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Effects of Withania Somnifera Standardized Root Extract on Serum Testosterone and Inflammatory Markers in Healthy Adults peoples

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Abstract

Background: Withania Somnifera also known as Winter Cherry is a prominent herb in Ayurveda medicine, commonly used to promote youthful vigor, longevity, and overall wellbeing. This paper focuses on Withania Somnifera as an ergogenic aid and presents the results of a randomized, double-blind, placebo-controlled clinical study on the effects of Withania Somnifera administered as an adjuvant to a resistance training program, on serum testosterone and inflammatory markers in healthy adults.

Aim: To investigate the effects of Withania Somnifera root extract on serum testosterone and inflammatory markers in healthy adults following resistance training.

Methods: This was a prospective, randomized, double-blind, placebo-controlled study in 80 healthy male and female adults between 18–45 years of age after obtaining informed consent. Enrolled participants were randomly allocated to receive capsule Withania Somnifera root extract 300 mg, or an identical placebo capsule containing starch. Both treatments were given twice daily for with milk or water for 8 weeks. Study assessments included serum testosterone (total and free), CD4 cell counts, and serum levels of inflammatory markers (IL-6, TNF-Alpha), done at baseline and after 8 weeks.

Results: Four participants in the placebo and 3 from Withania Somnifera group did not complete the study, and analyses were done on 73 (36 Withania Somnifera, 37 placebo) participants data. The free serum testosterone levels increased ($p<0.0001$) in males receiving Withania Somnifera compared to placebo. The levels of IL-6 and TNF-alpha were less in the Withania

Somnifera group, but these were statistically insignificant (p>0.05).

Conclusion: Withania Somnifera root extract supplementation in combination with resistance training is effective in improving free testosterone levels in men but not in women.

Keywords: Withania Somnifera, Resistance Training, Testosterone, Inflammatory

Introduction

Resistance training is a specific conditioning technique in which individual works against a broad spectrum of resistive loads to enhance general health, fitness, and performance. A resistance training program comprises a set of well-organized exercises and aids in rhythmic muscular contraction and relaxation against external resistance. Repetition of actions allows the human body to adapt to such resistance and induces strength and endurance over time.

In addition to strength development, resistance exercise improves immunity, bone, and muscle health, reduces inflammation and the overall function of all organs. Furthermore, regular exercise alters biochemical and physiological processes.

Reductions in steroid hormones in men occur as age advances. Males experience reduction in testosterone levels at the rate of 1%–2% per annum after the age of 40 years. Testosterone influences sexual health, lean body mass, mental health, cognition, bone density, cardiovascular function, and metabolic activity. Low serum testosterone levels in men are strongly associated with increased morbidity and reduced quality of life.

Withania Somnifera, popularly known as Withania Somnifera is a plant that belongs to the Solanaceae family and that grows in the arid or semi-arid regions. Withania Somnifera is one of the most frequently used medicinal plants in the Ayurvedic system of complementary medicine for a varied range of ailments. It has been used to treat musculoskeletal conditions and improve general vitality and quality of life. It has been demonstrated in several animal studies that Withania Somnifera can influence the hypothalamic–pituitary–gonadal hormonal axis and increase testosterone concentrations.

The present study aims to examine the effects of a standardized Withania Somnifera extract (as an adjunct to resistance training) on exercise recovery, concentrations of testosterone and levels of inflammatory/ immune markers in healthy, active participants of either sex.

Materials and Methods

80 participants met inclusion criteria and were enrolled to participate. All of them underwent randomization and were allocated respective medicinal packs of either treatment or placebo in a ratio of 1:1. The clinical study protocol followed in this study is provided in detail in the following section.

Study Design

An 8 week-long randomized, double-blind, placebo-controlled, prospective clinical study was designed to assess the efficacy and safety of the Withania Somnifera root extract on muscle mass, muscle strength, cardiorespiratory endurance and muscle recovery in healthy individuals.

Recruitment and Randomization

The recruitment of participants was performed by circulating printed fliers in the purlieu of the gymnasium which served as the site of the training program. Subjects were randomly and equally allocated into two groups using stratified randomization (male and female) to receive either an Withania Somnifera root extract or a placebo. The randomization code was computer-generated through randomly permuted blocks. Within

each block, the numbers of participants allocated to each of the two treatment arms were equal. The test and placebo capsules were manufactured and packed in identical containers and labeled equivalently to ensure blinding. The study centers received numbered and sealed randomization envelopes that contained no information about treatment allocation.

Study participants

All the participants read and signed the informed consent form prior to final selection and enrollment in the study. Healthy adults of either sex aged between 18 and 45 years engaged in regular physical activity (gymnasium/ strength training exercise at least 3 months before screening for this study) were included. Another inclusion mandate was those willing to comply with the protocol and likely to be compliant with the prescribed product. Females of child-bearing age, agreed to use appropriate birth control measures were eligible for the study. Those who were using any supplements, medications, steroids, or hormonal contraceptive were excluded from study. Smokers (more than 10 cigarettes a day) alcoholics (consuming more than 14 grams of alcohol per day) were not eligible for study. Exclusion was also made if participants had history of any orthopedic injury or surgery in the past 6 months. Those with weight loss of >5kg in the previous 3 months, history of heart disease, bronchial asthma, diabetes, depression, stroke, or other neurological disorder were not considered. Participants with known hypersensitivity to Withania Somnifera were excluded.

Investigational products

High-concentration Withania Somnifera root extract, KSM-66, manufactured by Ixoreal BioMed, Los Angeles, California, USA and placebo were used for the treatment in capsulated form. This extract was produced using a water-based process that does not use alcohol or solvents and was standardized to a 5 % concentration of with anolides as measured by HPLC. Both types of capsules, i.e., Withania Somnifera root extract and the placebo were weighing 300 mg and were produced in a Good Manufacturing Practice (GMP) certified facility. All the capsules used in this study were identical in appearance, shape, color, and packaging. Both the intervention and placebo were cellulose-based vegetarian capsule. The batch number of the test product used was KSM/ VG/18/ 1020 and the chemo profile of the study product was confirmed by a third party, an independent laboratory. Participants were also instructed to store the capsules at room temperature.

Interventions

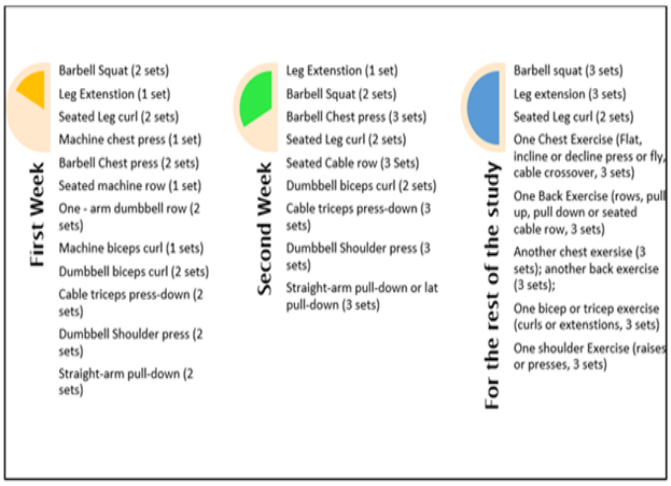
The treatment group received 300 mg of Withania Somnifera root extract twice daily, once shortly after awakening, and next before bedtime with milk or water for 8 weeks in capsule form. The control or placebo group received an identical dose of placebo capsules. Both the control and Withania Somnifera groups received a bottle of 60 pills at start of study and at 4 weeks. The pill count at 4 weeks allowed for a compliance check. All the participants were evaluated at baseline and after eight weeks with the outcome measures as described below. Data on safety and adverse effects were collected at the end of 8 weeks.

Study procedure

Informed consent was obtained from the participants during screening and enrollment. The participants were screened for brief medical history, general physical examination, and vital parameters. Once enrolled, Muscle strength, size measurements, cardiorespiratory endurance in form of VO_2 max were conducted at baseline (first day of training) and the end of the study after the completion of 8-weeks of training and supplementation. Resistance training exercise program

used in this study was focused on improving muscle strength, enhancing cardiorespiratory endurance, and increasing muscle mass. The various resistance exercises were chosen with the objective of training targeted muscle groups. Each participant was required to complete the training session every alternate day with a one-day complete rest per week. Therefore, participants were training 3 days per week. Each training session started with a warm-up of aerobic exercise of low intensity. Participants were instructed to perform maximum repetitions possible for each set until exhaustion. The exercise program is detailed in Figure 1, comprising exercises for week 1, week 2, and then the remainder of the study (weeks 3 to 8).

Figure 1: Exercise protocol



Clinical safety was assessed based on the frequency of adverse events reported by the participants /researcher and the PGATT (Physicians Global Assessment of Tolerability to Therapy) form. In addition to the subjective report, standard biochemistry tests were also performed along with measurement of vital signs.

Sample Size

The sample size was estimated using G*Power (Version 3.1.9.3). It was based on a previously published randomized controlled clinical study evaluating the effect of an Withania Somnifera root extract on muscle strength and recovery. A recently published systematic review on Withania Somnifera also supports this kind of improvement (effect size of 0.67) in physical performance. Considering the previous study, we hypothesized that Withania Somnifera treatment is better than placebo by an effect size of 0.6 with regards to change in the one-repetition maximum (1 RM) Chest press exercise after eight weeks. To detect an effect size = 0.6, in a two parallel group design (1:1), using independent Student t-test, with a 5 % risk of type 1 error (alpha) and 80% power, 40 subjects per group are required considering also a 10% drop-out rate. Thus, 80 healthy male and female subjects were recruited in the study.

Randomization and blinding

Following the screening, research coordinators randomized the eligible participants through computer-based predetermined randomization (Rando version 1.2) in a 1:1 ratio to receive either Withania Somnifera -root extract or placebo.

The randomization list had non-stratified blocks of the same length. The study was a double-blind one, i.e., doctors and participants were unaware of participants receiving the treatment and the placebo. The treatment and placebo medication packs were made tamper-proof and identical in appearance and weight.

After the participants were enrolled, they were provided with the medication pack having the corresponding serial number only. During data collection, the research coordinators, the study investigators, and the attending care personnel were not allowed to access the randomization codes and allocations. Unblinding was allowed only after completion of the entire data collection or in case of any serious adverse event. The randomization codes were covered in aluminum foil and placed in a separate sealed envelope for each patient.

Data analysts and responsible personnel of reporting study results were also unaware of the identity of the study groups. The data were double-entered and blinded to the statisticians as well.

Study outcomes

Serum Testosterone

Total and free blood testosterone serum levels were measured twice: at the study commenced and at the end of study. The blood withdrawal was timed to be between two hours and three hours of each subject's regular waking time, and prior to any substantial physical activity, in order to minimize the effects of the natural diurnal variation in testosterone level. The 20 ml blood withdrawn from an antecubital vein, punctured with a 20-gauge disposable needle connected to a Vacutainer tube. The blood serum samples were analyzed by an ELISA (enzyme-linked immunosorbent assay).

Immune markers

Resistance training exercise can increase in CD3, CD4, CD8 cells count. Test drug can enhance the effect of exercise.

Inflammatory markers

Resistance training can cause decrease inflammatory markers like IL-6 and TNF-Alpha. Test drug can enhance the effect of exercise.

Muscle recovery

Muscle recovery refers to the reduction in exercise-induced muscle damage over time. The level of creatine kinase, a protein, in the blood is a commonly used measure of muscle damage because this protein is specific to muscle tissue. The body on its own repairs such damage over 1 to 10 days and serum creatine kinase return to baseline levels. Serum creatine kinase was measured at 24 h and at 48 h after the end of the first exercise session, and the last exercise session approximately 8 weeks later, from 20 ml blood draws using a 20-gauge disposable needle and a Vacutainer setup. The creatine kinase level was determined in a commercial laboratory using enzymatic analysis tracking nicotinamide adenine diphosphopyridine (NADPH). The increase in creatine kinase from the 24-h point to the 48-h point can be taken as a biomarker of recovery in that a smaller increase corresponds to faster stabilization of creatine kinase level and hence faster recovery of muscle tissue from exercise-induced damage.

Statistical Analysis

All the data were entered into two separate Microsoft Excel spreadsheets (i.e., manual double-key data entry), and compared to assure data quality before analysis. Then, all relevant statistical calculations were completed using Medcalc® (version 20.011). The efficacy analysis was done on the modified intention to treat (ITT) anonymized dataset (n=73), whereas the safety analysis was done on an intention to treat anonymized dataset (n=80). A summary statistic for all the parameters was performed and the results presented as mean with standard deviation (SD) for continuous variables. Categorical and discrete data are presented as counts with percentages. Change in values form baseline to 8 weeks are computed from and compared between the two groups using unpaired t-test. Since the baseline values were not similar for gender, BMI, chest circumference, CD4 counts, and serum testosterone (total and free), the effect of these parameters on the different parameters with respect to the change from baseline was analysed using analysis of covariance (ANCOVA). The dependent variables were the change from baseline in all parameters, the random variable was the treatment (KSM-66 or placebo), whereas the covariates were gender, BMI, chest circumference, CD4 counts, and serum testosterone (total and free). Adjusted means with 95% confidence intervals, and effect size

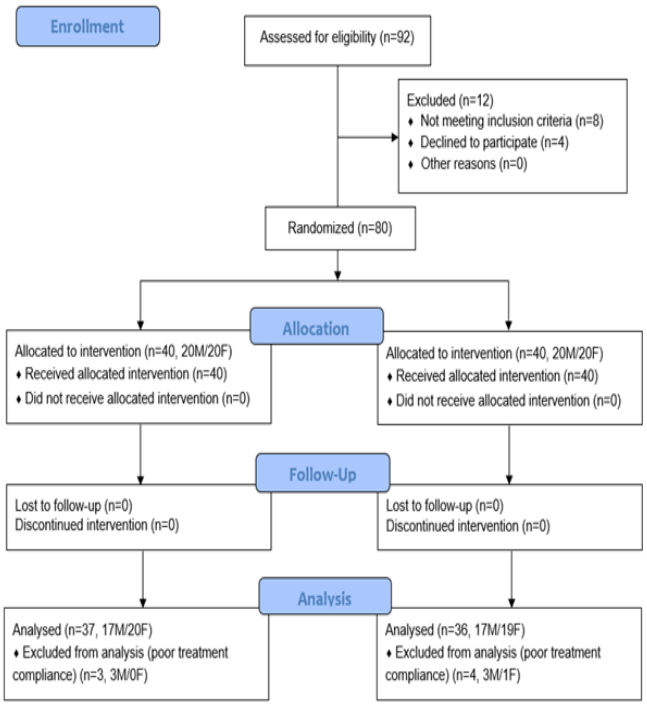
(Cohen's d) are presented for change from baseline values for the different parameters. The criteria for effect sizes are based on the standard criteria (<0.2, trivial; 0.2–0.6, small; 0.6–1.2, moderate; 1.2–2.0, large; 2.0–4.0, very large; and >4.0, nearly perfect).

Normality assumptions were checked on all variables using a one-sample Shapiro-Wilk test. Non-normal distributions were transformed using log10. An unpaired t-test was used to assess baseline differences and the between-group differences. Within-group effects were compared using a paired t-test. P-values were reported to all parameters with Bonferroni correction, where applicable to adjust for multiple comparisons. A p-value of less than 0.05 was considered the threshold to claim statistical significance.

Results

The study was initiated with 80 participants, 40 in each arm. Later, as the study progressed, 33 participants complied with the necessary treatment requirements, i.e., consumed capsules, for 8 weeks. During the study course, 3 and 4 participants dropped out of the treatment and placebo group, respectively, due to noncompliance. No participant withdrew from the study due to self-reported adverse effects because of the capsule intake (Figure 2). The final per-protocol analysis was done using the data of the 73 participants.

Figure 2: CONSORT flow chart



Participant Demographics

The mean age of participants was calculated using a per-protocol analysis of the 73 participants enrolled in the study. The mean (SD) age of the experimental and control group was documented as 25.22 (4.38) and 23.67 (4.33), respectively.

The deviation among the participants' age was less in both the groups; thus, we had homogeneous study participants of almost equivalent age groups. The demographic characteristics and baseline features of the two groups are represented in Table 1.

Table 1: Baseline demography and vital parameters in efficacy dataset.

		KSM66 (n=37)	Placebo (n=36)	Unpaired t-test
		M=17 / F=20	M=17 / F=19	
		Mean (SD)	Mean (SD)	p
Age (yrs.)	Male	25.18 (4.38)	23.35 (3.87)	0.165
	Female	25.25 (4.49)	23.95 (4.79)	0.528
	Total	25.22 (4.38)	23.67 (4.33)	0.155
Pulse (per min.)	Male	78.41 (3.37)	77.65 (5.13)	0.484
	Female	79.05 (4.52)	76.95 (2.12)	0.264

	Total	78.76 (4.00)	77.28 (3.81)	0.213
Systolic BP (mm Hg)	Male	126.76 (5.95)	124.59 (4.49)	0.589
	Female	126.00 (5.24)	127.11 (5.54)	0.476
	Total	126.35 (5.51)	125.92 (5.16)	0.321
Diastolic BP (mm Hg)	Male	79.18 (3.52)	78.18 (4.30)	0.936
	Female	78.30 (4.59)	79.63 (4.37)	0.439
	Total	78.70 (4.10)	78.94 (4.34)	0.165
BMI (kg/sq.m)	Male	23.52 (1.05)	22.48 (1.87)	0.059
	Female	23.02 (0.94)	22.73 (1.43)	0.382
	Total	23.25 (1.01)	22.62 (1.63)	0.040

Table 2: Inflammatory markers and serum testosterone in two groups at baseline

		KSM-66 (n=37)	Placebo (n=36)	Unpaired t-test
		M=17 / F=20	M=17 / F=19	
		Mean (SD)	Mean (SD)	p
Free Testosterone (ng/dL)	Male	13.76 (2.79)	13.84 (2.22)	0.197
	Female	0.40 (0.16)	0.38 (0.15)	0.133
	Total	6.54 (7.00)	6.74 (6.98)	0.607
Total testosterone (ng/dL)	Male	4.51 (1.13)	4.28 (1.34)	0.978
	Female	0.40 (0.16)	0.38 (0.15)	0.959
	Total	2.29 (2.21)	2.22 (2.17)	0.994
Sr CK (IU/L)	Male	139.26 (17.38)	136.30 (19.85)	0.998
	Female	123.81 (31.15)	132.72 (20.72)	0.536
	Total	130.91 (26.59)	134.41 (20.11)	0.610
CD3 (cell/µL)	Male	1384.41 (65.85)	1343.00 (82.02)	0.844
	Female	1332.90 (65.22)	1297.89 (79.63)	0.218
	Total	1356.57 (69.64)	1319.19 (82.82)	0.544
CD4 (cell/µL)	Male	858.18 (62.349)	825.35 (75.014)	0.042
	Female	813.15 (27.744)	782.05 (38.756)	0.021
	Total	833.84 (51.492)	802.50 (61.851)	0.006
CD8 (cell/µL)	Male	526.24 (37.933)	517.65 (36.455)	0.489
	Female	519.75 (54.930)	515.84 (67.086)	0.907
	Total	522.73 (47.357)	516.69 (54.064)	0.639
CD4/CD8 Ratio	Male	1.64 (0.19)	1.60 (0.19)	0.212

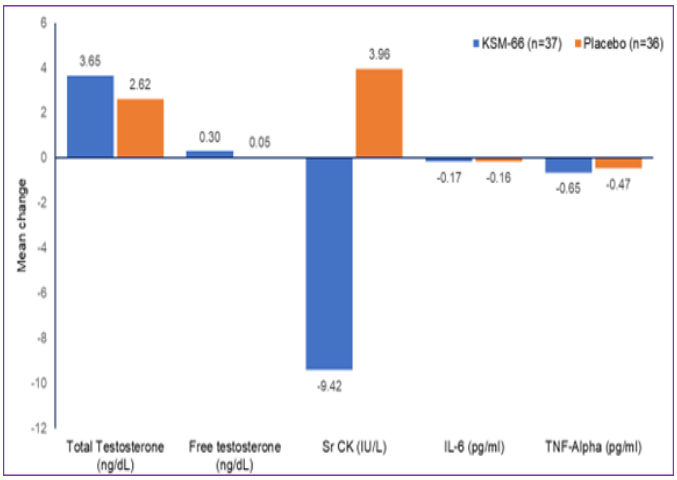
	Female	1.58 (0.18)	1.54 (0.23)	0.499
	Total	1.61 (0.18)	1.57 (0.21)	0.372
IL-6 (pg/ml)	Male	3.05 (0.94)	3.18 (1.19)	0.665
	Female	2.40 (0.51)	2.60 (0.92)	0.379
	Total	2.70 (0.80)	2.88 (1.08)	0.896
TNF-Alpha (pg/ml)	Male	3.43 (0.94)	3.56 (1.19)	0.665
	Female	2.80 (0.52)	2.98 (0.92)	0.429
	Total	3.09 (0.80)	3.26 (1.08)	0.933

Table 2: Change from baseline at 8 weeks in two groups (Univariate tests)

		KSM-66 (n=37)	Placebo (n=36)	Unpaired t-test
		M=17 / F=20	M=17 / F=19	
		Mean (SD)	Mean (SD)	'p'
Free Testosterone (ng/dL)	Male	0.631 (0.552)	0.105 (0.096)	<0.0001
	Female	0.006 (0.006)	0.003 (0.003)	0.053
	Total	0.319 (0.499)	0.054 (0.085)	0.001
Total testosterone (ng/dL)	Male	7.184 (26.062)	5.922 (4.959)	0.833
	Female	0.282 (0.330)	0.152 (0.118)	0.106
	Total	3.733 (18.525)	3.037 (4.530)	0.818
Sr CK (IU/L)	Male	-7.795 (15.706)	3.725 (10.797)	0.010
	Female	-10.290 (10.299)	4.490 (9.419)	<0.0001
	Total	-9.043 (13.170)	4.108 (10.008)	<0.0001
CD3 (cell/µL)	Male	-5.250 (14.714)	7.300 (43.918)	0.233
	Female	-6.350 (12.853)	4.000 (26.012)	0.119
	Total	-5.800 (13.648)	5.650 (35.666)	0.062
	Total	-2.500 (10.278)	4.050 (17.088)	0.041
CD8 (cell/µL)	Male	-3.300 (7.948)	-1.800 (14.902)	0.693
	Female	-3.300 (7.948)	-0.700 (23.015)	0.636
	Total	-3.300 (7.845)	-1.250 (19.146)	0.533
CD4/CD8 Ratio	Male	0.005 (0.039)	0.010 (0.064)	0.768
	Female	0.000 (0.000)	0.015 (0.067)	0.324
	Total	0.003 (0.028)	0.013 (0.065)	0.372
IL-6 (pg/ml)	Male	-0.175 (0.072)	-0.155 (0.170)	0.631
	Female	-0.160 (0.088)	-0.155 (0.224)	0.926
	Total	-0.168 (0.080)	-0.155 (0.196)	0.710

TNF-Alpha (pg/ml)	Male	-0.515 (0.254)	-0.435 (0.131)	0.218
	Female	-0.740 (0.751)	-0.500 (0.169)	0.171
	Total	-0.628 (0.565)	-0.468 (0.153)	0.088
Within group changes (baseline versus week 8) significant at p<0.05 (paired t-test)				

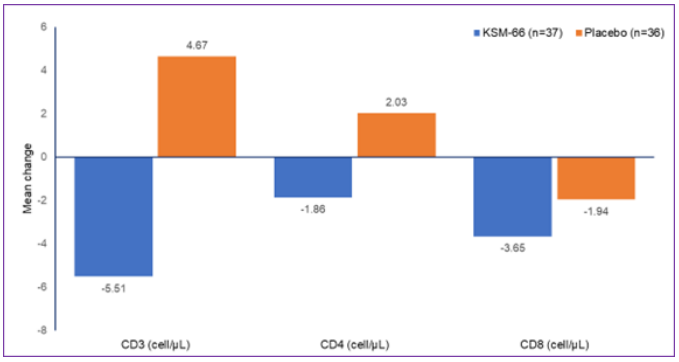
Figure 3: Mean change from baseline in laboratory parameters



Serum testosterone

Over the eight weeks, there was a significant increase in free testosterone level in the Withania Somnifera treatment group in males relative to the placebo group (p<0.0001). The level of total testosterone was greater with Withania Somnifera supplementation than with the placebo, the numbers are not detectable as statistically significantly different (Figure 4).

Figure 5: Mean change from baseline in CD4, CD3 and CD8 cell counts.



Immune cells & Inflammatory mediators

Reduction in levels of immune cells-CD3, CD4, CD8 cells has been observed in test group but was not statistically significant (Figure 4). Reduction in levels of inflammatory marker (IL-6 and TNF-Alpha) was less with Withania Somnifera compared to placebo, but these were not statistically significant (Table 3).

Serum creatine phosphokinase (CPK)

CPK levels were low in both the Withania Somnifera group and the placebo group, likely because of muscle tissue getting accustomed to the training regimen and developing greater integrity to resist any damage. Comparing the Withania Somnifera group and the placebo group, the results showed that muscle damage was substantially lower in the Withania Somnifera group. Total Serum creatinine kinase was reduced to significant level in test group (p<0.0001) as compared to placebo group (Figure 3).

Adverse events and safety parameters

The participants did not report any adverse events during the study period. Additionally, we conducted an array of routine clinical tests such as hematology, renal function, liver function, and thyroid function tests to evaluate the safety and tolerability of Withania Somnifera root extract supplementation in participants. None of the parameters in the study samples showed any abnormal changes at the end of the intervention.

Discussion

The present study focused to assess the impact of an Withania Somnifera root extract supplementation on resistance training adaptations such as serum

testosterone and inflammation (immune response). In healthy active adults, Withania Somnifera supplementation significantly increased testosterone levels. Also, it significantly attenuated the increases in serum creatine kinase levels and inflammatory mediators due to resistance training.

Withania Somnifera accelerates muscle recovery that is a collateral effect of resistance training. Compared to the placebo subjects, the subjects receiving Withania Somnifera also had significantly greater reduction of exercise-induced muscle damage as indicated by the reduction of serum creatinine kinase. It was also assessed by inflammatory markers. These objective and subjective markers reported significant improvement in muscle recovery. In other words, all the trained adults in the Withania Somnifera group are more likely than those in the placebo group to report that their muscle soreness was alleviated. This kind of benefit will be important for athletes who want to increase the frequency of training without the delayed onset of muscle soreness being the limiting factor.

Some studies have suggested that Withania Somnifera treatment is associated with increased serum testosterone in men. We did observe a statistically significant difference in the free testosterone in the Withania Somnifera group (male) compared to the placebo group, whereas there was no change in total and free testosterone in female groups. As far as we are concerned, this is the first study that measured free testosterone improvement with the Withania Somnifera root extract. The effects of Withania Somnifera in increasing levels of testosterone have been demonstrated in men undergoing resistance training, which leads to muscle growth. Testosterone production by testes is regulated by gonadotropin-releasing hormone (GnRH). It has been demonstrated in vitro and animal studies that Withania Somnifera enhances the activity of GnRH leading to increase in testosterone concentrations.

The present study demonstrated decrease in inflammatory markers IL-6 & TNF-α as also stated in a study done by Abudubari Sikandar et al with hot water extract of Withania Somnifera roots using the human keratinocyte cell line. Probable mechanism is Withania Somnifera significantly inhibited mRNA expression of inflammatory cytokines, including interleukin (IL)-8, IL-6, tumor necrosis factor (TNF-α), IL-1β and IL-12, and promoted the mRNA expression of the anti-inflammatory cytokine transforming growth factor (TGF)-β1 [20].

Suppression of inflammation by testosterone were observed in patients with coronary artery disease, prostate cancer and diabetes mellitus through the increase in anti-inflammatory cytokines (IL-10) and the decrease in pro-inflammatory cytokines (IL-1β, IL-6, and TNF-α) in a study done by Mohamad et al, through its influence on testosterone.

The mechanism for improvement in muscular strength appears to be increase in anabolic hormone (serum testosterone), which could be related to structural similarities with anolides (the major ingredients of Withania Somnifera root extract). However, since the female group did not show increased testosterone, it can be hypothesized that other factors such as anti-inflammatory and antioxidant effects also contribute significantly. In addition, as previously shown, reduced stress and improved sleep associated with Withania Somnifera does help perform better even though it was not measured in this study. Thus, it could be a safer alternative to improve and maintain physical performance.

Conclusions

Withania Somnifera root extract supplementation for 8 weeks in combination with resistance training demonstrated increase in free testosterone in healthy males with mean age 25 but not in females. The study also indicated that the participants have tolerated the Withania Somnifera root extract well. Further studies with larger sample sizes are required to substantiate the current findings. Future studies utilizing larger sample sizes, varying treatment doses and duration, are necessary to further understand the potential therapeutic and adaptogenic effects of Withania Somnifera.

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