10-28-2016

Effects of Eurycoma Longifolia and Maca Root on Libido and Mood in Premenopausal Women with Hypoactive Sexual Desire Disorder: A Case Study Design

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EFFECTS OF EURYCOMA LONGIFOLIA AND MACA ROOT ON LIBIDO AND MOOD IN PREMENOPAUSAL WOMEN WITH HYPOACTIVE SEXUAL DESIRE DISORDER: A CASE STUDY DESIGN

by

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A Thesis

Submitted in Partial Fulfillment of the

Requirements for the Degree of

Master of Science

Major: Health and Sport Sciences

The University of Memphis

December 2016

ABSTRACT

The aim of this study was to determine if *Eurycoma longifolia* in combination with maca root could be effective in treating women with hypoactive sexual desire disorder. Using a randomized, placebo-controlled, cross-over, case study design we evaluated the hypothesis that *E. longifolia* and maca root (3400 total mg/day) supplementation by premenopausal women with hypoactive sexual desire disorder would improve mood, libido, overall quality of life, muscular strength, and aerobic capacity. *E. longifolia* and maca root supplementation had little effect on the measured variables. It did not improve overall well-being and libido but had a slight effect on decreasing feelings of tension and anxiety, as well as increasing feelings of energy and physical appearance. *E. longifolia* and maca root supplementation did not elicit positive changes in muscular strength or aerobic capacity. Further investigation using a larger sample size may evaluate the aphrodisiac properties of *E. longifolia* and maca root.

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Introduction

In the presence of low testosterone, men and women may experience hypoactive sexual desire disorder (HSDD), which is characterized as a lack or absence of sexual fantasies and desire for sexual activity (Leiblum, Koochaki, Rodenberg, Barton, & Rosen, 2006). HSDD affects a higher percentage of women than men, and it affects women at all reproductive stages (Sowers, Beebe, McConnell, Randolph, & Jannausch, 2001). HSDD is prevalent among younger surgically postmenopausal women (26%) but can also be found in premenopausal women (14%) and naturally menopausal women (9%) (Sowers et al., 2001). Many women experience distress due to the lack or decline of sexual desire, which may affect personal relationships. Low testosterone levels in women may have negative impacts on body composition (Gasperino, 1995), bone health (Brincat et al., 1985), libido (Goldstat, Briganti, Tran, Wolfe, & Davis, 2003), skin appearance (Ng Tang Fui et al., 2013), and overall health (Pluchino et al., 2013). Many of the above problems lead to a further loss of sexual interest, as women experience decreased self-esteem based on their thoughts of poor personal physical appearance.

Dietary and herbal supplementation is an alternative to pharmaceutical products such as the transdermal patches and gels. One herbal supplement, *Eurycoma longifolia*, has been of great interest with research studies conducted in animals (Ang & Sim, 1997, 1998) and humans (Hamzah & Yusof, 2003; Henkel et al., 2014; Muhamad, Chen, Ooi, & Abdullah, 2009; Muhamad, Chen, Ooi, Abdullah, & Lam, 2010; Sarina, Zaiton, Aminudin, Nor, & Azizol, 2009; Tambi, Imran, & Henkel, 2012). The roots of *E. longifolia* are of particular interest, as chemical compounds have been extracted from the roots. These compounds have anti-tumor promoting

and anti-parasitic properties, as well as the ability to increase circulating testosterone (Bhat & Karim, 2010). The use of an *E. longifolia* supplementation in both elderly men and women (57-72 years of age) promotes increases in muscular strength and circulating testosterone (Henkel et al., 2014). Women experienced a 49% increase in total testosterone (0.35 ± 0.17 to 0.52 ± 0.30 ng/mL) and a 32% increase in free testosterone (0.50 ± 0.24 to 1.11 ± 0.66 pg/mL). Men also experienced a 15% significant increase in total testosterone (3.84 ± 0.79 to 4.42 ± 1.15 ng/mL) and a 61% increase free testosterone (5.20 ± 1.60 to 8.38 ± 2.18 pg/mL).

Additionally, maca root, has shown the potential to be an aphrodisiac in animals (Zheng et al., 2000) and humans (Brooks et al., 2008). Maca, or *Lepidium meyenii*, is a plant indigenous to the Andes Mountains, and extracts of the root have been used to improve sexual function for centuries (Shin, Lee, Yang, Lim, & Ernst, 2010). Phytosterols or phytoestrogens, which are two compounds found in maca, may be the mechanism for improving sexual function (Shin et al., 2010). In fact, when postmenopausal women were treated with 3.5g per day for 6 weeks of powdered maca, sexual dysfunction was reduced and psychological symptoms were improved (Brooks et al., 2008).

To date, it is has not been determined if premenopausal women with hypoactive sexual desire disorder can supplement with *E. longifolia* and maca root with positive outcomes. Since 14% of premenopausal women suffer from HSDD, understanding the effects of an herbal supplement may be a novel way to treat HSDD in women. Therefore, the purpose of this study was to determine the effect of *E. longifolia* and maca root on subjective feelings and libido in addition to muscle strength and aerobic capacity in premenopausal women. We hypothesized that supplementation of *E. longifolia* and maca root would improve subjective feelings such as mood, libido, and overall quality of life. The improved subjective feeling would be indicated via

scores on the psychological general well-being index and the brief profile of female sexual function. Secondarily, we hypothesized that a potential elevation in testosterone noted with treatment may lead to an increase in aerobic capacity (via treadmill testing) and muscle strength (via grip strength).

Methodology

Subjects

Three women with hypoactive sexual desire disorder were recruited to participate in this study. The study was exploratory in nature, as no studies have examined the effects of a botanical agent on premenopausal women with HSDD. Therefore, we had no empirical data to use in calculating a sample size based on power analysis. Moreover, at this stage of investigation the qualitative outcomes (subjective feelings of mood, quality of life, and libido) are of greater importance than potential quantitative outcomes (muscle strength and aerobic capacity).

Women were screened into the study using the brief profile of female sexual function. A score of less than 20 out of a possible 35 was needed to be classified as having hypoactive sexual desire disorder. Subjects needed to be in good overall health, not current smokers, and without a history of cardiovascular or metabolic disease. Subjects were not using hormonal replacement therapy (including birth control) or dietary supplements designed to increase testosterone. Subjects were not pregnant or nursing and a urine pregnancy test was administered to all subjects. Subjects were not diagnosed with depression or had a history of sleep disorders, as these conditions are known to negatively impact testosterone levels (Andersen & Tufik, 2008; Carnahan & Perry, 2004). Subjects were in a stable, sexually active relationship for a minimum of the past one year. Health history, medication and dietary supplement usage, and physical activity questionnaires were completed by all subjects and reviewed by an investigator to

determine eligibility. Subjects were informed of all procedures, potential risks, and benefits associated with the study through both verbal and written form. The University Institutional Review Board for Human Subject Research reviewed and approved the study procedures.

Initial Laboratory Visit: Screening Visit

During the initial lab visit, subjects completed all necessary paperwork, inclusive of the informed consent, health history and physical activity questionnaires. Subjects' heart rate, blood pressure, height, weight, waist, and hip circumference were measured and recorded. Subjects were given a urine pregnancy test. Subjects practiced the hand grip strength protocol in order to be familiarized with the protocol on test visits. They walked on a treadmill for 3-6 mins in order to be familiarized to the treadmill to be used to in the test visits. Subjects then scheduled their subsequent lab visits, as well as received all study instructions and a daily diary to complete.

Supplementation

Following the above assessments on day 1, subjects were assigned in a double blind manner, using a crossover design, to both the supplement and placebo. Each condition (two capsules twice daily) was ingested daily for a period of 28 days. The supplementation periods began at the start of the subject's menstrual cycle (within the first 3 days). Supplementation consisted of 400 mg of a standardized water-soluble extract of *E. longifolia* with 3g of maca root. The supplement was provided to each subject in a capsule bottle and produced under Good Manufacturing Practices by a dietary supplement manufacturer. Capsules were of similar appearance and provided to subjects in unlabeled bottles. Subject compliance to supplement intake was determined based on remaining capsules left in the bottles upon return.

Test Visit Procedures

Following the screening visit, subjects returned to the lab (before supplementation and after 28 days of supplementation for each condition) to complete the assessments indicated below. On each occasion, subjects reported to the lab in a 10-hour overnight fasted state without having consumed alcohol or caffeine within the past 24 hours. Subjects were instructed to obtain at least 7 hours of sleep during the night prior to testing. Subjects did not perform strenuous physical exercise within the past 24 hours.

Subjects reported to the lab in the morning hours (i.e., 6:00 – 9:00am) and the time of day was matched for each lab visit. On each visit, subjects completed the psychological general well-being index, the brief profile of female sexual function, another general questionnaire, hand grip strength test, and a maximal graded exercise test.

Psychological General Well-Being Index

The first questionnaire that was completed during each visit was the psychological general well-being index (PGWBI). The PGWBI is a self-administered quality of life assessment (22 total items), which has been validated (Dupuy, 1984). Subjects rated feelings of anxiety, depressed mood, positive well-being, self-control, general health, and vitality. The PGWBI can be found in appendix A.

The Brief Profile of Female Sexual Function

The second questionnaire administered is referred to as the brief profile of female sexual function (B-PFSF). The questionnaire scored sexual desire, arousal, orgasm, and problems affecting sexual function. The B-PFSF was designed to be a self-administered screening tool and is a valid tool in discriminating between women with or without hypoactive sexual desire disorder (Rust et al., 2007). According to women, the B-PFSF is easy to fill out and covers

relevant aspects of sexual function. Scores can be from 0 – 35 and any score below 20 was classified as having HSDD. This form can be found in appendix B.

Weekly Diary

The subjects were instructed to record their subjective feeling of energy levels, libido, and mental outlook using a Likert scale. There was also a space included for the subjects to provide comments as needed. This form was created to evaluate subjects' subjective feelings over the course of supplementation. The weekly diary can be found in appendix C.

Questionnaire

Due to the potential influence of *E. Longifolia* and maca root on subjective feelings, subjects completed a questionnaire on the morning of each test day. Using a scale of 1-10, with 1 representing the lowest rating and 10 representing the highest rating, subjects rated a number of variables pertaining to overall health with regards to how they felt over the past four weeks. The questionnaire can be found in appendix D.

Hand Grip Strength Test

For the hand grip strength test, the participant was instructed to take a standing position with arms at their side, not touching their body. The elbow was slightly bent. The test was conducted using the dominant hand. The subject squeezed the dynamometer with as much force as possible for approximately 3 s. Three trials were conducted with 30 s of rest between each trial to avoid the effects of muscle fatigue. If the difference between any two measures is more than 3 kg, another trial was conducted. In this case, the outlier was not used in data analysis.

Aerobic Fitness Test

A maximal graded exercise test (GXT) was conducted using a treadmill. The test began at a speed of 3.0 mph with 0% grade. It progressed either in speed or grade every two mins until

fatigue. The test continued until one of the following occurred, in accordance with the guidelines of the American College of Sports Medicine (ACSM): subject could no longer continue due to fatigue and requests to stop, or subject showed signs/symptoms that indicated the test is stopped. These include signs of distress beyond what is typical during acute exercise bouts (e.g., unusual and rapid breathing patterns, severe shortness of breath, profuse sweating, cold and clammy skin), lightheadedness or dizziness, or moderate to severe chest pain. Heart rate was monitored during testing using a heart rate monitor. The Borg scale of exertion was used to allow subjects to indicate their level of perceived work. Subjects were allowed an active cool-down period (e.g., slow speed walking) for several minutes until their heart rate falls below 120 beats per min or stabilizes. We have used this same protocol in recent studies at it works well for the intended purpose. Both sedentary and active individuals can use this same protocol, as the initial workload is simply a slow walk. The sedentary individuals simply become fatigued earlier than the active individuals.

Dietary Intake and Physical Activity

Subjects were instructed to consume their usual diet and to record dietary intake during the 48 hours prior to each test day. Diets were examined for macro- and micro-nutrient content using food analysis software, as micronutrient and macronutrient intake may affect hormone levels. Physical activity should have remained similar for subjects throughout the study.

Results and Discussion

For this study, we had initially planned on recruiting a total of 15 subjects. However, there were issues recruiting subjects, as well as keeping subject enrolled for the duration of the study. Three subjects successfully completed all aspects of the study, and therefore the results of the three subjects are presented below using a case study format.

Subject 1

One subject was a 30-year-old Caucasian female, who has been married for 6 years. She is 168.5 cm tall, weighs 82.6 kg, has a resting heart rate of 72 beats per min, and her resting blood pressure was 132/94 mmHg. She had no history of cardiovascular disease, metabolic disease, depression, anxiety, or sleep disorders. She was in a sexually active relationship but not currently using any birth control, nor was she pregnant or nursing. She is not a current smoker. For aerobic training, she has been completing two 45 mins sessions per week with a self-described intensity of "somewhat hard" for a total of 10 years. She does not partake in recreational sports or in anaerobic training.

The psychological general well-being index (PGWBI) was used to assess changes in quality of life with supplementation. For the placebo condition, the score increased 13 points while the score decreased 6 points for the *E. longifolia* and maca root (EL+MR) condition, (Figure 1). The decrease in overall well-being does not agree with findings of previous research as both *E. longifolia* and aca root have been shown to increase overall well-being (Brooks et al., 2008; Talbott, Talbott, George, & Pugh, 2013). The age of the subject is lower than the age of subject in the previous research, so the difference in age may be the reason the subject did not respond positively to supplementation.

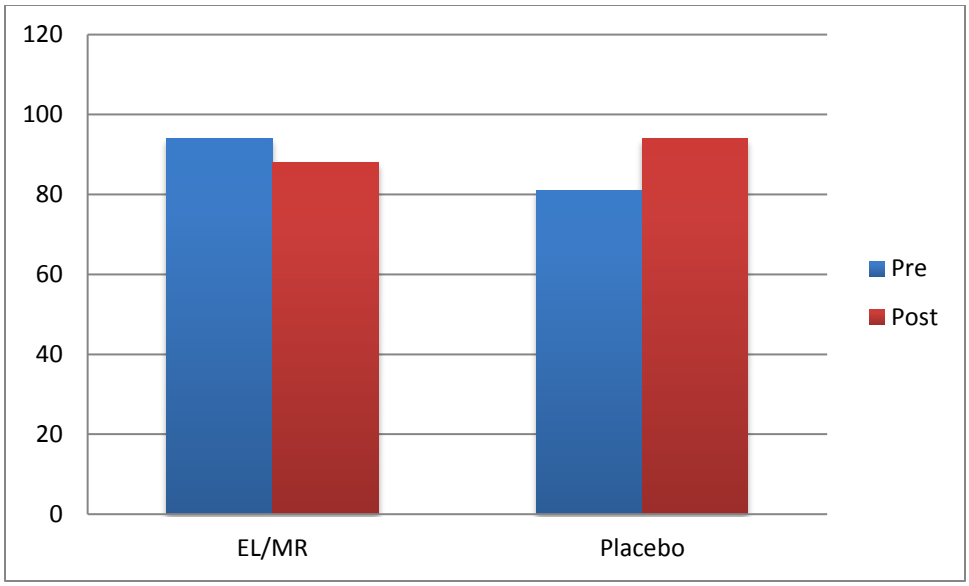

Figure 1. Psychological General Well Being Index for Subject 1

The brief profile of female sexual function (B-PFSF) was used to determine sexual desire, arousal, orgasm, and problems affecting sexual function after supplementation. For the placebo condition, the B-PFSF score increase by 2 points while it dropped by 3 points for the EL+MR condition (Figure 2). These results are similar to those seen in the PGWBI. The decrease in libido does not agree with findings of previous research as both *E. longifolia* and maca root have been shown to increase libido (Brooks et al., 2008; Talbott et al., 2013). The results from the PGWBI and the B-PFSF show that EL+MR supplementation did not have a positive effect in this subject. One reason this subject may have not seen an increase in either the PGWBI or the B-PFSF is the stressors from completing exams and other projects while enrolled in college courses. The compounds in the EL+MR supplement may not have able to influence libido and overall well-being because the potential negative effects of stress in the subject.

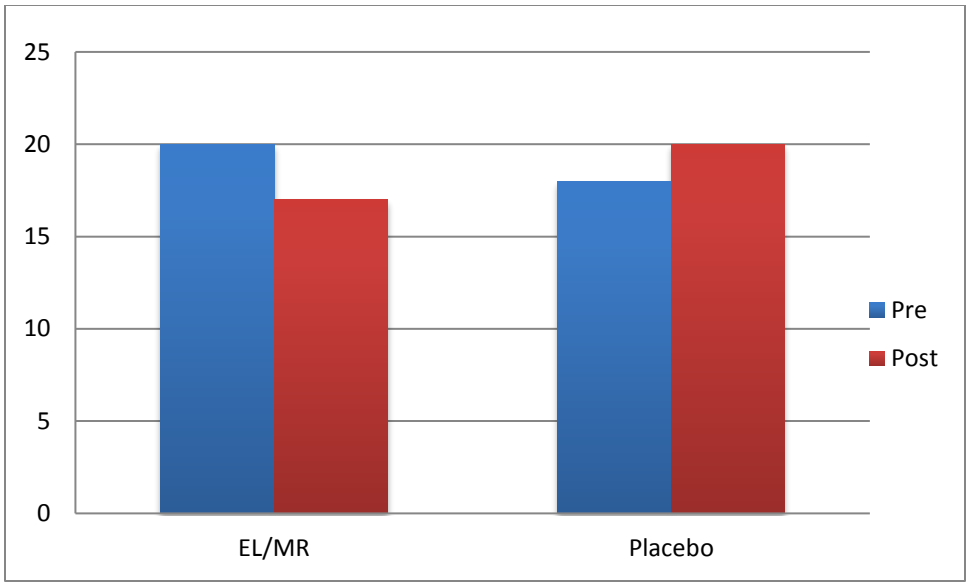

Figure 2. Brief Profile of Female Sexual Function for Subject 1

The weekly diary was used to evaluate subjects' subjective feelings of energy levels, libido, and mental outlook over the course of supplementation. For the subject, the diary energy mean, the diary libido mean, and the diary outlook mean were higher during the placebo condition than during the EL+MR condition (Figure 3). The results from the weekly dairy follows the same trend as the results from the PGWBI and the B-PFSF.

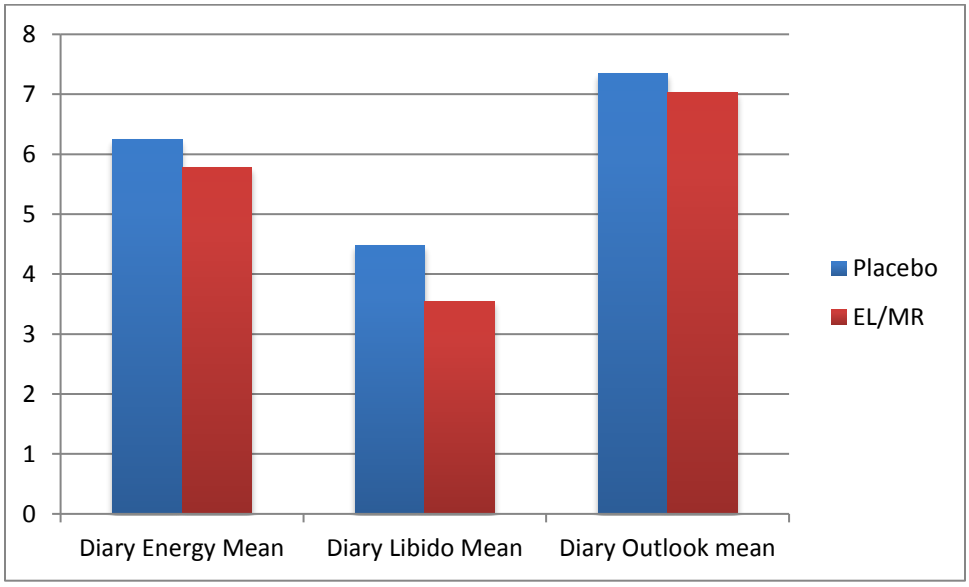

Figure 3. Weekly Diary Means for Subject 1

The general questionnaire was used to determine changes in a number of variables pertaining to overall health with supplementation. In regards to the general questionnaire, the subject noted no changes in alertness for either of the conditions with a rating of 8 at each time point (Table 1). For energy, there were increases seen for the placebo condition and the EL+MR condition. In terms of aggressiveness, this subject experience an increase in the placebo condition, but ratings did not change for the EL+MR condition. Increases in vitality were observed for the EL+MR condition while the ratings remained unchanged for the placebo condition. The only changed noted by the subject regarding libido was seen in the EL+MR condition. The lowest rating for sleep quality was seen at the end of the EL+MR condition. Mental outlook decreased for the EL+MR condition and remained unchanged for the placebo condition. Mental clarity was similar to mental outlook as ratings decreased in the EL+MR condition and remained unchanged in the placebo condition. This subject rated physical appearance highest in the EL+MR condition and did not note any changes with the placebo condition. Rating of subjective muscle strength increased following placebo supplementation but decreased following the EL+MR condition. Lastly, she had no change in ratings of tension and anxiety in the placebo condition, and noted an increase with the EL+MR condition. Again, these results are similar to those found with the PGWBI, the B-PFSF, and the weekly dairy.

Table 1

General Questionnaire for Subject 1

	Placebo		**EL/MR**	
	Pre	Post	Pre	Post
Alertness	8	8	8	8
Energy	5	6	6	8
Aggressiveness	3	6	6	6
Vitality	6	6	6	7
Libido	5	5	5	4
Sleep Quality	6	5	5	4
Mental Outlook	8	8	8	6
Mental Clarity	8	8	8	7
Physical Appearance	6	6	6	7
Muscle Strength	5	8	8	7
Muscle Endurance	5	5	5	7
Tension/Anxiety	4	4	4	5

The hand grip strength test was used to assess changes in muscular strength with supplementation. Muscle strength using the hand grip strength test increased by 1 kg after the placebo condition by reduced by 2 kg after the EL+MR condition (Figure 4). From these findings, it appears that *E. longifolia* had no influenced on muscular strength. *E. longifolia* has been shown to increase muscle strength in previous research, whereas maca root has been shown to only influence psychological well-being and sexual dysfunction and not hormone levels (Brooks et al., 2008; Henkel et al., 2014).

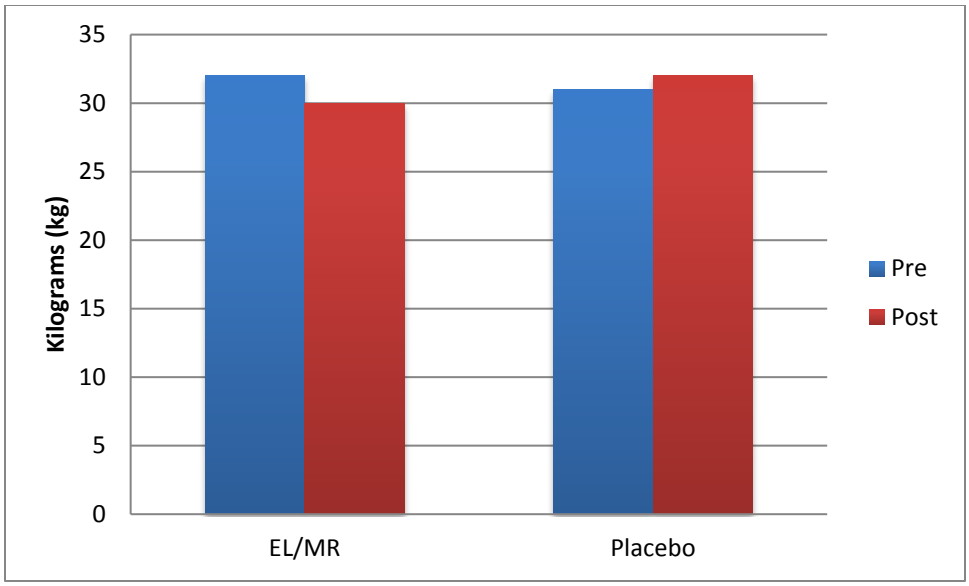

Figure 4. Hand Grip Strength for Subject 1

The aerobic fitness test was used to assess changes in aerobic capacity with supplementation. Neither the placebo or supplementation condition had a positive impact on total treadmill time (Figure 5). Aerobic capacity was not affected by supplementation, which is similar to what is seen with the hand grip strength test.

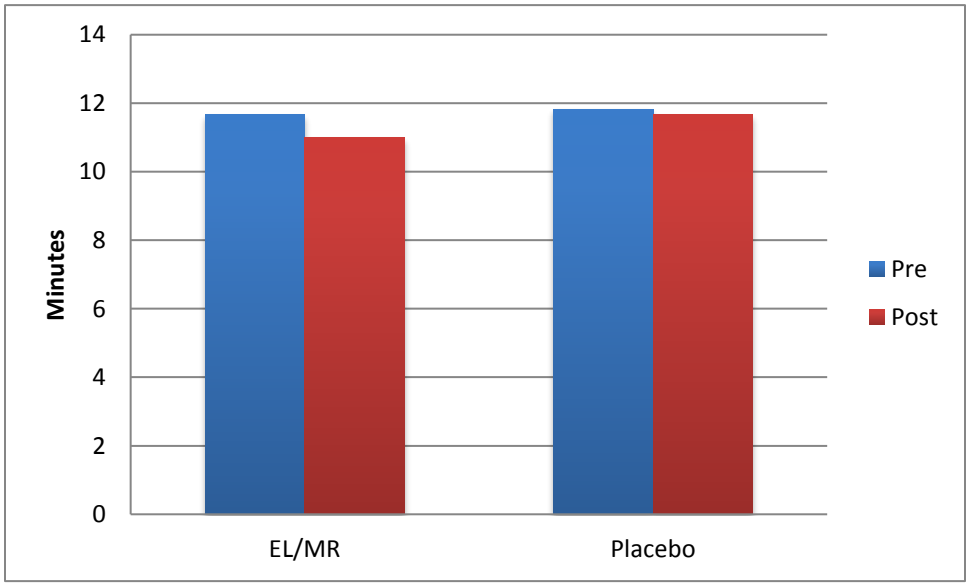

Figure 5. Treadmill Time to Fatigue for Subject 1

Subject 2

A second subject was a 31-year-old African American female, who has been in a relationship for a year and a half. She is 163.5 cm tall, weighs 81.2 kg, has a resting heart rate of 78 beats per min, and her resting blood pressure was 113/76 mmHg. She had no history of cardiovascular disease, metabolic disease, depression, anxiety, or sleep disorders. She was in a sexually active relationship but not currently using any birth control, nor was she pregnant or nursing. She is not a current smoker and has never smoked in the past. This subject has been performing light intensity aerobic exercise 5 days a week lasting 30 mins for 2 years. She has no history of organized or recreational sports or anaerobic training.

The psychological general well-being index (PGWBI) was used to assess changes in quality of life with supplementation. For the placebo condition, the score increased 12 points while the score increased 2 points for the EL+MR condition, (Figure 6). The increase in overall well-being is similar to previous research but not the same magnitude (Brooks et al., 2008; Talbott et al., 2013).

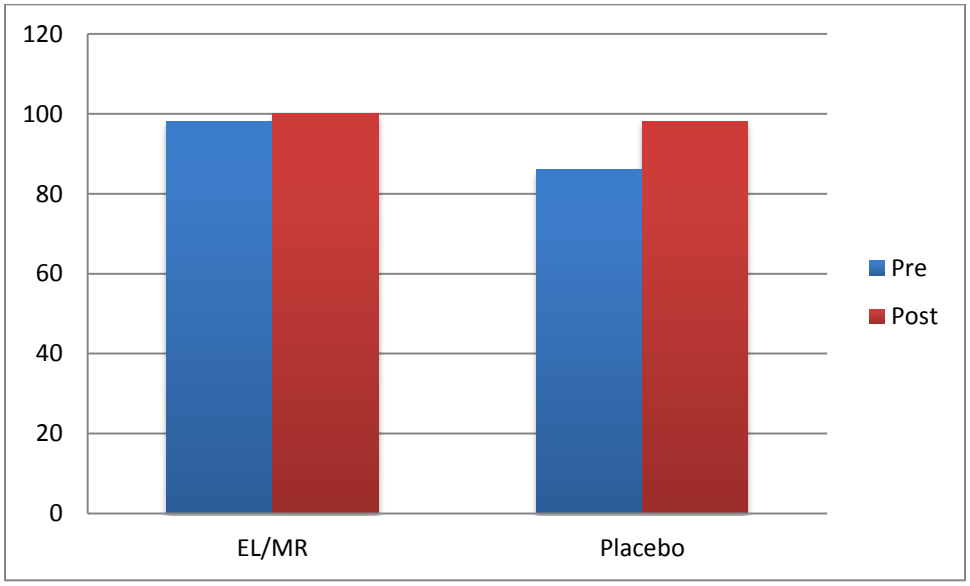

Figure 6. Psychological General Well Being Index for Subject 2

The brief profile of female sexual function (B-PFSF) was used to determine sexual desire, arousal, orgasm, and problems affecting sexual function after supplementation. For the placebo condition, the B-PFSF score did not change while it increased 4 points for the EL+MR condition (Figure 7). The increase in libido is similar to previous research but not the same magnitude (Brooks et al., 2008; Talbott et al., 2013). The results from the PGWBI and the B-PFSF show that EL+MR supplementation had a greater effect for this subject's libido than overall well-being.

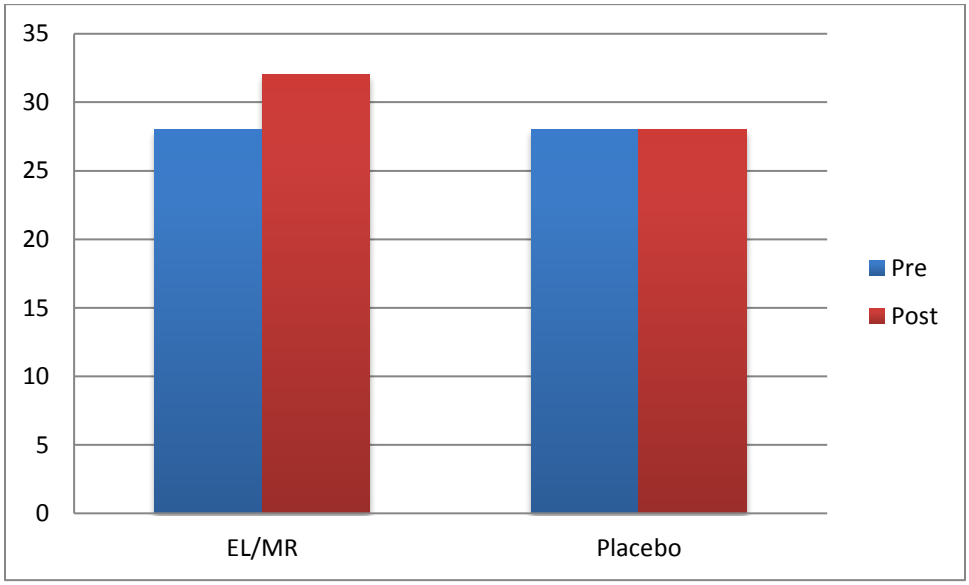

Figure 7. Brief Profile of Female Sexual Function for Subject 2

The weekly diary was used to evaluate subjects' subjective feelings of energy levels, libido, and mental outlook over the course of supplementation. For the subject, the diary energy mean, the diary libido mean, and the diary outlook mean were higher during the EL+MR condition than during the placebo condition (Figure 8). The results from the weekly diary show that the EL+MR condition had a positive effect for the subjective feelings of energy, libido and outlook, which is similar to previous research (Brooks et al., 2008; Talbott et al., 2013). The weekly dairy strengthened the case that the EL+MR condition had a positive effect for the

subject's libido as both the weekly diary and B-PFSF have the same trends of higher libido with EL+MR supplementation.

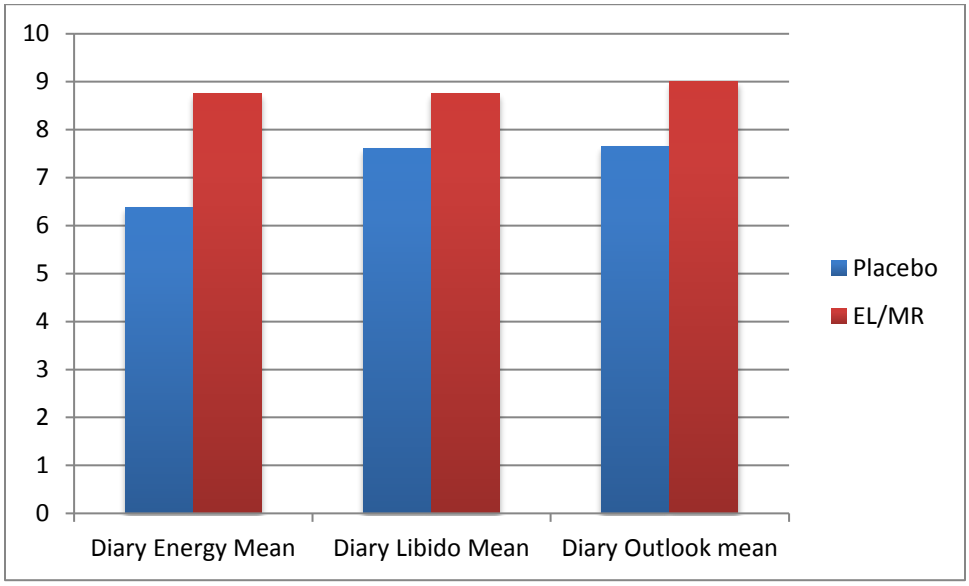

Figure 8. Weekly Diary Means for Subject 2

The general questionnaire was used to determine changes in a number of variables pertaining to overall health with supplementation. In regards to the general questionnaire, this subject noted a change an increase in alertness for the placebo condition, but there were no changes observed for the EL+MR condition (Table 2). For this subject, energy ratings increased for the EL+MR condition and the placebo, but the placebo condition saw a greater increase. With aggressiveness, she experienced an increase in the EL+MR condition but saw no change in the placebo condition. Vitality ratings increased the same amount for the placebo condition and the EL+MR condition. This subject noted the increase in libido for the placebo condition but remained unchanged for the EL+MR condition. As with libido, sleep quality had the largest increase in the placebo condition. Similar increases were noted by this subject in mental outlook and mental clarity in the placebo condition. As for physical appearance, the subject noted no change in the EL+MR condition. As with vitality ratings, subjective muscle strength increased

the same amount for the placebo condition and the EL+MR condition. Subjective muscle endurance increased in the placebo condition but not the EL+MR condition. Lastly, ratings of tension and anxiety decreased in the EL+MR condition. The slight decrease in tension and anxiety is similar to previous research (Brooks et al., 2008; Talbott et al., 2013).

Table 2

General Questionnaire for Subject 2

	Placebo		EL/MR	
	Pre	Post	Pre	Post
Alertness	7	8	8	8
Energy	6	8	8	9
Aggressiveness	5	5	5	8
Vitality	5	7	7	9
Libido	5	9	9	9
Sleep Quality	4	9	9	8
Mental Outlook	6	9	9	9
Mental Clarity	6	9	9	9
Physical Appearance	7	10	10	10
Muscle Strength	5	6	6	7
Muscle Endurance	5	6	6	6
Tension/Anxiety	2	2	2	1

The hand grip strength test was used to assess changes in muscular strength with supplementation. Muscle strength using the hand grip strength test did not change after the placebo condition by increased by 1 kg after the EL+MR condition (Figure 9). There was little change in muscle strength and aerobic capacity. From these findings, it appears that the maca root had an influenced the changes in subjective feelings and not the *E. longifolia*. *E. longifolia* has been shown to increase muscle strength in previous research, whereas maca root has been shown to only influence psychological well-being and sexual dysfunction and not hormone levels (Brooks et al., 2008; Henkel et al., 2014). It is possible that *E. longifolia* had a small, positive effect on testosterone as grip strength did have a small increase with EL+MR

supplementation. However, it would be unlikely that a small increase in testosterone would positively influence libido and overall well-being. This subject appeared to respond more favorable to compounds found in the maca root extract.

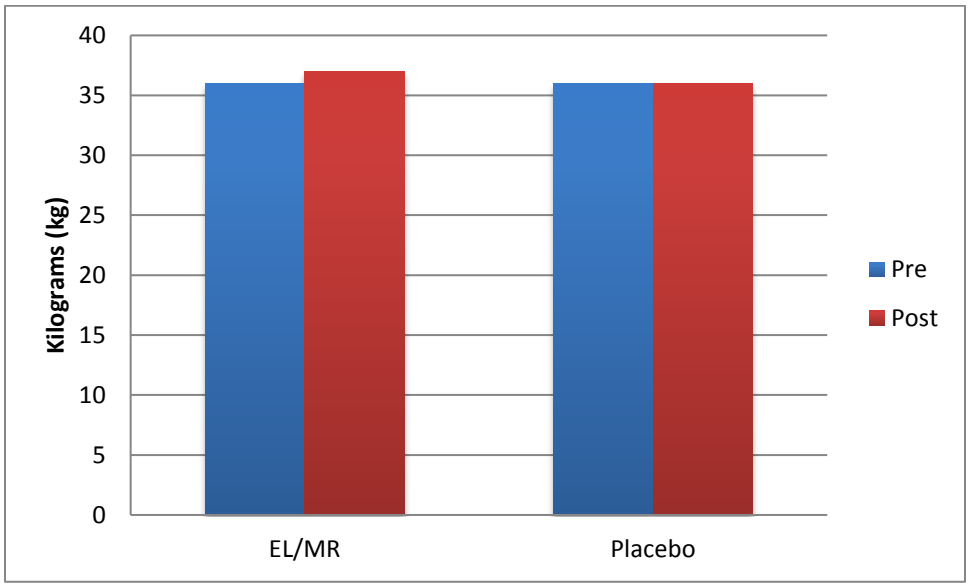

Figure 9. Hand Grip Strength for Subject 2

The aerobic fitness test was used to assess changes in aerobic capacity with supplementation. The subject experienced an increase in total treadmill time from the placebo condition but a decrease after the EL+MR condition (Figure 10). The EL+MR condition did not have a positive effect on aerobic capacity as expected.

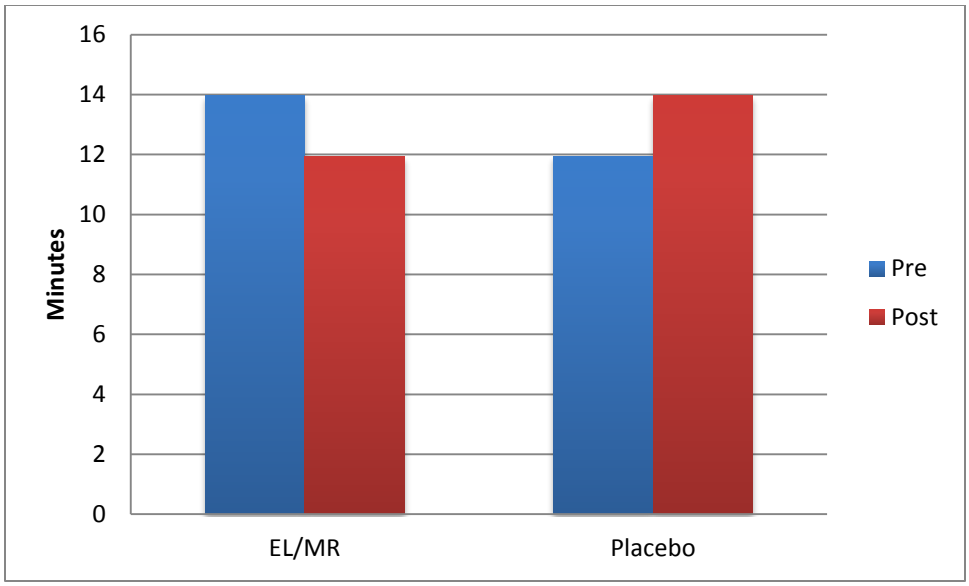

Figure 10. Treadmill Time to Fatigue for Subject 2

Subject 3

The third subject was a 47-year-old African American female, who has been married for 4 years. She is 158 cm tall, weighs 70.6 kg, has a resting heart rate of 93 beats per minute, and her resting blood pressure was 118/82 mmHg. She had no history of cardiovascular disease, metabolic disease, depression, anxiety, or sleep disorders. She was in a sexually active relationship but not currently using any birth control, nor is she pregnant or nursing. She is not a current smoker and has never smoked in the past. This subject has been performing light intensity aerobic exercise 5 days a week lasting 10 mins, for 10 or more years. She has no history of organized or recreational sports or anaerobic training.

The psychological general well-being index (PGWBI) was used to assess changes in quality of life with supplementation. The subject experienced slight decreases in the PGWBI for both conditions (Figure 11). The decrease in overall well-being does not agree with findings of previous research as both *E. longifolia* and maca root have been shown to increase overall well-being (Brooks et al., 2008; Talbott et al., 2013).

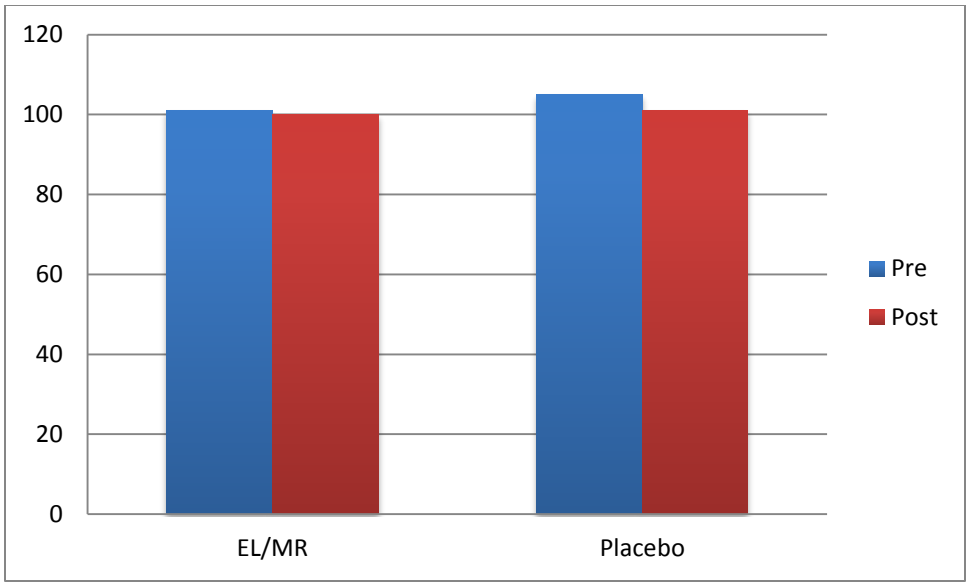

Figure 11. Psychological General Well Being Index for Subject 3

The brief profile of female sexual function (B-PFSF) was used to determine sexual desire, arousal, orgasm, and problems affecting sexual function after supplementation. For the placebo condition, the B-PFSF score increased 4 points while it decreased 5 points for the EL+MR condition (Figure 12). The decrease in libido does not agree with findings of previous research as both *E. longifolia* and maca root have been shown to increase libido (Brooks et al., 2008; Talbott et al., 2013). The results from the B-PFSF and the PGWBI indicate that EL+MR supplementation did not have a positive effect on libido and overall well-being in this subject.

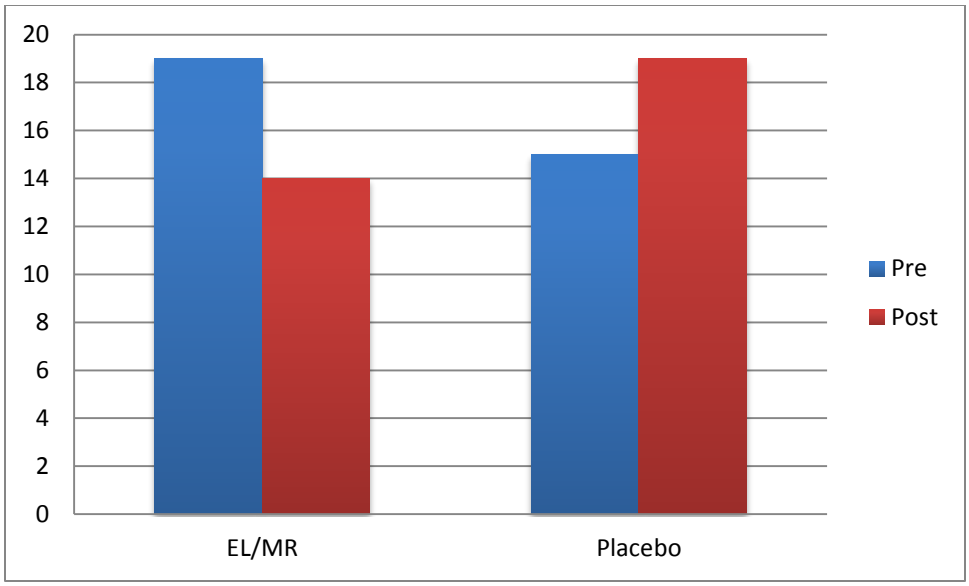

Figure 12. Brief Profile of Female Sexual Function for Subject 3

The weekly diary was used to evaluate subjects' subjective feelings of energy levels, libido, and mental outlook over the course of supplementation. The subject had no change in the diary energy mean, but the diary libido mean was higher in the EL+MR condition. However the was the diary outlook mean was lower during the EL+MR condition (Figure 13). The libido mean from the weekly questionnaire was higher for the EL+MR condition than the placebo condition, which may indicate that her libido was on average higher during the EL+MR condition. The EL+MR supplement may have not had a positive effect, as the subject's energy levels mental outlook were high before supplementation and therefore no room for improvement.

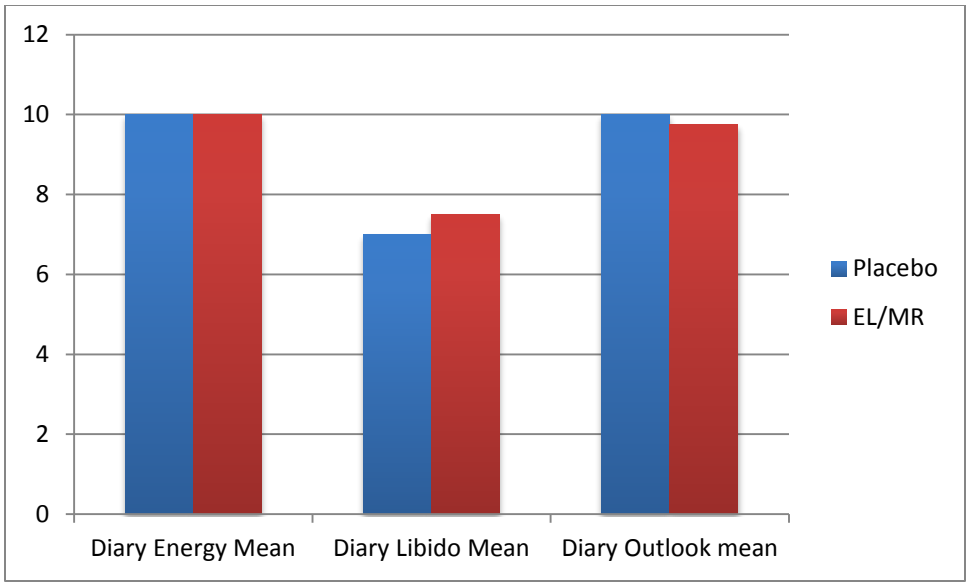

Figure 13. Weekly Diary Means for Subject 3

The general questionnaire was used to determine changes in a number of variables pertaining to overall health with supplementation. From the general questionnaire, alertness, energy, and vitality ratings were the same for both conditions (Table 3). Mental outlook, mental clarity, and physical appearance are the same for both conditions. Aggressiveness ratings decreased in the placebo condition and increased in the *E. longifolia* and maca root condition. The subject, for the EL+MR condition, noted an increase in libido. Conversely, libido decreased in the placebo condition. For sleep quality, the subject noted no change for either condition. Subjective muscle strength and muscle endurance remained the same for the EL+MR condition and decreased in the placebo condition. Lastly, this subject noted a noted a decrease in tension and anxiety for the EL+MR condition, but an increase for the placebo condition. There was a slight decrease in tension and anxiety, which is similar to previous research (Brooks et al., 2008; Talbott et al., 2013).

Table 3

General Questionnaire for Subject 3

	Placebo		EL/MR	
	Pre	Post	Pre	Post
Alertness	10	10	10	10
Energy	10	10	10	10
Aggressiveness	8	7	7	8
Vitality	10	10	10	10
Libido	8	7	7	8
Sleep Quality	6	6	6	6
Mental Outlook	10	10	10	10
Mental Clarity	10	10	10	10
Physical Appearance	10	10	10	10
Muscle Strength	9	8	8	8
Muscle Endurance	9	8	8	8
Tension/Anxiety	0	1	1	0

The hand grip strength test was used to assess changes in muscular strength with supplementation. Muscle strength using the hand grip strength test did not change after the placebo condition by increased by 1 kg after the EL+MR condition (Figure 14). Previous research has shown *E. longifolia* supplementation can increase muscular strength, as well as have a positive influence on testosterone levels (Henkel et al., 2014). It is possible that *E. longifolia* had a small, positive effect on testosterone as this subject did experience a small increase in grip strength with EL+MR supplementation. It would be hard to determine if EL+MR supplementation influenced subjective feelings of libido and overall well-being as many subjective feelings were given the highest rating before and after EL+MR supplementation. If there were changes in the subjective feelings, the changes were minimal. This subject did not appear to respond in a positive or negative manner to the compounds found in the EL+MR supplement as few changes were observed in outcome variables.

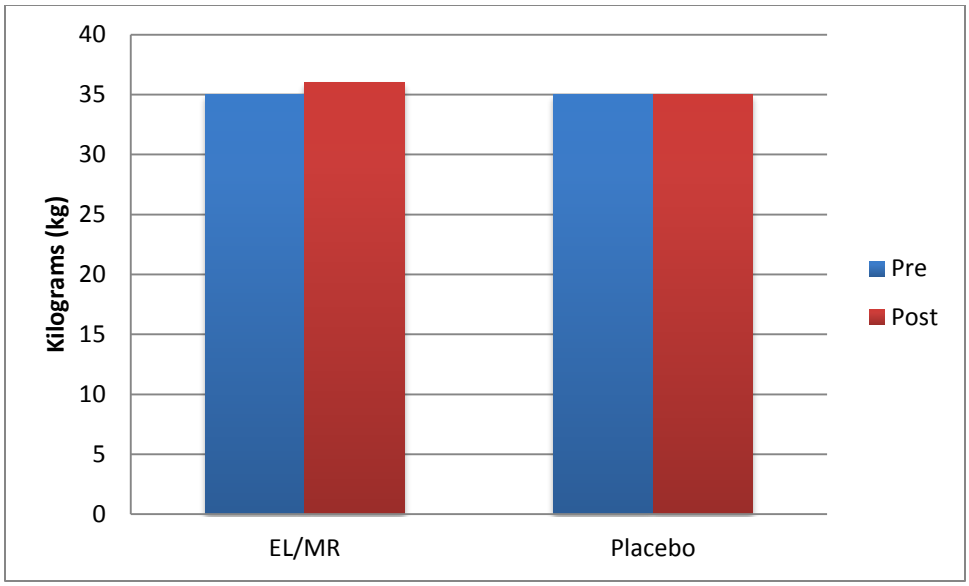

Figure 14. Hand Grip Strength for Subject 3

The aerobic fitness test was used to assess changes in aerobic capacity with supplementation. This subject experienced decreases in total treadmill time across for both the placebo condition and the EL+MR condition (Figure 15). As with muscle strength, there was little change in aerobic capacity.

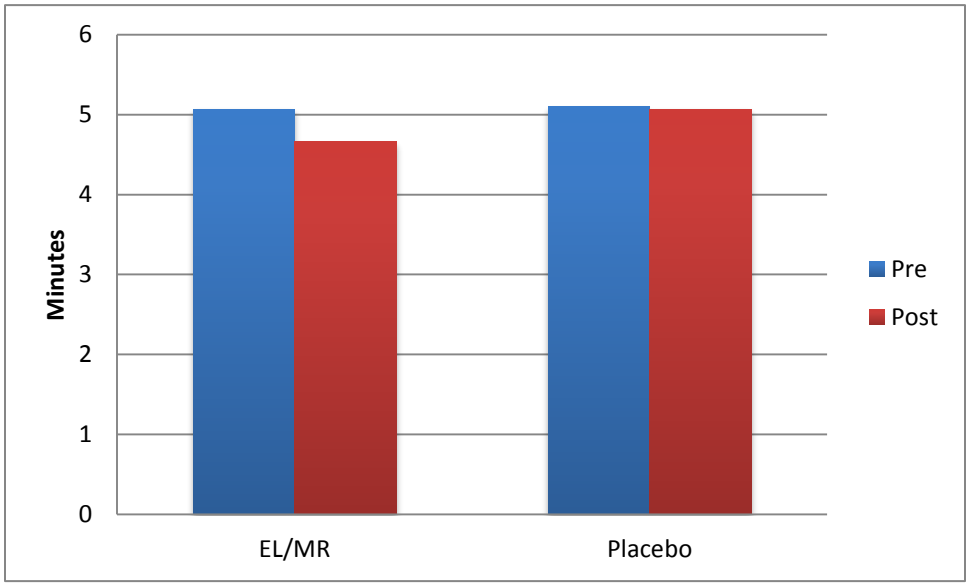

Figure 15. Treadmill Time to Fatigue for Subject 3

Further Investigation

The present study was initially designed to include a sample of 15 women. The study will be continued until an adequate sample of women is included. Testosterone in saliva samples will be determined using enzyme linked immunosorbent assay (ELISA) procedures. At that time, statistical analysis will be used to determine any statistical significance between conditions for all variables. The results from the statistical analysis may support our present findings of the influence of *E. longifolia* and maca root supplementation on feelings of tension, anxiety, energy, and physical appearance. Further investigation will provide more insight on how *E. longifolia* and maca root supplementation affects muscle strength, muscle endurance, and testosterone.

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Appendix A

Psychological General Well Being Index

1. How have you been feeling in general during the past month?

In excellent spirits……	☐ 5
In very good spirits……..	☐ 4
In good spirits mostly……..	☐ 3
I have been up and down in spirits a lot……..	☐ 2
In low spirits mostly……	☐ 1
In very low spirits……	☐ 0

2. How often were you bothered by any illness, bodily disorder, aches or pains during the past month?

Every day……	☐ 0
Almost every day……	☐ 1
About half of the time…….	☐ 2
Now and then, but less than half the time……...	☐ 3
Rarely……..	☐ 4
None of the time……..	☐ 5

3. Did you feel depressed during the past month?

Yes – to the point that I felt like taking my life……..	☐ 0
Yes – to the point that I did not care about anything……..	☐ 1
Yes – very depressed almost every day……..	☐ 2
Yes – quite depressed several times…….....	☐ 3
Yes – a little depressed now and then…….	☐ 4
No – never felt depressed at all……	☐ 5

4. Have you been in firm control of your behaviour, thoughts, emotions or feelings during the past month?

Yes, definitely so……	☐ 5
Yes, for the most part…….	☐ 4
Generally so……	☐ 3
Not too well…….....	☐ 2
No, and I am somewhat disturbed……..	☐ 1
No, and I am very disturbed……	☐ 0

5. Have you been bothered by nervousness or your "nerves" during the past month?

Extremely so – to the point where I could not work or take care of things……	☐ 0
Very much so……..	☐ 1
Quite a bit……	☐ 2
Some – enough to bother me…….	☐ 3
A little…….	☐ 4
Not at all……..	☐ 5

6. How much energy, pep, or vitality did you have or feel during the past month?

Very full of energy – lots of pep……. ☐ 5
Fairly energetic most of the time…… ☐ 4
My energy level varied quite a bit……... ☐ 3
Generally low in energy or pep…….…… ☐ 2
Very low in energy or pep most of the time…… ☐ 1
No energy or pep at all – I felt drained, sapped……... ☐ 0

7. I felt downhearted and blue during the past month.

None of this time…… ☐ 5
A little of the time……..…….. ☐ 4
Some of the time…….…… ☐ 3
A good bit of the time…….……... ☐ 2
Most of the time…….. ☐ 1
All of the time…….…… ☐ 0

8. Were you generally tense or did you feel any tension during the past month?

Yes – extremely tense, most or all of the time……. ☐ 0
Yes – very tense most of the time…….. ☐ 1
Not generally tense, but did feel fairly tense several times…….. ☐ 2
I felt a little tense a few times…… ☐ 3
My general tension level was quite low……. ☐ 4
I never felt tense or any tension at all…….. ☐ 5

9. How happy, satisfied, or pleased have you been with your personal life during the past month?

Extremely happy – could not have been more satisfied or pleased…… ☐ 5
Very happy most of the time…….. ☐ 4
Generally satisfied, pleased…… ☐ 3
Sometimes fairly happy, sometimes fairly unhappy…….. ☐ 2
Generally dissatisfied or unhappy……. ☐ 1
Very dissatisfied or unhappy most or all the time…….. ☐ 0

10. Did you feel healthy enough to carry out the things you like to do or had to do during the past month?

Yes – definitely so……..…… ☐ 5
For the most part……..……..…….. ☐ 4
Health problems limited me in some important ways…… ☐ 3
I was only healthy enough to take care of myself …….. ☐ 2
I needed some help in taking care of myself.…… ☐ 1
I needed someone to help me with most or all of the things I had to do..…….. ☐ 0

11. Have you felt so sad, discouraged, hopeless, or had so many problems that you wondered if anything was worthwhile during the past month?

Extremely so – to the point that I have just about given up..……..…… ☐ 0
Very much so….……..…….. ☐ 1
Quite a bit…… ☐ 2
Some – enough to bother me…….. ☐ 3
A little bit……..…….……. ☐ 4
Not at all……...…….. ☐ 5

12. I woke up feeling fresh and rested during the past month.

None of the time	☐ 0
A little of the time	☐ 1
Some of the time	☐ 2
A good bit of the time	☐ 3
Most of the time	☐ 4
All of the time	☐ 5

13. Have you been concerned, worried, or had any fears about your health during the past month?

Extremely so	☐ 0
Very much so	☐ 1
Quite a bit	☐ 2
Some, but not a lot	☐ 3
Practically never	☐ 4
Not at all	☐ 5

14. Have you had any reason to wonder if you were losing your mind, or losing control over the way you act, talk, think, feel or of your memory during the past month?

Not at all	☐ 5
Only a little	☐ 4
Some – but not enough to be concerned or worried about	☐ 3
Some and I have been a little concerned	☐ 2
Some and I am quite concerned	☐ 1
Yes, very much so and I am very concerned	☐ 0

15. My daily life was full of things that were interesting to me during the past month.

None of the time	☐ 0
A little of the time	☐ 1
Some of the time	☐ 2
A good bit of the time	☐ 3
Most of the time	☐ 4
All of the time	☐ 5

16. Did you feel active, vigorous, or dull, sluggish during the past month?

Very active, vigorous every day	☐ 5
Mostly active, vigorous – never really dull, sluggish	☐ 4
Fairly active, vigorous – seldom dull, sluggish	☐ 3
Fairly dull, sluggish – seldom active, vigorous	☐ 2
Most dull, sluggish – never really active, vigorous	☐ 1
Very dull, sluggish every day	☐ 0

17. Have you been anxious, worried, or upset during the past month?

Extremely so – to the point of being sick or almost sick	☐ 0
Very much so	☐ 1
Quite a bit	☐ 2
Some – enough to bother me	☐ 3
A little bit	☐ 4

Not at all……..……..……. ☐ 5

18. I was emotionally stable and sure of myself during the past month.

None of the time……...……..……... ☐ 0
A little of the time……..……..…….... ☐ 1
Some of the time……. ☐ 2
A good bit of the time…… ☐ 3
Most of the time……..……..……. ☐ 4
All of the time……...……. ☐ 5

19. Did you feel relaxed, at ease or high strung, tight, or keyed-up during the past month?

Felt relaxed and at ease the whole month……..…….. ☐ 5
Felt relaxed and at ease most of the time…….…….... ☐ 4
Generally felt relaxed but at times felt fairly high strung...……. ☐ 3
Generally felt high strung but at times felt fairly relaxed…… ☐ 2
Felt high strung, tight, or keyed-up most of the time..……. ☐ 1
Felt high strung, tight, or keyed-up the whole month.……...……. ☐ 0

20. I felt cheerful, lighthearted during the past month.

None of the time……...……..……... ☐ 0
A little of the time……..……..…….... ☐ 1
Some of the time……. ☐ 2
A good bit of the time…… ☐ 3
Most of the time……..……..……. ☐ 4
All of the time……...……. ☐ 5

21. I felt tired, worn out, used up, or exhausted during the past month.

None of the time……...……..……... ☐ 5
A little of the time……..……..…….... ☐ 4
Some of the time……. ☐ 3
A good bit of the time…… ☐ 2
Most of the time……..……..……. ☐ 1
All of the time……...……. ☐ 0

22. Have you been under or felt you were under any strain, stress, or pressure during the past month?

Yes – almost more than I could bear or stand……..…….. ☐ 0
Yes – quite a bit of pressure……..…….... ☐ 1
Yes, some – more than usual……...……. ☐ 2
Yes, some – but about usual……... ☐ 3
Yes – a little……...……. ☐ 4
Not at all……..……...……. ☐ 5

Appendix B

The Brief Profile of Female Sexual Function

Below you can see a list of statements regarding thoughts and feelings that were found to be related to Hypoactive sexual desire disorder (HSDD). Please indicate the extent to which you agree or disagree with each statement by clicking the corresponding checkbox.

	Always				Never
I felt like having sex	☐	☐	☐	☐	☐
I was unhappy about my lack of interest in sex	☐	☐	☐	☐	☐
Getting aroused took forever	☐	☐	☐	☐	☐
I felt sexually numb	☐	☐	☐	☐	☐
I felt disappointed by my lack of interest in sex	☐	☐	☐	☐	☐
I lacked sexual desire	☐	☐	☐	☐	☐
I reached orgasm easily	☐	☐	☐	☐	☐

Appendix C

Weekly Diary

Directions: This questionnaire asks about your current feelings of the below indicated items. Therefore, it is important that you focus on how you feel for that particular day. Please make a vertical line on the horizontal line below which best describes the overall feelings. 0 represents no feelings or the lowest possible rating. 10 represents extreme feelings or the highest possible rating.

Day 1

Energy levels (0 = EXTREMELY LOW 10 = EXTREMELY HIGH)

1 2 3 4 5 6 7 8 9 10

Libido (0 = EXTREMELY LOW 10 = EXTREMELY HIGH)

1 2 3 4 5 6 7 8 9 10

Mental outlook (0 = EXTREMELY NEGATIVE 10 = EXTREMELY POSITIVE)

1 2 3 4 5 6 7 8 9 10

Comments:

Appendix D

Using a rating of 1-10, with *1 representing the lowest rating and 10 representing the highest rating*, please rate the following variables, with consideration of how you felt over the past TWO WEEKS.

Variable	Rating (1-10)	Provide Comments as Needed
Alertness		
Energy Level		
Aggressiveness		
Vitality		
Libido		
Sleep Quality		
Mental Outlook and Mood		
Mental Clarity		
Physical Appearance		
Muscle Strength		
Muscle Endurance		
Tension or Anxiety		
Other (provide comments)		

CONDITION 1 DAY 1

NAME:_____

ID:_____

Appendix E

From: Christopher Wayne Whitehead (cwhitehd) on behalf of Institutional Review Board
Sent: Wednesday, September 23, 2015 4:47 PM
To: Richard J Bloomer (rbloomer)
Subject: IRB Approval 3821

Hello,

The University of Memphis Institutional Review Board, FWA00006815, has reviewed and approved your submission in accordance with all applicable statuses and regulations as well as ethical principles.

PI NAME: Richard Bloomer
CO-PI: Ryan Moran, Matt Butawan, Brooks Crone
PROJECT TITLE: Effects of Herbal Supplements on Testosterone, Libido, and Mood Premenopausal Women with Hypoactive Sexual Desire Disorder
FACULTY ADVISOR NAME (if applicable):
IRB JD: #3821
APPROVAL DATE: 9/23/2015
EXPIRATION DATE: 9/23/2016
LEVEL OF REVIEW: Full Board
RISK LEVEL DETERMINATION: More than minimal
Please Note: Modifications do not extend the expiration of the original approval
Approval of this project is given with the following obligations:
1. If this .IRB approval has an expiration date, an approved renewal must be in effect to continue the project prior to that date. If approval is not obtained, the human consent form(s) and recruiting materials are no longer valid and any research activities involving human subjects must stop.
2. When the project is finished or terminated, a completion form must be completed and sent to the board.
3. No change may be made in the approved protocol without prior board approval, whether the approved protocol was reviewed at the Exempt, Exedited or Full Board level.
4. Exempt approval are considered to have no expiration date and no further review is necessary unless the protocol needs modification.
Approval of this project is given with the following special obligations:

Thank you,

James P. Whelan, Ph.D.

Institutional Review Board Chair

Appendix F

Statement of the Problem

Maintaining normal concentrations of hormones, such as testosterone, is important as related to overall quality of life. Lower than normal concentrations of testosterone can lead to a decline in metabolism, libido, muscle mass, and bone density. These lower concentrations of testosterone may also contribute to the increase in fat mass, depression, and erectile dysfunction (Harman, Metter, Tobin, Pearson, & Blackman, 2001; Schulman et al., 2009). Both men and women can experience a decrease in testosterone with age (Horstman, Dillon, Urban, & Sheffield-Moore, 2012). In men, testosterone levels remain stable until the age of approximately 40 years, when testosterone concentrations begin to decline (Harman et al., 2001) and levels can decline by approximately 50% by the age of 60 years. This decline causes an androgen deficiency, which can be problematic in older populations (Matsumoto, 2003).

Research shows that women with symptoms of low testosterone can be treated with hormone replacement therapy with positive outcomes (Pluchino et al., 2013). Up to 43% of women note having sexual problems, with hypoactive sexual desire disorder being commonly reported (Laumann, Paik, & Rosen, 1999). Hypoactive sexual desire disorder is defined by disturbances, decreases or absence in sexual desire, which can be apparent in both women and men (Laumann et al., 1999) (with more women affected than men). Hypoactive sexual desire disorder in women can be caused by natural menopause and bilateral oophorectomy (Pluchino et al., 2013). Experiments have shown that a transdermal patch or spray testosterone (alone or in conjunction with estrogen) can be effective for women who are characterized as having hypoactive sexual desire disorder due to natural or surgical menopause (S. R. Davis et al., 2008a; S. Davis et al., 2008; Simon et al., 2005). Therefore, it is believed that testosterone replacement therapy can

benefit women who have low concentrations of testosterone and can alleviate the aforementioned symptoms of low testosterone related specifically to libido. The question remains as to whether or not non-pharmaceutical agents can prove beneficial to improving libido in women with hypoactive sexual desire disorder.

Literature Review

The present review is focused on the influence that circulating testosterone has on overall health and well-being in adults, with a specific emphasis on women. The review begins with a brief overview of herbal supplements and testosterone. The review also emphasizes the impact of dietary and herbal supplementation on feelings of well-being.

Overview of Herbal Supplements

Western medicine, which developed from the philosophy and science of Hippocrates some 2,400 years ago, took an analytical or theoretical approach to medicine (Robson & Baek, 2009). On the other hand, eastern countries such as China dealt with medicine in a much more applied manner, observing self-experiments and anecdotal reports over hundreds of years. During the 1st century AD, the Chinese scientist, Shen Nong Ben Cao Jing, began to record herbal medicines as superior or inferior, as well as their effect on various diseases (Hong, 2004). Herbal medicines have been used for several hundred years to improve overall health of individuals (Ackerknecht, 1982; Nunn, 2002).

Indeed, herbal supplementation *potentially* treats a variety of disorders and diseases such as cardiovascular disease (Fugh-Berman, 2000; Yeh, Davis, & Phillips, 2006), prostate disease (Feifer, Fleshner, & Klotz, 2002; Small et al., 2000), chronic liver disease (Levy, Seeff, & Lindor, 2004), diabetes (Modak, Dixit, Londhe, Ghaskadbi, & Devasagayam, 2007), and eye diseases (West, Oren, & Moroi, 2006). There has been a growing interest in using dietary

supplements in the U.S. over the past forty years. With the potential ability to prevent or treat a variety of diseases, herbal supplement use has become more common across age ranges, with approximately 20% of adults reporting use of herbal supplements (Bailey et al., 2011). The effectiveness of herbal supplementation has been investigated for improving various aspects of human health, from pregnancy (Smeriglio, Tomaino, & Trombetta, 2014) and obesity (Greenway & Heber, 2012) to depression (Lee & Ji, 2014) and physical performance (Qureshi, Naughton, & Petroczi, 2014a). Investigations have also been conducted using herbal supplements as treatments for a variety of human diseases (Feifer et al., 2002; Levy et al., 2004; West et al., 2006).

With this growing interest in using herbal supplements, more research has been devoted to determining the effects of herbal supplementation on specific hormone concentrations (Bidwell, 2013; George & Henkel, 2014; Qureshi et al., 2014a). Much of this research focuses on the effects of dietary supplements in the respect to testosterone and growth hormone (Bidwell, 2013; George & Henkel, 2014). Specific herbal and botanical agents may aid the body to produce these hormones naturally, which may be preferred over taking other medicinal products. Botanical agents and dietary supplements that have been reported to increase testosterone and libido include *Eurycoma longifolia* (Hamzah & Yusof, 2003; Henkel et al., 2014; Muhamad, Chen, Ooi, & Abdullah, 2009; Muhamad, Chen, Ooi, Abdullah, & Lam, 2010; Sarina, Zaiton, Aminudin, Nor, & Azizol, 2009; Tambi, Imran, & Henkel, 2012) and D-aspartic acid (Topo, Soricelli, D'Aniello, Ronsini, & D'Aniello, 2009), respectively. Maca root is another botanical agent, which has been reported to increase libido, but it does not appear to influence testosterone levels (Zheng et al., 2000).

Overview of Testosterone

Testosterone plays an important role in human physiology, as it can affect muscle growth, muscle strength, and overall well-being and vitality (Finkelstein et al., 2013). Testosterone is a steroid hormone, which is responsible for the development of male secondary sexual characteristics (Finkelstein et al., 2013). Testosterone is naturally produced in males mainly by the Leydig cells located in testicles, which is initiated by the pituitary gland. Testosterone concentrations begin to decline as men age for several reasons, including decreases in the number of Leydig cells, diminishing response from the pituitary, and an increase in sex hormone binding globulin (SHBG) (Finkelstein et al., 2013). As men age, there is an increase of SHBG, which binds to free testosterone in the blood stream. Free testosterone is the form most utilized by the body. As testosterone levels decline, androgen deficiencies may occur, causing serious health issues as testosterone is used in many different processes (Matsumoto, 2003). The specific cause of the decline in testosterone with age may be initiated by chrono-biological factors, as well as lifestyle factors such as increased body fat gain and lack of physical activity.

Effects of testosterone therapy on muscle growth have been thoroughly investigated in humans and animals (Dayal et al., 2005; Kenny et al., 2010; Serra et al., 2013; Storer et al., 2008). One study investigated the effects of supra-physiologic doses of testosterone, injections of 600 mg of testosterone enanthate, on muscle size and strength in healthy men. The results show that when combined with strength training, these supra-physiologic doses of testosterone increase muscle size (Bhasin et al., 1996). Another investigation noted that the increase in muscle mass is dependent on the dose of testosterone received (Storer et al., 2008).

Studies also evaluated the effects of muscle strength as related to testosterone dose (Bhasin et al., 1996; Dayal et al., 2005; Kenny et al., 2010; Storer et al., 2008). One study

showed that testosterone supplementation increased muscle mass but did not change muscle strength in older men (Kenny et al., 2010). Testosterone was found to impact muscle strength when administration occurred with greater weekly or monthly doses rather than smaller daily doses.

Overall well-being and vitality, along with muscle size and strength, is affected by testosterone. A study on the effects of a transdermal testosterone gel, which is applied daily, found improvements in quality of life over a six month period with greater improvements occurring after twelve months (Behre et al., 2012). Another study of transdermal testosterone gel, also applied daily, concluded that the gel improves sexual function and mood as well as other physical characteristics, such as muscle mass and strength (Wang et al., 2000). The transdermal studies used hypogonadal men, or men who suffered from low concentrations of testosterone. If men with normal testosterone concentrations were recruited for the same study, the observed effects may not be the same.

Women have less circulating testosterone than men, but this hormone still plays a key role in overall health. In women, testosterone is produced by the theca cells of the ovaries, the adrenal glands, and tissues such as adipose and muscle (Pluchino et al., 2013). The ovaries are responsible for 25% of testosterone production, the adrenal glands another 25%, and the remainder from local tissue. After menopause, the ovaries are responsible for 50% of testosterone, whereas the adrenal gland production decreases to 10% (Pluchino et al., 2013). As women mature, testosterone levels decrease; circulating testosterone in women approximately 40 years of age is roughly half of that of women in their 20's (Goldstat, Briganti, Tran, Wolfe, & Davis, 2003). Both pre- and postmenopausal women experience low libido and other symptoms due to low testosterone (Goldstat et al., 2003). Many postmenopausal women receive estrogen

therapy but still experience symptoms that include decreased sexual desire, pleasure, and overall well-being (S. R. Davis et al., 2008b; Goldstat et al., 2003; Shifren et al., 2000).

In women who have undergone oophorectomy and hysterectomy, treatment with transdermal testosterone patches and estrogen improved sexual function and psychological well-being (Shifren et al., 2000). Transdermal testosterone patches have improved sexual function in postmenopausal women, who are not also receiving estrogen (S. R. Davis et al., 2008b). Premenopausal women, who have low libido and testosterone, treated with a testosterone cream, experienced improvements in well-being, mood, and sexual function (Goldstat et al., 2003). Although the US Food and Drug Administration has not yet approved testosterone therapy for women, doctors have the ability to prescribe testosterone to women to counteract symptoms of low libido and poor body composition. Hypoactive sexual desire disorder in both post- and premenopausal women has been treated with hormone placement therapy with positive outcomes (Goldstat et al., 2003).

Methods of Increasing Testosterone

Resistance Exercise Training

Chronic resistance exercise training has a positive effect on muscle mass and strength (Kosek, Kim, Petrella, Cross, & Bamman, 2006), but the effect of resistance training, both acute and chronic, on testosterone is less clear (Arazi, Damirchi, Faraji, & Rahimi, 2012; Hakkinen, Pakarinen, Kraemer, Newton, & Alen, 2000; Weiss, Cureton, & Thompson, 1983). Research has shown that testosterone response, due to an acute bout of heavy resistance exercise, is greater in men than in women (Weiss et al., 1983). Testosterone response to chronic resistance exercise is not the same as responses to acute exercise. After 6 months of heavy resistance training, neither men nor women experienced any changes in concentrations of testosterone or growth hormone

(Hakkinen et al., 2000). The exact mechanism for increased concentrations of testosterone is unknown, warranting more research in this area.

Pharmaceuticals and Pro-hormones

Another method of increasing circulating testosterone is the use of pharmaceutical agents such as transdermal testosterone patches and gels (S. R. Davis et al., 2008b; Kenny et al., 2010; Storer et al., 2008; Wang et al., 2000). Other common methods of increasing testosterone include mouth patches (Venkatalakshmi et al., 2012), injections (Kamischke, Venherm, Plöger, von Eckardstein, & Nieschlag, 2001) and subcutaneous testosterone pellet implants (McCullough et al., 2012). If men or women experience symptoms of low libido, chronic fatigue, or depression due to low concentrations of testosterone, one of these pharmaceutical agents may be prescribed.

Testosterone pro-hormone supplements such as DHEA, androstenedione, and androstenediol have also been marketed to increase testosterone concentrations, but research has shown no positive outcomes with administration of these pro-hormone supplements in otherwise healthy individuals (Brown, Vukovich, & King, 2006). These testosterone supplements, as well as anabolic steroids, are of great interest for both bodybuilders and athletes looking to improve muscle mass and physical performance, respectively (Arazi & Hosseini, 2011). Use or abuse of these products for sport may be due to the lack of knowledge of adverse effects.

Nutritional Intake

Circulating testosterone can be manipulated naturally through nutritional interventions such as alterations in macronutrient and micronutrient content of a diet. Acute changes to macronutrient content of a meal produce little to no changes in hormone concentrations immediately following ingestion (Alleman Jr & Bloomer, 2011). Chronic changes in macronutrient content have shown more positive results in influencing hormonal changes

(Hämäläinen, Adlercreutz, Puska, & Pietinen, 1984). Increasing carbohydrate intake or saturated fat intake may produce increases in testosterone in certain individuals (Anderson et al., 1987).

Alterations of micronutrient content may produce favorable outcomes in regards to circulating testosterone. One micronutrient associated with testosterone production is zinc. Zinc deficiencies have been linked to low testosterone concentrations, but studies are inconclusive on the effects of zinc magnesium aspartate, or ZMA, in relation to testosterone concentrations (Brilla & Conte, 2000; Koehler, Parr, Geyer, Mester, & Schänzer, 2007). ZMA supplementation may be more effective for individuals with low zinc levels. Vitamin D is another macronutrient that is directly related to testosterone levels. Research indicates vitamin D may have positive effects on testosterone levels (Pilz et al., 2011), but more trials are needed.

Herbal and Dietary Supplements

Dietary supplements and botanical agents, which are widely available on the market, may have a positive effect in raising testosterone levels. One dietary supplement of recent interest is D-aspartic acid (DAA) (Topo et al., 2009). One product, N-methyl-D-aspartic acid or NMDA, combines the dietary supplement DAA with the botanical agents *E. longifolia* and *Mucuna pruriens* to potentially increase testosterone (Willoughby, Spillane, & Schwarz, 2014). Other botanical agents which have been investigated include *Ginkgo bilboa* (Ahmed, Abdel-Rahman, Ali, & Moniem, 2009), fenugreek (Bushey et al., 2009), *Tribulus terrestris* (Neychev & Mitev, 2005; Qureshi, Naughton, & Petroczi, 2014b; Singh, Nair, & Gupta, 2012), *Bulbine natalensis* (M. Yakubu & Afolayan, 2009; M. T. Yakubu & Afolayan, 2010), ecdysterone (Chermnykh, Shimanovskii, Shutko, & Syrov, 1988; Wilborn et al., 2006), and shilajit (70-72). *E. longifolia*, *Ginkgo bilboa*, fenugreek, and *Tribulus terrestris* have been thoroughly reviewed (72). *Bulbine natalensis*, ecdystrone, *Mucuna pruriens*, and shilajit have shown promise in animal studies, but

no human studies have been performed. *E. longifolia* is one botanical agent that has shown the greatest potential to increase testosterone levels. The botanical agents *E. longifolia* and maca root, and the amino acid DAA have shown potential and will be reviewed in more detail below.

Eurycoma Longifolia

One herbal supplement, *E. longifolia*, has been of great interest being researched in animals (73-75) and humans (Hamzah & Yusof, 2003; Henkel et al., 2014; Muhamad et al., 2009; Muhamad et al., 2010; Sarina et al., 2009; Tambi et al., 2012). *E. longifolia* is a tropical plant, which grows in southwest Asian countries such as Malaysia, Indonesia, and Vietnam. Common names for *E. longifolia* include Tongkat Ali, long jack root, Malaysian ginseng, and many others. The roots of *E. longifolia* are of particular interest, as chemical compounds have been extracted from the roots. These compounds have anti-tumor promoting and anti-parasitic properties, as well as the ability to increase circulating testosterone (77). *E. longifolia* commercial products are available either in the form of raw crude powder of the root, as a capsule with other ingredients, and as an additive mixed with coffee.

In vitro experiments have examined the effects of *E. longifolia* on human spermatozoa and rat testicular Leydig cells (Erasmus, Solomon, Fortuin, & Henkel, 2012; B. Low, Choi, Wahab, Das, & Chan, 2013). Therapeutically used concentrations ($<2.5\ \mu g \cdot ml^{-1}$) of *E. longifolia* extract had no deleterious effects on sperm function, but harmful effects may be seen at very high concentrations (B. Low et al., 2013). Rat Leydig cells incubated with Eurycomanone, a quassinoid found in the root extract of *E. longifolia*, for two hours experienced dose dependent increases in testosterone production. Inhibiting aromatase conversion of testosterone to estrogen brought about the increase in testosterone production (S. M. Talbott, Talbott, George, & Pugh,

2013). Phosphodiesterase inhibition was seen at the higher concentration (S. M. Talbott et al., 2013).

Animal studies show that *E. longifolia* can enhance libido and sexual motivation in male rats (Ang & Sim, 1997, 1998). One study used 240 sexually experienced male rats, as the male rats were housed in a cage with a non-experimental female. The rats were treated with fractions of *E. longifolia*: 200, 400, and 800 mg/kg body weight twice daily. The results showed a positive correlation between mounting frequency and dose of *E. longifolia* (Ang & Sim, 1997). Another study employed 260 sexually naïve male rats and were treated at the same fractions of the previous study. The results showed *E. longifolia* enhanced crossovers and mountings (Ang & Sim, 1998), but there were no differences between fractions as found in previous research. These two studies support the claimed aphrodisiac qualities of *E. longifolia.*

A pilot study examined the effects of *E. longifolia* on body composition, muscle size, and muscle strength in fourteen healthy men (Hamzah & Yusof, 2003). For five weeks, subjects performed an intense strength training program while ingesting 100 mg/day of an *E. longifolia* water soluble extract or a placebo. The results showed a significant decrease in body fat for both groups. The increases in lean body mass, arm circumference and strength were significant in the treatment group but not the placebo group. These results show that supplementation of *E. longifolia* has favorable outcomes for body composition, muscle size, and muscle strength when combined with a strength training program.

A recent study examined the ergogenic effects of *E. longifolia* had on an elderly population, 13 male and 12 female subjects aged 57-72 years and physically active (Henkel et al., 2014). Subjects were treated with a 400 mg *E. longifolia* supplement daily for 5 weeks, and concentrations of total and free testosterone, DHEA, cortisol, insulin-like growth factor-1, and

SHBG were analyzed. Additional biochemical parameters were taken and muscle strength was determined by a hand grip test. Results showed treatment with a 400 mg dose of *E. longifolia* significantly increases total and free testosterone concentrations and muscle strength followed a similar trend. In women, free testosterone rose from 0.50 ± 0.24 pg/mL to 1.11 ± 0.66 pg/mL. Muscle strength in women increased from 29.61 ± 7.28 kg to 33.67 ± 8.38 kg. In men, free testosterone increased from 5.20 ± 1.60 pg/mL to 8.38 ± 2.18 pg/mL. Muscular strength in men increased from 46.03 ± 11.30 kg to 53.67 ± 9.86 kg. SHBG concentrations declined significantly in women (59.66 ± 17.18 nmol/L to 47.26 ± 16.65 nmol/L), possibly affecting the increase in free testosterone (Henkel et al., 2014)

Another recent experiment examined the effects of *E. longifolia* on stress hormones and mood in subjects who were moderately stressed. A total of 63 subjects (32 men and 31 women) with moderate stress ingested an *E. longifolia* root extract (200 mg/day) or placebo for 4 weeks (S. Talbott et al., 2006). Improvements in subjective feelings of tension (-11%), anger (-12%) and confusion (15%) were observed in the supplement group. The supplement group also experienced a significant decrease in cortisol levels (-16%) and a concomitant increase in testosterone levels (+37%). These results support other findings in which daily supplementation of *E. longifolia* can increase testosterone levels and improve subjective feelings (S. Talbott et al., 2006).

Similar findings were seen on stress hormones when *E. longifolia* was consumed prior to a bout of endurance exercise. Thirty male subjects consumed 100mg of *E. longifolia* or a placebo 30 mins prior to a mountain biking event (B. S. Low, Ng, Choy, Yuen, & Chan, 2005). Cortisol levels were significantly lower in the supplement group (0.552 ± 0.665 μg/dL) when compared to the placebo group (0.816 ± 0.775 μg/dL). Testosterone levels were significantly higher in the

supplement group (86.72 ± 40.9 pg/mL) than the placebo group (72.47 ± 33.77 pg/mL). Researchers concluded that even during intense exercise, *E. longifolia* might help maintain an anabolic hormone state. However, when examining the ergogenic effects of *E. longifolia* on endurance running capacity in 12 healthy male recreational athletes (Muhamad et al., 2010), endurance running capacity was not affected by the supplementation of *E. longifolia* (two 75 mg capsules twice per day) for seven days. Discrepancies in findings may be in part due to the difference in dosing across studies, as well as the concentration of the *E. longifolia* supplied in the supplement.

One explanation for the increase in testosterone and spermatogenesis with supplementation of *E. longifolia* is the presence of eurycomanone, a major quassinoid present in *E. longifolia* root extract. Unfortunately, *E. longifolia* has low bioavailability when ingested orally as compared to intravenous administration (Shin, Lee, Yang, Lim, & Ernst, 2010). Decreased levels of SHBG may be another reason for increasing testosterone values. As mentioned earlier, Henkel et al. found that concentrations of SHBG decreased with *E. longifolia* supplementation, which may have impacted the increase in testosterone (Henkel et al., 2014). Eurypeptides may also exhibit an effect on biosynthesis of testosterone (Tambi et al., 2012). Eurypeptides are bioactive compounds consisting of large chain amino acids found within the root extract. Eurypeptides activates the CYP17 enzyme to increase the metabolism of pregnenolone and 17-OH-pregnenolone to yield more dehyodroepiandrosterone. Metabolism of progesterone and 17-OH-progestrone to 4-androstenedione and to testosterone is also increased (Tambi et al., 2012). With these identified mechanisms and with more work documenting the benefit of *E. longifolia*, it may become a viable alternative to testosterone replacement therapy.

Maca Root

Maca, or *Lepidium meyenii*, is a plant indigenous to the Andes Mountains, and extracts of the root have been used to improve sexual function for centuries (G. F. Gonzales, Ruiz, Gonzales, Villegas, & Cordova, 2001). In controlled studies, maca root has been used to treat sexual dysfunction in humans and animals. Phytosterols or phytoestrogens, which are two compounds found in maca, may be the mechanism for improving sexual function (G. F. Gonzales et al., 2001). Maca is commercially available in stores and online in different forms, such as tablets.

Maca root supplementation has been examined in both rats and mice with favorable outcomes (Zheng et al., 2000). In normal mice, maca (orally administered for 22 days) significantly increases libido and sexual potency (Zheng et al., 2000). One-time oral administration in mice showed that the active ingredients were immediately bioavailable. Maca also improved erectile function and the latent period of erection in rats with erectile dysfunction and with removed testes, respectively (Zheng et al., 2000). Other experiments with rats have also reported aphrodisiac effects with maca administration (G. Gonzales et al., 2002).

The aphrodisiac properties of maca have been shown in healthy men as well as men with mild erectile dysfunction. Healthy men were administered 1.5g or 3g of maca and the effects on sexual desire, mood, and serum testosterone were measured at 4, 8, and 12 weeks (Zenico, Cicero, Valmorri, Mercuriali, & Bercovich, 2009). Of the men administered maca, 42.2% experienced an increase in sexual desire after 12 weeks of supplementation (Zenico et al., 2009). However, serum testosterone and scores of depression and anxiety were not changed with treatment. In addition, men with mild erectile dysfunction experienced an increase in sexual

desire as well as an increase in quality of life with administration of maca (2400mg/day for 12 weeks) (Zenico et al., 2009).

Another study has shown that both men and women experience improvements in sexual desire with supplementation of maca. A total of 3 Men and 17 women with selective-serotonin reuptake inhibitor (SSRI)-induced sexual dysfunction ingested either 1.5g or 3g of maca per day for 12 weeks with assessments of sexual function and depression being made every 2 weeks (Brooks et al., 2008). There was a significant increase in libido in the supplement groups, with the higher dose group having a greater improvement. There was also a downward trend seen in depression scores over the course of supplementation, which may be attributed to the increases in libido. These results may be more generalizable to women than men, as women made up 85% of the subject pool.

Postmenopausal women were treated with 3.5g per day of powdered maca and assessments were made at the end of supplementation of psychological symptoms, sexual dysfunction, and hormone concentrations (D'Aniello et al., 1996). Maca supplementation reduced sexual dysfunction and improved psychological symptoms. No differences were seen in serum concentrations of estradiol, follicle-stimulating hormone, luteinizing hormone, and SHBG between groups. These data add to other findings supporting maca root as an aphrodisiac.

D-aspartic acid

One dietary supplement, DAA, has been marketed and researched for its ability to increase testosterone levels. DAA occurs naturally in animals and appears to be able to stimulate the release of sex hormones from the pituitary and testes. Early *in vitro* experiments, where DAA was introduced to isolated rat testes, have shown DAA can activate synthesis of testosterone

(D'Aniello et al., 1996). Studies employing male rats have demonstrated the involvement of DAA in steroidogenesis (Nagata, Homma, Lee, & Imai, 1999; Topo et al., 2009).

Human studies involving DAA supplementation have found conflicting evidence on the effects of DAA on circulating testosterone. The first human study found that DAA supplementation significantly increased testosterone levels when compared to the placebo (Topo et al., 2009). Twenty-three healthy male subjects (27 to 37 years of age) received a 10 ml 2.0 M solution of sodium D-aspartate solution to be taken in the morning for 12 days, while 20 other males received a placebo. Levels of testosterone and luteinizing hormone were monitored after 6 and 12 day of supplementation and again 3 days after the cessation of treatment. At 12 days of supplementation, 20 of 23 subjects in the experimental group had increased concentrations of luteinizing hormone and testosterone. Researchers concluded DAA plays a role in the release and synthesis of testosterone and luteinizing hormone (Topo et al., 2009).

A more recent human study evaluated the influence of DAA on circulating testosterone (Willoughby & Leutholtz, 2013). In this randomized, double-blind manner, 20 healthy, recreationally active, resistance trained men (~23 years of age) took part in 28 days of heavy resistance training while ingesting 3 grams of DAA or placebo daily. Assessments of body composition, muscle strength, and serum hormones (total and free testosterone, luteinizing hormone, estrogen, and gonadotropin-releasing hormone) were made on day 0 and day 29. These results show there were similar gains in muscle mass and strength in both groups. Contrary to previous research, this study did not find any effects of DAA supplementation on testosterone levels. The differences these findings may be due to the age differences in subject's age and training status, as well as different baseline testosterone values.

Another recent study examined the effects of a DAA supplement on blood testosterone, along with subjective measures of health indicators (Bloomer, Gunnels, Moran, & Schriefer,). Ten overweight or obese men (mean age of 42 years) were assigned to groups where one group ingested one severing per day and the other ingested two servings per day of the supplement. One serving of the supplement contained 3120mg of DAA, 480mg of sodium nitrate, and 4000IU of vitamin D. After the supplementation period, subjects experienced an increase in subjective feeling of vitality and libido (Bloomer et al.). Testosterone values were impacted in subjects with low basal testosterone levels, but the impact was not seen in men with higher testosterone levels. DAA supplements may have positive outcome on testosterone concentrations if starting testosterone levels are low.

Conclusion

Maintaining normal levels of testosterone may provide several benefits for men and women of all ages. If testosterone levels are low, undesired effects may be seen in body composition, overall health and well-being. Pharmaceutical agents, dietary supplements, and herbal supplements have been used to remedy low testosterone concentrations and associated health related issues with moderate success. Common symptoms of low testosterone seen in men and women include low libido, chronic fatigue, and a decrease in overall well-being.

These symptoms may be treated with testosterone replacement therapy with pharmaceutical drugs such as transdermal testosterone patches or gels, injections, and implants. The use of dietary or herbal supplements instead of drugs may be used as an alternative to testosterone replacement therapy. DAA is one dietary supplement of great interest as it has shown to increase testosterone in some men, mainly those with low concentrations of testosterone. A daily dose of 3g of DAA may be enough to increase testosterone concentrations

in some men. More human research is warranted to determine the most effective dose and treatment period of DAA to raise testosterone levels. There is evidence for the use of *E. longifolia*, an herbal supplement, to elevate circulating testosterone and improve libido in men and women. While a 100mg/day dose of *E. longifolia* has been ineffective in raising testosterone levels, a 200mg/day dose has been shown to increase circulating testosterone. There is also evidence that maca root improves sexual desires, but it does not appear to have an effect on circulating testosterone. Effective doses of maca may be 1.5g or 3g per day. These herbal and dietary supplements may be effective in improving sexual desire and overall quality of life and require additional research.

Literature Gaps and Limitations

It appears that both women and men can benefit from testosterone replacement therapy. Both postmenopausal and premenopausal women with low basal testosterone have experienced increases in overall well-being, mood, and sexual function from testosterone replacement therapy. It is also possible that women may benefit in a similar manner as men from dietary or herbal supplementation. There is a need for a study to evaluate the use of botanical agents in women, as supplementation may elevate circulating testosterone and improve associated measures of sexual health and vitality. One study has shown how supplementation of *E. longifolia* in older women can increase testosterone, as well as muscle size and muscle strength (Henkel et al., 2014). Another study has shown that maca supplementation in postmenopausal women leads to improvements in mood and libido (Brooks et al., 2008).

Future research of botanical supplementation should focus on the population of premenopausal women suffering from low sexual desire. A proposed study would evaluate the ability of *E. longifolia* (400mg/day) to improve perceived quality of life and libido. Maca root

supplementation (1.5g to 3g/day) may also promote positive changes in subjective feelings of mood in this population. Another potential study would evaluate the effects of a combination of *E. longifolia* and maca, which may produce greater change in subjective feeling than one herbal agent alone.

Research Question and Hypothesis

The following research questions and hypothesis were formed based on current literature findings.

Question 1.

Does supplementation of *E. Longifolia* in combination with maca root by premenopausal women with hypoactive sexual desire disorder induce positive changes in the scores of the psychological general well-being index, the brief profile of female sexual function, and within a self-reported daily diary?

Question 2.

Does supplementation of *E. Longifolia* in combination with maca root by premenopausal women with hypoactive sexual desire disorder induce changes in muscular strength and endurance?

We hypothesize that supplementation of *E. longifolia* in combination with maca root by premenopausal women with hypoactive sexual desire disorder will improve subjective feelings such as mood, libido, and overall quality of life. A potential elevation in testosterone may be associated with an increase muscular strength and endurance. This novel approach to treating hypoactive sexual disorder may prove to be an alternative to the traditional pharmaceutical treatment.

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