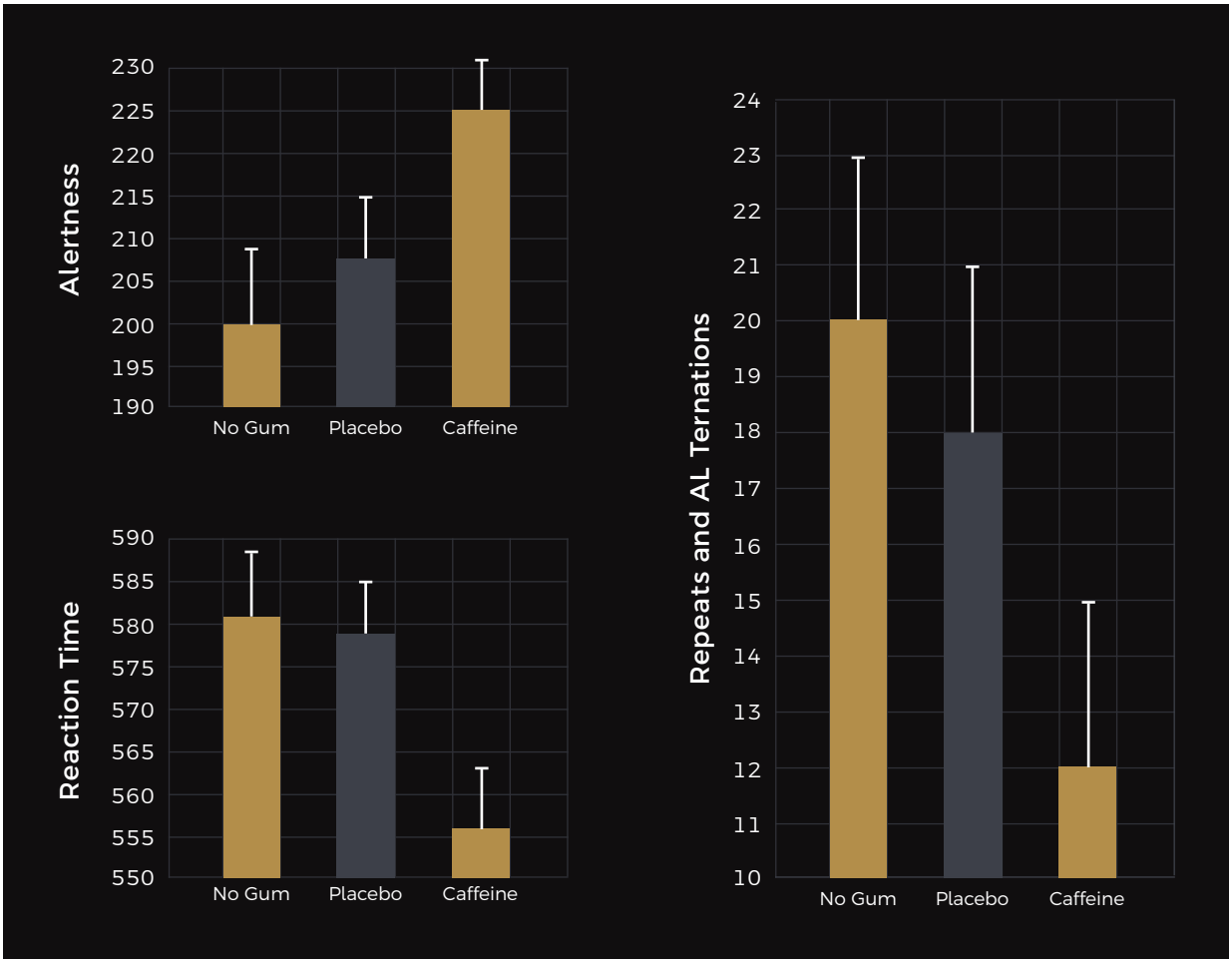


FIG. 5. Response latency (RL) and Peakforce variability (PFVAR) differences at each CAFFEINE level. Bar graph illustrates the moderate increases in RL from PLACEBO to LOWCAF and PLACEBO to MODCAF; and the decrease in PFVAR from PLACEBO to MODCAF and LOWCAF to MODCAF.

Caffeine study 6

To compare the effects of caffeinated gum (40 mg), placebo gum and no gum conditions on mood and attention, a double-blind placebo controlled study[28] was conducted with volunteers (18-30 yrs) being randomly assigned to one of the three conditions. Baseline measures of mood and attention were taken prior to chewing and a test session was then conducted. One hundred and eighteen young adults participated in the study. Those in the gum groups chewed the gum for 20 minutes. The results were: 1) T-tests showed that the caffeinated gum group gave higher alertness ratings than the other groups; 2) those in the caffeinated gum conditions had faster reaction times than the other two groups; and 3) T-tests revealed that the caffeine condition was better than the other two in repeats and alternations[e] (see charts below). In conclusion, the implications of the present study are that chewing caffeinated gum has been shown to improve performance efficiency and mood by its alerting and energizing effects.



Notes:

The basis for the "Lasts up to 5 hours" claim is the fact that caffeine's half-life is generally considered to be about 5 hours.

Caffeine study 7

In a double-blind, cross-over study[29] in nine healthy subjects, Bruce et al found that the half-life of single doses of anhydrous caffeine (250 mg and 500 mg) was approximately 5 hours.

S7 study 1

Recent interest has focused on maintenance of healthy levels of redox signaling and the related oxidants; these parameters are crucial for providing us with concrete nutritional targets that may help us to better understand and maintain “optimal health”. Following the above hypothesis, we performed a pilot double-blind, crossover, placebo-controlled, single dose study[30] to measure the dose-dependent effects of a proprietary plant-based dietary supplement labelled here as S7 (SPECTRA7), related to how it affected the cellular metabolic index (CMI) in healthy human participants (n ¼ 8). We demonstrated using the electron spin resonance/electron paramagnetic resonance spectrometer NOXYSCAN that the administration S7 resulted in statistically significant, long-term, dose-dependent inhibition of mitochondrial and cellular reactive oxygen species generation by as much as 9.2 or 17.7% as well as 12.0 or 14.8% inhibition in extracellular nicotinamide-dinucleotide-phosphate oxidase system-dependent generation of O2□, and 9.5 or 44.5%inhibition of extracellular H2O2 formation. This was reflected with dose-dependent 13.4 or 17.6%inhibition of tumor necrosis factor alpha induced cellular inflammatory resistance and also 1.7 or 2.3-times increases of bioavailable NO concentration. In this pilot study, we demonstrated the ability of a natural supplement to affect cellular redox signaling, which is considered by many researchers as oxidative stress. The design and activity of this proprietary plant-based material, in combination with the newly developed “CMI” test, demonstrates the potential of using dietary supplements to modulate redox signaling. This opens the door to future research into the use of S7 for modulation of inflammatory markers, for sports endurance or recovery applications.

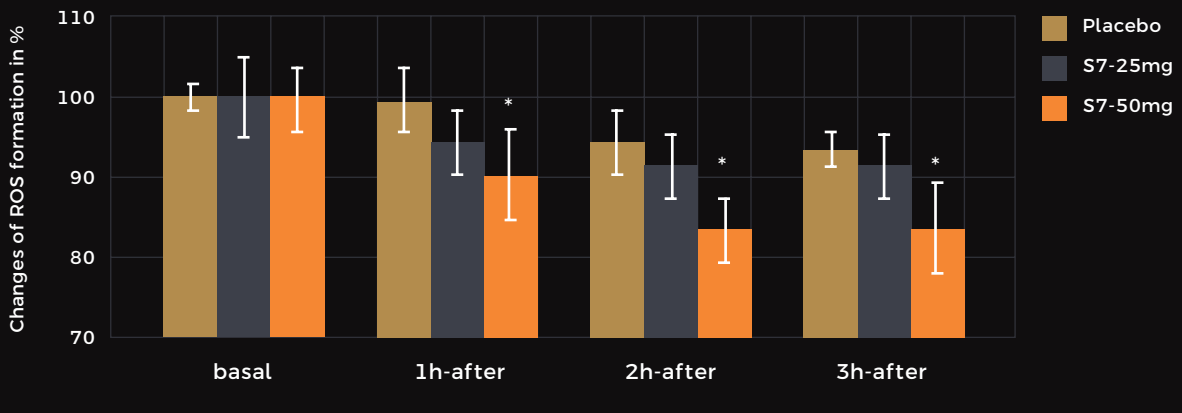


Figure 1. Effect of single dose of S7 on cellular metabolic index “total ROS generation” in human participants. CMI value for a healthy person is age and gender dependent and equal the value 220-240 nm/s. Detection of reactive oxygen species was performed using spin probe CMH (200μm) and bench-top EPR spectrometer NOXYSCAN in eight generally healthy, fasted (minimum 12h) participants. Gold columns (placebo); prior to and 60, 120, 180 min after consumption of standard breakfast (bread roll with glass of water); Dark Grey columns (25 mg S7): after consumption of standard breakfast and capsule with 25 mg of S7; and Orange columns (50 mg S7): after consumption of standard breakfast and capsule with 50 mg of S7. For EPR settings please refer to “Material and methods” section. Data are mean (n=8) ± SEM, *p<.05 vc. placebo.

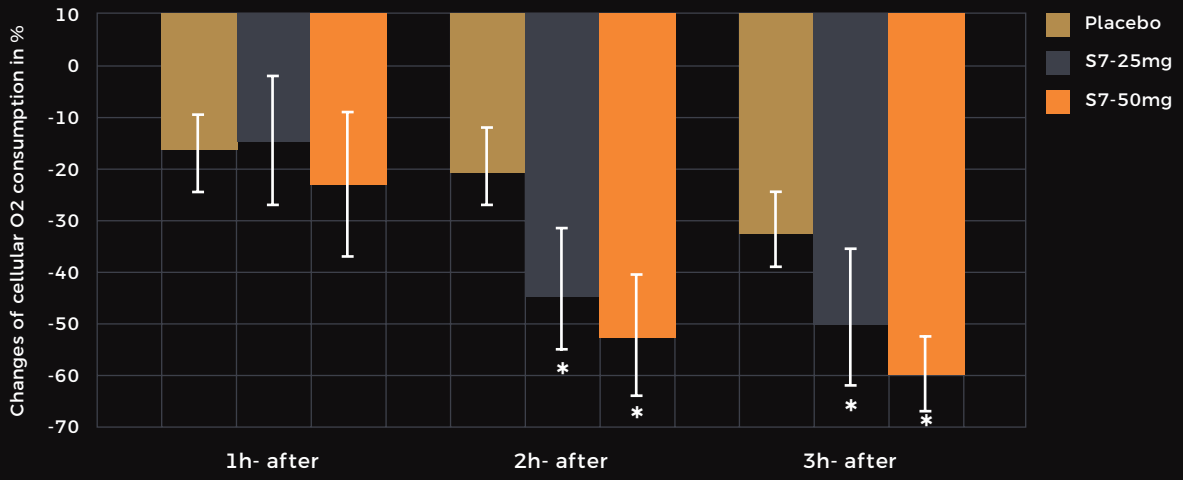
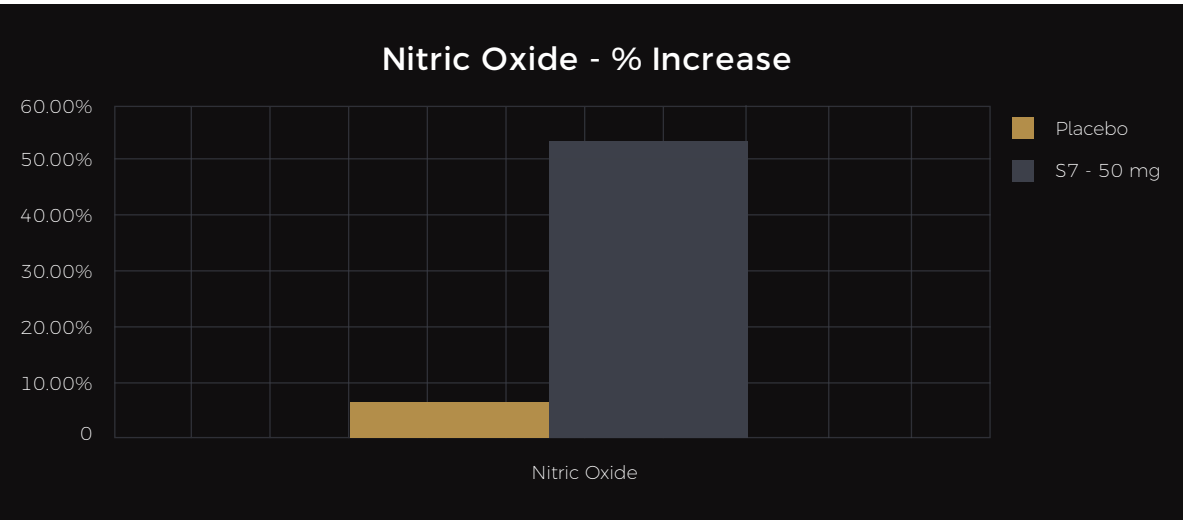


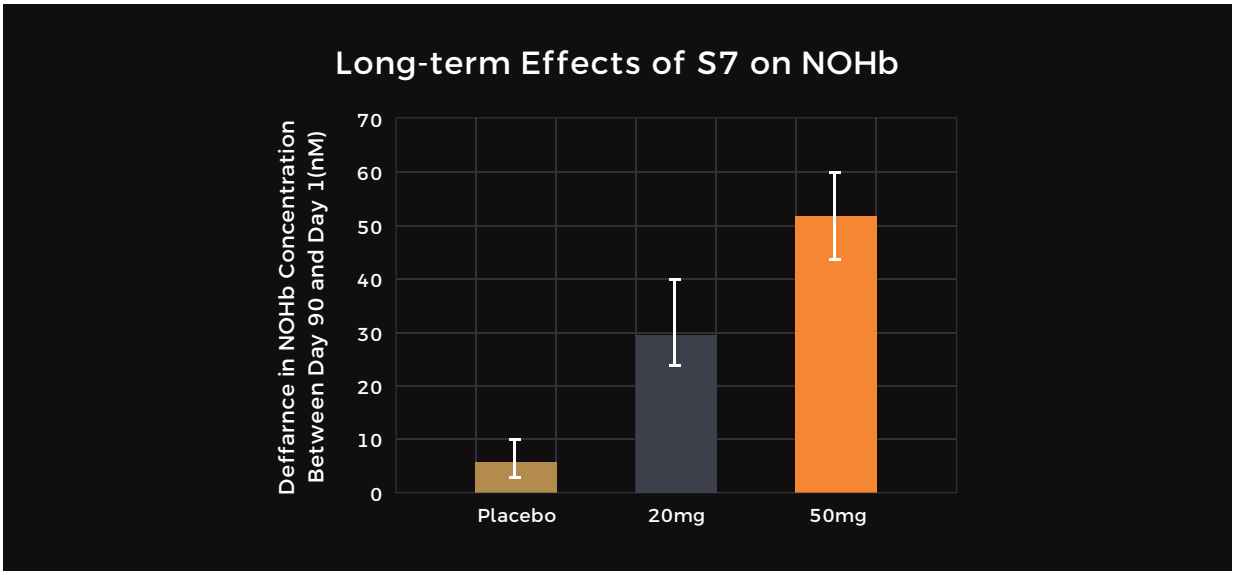
Figure 2. Effect of S7 on cellular oxygen consumption of bloov cells. Oxygen consumption analysis was performed simultaneously with detection of ROS using spin-label NOX-15.1 (5 µm) and bench-top EPR spectrometer NOXYSCAN in eight generally healthy, fasted (minimum 12h) participants. Gold columns (placebo): 60, 120, 180 min after consumption of standard breakfast (bread roll with glass of water) and placebo capsule; Dark Grey columns: after consumption of standard breakfast and capsule with 25 mg of S7; and Red columns: after consumption of standard breakfast and capsule with 50 mg of S7. Data are mean ± SEM (n=8), *p < .05 vc. placebo.

S7 study 2

Healthy endothelial function has been positively associated with elevated levels of circulating nitric oxide (NO). Consequently, a natural, plant-based material that may safely increase endogenous NO levels, reduce redox imbalance, and promote improved metabolic response could be of significant interest and benefit. In this first study of its kind, we conducted a longitudinal, randomized, double-blind, placebo-controlled study[31] of S7, a proprietary polyphenol-rich fruit, vegetable, and herb-based material previously reported to reduce reactive oxygen species (ROS) and to increase NO.



Specifically, we measured changes in real-time cellular generation of ROS and changes in levels of bioavailable NO (measured as circulating NOHb) in 42 overweight or slightly obese individuals who were recruited into one of three groups: placebo, 25mg of S7, and 50mg of S7. Results suggest that after 90 days of once-daily supplementation, the 25mg and 50mg S7 groups exhibited diminished mitochondrial ROS generation (~54% and ~75%, respectively) compared to placebo, which exhibited a slight increase (>12%) ($p = 0.049$). Furthermore, circulating NOHb levels significantly increased in the 25mg and 50mg S7 groups (33.87% and 53.43%, respectively) compared to placebo (6.67%) ($p < 0.001$)—8 times higher percentage with 50 mg than placebo. Together, these results suggest that long-term daily supplementation of S7 may provide potential benefits related to healthy endothelial function and reduced mitochondrial dysfunction.



Notes:

In the following three studies, 2 g, 3.2 g and 3 g, respectively of Lion's Mane (Hericium erinaceus) powder. In the current formula, a 1:8 extract of Lion's Mane is used, wherein 8 g of Lion's Mane is used to create 1 g of the extract. Consequently, 400 mg of the extract is equivalent to 3.2 g of the powder.

Lion's mane study 1

Hericium erinaceus, a well-known edible mushroom, has numerous biological activities. Especially hericenones and erinacines isolated from its fruiting body stimulate nerve growth factor (NGF) synthesis, which expects H. erinaceus to have some effects on brain functions and autonomic nervous system. A randomized, double-blind, placebo-controlled trial[32] was conducted to investigate the clinical effects of H. erinaceus on menopause, depression, sleep quality and indefinite complaints, using the Kupperman Menopausal Index (KMI), the Center for Epidemiologic Studies Depression Scale (CES-D), the Pittsburgh Sleep Quality Index (PSQI), and the Indefinite Complaints Index (ICI). Thirty females were randomly assigned to either the H. erinaceus (HE, 2g/day) group or the placebo group and took HE cookies or placebo cookies for 4 weeks. Each of the CES-D and the ICI score after the HE intake was significantly lower than that before.

In two terms of the ICI, “insentive” and “palpitatio”, each of the mean score of the HE group was significantly lower than the placebo group. “Concentration”, “irritating” and “anxious” tended to be lower than the placebo group. Our results show that HE intake has the possibility to reduce depression and anxiety and these results suggest a different mechanism from NGF-enhancing action of H. erinaceus.

Table 6: **Comparison before and after the trial**

	Before				After				In HE groups, before - and - after comparison	2 groups comparison
	HE		Placebo		HE		Placebo			
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
KMI	16.5	10.2	17.1	8.1	11.2	6.2	11.1	9.9	P = 0.090	n.s.
CES-D	13.9	7.8	15.1	9.6	10.3	7.3	12.6	8.3	P = 0.033	n.s.
PSQI	6.3	2.3	6.2	2.6	6.0	2.7	6.4	2.7	n.s.	n.s.
ICI	46.1	23.4	40.4	17.5	29.6	21.5	31.6	22.3	P = 0.004	n.s.
Total IC	13.8	8.9	11.5	7.1	8.1	7.8	8.4	7.5	P = 0.004	n.s.

- **HE :** Hericium eriaceus,
- **BMI :** Body-Mass Index,
- **KMI :** Kupperman Menopausal Index,
- **CES-D :** Center for Epidemiologic Studies Depression,
- **PSQI :** Pittsburgh Sleep Quality Index,
- **ICI :** Indefinite Complaints Index,
- **n.s. :** non-significant,

Lion’s mane study 2

Hericium erinaceus has been recognized as medical mushroom since ancient time, but its scientific evidence for human health has been still uncertain. In this study, we tested a randomized, double-blind, placebo-controlled parallel-group comparative study[33] to evaluate the improvement of the cognitive functions by taking supplements containing fruiting body of H. erinaceus (3.2 g/day) for 12 weeks. We performed three kinds of tests: Mini Mental State Examination (MMSE), Benton visual retention test, and Standard verbal paired-associate learning test (S-PA). MMSE alone showed that oral intake of H. erinaceus significantly improved cognitive functions and prevented from the deterioration. We speculate that various chemical compounds, including hericenones, in the mushroom have multiple effects to the brain neural networks and improve cognitive functions. Oral intake of H.erinaceus is safe and convenient method for dementia prevention so far.

Table 7: Comparison of MMSE scores between HE and Placebo groups

	Ex-ante			Interim			Ex-post		
	HE	Placebo	P-value	HE	Placebo	P-value	HE	Placebo	P-value
Oriventain on place	5.00 (0.000)	5.00 (0.00)	ND	4.88 (0.085)	4.93 (0.07)	0.598	5.00 (0.000)	4.93 (0.07)	0.310
Oriventain on time	4.63 (0.155)	4.67 (0.16)	0.853	4.88 (0.085)	4.80 (0.14)	0.654	5.00 (0.000)	4.73 (0.15)	0.0824‡
Immediate recall	2.94 (0.063)	3.00 (0.00)	0.341	3.00 (0.000)	3.00 (0.00)	ND	3.00 (0.000)	3.00 (0.00)	ND
Calculation	4.75 (0.250)	4.13 (0.40)	0.196	4.88 (0.125)	4.47 (0.32)	0.252*	5.00 (0.000)	4.93 (0.07)	0.310
Delayed recall	2.88 (0.085)	3.00 (0.00)	0.167	3.00 (0.000)	2.93 (0.07)	0.310	3.00 (0.000)	3.00 (0.00)	ND
Naming objects	2.00 (0.000)	2.00 (0.00)	ND	2.00 (0.000)	2.00 (0.00)	ND	2.00 (0.000)	2.00 (0.00)	ND
Repeat a sentence	1.00 (0.000)	1.00 (0.00)	ND	1.00 (0.000)	1.00 (0.00)	ND	1.00 (0.000)	0.93 (0.07)	0.310
Oral command	3.00 (0.000)	3.00 (0.00)	ND	3.00 (0.000)	3.00 (0.00)	ND	3.00 (0.000)	3.00 (0.00)	ND
Writing Oral command	1.00 (0.000)	1.00 (0.00)	ND	1.00 (0.000)	1.00 (0.00)	ND	1.00 (0.000)	1.00 (0.00)	ND
Spontaneous writing of sentences	1.00 (0.000)	0.93 (0.07)	0.310	1.00 (0.000)	1.00 (0.00)	ND	1.00 (0.000)	1.00 (0.00)	ND
Graphic drawing	1.00 (0.000)	1.00 (0.00)	ND	1.00 (0.000)	1.00 (0.00)	ND	1.00 (0.000)	1.00 (0.00)	ND
Total score	29.19 (0.430)	28.73 (0.43)	0.462	29.63 (0.180)	29.13 (0.43)	0.310*	30.00 (0.000)	29.53 (0.22)	0.0328

- **ND :** Not defined because two values were coincidence.
- **( ) :** Brackets denote Standard Errors.
- † : The value suggests significant difference between HE and placebo groups.
- ‡ : The value suggests tendency to be significantly different.
- * : The value was calculated by Welch's t-test.

Lion's mane study 3

A double-blind, parallel-group, placebo-controlled trial[34] was performed on 50- to 80-year -old Japanese men and women diagnosed with mild cognitive impairment in order to examine the efficacy of oral administration of Yamabushitake (Hericium erinaceus), an edible mushroom, for improving cognitive impairment, using a cognitive function scale based on the Revised Hasegawa Dementia Scale (HDS-R). After 2 weeks of preliminary examination, 30 subjects were randomized into two 15-person groups, one of which was given Yamabushitake and the other given a placebo. The subjects of the Yamabushitake group took four 250 mg tablets containing 96% of Yamabushitake dry powder three times a day for 16 weeks. After termination of the intake, the subjects were observed for the next 4 weeks. At weeks 8, 12 and 16 of the trial, the Yamabushitake group showed significantly increased scores on the cognitive function scale compared with the placebo group. The Yamabushitake group's scores increased with the duration of intake, but at week 4 after the termination of the 16 weeks intake, the scores decreased significantly. Laboratory tests showed no adverse effect of Yamabushitake. The results obtained in this study suggest that Yamabushitake is effective in improving mild cognitive impairment.

Health Canada monograph[35]

Table 8: Proper name(s), Common name(s), Source material(s)

Proper name(s)	Common name(s)	Source material(s)		
		Proper name(s)	Part(s)	Preparation(s)
Agaricaus blazei	Himematsutake	Agaricus blazei	· Cultured mycelium · Fruiting body · Mycelium	Dried
Auricularia auricula- judae	Jelly ear	Auricularia auricula- judae	· Cultured mycelium · Fruiting body · Mycelium	Dried
Ganoderma applanatum	Artist's conk	Ganoderma applanatum	· Cultured mycelium · Fruiting body · Mycelium	Dried
Ganoderma lucidum	· Ganoderma · Ling zhi · Reishi	Ganoderma lucidum	· Cultured mycelium · Fruiting body · Mycelium	Dried
Grifola frondosa	Maitake	Grifola frondosa	· Cultured mycelium · Fruiting body · Mycelium	Dried
Hericium erinaceus	Lion's Mane	Hericium erinaceus	· Cultured mycelium · Fruiting body · Mycelium	Dried
Inonotus obliquus	Chaga	Inonotus obliquus	· Cultured mycelium · Fruiting body · Mycelium	Dried

Use(s) or Purpose(s)

All Products

Source of fungal polysaccharides with immunomodulating properties (Xu et al. 2014; Mizuno and Nishitani 2013; Dai et al. 2013; Jung et al. 2012; Won et al. 2011; Wang et al. 2009; Change and Miles 2004; Bensky et al. 2004; Hobbs 2003; Li et al. 2002; Wasser 2002; MHPRC 1998; Bin and Yang 1991).

Products containing Lentinula edodes fruiting body and/or (cultured) mycelium, a decocted fruiting body of Agaricus blazei, a decocted fruiting body of Hericium erinaceus, a decocted cultured mycelium of Paecilomyces hepiali and/or a decocted stroma of Ophiocordyceps sinensis

- Source of/Provides antioxidants (De Sa-Nakanishi et al. 2014; Zheng et al. 2014; Han et al. 2013; Qi et al. 2013; Wang et al. 2011; Bisen et al. 2010; Xu et al. 2010).
- Source of/Provides antioxidants that help fight/protect (cell) against/reduce (the oxidative effcts of/the oxidative damage caused by/cell damage casused by) fre adicals (De Sa-Nakanishi et al. 2014; Zheng et al. 2014; Han et al. 2013; Qi et al 2013; Wang et al. 2011; Bisen et al. 2010; Xu et al. 2010).

Maca study 1

The objective of this study was to assess the effect of maca on seminal parameters in infertile adult men. This is a double-blind, randomised, placebo-controlled pilot trial[36] in which sixty-nine patients diagnosed with mild asthenozoospermia and/or mild oligozoospermia were supplied by maca (n = 35) or placebo (n = 34) (2 g/day) for a period of 12 weeks. When compared patients treated with maca and patients treated with placebo, there were no significant differences in semen volume (2.95 ± 0.52 vs. 2.90 ± 0.52; p = .392), sperm motility (22.34 ± 2.22 vs. 23.05 ± 2.22; p = .462) and normal sperm morphology (7.89 ± 1.89 vs. 7.04 ± 2.28; p = .801), but there was a significant difference in sperm concentration (15.04 ± 5.61 vs. 10.16 ± 3.59, respectively; p = .011). In conclusion, patients treated with 2 g of maca for a period of 12 weeks showed a significant improvement in seminal concentration compared with patients treated with placebo. There were no significant differences in semen volume, sperm mobility and morphology when compared both groups.

Maca study 2

Lepidium meyenii (Maca) is a cultivated root belonging to the brassica family used in the Andean region for its supposed aphrodisiac properties. We carried out a double-blind clinical trial[37] on 50 Caucasian men affected by mild erectile dysfunction (ED), randomised to treatment with Maca dry powder, 2400 mg, or placebo. The treatment effect on ED and subjective well-being was tested administrating before and after 12 weeks the International Index of Erectile Function (IIEF-5) and the Satisfaction Profile (SAT-P). After 12 weeks of treatment, both Maca- and placebo-treated patients experienced a significant increase in IIEF-5 score ($P < 0.05$ for both). However, patients taking Maca experienced a more significant increase than those taking placebo (1.6 +/- 1.1 versus 0.5 +/- 0.6, $P < 0.001$).

Both Maca- and placebo-treated subjects experienced a significant improvement in psychological performance-related SAT-P score, but the Maca group higher than that of placebo group (+9 +/- 6 versus +6 +/- 5, P < 0.05). However, only Maca-treated patients experienced a significant improvement in physical and social performance-related SAT-P score compared with the baseline (+7 +/- 6 and +7 +/- 6, both P < 0.05). In conclusion, our data support a small but significant effect of Maca supplementation on subjective perception of general and sexual well-being in adult patients with mild ED.

Maca study 3

This study was a 12-week double blind placebo-controlled, randomized, parallel trial[38] in which active treatment with different doses of Maca Gelatinizada was compared with placebo. The study aimed to demonstrate if effect of Maca on subjective report of sexual desire was because of effect on mood or serum testosterone levels. Men aged 21-56 years received Maca in one of two doses: 1,500 mg or 3,000 mg or placebo. Self-perception on sexual desire, score for Hamilton test for depression, and Hamilton test for anxiety were measured at 4, 8 and 12 weeks of treatment. An improvement in sexual desire was observed with Maca since 8 weeks of treatment. Serum testosterone and oestradiol levels were not different in men treated with Maca and in those treated with placebo (P:NS). Logistic regression analysis showed that Maca has an independent effect on sexual desire at 8 and 12 weeks of treatment, and this effect is not because of changes in either Hamilton scores for depression or anxiety or serum testosterone and oestradiol levels. In conclusion, treatment with Maca improved sexual desire.

Maca dosing as it relates to this product and the data presented

Notes: 1

The previously summarized Maca studies used 2000 mg, 2400 mg, and 1500/3000 mg of Maca powder per day. This product uses only 224 mg of Maca extract. The rationale is that Maca powder provides a specific amount of the active marker compounds known as macamides and macaenes, while the 270 mg of Maca extract meets and exceeds that same amount of these compounds. The position being taken is that the maca extract provides phytoequivalancy to the active marker compounds in maca powder. A further discussion of this will take place after the following summaries.

Notes: 2

Botanically speaking, the term “hypocotyl” referes to the stem of a germinating seedling, found below the seed leaves) and above the root. However, Maca’s fleshy hypocotyl is a fused hypocotyl and taproot, so in the case of this particular plant the terms hypocotyl and root are interchangeable.

Maca dosing summary 1

According to USP[39] “Benzylated alkamides frequently referred to as macamides occur in maca at concentrations of 0.0016%–0.0123% in the dried hypocotyls.” Also, “Alkamides such as macamides and macaenes may be considered marker compounds for standardization of maca. Total alkamide content varies from 0.15%–0.84%.”

Maca dosing summary 2

The hypocotyls of Maca display various colors ranging from white to black. This study[40] analyzed the concentrations of major secondary metabolites in Maca hypocotyls (and leaves of maca). The results were as shown:

Table 9: **Effects plant orgab (O, hypocotyl/leaf), type of terrain (T: -, never cultivated; +, cultivated with maca 2 - 3 years ago) and colour type (C: Y, yellow; P, pink; V, violet; L, lead-coloured) on the concentrations of macaene, macamides and phytosterols (μmolg^{-1} dry matter) and total phenolic compounds (mg gallic acid equivalent g^{-1}) in maca**

			Macaene	Macamide 1	Macamide 2	Total Macamides	Campesterol	β-sitosterol	Total phenols
	T		- +	- +	- +	- +	- +	- +	- +
Hypocotyls	Color	Y	6.69a 7.21	0.47b 0.49b	1.40 1.30b	1.87 1.79b	0.14 0.07	0.23 0.13	5.65 5.85
		P	- 8.24	- 0.62ab	- 2.15ab	- 2.77ab	- 0.01	- 0.14	- 5.72
		V	4.86b 6.83	0.79a 0.92a	1.80 2.28a	2.60 3.21a	0.08 0.06	0.14 0.17	4.61 5.21
		L	4.93ab 6.03	0.65ab 0.40b	1.94 1.78ab	2.59 2.18ab	0.07 0.05	0.01 0.10	4.89 4.91
	P[a]	C	* 	** **	X *	* **			X X
	P across terrains[b]	C	*	***	***	***			**
		T	*				*		
		CxT		X	X	X			
Leaves	Color	Y	0.66 0.83	0.09 0.07	0.06 0.02	0.15a 0.09	0.13 0.11	0.43 0.45	16.84 16.19
		P	- 0.86	- 0.08	- 0.02	- 0.10	- 0.12	- 0.34	- 15.38
		V	0.80 0.88	0.08 0.07	tr. 0.02	0.10 0.08ab	0.09 0.06	0.52 0.41	15.27 15.70
		L	0.53 0.71	0.07 0.07	tr. 0.05	0.07b 0.12	0.12 0.14	0.44 0.43	15.61 14.73
	P[a]	C	X 			*			

Leaves	P across terrains[b]	C							
		T							
		CxT			X	X			
		SEM[d]	0.213	0.320	0.062	0.087	0.016	0.025	0.298
		C	*	***	***	***			*
	Overall P[c]	T	**						
		O	***	***	***	***		***	***
		CxO	X	***	***	***			
		TxO	*						

- **LS means within organ carrying no common letter are significantly different (P < 0.05) Significance of effects:** *** P < 0.001; ** P <0.01; * P < 0.05; x P < 0.1 (approaching significance). -, missing data; tr, trace; i.e. detected under limit of quantification.
- [a] **P-values for each row applying Model 1:** $Yij = \mu + Cl + \varepsilon ij$.
- [b] **P-values for each variable within organ applying Model:** $Yijk = \mu + C\,i + T\,j + C \times T\,ij + \varepsilon ijk$.
- [c] **P-values for each variable applying Model 3:** $Yijkl = \mu + Ci + Tj + Ok + C \times Oik + T \times Oik + \varepsilon ijkl$.
- [d] **SEM**, standard errors of the mean.

The average macaene and total macamide content from the seven various colors of cultivated/never cultivated hypocotyls listed is 6.40 and 2.43, respectively. The combined total is 8.83, of which the percentage of macaenes and total macamides is 72.48% and 27.51%, respectively.

Maca dosing summary 3

According to Melnikovova et al[41] "Some of the aphrodisiac activities of maca have been related to lipidic fraction of maca, which contains mainly fatty acids and macamides (Zheng et al., 2000), therefore content of macamides is used as the main quality markers in maca products."

Maca dosing summary 4

According to Ganzera et al[42] "Even though the biologically active principles of Maca are not fully known, extracts rich in macamides and macaenes showed promising pharmacological activity. These compounds are therefore used as quality markers (some products are standardized for their content)..."

Notes: 3

To determine the highest level of macamides that might be providing efficacy in in the highest daily intake of maca powder from published research, the higher level of 0.0123% macamides found in the dried maca hypocotyls (per USP) will serve as the basis for calculation. Likewise, highest daily dose of 3000 mg maca powder from the Gonzales et al study will also serve as the basis for calculation. Therefore, 3000 mg X 0.0123% = 0.369 mg of macamides.

The Maca extract being used in this formulation is 0.6% combined macamides and macaenes (the individual breakdown of these compounds is not provided). According to the Clément et al study, of the combined total macaene and macamide content in Maca hypocotyls, 72.48% is macaenes and 27.51% is macamides. On that basis then, 0.43488% of the Maca extract is macaenes and 0.16506% is macamides. Therefore, if 224 mg of the Maca extract is used, it should yield about 0. 369 mg of macamides, which is the dose of macamides calculated to the be amount found in 3000 mg of maca.

Using these calculations, 224 mg of Maca extract is estimated to be equivalent to whole Maca powder based upon macamide content.

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