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Research Article

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Effects of the Nuegra® from Male Silkworm Extract on Enhancement of the Masculine Function and Activation of Overall Physical Function

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The purpose of this investigation is to evaluate the effects of the Nuegra® on enhancement of the masculine and physical activities in general through measuring changes of the testosterone, FSH and subjective symptoms like fatigue, insomnia, urinary stream, muscular weakness, libido and erectile dysfunction. Total 168 male subjects were enrolled from 12 urology, internal medicine clinics and general practitioner. During the 6-week investigational period, 2 capsules of Nuegra® were given to the subjects right after meal for 4 weeks, and 1 capsule of Nuegra® was added each time in subjects with no or minimal effect. Testosterone and FSH levels were measured at first visit and last visit, for evaluating masculine activities. To avoid bias and standardize the test results, only one clinic was assigned as a central lab, and all blood samples were transferred. General information and subjective symptoms were evaluated at first visit and at 2 weeks interval, week 2, 4 and 6 using VAS (Visual Analogue Scale). The mean age of the subjects were 51.8±8.2 years old (range: 36.1−82.1). Based on the subjects who were tested on testosterone and FSH levels at day1 and week 6, the means were 4.4±1.4 nmol/L (range: 2.6−7.7), 8.6±9.6 mIU/mL (range: 0.3−40.4), respectively at day 1. At week 6, the results were 4.9 ±1.6 (2.6−8.9 range), 9.4±13.1 (1.0−53.9 range), respectively. Marginally significant difference between pre-dose and post-dose was present. Statistically significant differences were revealed in general assessment for subjective symptoms, fatigue, insomnia, erectile dysfunction, etc. In fatigue, response rates were 39.6, 65.4 and 76.4% at week 2, 4 and 6, respectively ($P < 0.0001$). Response rates for erectile dysfunction were 13.4, 41.2 and 72.7% at week 2, 4, and 6 ($P < 0.0001$), respectively. Response rates for libido were 13.6, 51.6 and 73.5% at week 2, 4, and 6 ($P < 0.0001$), respectively. For urinary stream response rates were 26.9, 44.7 and 66.8% at week 2, 4, and 6 ($P < 0.0001$), respectively. VAS for muscular weakness did not show significant results that response rates were 40, 60 and 80% at week 2, 4, and 6 from 8.2 ($P = 0.24$), respectively. Response rates for insomnia were 50, 60, 100% at week 2, 4, and 6 ($P < 0.0001$), respectively. The results shows that Nuegra® tends to enhance masculine activities including libido, erectile dysfunction and urinary stream and also effective for improving general conditions especially insomnia, muscular weakness and fatigue. In conclusion, this investigation has demonstrated that Nuegra® does not only have tendency to increase masculine activities through increased secretion of the testosterone and FSH but also improve general conditions such as erectile dysfunction, libido, fatigue and muscular power.

Key word: Nuegra®, Masculine function, Testosterone

Introduction

Nuegra® is a combined natural medicine product effective for enhancement of masculinity with natural, non-toxic ingredients free from side effects. The product is developed from a substance patented by the Rural Development

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Administration. Nuegra® is another product that made a scientific achievement from a folk remedy as prescribed in Dongyebogam. It is designed as a soft capsule so that it is easy to take in and carry. Therefore, it is an effective health supplement product for young and old men with reduced physical function or strength, weak urinary function, or complaints for fatigue. Nuegra® is composed of male silkworm moth (*Bombyx mori*), Acanthopanax centicosus, Schizandra chinensis, Rubus Coreanum, L-glutamine, freeze-dried royal jelly, Lycium chinense Mill., tocopherol, and effects of each constutient on masculinity enhancement are recorded in other documents. According to Dongyebogam, male silkworm moth that just came out into the world with penetration of cocoon, can be killed instantly and dried to be used as a aphrodisiac called male silkworm moth (*Bombyx mori*). A male moth starts mating as soon as it comes out into the world and has enough stamina to continue for a whole day mating with hundreds of female moths. Wings and legs taken off, two aged male silkworm moth (*Bombyx mori*) is lightly roasted so that it does not burn and then use as a medication. It enhances male stamina, prevent nocturnal ejaculation and hematuria and stimulate renal and urinary functions by warming them. It makes sexual intercourse strong by helping with stamina, thus making a tireless man after many intercourses.

Eleutheroside E, major constituent of Acanthopanax centicosus, is a lignan compound that prevents sexual activity from reducing due to stress and strengthens memory. Also according to a book called Shinnongbonchokyeong (New Agricultural Cultivation) written around the 1st century, it is well-known that Acanthopanax centicosus makes musculoskeletal system stronger, body lighter, prevents aging process, endure the cold, makes up for shortage in spirit and energy, and makes a person live long if exposed for a log time.

This research attempted to examine the efficacy and the effect of Nuegra® capsule on FSH (folliclestimulating hormone) and testosterone secretion which are one of the variables for masculinity and on general physical functions.

In an animal experiment with rats (Ryu *et al.*, 2002), effects of Nuegra® and Viagra on male hormone, NO content, sperm counts and endurance were compared. Ryu *et al.* (2002) reported 32.8% male hormone increase with Nuegra® compared to 9.9% increase with Viagra-administered group. NO content increased by 16.6% with Nuegra® compared to 5.4% increase with Viagra-administered group. Sperm counts increased by 41% with Nuegra® administration compared to 11.9% with Viagra-administered group. They also reported 60.0% increase of endurance in Nuegra®-administered group.

In a clinical trial conducted overseas, Lavallet *et al.* (1999) reports that FSH together with testosterone react on progesterone, are secreted from Leydig cells, and has synergistic action on proliferation of spermatogonia and maintaining quality and quantity of spermatogenesis. FSH is required to make testosterone also. It is reported that FSH is secreted throughout life in male, and is secreted into seminiferous tubule of testis to stimulate the production of testosterone and spermatogenesis as Dunfield *et al.* (2000) reported. Ben-Rafael *et al.* (2000) reported, in fertility and sterility, that rate of successful pregnancy for 40 male sterile patients treated with FSH replacement were significantly higher than the trial group.

Materials and Method

Experimental subjects

The purpose of this research was explained to outpatients and healthy males at 12 urology clinics and hospitals located in Seoul and its suburbs. 168 subjects who gave consent were registered with the consecutive test method and investigations were carried out. Effectiveness evaluation was possible in 153 patients who had their testosterone and FSH level checked before and after application. Safety evaluation was possible in 168 subjects who had taken Nuegra® at least once.

Administration method

Subjects were provided with two-week supply of soft Nuegra® capsule in the first visit, and were advised to take the capsule 3 times a day, 2 capsules at a time after meal. Where there is no or insignificant improvement of symptoms at a visit 4 weeks later, the dose was increased by one capsule, thus 3 capsules at a time, 3 times a day, for subsequent two weeks. Where a subject has other complications or pre-existing conditions, he/she was advised to continue appropriate dosage, and other special dietary treatment or administration of vitamins and digesters were not restricted.

Blood sampling

2cc of blood were collected from the subjects at initial visit and 6th week visit to measure Testosterone and FSH levels. For standardization and quality control of methods and values, specimen were taken into a hospital chosen as the Examination Center and measured there.

Data management and statistical analysis

All data recorded in charts were fed into computers and database for post-marketing surveillance study was established. For input, MS-ACCESS® was used. For data anal-

ysis, MS-Excel® SAS were used. Before establishing the database for post-marketing surveillance study, errors and defects in charts were extrapolated by comparing all the data in database 3 times. Descriptive analysis for each field was performed on finalized database. Then, appropriate contingency table was formed and analysis results were presented. Statistical analysis for cases was done on incidence of abnormal reactions and effectiveness under each factor. Significance of Nuegra®s effects on hormones were analyzed using repeated measures ANOVA test. Onset of effects under each factor and at each period was calculated using Chi-square test or Fishers exact test.

Results

General characteristics of subjects

A total of 168 subjects from 12 clinics were registered, as in following Table 1. Looking at the background information of the subjects, average age was 51.8±8.2 (range: 36.1–82.1). Average height was 170±5.3 cm (range: 154.0–184 cm). Average weight was 70.1±8.0 kg (range: 52.0–96.0 kg). Average BMI was 24.1±2.3 (range: 18.0–32.2) Past medical history was found in 33 subjects who suffered from conditions such as hypertension, diabetes, bronchitis, gastritis, hepatitis. With the exception of two unknown cases, there was no past medical history in remaining 133 patients requiring attention. Complications the subjects were suffering from included hypertension, diabetes mellitus, gastritis, chronic prostatitis, asthma and others in 24 subjects. With the exception of two unknown cases, there were no complications requiring attention in remaining 142 subjects. Idiosyncrasies such as allergies were present in 13 subjects, 3 were unknown, and remaining 152 did not show allergies. Alcoholism and smoking history were also investigated. 62 subjects smoked and 106 subjects did not smoke. 116 subjects had alcoholism and 51 subjects (with the exception of 1 unknown case) said that they did not have alcoholisms. 14 cases of pre-existing symptoms including sputum, cough, hypertension, diabetes mellitus, fatigue and others were complained about. 6 cases were mild, 7 cases were intermediate, and 1 case of severe erectile dysfunction was reported. To treat intercurrent diseases, 47 different types of medications including an anti-hypertensive drug were administered. Details are shown in Table 2, 3, 4, 5, 6, 7, 8. Most popular reasons for using Nuegra® was fatigue with 118 cases. There were 70 cases of erectile dysfuction, 105 cases of impotence, 42 cases of thinning and lacking strength in urinary stream. Overall most complaints were concerning declined virility. Details are described in Table 9.

Table 1. Number of cases

Research institutes	Frequency	Percentage
Korea Ace Urology Clinic	11	6.55
Dr. Kim, Doo-Chuns Urology Clinic	5	2.98
Dr. Kims Clinic	21	12.5
Dr. Kim, Jung-Kwon's Internal Medicine Clinic	8	4.76
Myeong Internal Medicine Clinic	11	6.55
Big Man Urology Clinic	20	11.9
Dr. Song, Young-Seok's Urology Clinic	30	17.86
Ye Urology Clinic	5	2.98
Dr. Cheons Urology Clinic	15	8.93
Dr. Chung, Byeong-Dong's Urology Clinic	11	0.6
Dr. Chin, Kil-Nams Urology Clinic	20	11.9
Dr. Han, Hos Urology Clinic	11	6.55
Total	168	100

Administration conditions

On average, 278.8±61.0 capsules (range 84.0–510) were administered to each case of 168 patients for 46.5±9.9 days (range: 14.0–85 days). Dosage increase occurred in 6 cases.

Effectiveness Evaluation

1) Change of testosterone and FSH

Testosterone levels decreased from 4.8 nmol/L before Nuegra® application to 4.5 nmol/L after Nuegra® administration, showing a reduction by 0.3 nmol/L with paired t-test analysis. However, there were many cases where the end-date for administration and the measuring date were different, reducing the accuracy of the measurements. Therefore, a paired t-test analysis for the before-after difference was done again using 80 cases where measurement was done on the end-date for administration. Testosterone level on average increased from 4.4 nmol/L to 4.9 nmol/L, which was marginally significant (P = 0.06), and in 80 cases where the measurements were made 3 days within the end of administration, average levels

Table 2. Demographical details

Average Age (yrs): 51.8±8.2 (36.1–82.1)	(N = 166)
Average Height (cm): 170.5±5.3 (154.0–184.0)	(N = 166)
Average Weight (kg): 70.1±8.0 (82.0–96.0)	(N = 166)
Average BMI (kg/square meter): 24.1±2.3 (18.0–32.2)	(N = 166)

*unrecorded: 2 subjects.

Table 3. Patients background

All patients		No. of cases
Sex	Male	168 (100%)
Age	< 40	14 (8.3)
	40 ~ 49	71 (42.3)
	50 ~ 59	54 (32.1)
	60 ~ 69	25 (14.9)
	> 71	4 (2.4)
	Total	168 (100%)
BMI	< 25	116 (69.0)
	> 25	52 (31.0)
	Total	168 (100%)
Admission or Outpatient	Outpatient	168 (100%)
	Yes	33 (19.9)
Past medical history	No	133 (80.1)
	Unknown	2 (1.5)
	Total	168 (100%)
	Yes	24 (14.5)
intercurrent diseases	No	142 (85.5)
	Unknown	2 (1.4)
	Total	168 (100%)
	Yes	13 (7.9)
Idiosyncrasy	No	152 (92.1)
	Unknown	3 (1.9)
	Total	168 (100%)
Smoking history	Yes	62 (36.9)
	No	106 (63.1)
	Total	168 (100%)
Alcoholism	Yes	116 (69.5)
	No	51 (30.5)
	Unknown	1 (1.9)
	Total	168 (100%)
Pre-existing symptoms	Yes	14 (8.1)
(overlap allowance)	No	159 (91.9)
	Total	173 (100%)
Combined drugs	Yes	47 (26.6)
(Overlap allowance)	No	130 (73.4)
	Total	177 (100%)

Table 4. Past medical history (no. of cases)

Hypertension	14
Diabetes	5
Bronchitis	3
Gastritis	3
Hepatitis	3

Table 5. Intercurrent disease (no. of cases)

Hypertension	9
diabetes	4
Gastritis	2
chronic prostatitis	4
asthma	2

*3 cases unrecorded.

Table 6. Allergies (no. of cases)

chronic urticaria	2
Nickel allergy	1
Slight psoriasis	1
Pollen	1
chronic urticaria, itchiness	1
chrysalis, Aspirin	1
Peach	1
rhinitis	1
Allergy to mugworts	1
Allergic asthma	1
Allergic rhinitis	1

Table 7. Pre-existing symptoms

Sputum, cough (Dry Cough)	1
Hypertension	2
Costal neuralgia	1
diabetes	1
chronic prostatitis	1
Athletes foot	1
erectile dysfuction	1
Lack of strength in urinary stream	1
stomach cancer	1
prostatic hyperplasia	1
Impotence	1
fatigue	2
Total (no. of cases)	14

decreased 4.7 to 4.6, which was not a statistically significant difference, nevertheless there was a tendency for rebound effect. On the other hand, FSH level which enhances the sperm function increased from 7.7 mIU/mL to 8.0 mIU/mL, however the difference was not statistically significant. (P=0.16). Also, in 80 cases where measurements were made on the end-date for administration, average FSH levels increased from 8.6 to 9.6, with no statistically significant difference (P=0.4). In 80 cases where measurements were made within 3 days of the end of administration, average FSH levels increased by 0.3 from 7.8 to 8.2, again with no statistically significant difference (P=0.3). Details are described in Table 10, 11 and 12.

2) Changes in subjective symptoms

Effectiveness evaluation according to reasons for using Nuegra® were performed with repeated measure ANOVA

Table 8. Degree of Pre-existing symptoms

Types of Pre-existing symptoms	Degree of symptoms (no. of cases)			
	Mild	Moderate	Severe	Total
sputum,cough (dry cough)	1	0	0	1
Hypertension	1	1	0	2
Costal neuralgia	1	0	0	1
Diabetes	0	1	0	1
chronic prostatitis	1	0	0	1
Athletes foot	1	0	0	1
erectile dysfunction	0	0	1	1
Lack of strength in urinary stream	0	1	0	1
stomach cancer	1	0	0	1
prostatic hyperplasia	0	1	0	1
Impotence	0	1	0	1
Fatigue	0	2	0	2
Total (no. of cases)	6	7	1	14

test. There were statistically significant improvement in all symptoms mentioned-fatigue, erectile dysfuction, impotence, weak urinary stream, muscular atrophy, sleep disturbance (refer to Table 11). Such symptoms showed significant improvement from 2 weeks after administration, and details are described in Table 13 and 14.

For onset of effect by reasons for usage as shown in Table 15, muscular atrophy and sleep disturbance showed distinctive improvement from 2 weeks after administration, and its effectiveness continues to through 4 and 6 weeks after administration.

Table 9. Reasons for usage

Reasons for usage	Cases (%)
Fatigue	118 (33.9)
erectile dysfunction	70 (20.1)
Impotence	105 (30.2)
Thinning and lack of strength for urinary stream	42 (12.1)
muscular atrophy	5 (1.4)
sleep disturbance	7 (2.0)
Others	1 (0.3)
Total	348 (100%)

Looking at overall response, cases that showed improvement at two weeks after administration were 99 cases (62.6%) out of total 159 cases with one exceptional case that could not be determined. This figure increased to 136 cases (86.1%) at 4 weeks and 134 cases out of 154 (87%) at 6 weeks after administration.

The degree of improvement of overall response rate at each administration period are shown in Table 16 and 17.

The degree of improvement of subjective symptoms at each administration period are described in Table 14, 15, 16, 17, 18 and 19. Looking at the degree of improvement

Table 10. Changes in effectiveness variables

Variables	Period	No. of cases	Average	S. D.	Minimum value	Maximum value	Paired t-test	
Testosterone (nmol/L)	Before administration	168	4.8	1.9	1.6	12.9	t-value	Pr > |t|
	After administration	153	4.5	1.6	1.5	10.1		
	Difference	153	−0.3	1.9	−10.0	8.0	-2.09	0.04
FSH (mIU/L)	Before administration	168	7.7	5.9	0.01	48.5	t-value	Pr > |t|
	After administration	153	8.0	6.5	0.1	53.9		
	Difference	153	0.3	2.9	−13.3	13.6	1.42	0.16

Table 11. The change of Testosterone and FSH level examined on the date of administration

Variables	Period	No. of cases	Average	S. D.	Minimum value	Maximum value	Paired t-test	
Testosterone	Before administration	53	4.4	1.4	2.6	7.7	t-value	Pr > |t|
	After administration	51	4.9	1.6	2.6	8.9		
	Difference	51	0.5	1.0	−2.4	1.5	2.05	0.06
FSH	Before administration	53	8.6	9.6	0.30	40.4	t-value	Pr > |t|
	After administration	51	9.4	13.1	1.0	53.9		
	Difference	51	0.8	4.0	−4.0	13.6	0.8	0.4

Table 12. The change of Testosterone and FSH level examined within 3 days of the end of administration

Variables	Period	No. of Cases	Average	S. D.	Minimum value	Maximum value	Paired t-test	
Testosterone	Before administration	82	4.7	1.6	2.0	12.7	t-value	Pr > |t|
	After administration	80	4.6	1.5	2.1	9.1		
	Difference	80	−0.1	1.8	−9.8	5.6	−0.57	0.6
FSH	Before administration	82	7.8	7.1	0.01	48.5	t-value	Pr > |t|
	After administration	80	8.2	7.0	0.1	54.0		
	Difference	80	0.3	2.9	−9.4	13.6	1.05	0.3

Table 13. Effectiveness due to reasons for usage (VAS Change)

Variables	Period	No. of cases	Average (cm)	S. D.	Minimum value	Maxinum Value	F-value*	Pr > F
Fatigue	Before administration	119	5.8	2.4	0.0	10.0	146.6	<.0001
	After 2 weeks	117	4.7	2.4	0.0	9.0		
	After 4 weeks	114	3.7	2.6	0.0	9.5		
	After 6 weeks	111	3.0	2.5	0.0	9.0		
Erectile dysfunction	Before administration	69	6.8	2.6	0.5	10.0	84.7	<.0001
	After 2 weeks	67	6.0	2.2	2.0	10.0		
	After 4 weeks	63	5.1	2.2	1.0	10.0		
	After 6 weeks	62	4.2	2.3	0.0	10.0		
Impotence	Before administration	105	6.1	2.4	2.0	10.0	136.8	<.0001
	After 2 weeks	103	5.2	2.0	2.0	9.0		
	After 4 weeks	101	4.3	2.3	0.0	9.5		
	After 6 weeks	98	3.3	2.6	0.0	9.0		
Weak urinary stream	Before administration	42	5.9	1.9	2.0	9.5	37.9	<.0001
	After 2 weeks	41	4.9	2.1	1.7	9.0		
	After 4 weeks	38	4.1	1.8	0.9	9.0		
	After 6 weeks	36	3.4	1.7	0.5	9.0		
Muscular atrophy	Before administration	5	8.2	1.3	7.0	10.0	5.4	0.01
	After 2 weeks	5	4.8	2.8	0.0	7.0		
	After 4 weeks	5	4.6	2.7	0.0	7.0		
	After 6 weeks	5	4.4	2.6	0.0	7.0		
Sleep disturbance	Before administration	7	7.0	1.6	3.6	8.3	6.5	0.008
	After 2 weeks	6	4.8	1.7	2.0	7.0		
	After 4 weeks	5	4.0	1.6	2.0	6.0		
	After 6 weeks	5	2.8	1.4	1.5	5.0		

*Results of Repeated measures ANOVA test.

of subjective symptoms at each administration period, fatigue showed 39.6% improvement after 2 weeks of administration, and 65.4% and 76.4% after 4 and 6 weeks respectively ($P < 0.0001$). Erectile dysfunction showed 13.4% improvement after 2 weeks of administration, and, 41.2% and 72.7% after 4 and 6 weeks, respectively ($P < 0.0001$). Impotence showed 13.6% improvement after 2 weeks of administration, and 51.6% and 73.5% after 4 and 6 weeks respectively ($P < 0.0001$). Weak urinary stream showed 26.9% improvement after 2 weeks of administration, and 44.7% and 66.8% after 4 and 6 weeks respectively ($P < 0.0001$). Thus, all of the above values showed statistical significance. For muscular atrophy and sleep disturbance, significance could not be proved because of small sample size, however improvement rate was 60% at 4 weeks of administration for both symptoms, and rates were 80% and 100% at 6 weeks of administration for muscular atrophy and sleep disturbance respectively

Table 14. Response rate due to reasons for usage (VAS scale % change)

Variables	period	No. of cases	Average (%)	S. D.	Mininum value	Maximum value	F-value*	Pr > F
Fatigue	After 2 weeks	116	−19.0	21.1	−100.0	29.0	97.01	<.0001
	After 4 weeks	113	−38.6	30.4	−100.0	25.0		
	After 6 weeks	110	−52.5	33.5	−100.0	0.0		
Impotence	After 2 weeks	67	−12.1	14.8	−75.0	9.3	65.7	<.0001
	After 4 weeks	63	−25.1	20.3	−78.3	0.0		
	After 6 weeks	62	−39.7	24.8	−100.0	0.0		
Impotence	After 2 weeks	103	−11.0	16.7	−76.5	7.9	99.2	<.0001
	After 4 weeks	101	−29.0	24.0	−100.0	16.7		
	After 6 weeks	98	−49.1	33.5	−100.0	0.0		
Weak Urinary	After 2 weeks	41	−14.6	23.0	−75.0	25.0	31.8	<.0001
Stream	After 4 weeks	38	−26.0	24.6	−85.7	0.0		
	After 6 weeks	36	−38.7	27.7	−90.0	0.0		
Muscular	After 2 weeks	5	−38.2	38.0	−100.0	−12.5	1.7	0.24
Atrophy	After 4 weeks	5	−41.1	36.2	−100.0	−12.5		
	After 6 weeks	5	−43.9	34.1	−100.0	−12.5		
Sleep	After 2 weeks	6	−27.7	27.8	−75.9	5.6	3.1	0.01
Disturbances	After 4 weeks	5	−35.4	34.1	−71.4	11.1		
	After 6 weeks	5	−55.3	24.1	−78.6	−28.6		

*Result of repeated measures ANOVA test.

Table 15. Onset of effect and effectiveness due to reasons for usage (VAS)

Period	Fatigue	Erectile dysfunction	Impotence	Urinary stream	Muscular atrophy	Sleep disturbance
Before Administration	5.8	6.8	6.1	5.9	8.2	7.0
After 2 weeks	4.7	6.0	5.2	4.9	4.8	4.8
After 4 weeks	3.7	5.1	4.3	4.1	4.6	4.0
After 6 weeks	3.0	4.2	3.3	3.4	4.4	2.8

Table 16. Overall response at 4 weeks after administration

Frequency		Overall response 4 weeks after administration					Total
		Marked improvement	Improvement	Some improvement	Some change	Unable to determine	
Overall response 2 weeks after administration	Marked improvement	3	1	0	0	0	4
	Improvement	0	17	4	0	0	21
	Some improvement	0	21	49	4	0	74
	Some change	0	3	38	18	0	59
	Unable to deyermine	0	0	0	0	1	1
Total		3	42	91	22	1	159

(muscular atrophy: P=0.24, sleep disturbance: P=0.01).

When Nuegra® was administered to a patient specifically complaining about erectile dysfunction, and the degree of improvement marked on VAS scale, 8 out of 63 total cases (12.7%) showed improvement at two weeks of administration. At 4 and 6 weeks of administration, 16 (25.4%) and 45 (72.6%) cases showed improvement respectively (Refer to Tables 20, 21). Increase in the degree of improvement at 4 weeks and 6 weeks of administration from 2 weeks of administration can be clearly observed in Table 20 and Table 21 showing improvements of all symptoms.

Table 17. Overall response 6 weeks after administration

Frequency		Overall response 6 weeks after administration					Total
		Marked improvement	Improvement	Some improvement	Some change	Unable to determine	
Overall response 2 weeks After administration	Marked improvement	2	1	0	0	0	3
	Improvement	3	14	3	0	0	20
	Some improvement	5	31	30	7	0	73
	Some change	4	20	21	13	0	58
	Unable to determine	0	0	0	0	1	1
Total		14	66	54	20	1	155

Table 18. The degree of improvement of subjective symptoms at each administration period fatigue

Degree of improvement	No. of cases (%)		
	2 weeks after administration	4 weeks after administration	6 weeks after administration
Marked improvement	2 (1.7)	11 (9.7)	29 (26.4)
Improvement	3 (2.6)	24 (21.2)	23 (20.9)
Some improvement	41 (35.3)	39 (34.5)	32 (29.1)
No change	70 (60.3)	39 (34.5)	26 (23.6)
Total	116 (100%)	113 (100%)	110 (100%)

Table 19. The degree of improvement of subjective symptoms at each administration period-erectile dysfuction

Degree of improvement	No. of cases (%)		
	2 weeks after administration	4 weeks after administration	6 weeks after administration
Marked improvement	0 (0.0)	1 (1.6)	4 (6.5)
Improvement	1 (1.5)	4 (6.3)	13 (21.0)
Some improvement	8 (11.9)	21 (33.3)	28 (45.2)
No change	58 (86.6)	37 (58.7)	17 (27.4)
Total	67 (100%)	63 (100%)	62 (100%)

Table 20. The degree of improvement of subjective symptoms at each administration period Impotence

Degree of improvement	No. of cases (%)		
	2 weeks after administration	4 weeks after administration	6 weeks after administration
Marked improvement	1 (1.0)	3 (3.0)	24 (24.5)
Improvement	4 (3.9)	15 (14.9)	16 (16.3)
Some improvement	9 (8.7)	34 (33.7)	32 (32.7)
No change	89 (86.4)	49 (48.5)	26 (26.5)
Total	103 (100%)	101 (100%)	98 (100%)

Table 21. The degree of improvement of subjective symptoms at each administration periodWeak urinary stream

Degree of improvement	No. of cases (%)		
	2 weeks after application	4 weeks after application	6 weeks after application
Marked improvement	0 (0.0)	1 (2.6)	2 (5.6)
Improvement	4 (9.8)	5 (13.2)	11 (30.6)
Some improvement	7 (17.1)	11 (28.9)	11 (30.6)
No change	30 (73.2)	21 (55.3)	12 (33.3)
Total	41 (100%)	38 (100%)	36 (100%)

Table 22. The degree of improvement of subjective symptoms at each administration period muscular atrophy

Degree of improvement	No. of cases (%)		
	2 weeks after administration	4 weeks after administration	6 weeks after administration
Marked improvement	1 (20.0)	1 (20.0)	1 (20.0)
Improvement	0 (0.0)	0 (0.0)	0 (0.0)
Some improvement	1 (20.0)	2 (40.0)	3 (60.0)
No change	3 (60.0)	2 (40.0)	1 (20.0)
Total	5 (100%)	5 (100%)	5 (100%)

Table 23. The degree of improvement of subjective symptoms at each administration periodsleep disturbance

Degree of improvement	No. of cases (%)		
	2 weeks after administration	4 weeks after administration	6 weeks after administration
Marked improvement	1 (16.7)	0 (0.0)	1 (20.0)
Improvement	0 (0.0)	2 (40.0)	2 (40.0)
Some improvement	2 (33.3)	1 (20.0)	2 (40.0)
No change	3 (50.0)	2 (40.0)	0 (0.0)
Total	6 (100%)	5 (100%)	5 (100%)

Table 24. The degree of improvement of subjective symptoms at each administration period- overview

Symptoms	No. of cases (%)		
	2 weeks after administration	4 weeks after administration	6 weeks after administration
Fatigue	46 (39.6)	74 (65.4)	84 (76.4)
erectile dysfunction	9 (13.4)	26 (41.2)	45 (72.7)
Impotence	14 (13.6)	52 (51.6)	72 (73.5)
Urinary stream	11 (26.9)	17 (44.7)	24 (66.8)
muscular atrophy	2 (40.0)	3 (60.0)	4 (80.0)
sleep disturbance	3 (50.0)	3 (60)	5 (100%)

Table 25. Improvement in patients with erectile dysfuction (VAS scale category)

Frequency		Improvement 4 weeks after administration				Total
		Marked improvement	Improvement	Some improvement	No change	
Improvement 2 weeks after administration	Marked improvement	0	0	0	0	0
	Improvement	0	1	0	0	1
	Some improvement	0	2	4	1	7
	No change	1	1	17	36	55
Total		1	4	21	37	63

Frequency		Improvement 6 weeks after administration				Total
		Marked improvement	Improvement	Some improvement	No change	
Improvement 2 weeks after administration	Marked improvement	0	0	0	0	0
	Improvement	0	1	0	0	1
	Some improvement	1	2	4	0	7
	No change	3	10	24	17	54
Total		4	13	28	17	62

Table 26. Overall Improvement (patient with erectile dysfunction)

Frequency		Overall response 4 weeks after administration				
		Marked improvement	Improvement	Some improvement	No change	Unable to determine
Overall response 2 weeks after administration	Marked improvement	1	1	0	0	0
	Improvement	0	6	1	0	0
	Some improvement	0	8	17	3	0
	No change	0	1	16	8	0
	Unable to determine	0	0	0	0	1
Total		1	16	34	11	1

Frequency		Overall response 6 weeks after administration				
		Marked improvement	Improvement	Some improvement	No change	Unable to determine
Overall response 2 weeks after administration	Marked improvement	1	1	0	0	0
	Improvement	0	6	1	0	0
	Some improvement	1	14	9	3	0
	No change	0	7	12	6	0
	Unable to determine	0	0	0	0	0
Total		2	28	22	9	0

Table 27. Abnormal Symptoms and Patient Profile

Chart no.	Abnormal symptoms	SAE	Degree	Discovered date	Recovery date	Action	Result	Association with Nuegra®
360317	Digestive difficulty	no	mild	2001-12-12	2001-12-14	none	recovered	unable to determine
540315	Sputum	no	mild	2001-12-13	2001-12-15	none	recovered	unable to determine
570208	Temporary chest palpitation	no	mild	2001-12-25	2001-12-27	none	recovered	unable to determine
570501	Drowsiness	no	mild			none	recovered	low
601021	Increased stool frequency	no	mild	2001-12-15	2001-12-17	none	recovered	unable to determine

In 6 cases with increased dosage, improvements were shown in 3 cases at 2 weeks and 4 weeks of administration. However, after the actual dosage increase, at 6 weeks of administration, improvements were shown in 5 cases therefore enhancement of effectiveness was clarafied, even though statistical significance could not be proven because of small sample size.

Safety Evaluation

For abnormal symptoms, digestive difficulty, sputum, temporary chest palpitation, drowsiness and increased stool frequency occurred once each. All abnormal symptoms were mild, and association with Nuegra® could not be determined with the exception of one drowsiness case in which association was determined to be low. Therefore, Nuegra® is considered as a relatively safe medication with hardly any abnormal symptoms.

Discussion

Nuegra® containing extracts from male silkworm cocoon has been known for its effectiveness on the enhancement of males stamina and the improvement of physical activity. According to Cho *et al.* (1998) taking 500 mg of silkworm powder 3 times a day after meals for four weeks is effective in lowering blood glucose and blood lipid levels. Also, Eleutheroside E, major constituent of Acanthopanax centicosus, is a lignan compound that prevents sexual activity from reducing due to stress and strengthens mem-

ory. Also according to a book called Shinnongbon-chokyeong (New Agricultural Cultivation) written around the 1st century, it is well-known that acanthopanax centicosus makes musculoskeletal system stronger, body lighter, prevents aging process, endure the cold, makes up for shortage in spirit and energy, and makes a person live long if exposed for a log time.

Nuegra® is a new artificial combinant substance containing extracts from male silkworm (Ryu *et al.*, 2002). This product scientifically demonstrates the effect of silkworm in folk medicine.

According to an animal experiment with white rats by Ryu *et al.* (2002) where effects by Nuegra® and Viagra on male hormone, NO content, sperm counts and endurance were compared. Male hormone increased by 32.8% with Nuegra® compared to 9.9% increase with Viagra-administered group. NO content increased by 16.6% with Nuegra® compared to 5.4% increase with Viagra-administered group. Sperm counts increased by 41% with Nuegra® compared to 11.9% with Viagra-administered group. Ryu *et al.* (2002) also reported 60.0% increase of endurance in Nuegra®-administered group.

In a clinical trial conducted overseas, Lavallet *et al.* (1999) reported that FSH together with Testosterone react on progesterone, are secreted from Leydig cells, and has synergistic action on proliferation of spermatogonia and maintaining quality and quantity of spermatogenesis.

Dirnfield *et al.* (2000) reported, the results of a clinical trial that FSH replacement therapy were effective on 178 male sterile patients. Ben-Rafael *et al.* (2000) reported, that rate of successful pregnancy for 40 male sterile patients treated with FSH replacement were significantly higher than the trial group.

This research also looked at efficacy and effect of Nuegra® capsules on overall physical function and the secretion of FSH and Testosterone two variables for virility. The testosterone level showed increase from 4.4 nmol/L before Nuegra® administration to 4.9 nmol/L after Nuegra® administration with paired t-test analysis of before-after difference, and this difference was marginally significant ($P=0.06$). In 80 cases where measurement took place within 3 days of the end of administration, average levels decreased from 4.7 to 4.6 and thus statistically insignificant, however there was tendency for rebound effect and thus it is considered as requiring more deep observation.

On the other hand, FSH level which enhances the sperm function increased from 7.7 mIU/mL to 8.0 mIU/mL. Even though the difference was not statistically significant ($P=0.16$), there was a significant clinical change.

In addition in cases where measurements were made on the end-date for administration, average FSH levels increased from 8.6 to 9.6, with no statistically significant difference ($P=0.4$). In 80 cases where measurements were made within 3 days of the end of administration, average FSH levels increased by 0.3 from 7.8 to 8.2, again with no statistically significant difference ($P=0.3$).

Such results shows that Nuegra® makes statistically and clinically significant improvement on FSH and testosterone secretion, scientifically proving its actual effectiveness on enhancing virility. These results correspond to animal experiments performed by Ryu *et al.* (2002).

Effects of Nuegra® on symptoms such as impotence, sleep disturbance, weak urinary stream increase more significantly at 4 and 6 weeks of administration than at 2 weeks of administration. Looking at the degree of improvement of subjective symptoms at each period, fatigue showed 39.6% improvement rate at 2 weeks, 65.4% and 76.4% at 4 and 6 weeks respectively, thus showing a clear improvement after 4 weeks of administration ($P < 0.0001$). Erectile dysfunction showed 13.4% improvement rate at 2 weeks, 41.2% and 72.7% at 4 and 6 weeks respectively, thus long-term administration is recommended ($P < 0.0001$). Impotence showed 13.6% improvement rate at 2 weeks of administration, 51.6% and 73.5% at 4 and 6 weeks respectively, thus here long-term administration is also recommended ($P < 0.0001$). The symptom of weak urinary stream showed 26.9% improvement rate at two weeks of administration, 44.7% and 66.8% at 4 and 6 weeks respectively, showing relatively low rate of improvement ($P < 0.0001$).

There were small number of cases with muscular atrophy symptoms and sleep disturbance therefore it is not possible to determine the significance of improvements. Nevertheless, improvement rate was 60% at 4 weeks of administration, 80% and 100% for muscular atrophy and sleep disturbances respectively at 6 weeks of administration, showing the effectiveness of the substance on these symptoms (muscular atrophy: $P=0.24$, sleep disturbance: $P=0.01$).

These results show that Nuegra® has significant effects on the subjective symptoms listed above, and for enhancement of masculinity in conditions such as impotence or erectile dysfunction, long-term administration is considered to be effective.

When Nuegra® was administered in a patient specifically complaining about erectile dysfunction, and a degree of improvement marked on VAS scale, 8 out of 63 total cases (12.7%) showed improvement at two weeks of administration. At 4 and 6 weeks of administration, 16 (25.4%) and 45 (72.6%) cases showed improvement respectively

Overall response from these patients regarding degree of improvement also shows that 24 out of 62 cases

(38.7%) indicated more improvement than "little improvement" category. At 4 and 6 weeks of administration, figures were 51 out of 62 (82.3%) and 52 out of 61 (85.2%) respectively, showing that Nuegra® is effective for erectile dysfunction.

Increasing dosage was carried out in only 6 subjects out of a total of 168. Improvements were shown in 3 subjects at 2 weeks and 4 weeks of administration, however after the actual dosage increase took place, improvements were shown in 5 subjects at 6 weeks of administration. Thus, the relation of increased effect to increased dosage was clearly shown, even though significance could not be proven because of small number of cases. This suggests that effectiveness of Nuegra® may be dose-dependent and further research on this area will be required. On the other hand, where subjects had a past history of hypertension, diabetes, or other complications, or even where subjects had smoking history, alcohlisml, or determined as obese (BMI > 25), effects of Nuegra® did not deteriorate in these subjects (refer to Appendix).

In Summary, Nuegra® can be expected to have effects such as improving physical strength, losing the feeling of fatigue and increasing stamina in middle-aged men who frequently complain general fatigue because of decreased in physical strength and stamina. Even though excluded from this particular investigation, young men and even women are expected to have beneficial effects from this medication. However, as of present, clinical data on effectiveness and scientific bases for dose configuration are not sufficient, and thus more in-depth observation will be required.

Summary

1. When effects of Nuegra® on variables for virility FSH and Testosterone are compared before and after administration, there was statistically and clinically significant increase after the administration, and there was a rebound effect after the end of aadministration.
2. When effects of Nuegra® on subjective symptoms are compared for before and 2, 4, and 6 weeks after administration, the percentage of cases showing improvement at 2-week after overall response was 62.6%. At 4 weeks and 6 weeks, the percentages were 86.1% and 87.0% respectively, showing a statistically significant improvement and clinical significance could be discovered.

Looking at overall degree of improvement of subjective symptoms at each administration period, fatigue showed 39.6% improvement after 2 weeks of administration, and 65.4% and 76.4% after 4 and 6 weeks respectively ($P < 0.0001$). Erectile dysfunction showed 13.4% improvement

Appendix 1. Validity comparison by smoking habit for each period after application

(2 weeks after administration)

Effectiveness	No. of cases (%)	
	Smoker	Non-smoker
Effective	38 (63.3)	62 (59.6)
Non-effective	22 (36.7)	42 (40.4)
Total	60 (100%)	104 (100%)

(4 weeks after administration)

Effectiveness	No. of cases (%)	
	Smoker	Non-smoker
Effective	53 (91.4)	83 (82.2)
Non-effective	5 (8.6)	18 (17.8)
Total	58 (100%)	101 (100%)

(6 weeks after administration)

Effectiveness	No. of cases (%)	
	Smoker	Non-smoker
Effective	52 (89.7)	82 (84.5)
Non-effective	6 (10.3)	15 (15.5)
Total	58 (100%)	97 (100%)

Appendix 2. Effectiveness comparison due to alcoholism at each administration period

(2 weeks after administration)

Effectiveness	No. of cases (%)	
	Alcoholism	Non-alcoholism
Effective	68 (60.2)	32 (62.7)
Non-effective	45 (39.8)	19 (37.3)
Total	113 (100%)	51 (100%)

(4 weeks after administration)

Effectiveness	No. of cases (%)	
	Alcoholism	Non-alcoholism
Effective	94 (84.7)	42 (87.5)
Non-effective	17 (15.3)	6 (12.5)
Total	111 (100%)	48 (100%)

(6 weeks after administration)

Effectiveness	No. of cases (%)	
	Alcoholism	Non-alcoholism
Effective	98 (89.9)	36 (78.3)
Non-effective	11 (10.1)	10 (21.7)
Total	109 (100.0)	46 (100.0)

Appendix 3. Effectiveness comparison of BMI at each administration period

BMI (2 weeks after administration)

Effectiveness	No. of cases (%)	
	<25	>25
Effective	66 (59.5)	34 (66.7)
Non-effective	45 (40.5)	17 (33.3)
Total	111 (100%)	51 (100%)

BMI (4 weeks after administration)

Effectiveness	No. of cases (%)	
	<25	>25
Effective	97 (89.8)	37 (75.5)
Non-effective	11 (10.2)	12 (24.5)
Total	108 (100%)	49 (100%)

BMI (6 weeks after administration)

Effectiveness	No. of cases (%)	
	<25	>25
Effective	93 (87.7)	39 (83.0)
Non-effective	13 (12.3)	8 (17.0)
Total	106 (100%)	47 (100%)

Appendix 4. Effectiveness comparison at each administration period in cases with previous history of hypertension

Hypertension (2 weeks after administration)

Effectiveness	No. of cases (%)	
	Hypertension	No hypertension
Effectiveness	5 (41.7)	95 (62.5)
Non-effectiveness	7 (58.3)	57 (37.5)
Total	12 (100%)	152 (100%)

Hypertension (4 weeks after administration)

Effectiveness	No. of cases (%)	
	Hypertension	No hypertension
Effectiveness	9 (81.8)	127 (85.8)
Non-effectiveness	2 (18.2)	21 (14.2)
Total	11 (100%)	148 (100%)

Hypertension (6 weeks after administration)

Effectiveness	No. of cases (%)	
	Hypertension	No hypertension
Effectiveness	9 (81.8)	125 (86.8)
Non-effectiveness	2 (18.2)	19 (13.2)
Total	11 (100%)	144 (100%)

Appendix 5. Effectiveness comparison at each administration period in cases with previous history of diabetes

Diabetes (2-weeks after administration)

Effectiveness	No. of cases (%)	
	Diabetic	Non-diabetic
Effective	3 (50.0)	97 (61.4)
Non-effective	3 (50.0)	61 (38.6)
Total	6 (100%)	158 (100%)

Diabetes (4-weeks after administration)

Effectiveness	No. of cases (%)	
	Diabetic	Non-diabetic
Effective	4 (80.0)	132 (85.7)
Non-effective	1 (20.0)	22 (14.3)
Total	5 (100%)	154 (100%)

Diabetes (6 weeks after administration)

Effectiveness	No. of cases (%)	
	Diabetic	Non-diabetic
Effective	4 (100.0)	130 (86.1)
Non-effective	0 (0.0)	21 (13.9)
Total	4 (100.0)	151 (100.0)

after 2 weeks of administration, and, 41.2% and 72.7% after 4 and 6 weeks respectively ($P < 0.0001$). Impotence showed 13.6% improvement after 2 weeks of administration, and 51.6% and 73.5% after 4 and 6 weeks respectively ($P < 0.0001$). Weakness of urinary stream showed 26.9% improvement after 2 weeks of administration, and 44.7% and 66.8% after 4 and 6 weeks respectively ($P < 0.0001$). As for muscular atrophy and sleep disturbance, there was no significance in the differences because of small number of cases, however improvement rate was 60% at 4 weeks of administration for both symptoms, and rates were 80% and 100% at 6 weeks of administration for muscular atrophy and sleep disturbance, respectively.

3. Effect changes in cases of increased dosage

Significance could not be shown because of small number of cases (6 cases). Nevertheless, increased effects were evident in 5 of the 6 cases.

4. Summary of Onset of the effects

Improvement of symptoms appeared at 2 weeks after Nuegra® administration, however the degree of improvement is very low compared to 4 or 6 weeks after administration. Therefore at least 4 weeks of administration is recommended.

5. Evaluation on erectile dysfuction patients.

When Nuegra® was administered in a patient specifically complaining about erectile dysfunction, and a degree of improvement marked on VAS scale, 8 out of 63 total cases (12.7%) showed improvement two weeks after administration. At 4 and 6 weeks after administration, 16 (25.4%) and 45 (72.6%) cases showed improvement respectively, thus it was shown that Nuegra® is effective on erectile dysfunction patients.

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