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# Efficacy and Safety of Two Polyherbal Combinations: E-MA-H and E-MA-HP in Male Sexual Dysfunction

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Efficacy and safety of 2 herbal products—E-MA-H at 2 dose levels, low (HLD) and high (HHD), and E-MA-HP (HP) capsules—versus placebo (PL) was evaluated in subjects with male sexual dysfunction. Males aged 21–60 with erectile dysfunction, premature ejaculation, or other form of sexual dysfunction were studied in this triple-blind, randomized, placebo-controlled, parallel-groups trial. Subjects received any one of the following 4 interventions: E-MA-H 2 capsules at night (HLD) for 60 days; E-MA-H 2 capsules twice daily for 30 days, followed by 2 capsules at night for 30 days (HHD); E-MA-HP (HP) 2 capsules twice daily for 60 days; or placebo (PL) 2 capsules twice daily for 60 days. All dosage regimens were standardized to 2 capsules twice daily by using 2 matching placebo capsules as the morning dose for HLD and on days 31–60 for HHD. Efficacy outcome measures were the international index of erectile function; index for premature ejaculation; erectile dysfunction inventory of treatment satisfaction; subjects' and investigators' global assessment. Safety was assessed through adverse events; hematology; blood chemistry. Of 148 subjects enrolled, 1 was excluded from analysis; data on the intention-to-treat population of 147 (PL = 36, HLD = 38, HHD = 37, HP = 36) were analyzed. There was a significant ($P < 0.01$) increase in the total international index of erectile function score (mean ± SEM) in subjects receiving HLD (16.28 ± 1.39), HHD (15.40 ± 1.22), and HP (18.55 ± 1.36) compared with PL (6.83 ± 1.52). The same pattern was seen with increase in index for premature ejaculation scores: HLD (9.68 ± 1.17), HHD (10.27 ± 1.05), HP (11.36 ± 1.20) versus PL (3.77 ± 1.04). There was no significant difference in effect among the active treatment groups. The incidence of adverse events was similar in all the groups. Laboratory evaluations did not show any clinically significant abnormality in any of the groups. Treatment with HLD, HHD, and HP is well tolerated, and more effective than placebo ($P < 0.01$), in subjects with erectile dysfunction, premature ejaculation, and other forms of sexual dysfunction.

*Keywords:* E-MA-H, erectile dysfunction, herbal, premature ejaculation, randomized controlled

## INTRODUCTION

Delivering an ultimate sexual performance has been an eternal quest for men. Despite the advent of Sildenafil being largely successful in erectile dysfunction (ED), its safety concerns continue to fuel the research drive in sexual medicine.

Although the focus so far has been on evaluation of patients with single conditions, a contrasting situation is encountered in clinical practice, where men frequently present with varying forms of sexual

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dysfunction entrapped in a vicious cycle. Erectile dysfunction the most prevalent form of sexual dysfunction in men is often accompanied by problems of premature ejaculation (PE) and low sexual desire.[1] To treat these conditions with a complex regimen is demanding on the clinician and may adversely affect patient compliance and ultimately his relief. There is a need for a treatment option which empowers the physician to simplify the prescription for successful management of multiple aspects of male sexual dysfunction (MSD).

Use of Alternative and complementary therapies is being increasingly contemplated to plug the lacunae in the existing approaches of conventional medicine. Apparently men with sexual dysfunction too, resort to therapies claiming a complete and natural restoration of sexual function. However, lack of strong scientific evidence does not support the usage of natural aphrodisiacs[2] and, therefore, inhibits the acceptance of such therapies by the scientific community.

E-MA-H (H) and E-MA-HP (HP) are two novel formulations comprised of traditional herbs and minerals (Table 1.) documented for their aphrodisiac and sexual enhancement properties. In an uncontrolled study of nine men, E-MA-H was found to significantly improve the erectile function and other aspects of sexual function (unpublished data). It was thus necessary to examine in a double blind randomized, placebo controlled trials, the efficacy and safety of E-MA-H and E-MA-HP (with two additional ingredients) in subjects with MSD. In order to arrive at a convenient, less frequent, ''user-friendly'' dosage regimen that would facilitate patient compliance, study objectives included the evaluation of E-MA-H high dose (HHD) versus E-MA-H low dose (HLD). A subgroup analysis was also incorporated to examine whether the effect of the treatments differed between three study populations pre-identified on the basis of predominance of a sexual condition (ED, PE or other than ED and PE).

**Table 1**. Composition of E-MA-H & E-MA-HP.

| E-MA-HP | | |
|---|---|---|
| Latin name | Common name | Part used |
| Tribulus terrestris | Gokhru | Fruit |
| Withania somnifera | Ashwagandha | Roots/Rhizomes |
| Asparagus adscendens | Safed musli | Roots/Rhizomes |
| Mucuna pruriens | Kawach | Seed |
| Asteracantha longifolia | Gokhulakanta | Entire plant |
| Curculigo orchioides | Kali musli | Roots/Rhizomes |
| Asphaltum | Shilajeet | Exudate |
| E-MA-HP contains 2 more ingredients as follows: | | |
| Anacyclus pyrethrum | Akarkarbh | Root |
| Piper longum | Pippali | Fruit |

## MATERIALS AND METHODS

### Administration

Before initiation, the study was approved by Intersystem Biomedica Ethics Committee, Mumbai, India. Rigorous measures were adopted to ensure the authenticity and unbiased nature of the trial. Blinding and randomization were performed by a research coordinator, not otherwise involved in trial related activities. During site initiation visits, it was ensured that all personnel involved in execution of the trial were adequately trained in ICH- GCP and protocol required procedures. Freely given informed consent was obtained from male subjects and their female partners before they entered the trial. Regular monitoring visits were made to sites to check trial compliance with approved protocol and ICH-GCP.

### Study population

Males 21-60 years of age, suffering from mild to moderate form of sexual dysfunction as evidenced by at least one of the following conditions– an international index of erectile function (IIEF)–erectile function (EF) domain score in the range of 11-21, IIEF-remaining part score (sum of scores for sexual desire, intercourse satisfaction, orgasmic function, and overall satisfaction) between 21-30, and index for premature ejaculation (IPE) score between 18-28 – were eligible for this study. Those with hormonal abnormalities (including low serum testosterone, i.e., $<$200 ng/dl), major psychiatric or systemic disorders, uncontrolled diabetes mellitus, cardiovascular complications, AIDS, or a history of alcohol and substance abuse were excluded. Patients in whom sexual dysfunction could be attributable to spinal cord injury, penile fibrosis, phimosis, or medications known to cause sexual dysfunction were also excluded.

One hundred fourty-eight eligible subjects were randomized to receive any one of the following 4 regimens for 2 months: (1) placebo 2 capsules twice a day; (2) E-MA-H 2 capsules at night and 2 placebo capsules at morning (HLD); (3) E-MA-H 2 capsules twice a day initially for 1 month and then E-MA-H 2 capsules at night and placebo 2 capsules in the morning for the next month (HHD); or (4) E-MA-HP 2 capsules twice a day. No other medication for sexual dysfunction was allowed during the study. After an initial visit in 7 days, subsequent follow-up visits were scheduled at fortnightly intervals. IIEF and IPE questionnaires were administered at each follow-up visit. On

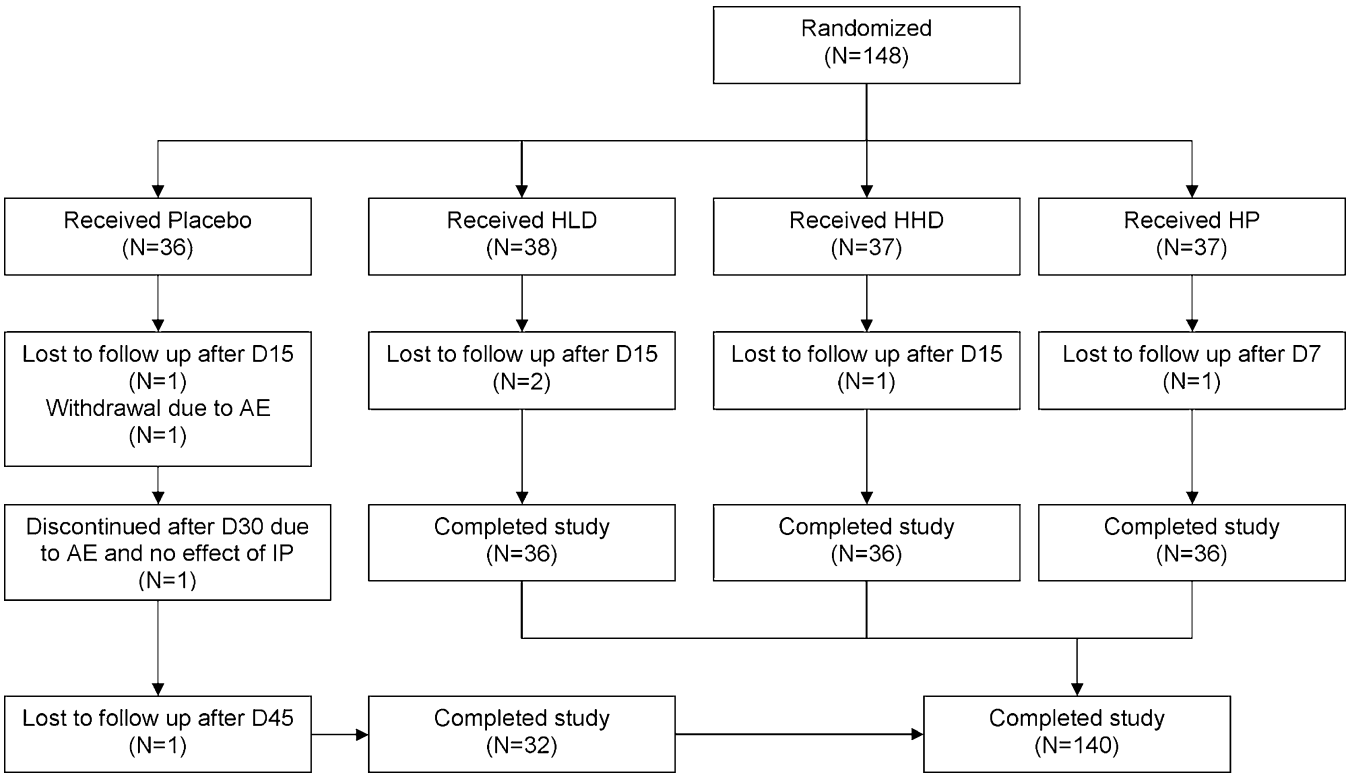


**FIGURE 1.** Disposition of patients.

completion of 1 month, and at study end, subject and partner satisfaction were assessed by the Erectile Dysfunction Inventory for Treatment Satisfaction (EDITS). Additionally at study end, investigators performed global assessment of treatment, and subjects gave their opinion regarding continuation of treatment. Adverse events (AEs) were recorded at each visit.

# RESULTS

One hundred forty subjects completed the study duration of 2 months (Figure 1). Treatment groups were well balanced in terms of demographics and baseline scores of IIEF, IPE (Table 2).

### Safety

Safety analysis was conducted in an intent-to-treat population of 147 subjects in whom at least a single postbaseline assessment was available. Last observation carried forward method was used to treat missing data.

Vital parameters, laboratory parameters, urine, and electrocardiogram were analyzed for changes from baseline to end of treatment, using paired *t* test. No clinically significant changes were seen in any of the groups during the study period (Table 3).

A total of 80 AEs occurred during the study (Table 4). The nature of AEs was mild to moderate in most cases. No Serious AE was reported during the entire study

**Table 2.** Baseline comparison of groups.

| Variable<br>N | PL<br>36 | HLD<br>38 | HHD<br>37 | HP<br>36 | *P** |
|---|---|---|---|---|---|
| Age (yrs) | 40.1 ± 1.49 | 39.7 ± 1.09 | 40.2 ± 1.51 | 39.6 ± 1.21 | 0.98 |
| Weight (kg) | 64.2 ± 1.89 | 67.9 ± 1.36 | 67.8 ± 2.18 | 67.6 ± 2.26 | 0.47 |
| Erectile function score | 17.69 ± 0.54 | 18.15 ± 0.83 | 19.45 ± 0.60 | 17.61 ± 0.74 | 0.20 |
| Remaining 4 domain of IIEF | 27.44 ± 0.77 | 26.31 ± 0.83 | 26.97 ± 0.74 | 26.97 ± 0.84 | 0.79 |
| PE scale score | 26.47 ± 1.03 | 27.18 ± 0.93 | 27.40 ± 0.82 | 26.88 ± 0.98 | 0.90 |

Data are expressed as mean ± SEM.
*For comparison among the groups by 1-way analysis of variance.
PL, placebo.

**Table 3**. Effect on hematological parameters.

| Variable | Group | N | Day Sc | Day 60 | Change | $P_w$ | $P_b$ |
|---|---|---|---|---|---|---|---|
| Hb, (g/dL) | PL | 36 | 14.59 ± 0.29 | 14.43 ± 0.30 | −0.16 ± 0.11 | 0.157 | 0.079 |
| | HLD | 38 | 15.17 ± 0.24 | 14.19 ± 0.22 | −0.25 ± 0.12 | 0.042 | |
| | HHD | 37 | 15.23 ± 0.16 | 14.89 ± 0.15 | −0.34 ± 0.11 | 0.004 | |
| | HP | 36 | 14.55 ± 0.24 | 14.69 ± 0.19 | 0.14 ± 0.19 | 0.468 | |
| RBC, ($m/mm^3$) | PL | 36 | 5.12 ± 0.09 | 5.02 ± 0.08 | −0.09 ± 0.06 | 0.137 | 0.063 |
| | HLD | 38 | 5.16 ± 0.09 | 5.06 ± 0.09 | −0.10 ± 0.04 | 0.011 | |
| | HHD | 37 | 5.09 ± 0.08 | 4.93 ± 0.10 | −0.16 ± 0.06 | 0.007 | |
| | HP | 36 | 4.91 ± 0.11 | 4.96 ± 0.10 | 0.05 ± 0.07 | 0.480 | |
| Total WBC, ($000/mm^3$) | PL | 36 | 7.01 ± 0.26 | 7.21 ± 0.26 | 0.20 ± 0.20 | 0.325 | 0.648 |
| | HLD | 38 | 7.37 ± 0.29 | 7.21 ± 0.26 | −0.16 ± 0.29 | 0.589 | |
| | HHD | 37 | 7.80 ± 0.34 | 7.86 ± 0.39 | 0.06 ± 0.25 | 0.824 | |
| | HP | 36 | 7.13 ± 0.27 | 7.44 ± 0.28 | 0.31 ± 0.34 | 0.360 | |
| Neutrophils, (%) | PL | 36 | 59.05 ± 1.49 | 57.72 ± 1.28 | −1.33 ± 1.33 | 0.325 | 0.267 |
| | HLD | 38 | 59.21 ± 1.26 | 58.68 ± 1.13 | −0.53 ± 1.00 | 0.602 | |
| | HHD | 37 | 59.62 ± 1.58 | 56.86 ± 1.58 | −2.76 ± 1.53 | 0.079 | |
| | HP | 36 | 59.44 ± 1.54 | 60.33 ± 1.31 | 0.89 ± 1.36 | 0.520 | |
| Lymphocytes, (%) | PL | 36 | 29.89 ± 1.10 | 31.42 ± 0.98 | 1.53 ± 1.22 | 0.219 | 0.471 |
| | HLD | 38 | 31.10 ± 1.08 | 30.92 ± 0.95 | −0.18 ± 0.81 | 0.820 | |
| | HHD | 37 | 29.76 ± 1.36 | 30.76 ± 1.23 | 1.00 ± 1.25 | 0.431 | |
| | HP | 36 | 29.47 ± 1.36 | 28.72 ± 1.17 | −0.75 ± 1.17 | 0.541 | |
| Eosinophils, (%) | PL | 36 | 4.39 ± 0.65 | 4.53 ± 0.73 | 0.14 ± 0.52 | 0.789 | 0.489 |
| | HLD | 38 | 3.55 ± 0.49 | 3.66 ± 0.50 | 0.11 ± 0.36 | 0.771 | |
| | HHD | 37 | 4.86 ± 1.04 | 5.94 ± 1.59 | 1.08 ± 0.64 | 0.101 | |
| | HP | 36 | 4.17 ± 0.57 | 4.50 ± 0.55 | 0.33 ± 0.41 | 0.422 | |
| Monocytes, (%) | PL | 36 | 6.25 ± 0.41 | 5.86 ± 0.39 | −0.39 ± 0.36 | 0.289 | 0.541 |
| | HLD | 38 | 5.68 ± 0.29 | 6.26 ± 0.34 | 0.58 ± 0.31 | 0.074 | |
| | HHD | 37 | 5.19 ± 0.35 | 5.89 ± 0.37 | 0.70 ± 0.42 | 0.102 | |
| | HP | 36 | 6.36 ± 0.30 | 6.03 ± 0.29 | −0.33 ± 0.34 | 0.328 | |
| Basophils, (%) | PL | 36 | 0.42 ± 0.08 | 0.39 ± 0.08 | −0.03 ± 0.10 | 0.786 | 0.931 |
| | HLD | 38 | 0.45 ± 0.08 | 0.47 ± 0.08 | 0.02 ± 0.09 | 0.768 | |
| | HHD | 37 | 0.62 ± 0.11 | 0.54 ± 0.08 | −0.08 ± 0.13 | 0.539 | |
| | HP | 36 | 0.56 ± 0.08 | 0.53 ± 0.12 | −0.03 ± 0.14 | 0.838 | |
| ESR, (mm at 1 h) | PL | 36 | 3.58 ± 0.40 | 4.00 ± 0.49 | 0.42 ± 0.55 | 0.450 | 0.309 |
| | HLD | 38 | 3.24 ± 0.31 | 4.84 ± 0.67 | 1.60 ± 0.77 | 0.043 | |
| | HHD | 37 | 4.81 ± 1.33 | 3.97 ± 0.34 | −0.84 ± 1.32 | 0.531 | |
| | HP | 36 | 4.11 ± 0.54 | 5.61 ± 0.79 | 1.50 ± 0.58 | 0.014 | |
| Serum creatinine, (mg/dL) | PL | 36 | 0.93 ± 0.02 | 0.93 ± 0.02 | 0.00 ± 0.02 | 0.904 | 0.646 |
| | HLD | 38 | 0.99 ± 0.02 | 0.98 ± 0.03 | −0.01 ± 0.02 | 0.653 | |
| | HHD | 37 | 0.90 ± 0.02 | 0.91 ± 0.02 | 0.01 ± 0.02 | 0.731 | |
| | HP | 36 | 0.89 ± 0.03 | 0.92 ± 0.03 | 0.03 ± 0.03 | 0.265 | |
| SGPT (AST), IU/mL | PL | 36 | 25.08 ± 1.86 | 24.47 ± 1.83 | −0.61 ± 0.99 | 0.542 | 0.334 |
| | HLD | 38 | 32.16 ± 2.47 | 27.82 ± 1.74 | −4.34 ± 2.18 | 0.054 | |
| | HHD | 37 | 27.27 ± 1.41 | 23.95 ± 1.58 | −3.32 ± 1.44 | 0.027 | |
| | HP | 36 | 30.47 ± 2.14 | 28.17 ± 2.32 | −2.30 ± 2.17 | 0.294 | |

Pw, analysis of baseline versus day 60 within each treatment group (paired *t* test).
Pb, analysis of change across 4 treatment groups (1-way analysis of variance).

duration. Incidence of gastrointestinal events was the highest in each group and more frequent in the placebo group.

Treatment groups were also assessed for incidence of any AEs commonly associated with Sildenafil namely: headache (10.8%), flushing (10.9%), abnormal vision (3.6%), dyspepsia (3%), nasal congestion (2.1%), dizziness (2.9%), and palpitation (1%).[3] In the present study, headache and heartburn (acidity) was reported at around 2% rate, whereas no cases of flushing or dizziness were reported. Upper respiratory tract

**Table 4.** Occurrence of AEs.

| | Total | Placebo | HLD | HHD | HP |
|---|---|---|---|---|---|
| GI | | | | | |
| Abdominal pain | 2 | 1 | 0 | 1 | 0 |
| Diarrhea | 1 | 0 | 1 | 0 | 0 |
| Acidity | 9 | 3 | 1 | 2 | 3 |
| Constipation | 3 | 1 | 2 | 0 | 0 |
| Flatulence | 9 | 2 | 1 | 3 | 3 |
| Hemorrhoids | 1 | 1 | 0 | 0 | 0 |
| Nausea and vomiting | 2 | 2 | 0 | 0 | 0 |
| Upset Stomach | 8 | 2 | 3 | 2 | 1 |
| Total GI | 35 | 12 | 8 | 8 | 7 |
| RT | | | | | |
| Allergic rhinitis | 2 | 1 | 0 | 1 | 0 |
| Common cold and cough | 10 | 3 | 2 | 3 | 2 |
| Pharyngitis | 2 | 1 | 0 | 0 | 1 |
| Breathlessness | 1 | 0 | 0 | 0 | 1 |
| Total RT | 15 | 5 | 2 | 4 | 4 |
| Skin | | | | | |
| Skin reaction | 4 | 1 | 2 | 1 | 0 |
| Herpes zoster | 1 | 0 | 1 | 0 | 0 |
| Total skin | 5 | 1 | 3 | 1 | 0 |
| Others | 25 | 6 | 4 | 7 | 8 |
| Total | 80 | 24 | 17 | 20 | 19 |

GI, gastrointestinal; RT, respiratory tract.

conditions, which may have resulted in nasal congestion (if any), were reported at comparatively lower rate.

## Efficacy

The intent-to-treat population for efficacy consisted of 147 patients. Efficacy evalution was conducted by applying analysis of variance and then Scheffe test for multiple comparisons. In the analysis of Global assessments by investigator and subjects' opinion, active treatments were compared against placebo using Fisher exact test and Pearson $\chi^2$ test.

### *Improvement in IIEF-erectile function domain*

E-MA-H (HLD and HHD) and E-MA-HP showed statistically significant increases in IIEF-EF scores as compared with placebo (Table 5). In subjects receiving low dose of E-MA-H, the ability to get an erection during sexual activity (question1 of IIEF) increased by 48.52% and was the highest amongst all groups. Subjects treated with E-MA-HP saw a maximum increase (48%) in the ability to maintain erections after penetration (question 4 of IIEF).

### *Improvement in IIEF-other than EF domains*

Mean increases in the remaining part of the IIEF were significantly higher in subjects treated with E-MA-H (both doses) and E-MA-HP as compared with placebo. The improvement, however, did not vary significantly across the active treatment groups.

The percentage improvement in individual domains was always higher in the active groups than with placebo; the highest increase occurring in the E-MA-HP group each time.

### *Improvement in IPE scores*

Mean increases in IPE scores were significantly greater in subjects treated with either dose of E-MA-H and E-MA-HP as compared with those who received placebo. No significant differences were observed in the increased IPE scores between the active treatment groups.

**Table 5.** Effect on efficacy variables.

| Efficacy variable | Group | N | Baseline | Day 60 | *P* |
|---|---|---|---|---|---|
| IIEF (erectile function domain) | PL | 36 | 17.69 ± 0.54 | 20.75 ± 0.82 | |
| | HLD | 38 | 18.15 ± 0.83 | 24.86 ± 0.81 | 0.004 |
| | HHD | 37 | 19.45 ± 0.60 | 25.45 ± 0.62 | 0.042 |
| | HP | 36 | 17.61 ± 0.74 | 25.25 ± 0.71 | 0.000 |
| IIEF (sexual desire, intercourse satisfaction, orgasmic function, overall satisfaction domain) | PL | 36 | 27.44 ± 0.77 | 31.16 ± 0.97 | — |
| | HLD | 38 | 26.31 ± 0.83 | 35.84 ± 0.94 | 0.000 |
| | HHD | 37 | 26.97 ± 0.74 | 36.29 ± 0.77 | 0.000 |
| | HP | 36 | 26.97 ± 0.84 | 37.52 ± 0.76 | 0.000 |
| IPE (index of premature ejaculation) | PL | 36 | 26.47 ± 1.03 | 30.25 ± 1.33 | — |
| | HLD | 38 | 27.18 ± 0.93 | 36.86 ± 1.17 | 0.005 |
| | HHD | 37 | 27.40 ± 0.82 | 37.67 ± 0.91 | 0.002 |
| | HP | 36 | 26.88 ± 0.98 | 38.25 ± 0.96 | 0.000 |

The *P* value is for change in mean score from baseline as compared with placebo, using analysis of variance and Scheff test. IIEF and IPE data are expressed as mean ± SEM.

**Table 6**. Effect on serum testosterone levels.

| | Baseline | Day 60 | *P* |
|---|---|---|---|
| PL (n = 36) | 538.23 ± 34.06 | 529.75 ± 34.19 | — |
| HLD (n = 38) | 553.13 ± 34.45 | 507.37 ± 30.67 | 0.799 |
| HHD (n = 37) | 579.10 ± 28.61 | 477.11 ± 28.49 | 0.104 |
| HP (n = 37) | 513.84 ± 24.99 | 480.07 ± 32.31 | 0.929 |

Data are expressed as Mean ± SEM.
The *P* value is for changes in mean testosterone levels as compared with placebo, using analysis of variance and Scheff test.

Serum testosterone levels were found to be decreased in all study groups at study end; the changes, however, were not of clinical relevance (Table 6). Subjects and female partners of active group demonstrated greater scores of treatment satisfaction by EDITS as compared with those of the placebo group (Table 7).

All of the 3 active treatments received significantly greater number ($P = 0.00$) of satisfactory responses (including excellent, very good and good) from the investigators for their efficacy as compared with placebo (Table 8). The proportion of subjects who wanted to continue therapy was significantly larger in the active groups than that in the placebo group (Table 9). Results obtained from subgroup analyses corresponded with those of the overall analysis.

## DISCUSSION

Results of this study demonstrate that E-MA-H (at low and high dose) and E-MA-HP were effective in subjects with mild to moderate MSD. The methodological rigor that yielded these results deserves attention, especially in the context of concerns over the quality of clinical trials of herbal medicines. Reviews of previous studies evaluating the effect of herbs commonly used in MSD cite several methodological flaws. Though trials examining the efficacy of Korean red ginseng have found it to be better than placebo, these trials were generally burdened with issues of inadequate reporting of ethical approval, blinding, randomization and baseline comparisons,[4] Another popular herbal ingredient Yohimbine (the primary active constituent in the bark of an African tree), has been shown to be superior to placebo in treating men with ED.[5] However, the size of the trials evaluating Yohimbine was generally small (only 1 of 7 trials studied 100 men), and statistical benefit for Yohimbine over placebo was detected in only 1 trial. In comparison, the present study seems to have considerably addressed these shortcomings.

The efficacy and safety results of this study are in support of the traditionally acclaimed role and add to the existing body of evidence for the aphrodisiac properties of the herbs present in E-MA-H and E-MA-HP. Curculigo orchioides when administered to rats demonstrated a pronounced effect on the spermatogenesis and sexual orientation toward female rats.[6–8] The sexually invigorating effect of Mucuna pruriens was evidenced in 2 studies showing significant improvements in sexual behavior, libido, and potency of diabetic and healthy rats.[9,10] Tribulus terrestris was shown to have a marked aphrodisiac effect through improvement in sexual behavior, increase in prostrate weight, and intracavernous pressure.[11,12]

Current understanding of sexual dysfunction in men considers it to be an alteration in any 1 or more phases

**Table 7**. Effect on patient and partner satisfaction.

| | Patient | | Partner | |
|---|---|---|---|---|
| EDITS | Day 60 | *P* | Day 60 | *P* |
| PL | 54 ± 4.25 (n = 34) | — | 61.5 ± 6.80 | — |
| HLD | 78.55 ± 3.04 (n = 36) | 0.000 | 77.36 ± 4.36 | 0.211 |
| HHD | 75.83 ± 2.56 (n = 36) | 0.000 | 77.35 ± 3.86 | 0.234 |
| HP | 73.16 ± 3.51 (n = 36) | 0.000 | 77.38 ± 5.11 | 0.193 |

Data are expressed as Mean ± SEM.
*P* value is for comparison with placebo, using ANOVA and Scheff test.

**Table 8**. Global assessment by investigator.

| | PL | HLD | HHD | HP |
|---|---|---|---|---|
| Satisfactory (excellent, very good, or good) | 14 | 34* | 30† | 30† |
| Unsatisfactory (fair or poor) | 18 | 1* | 6† | 6† |

*The value of $P = 0.00$ is significant when compared with placebo using 1-sided Fischer test.
†The value of $P = 0.001$ is significant when compared with placebo using Pearson $\chi^2$ test.

**Table 9**. Subject's opinion.*

| | Yes | No |
|---|---|---|
| PL (n = 30) | 14 | 16 |
| HLD (n = 35) | 32† | 3† |
| HHD (n = 36) | 29‡ | 7‡ |
| HP (n = 35) | 28‡ | 7‡ |

*As assessed by a yes or no response to the question: Would you take the same product in future if you suffer from the same condition?
†The value of $P < 0.001$ compared with placebo using 1-sided Fischer test.
‡The value of $P < 0.01$ compared with placebo using Pearson $\chi^2$ test.

of the sexual response cycle as follows: libido, erection, ejaculation, and orgasm. The IIEF is a validated instrument equipped to measure each of these constituent domains. Thus a significant increase in all domains of the IIEF accompanied by a significant increase in the IPE scores indicates an all-round improvement in the quality of sexual functioning (libido, erection, orgasm, and ejaculation) in subjects receiving E-MA-H and E-MA-HP. This implies that E-MA-H and E-MA-HP could have a regulatory influence on the physiological functioning and integration of numerous processes that go into the satisfactory sexual functioning of men. Such versatile ability to improve all aspects of sexual function is most warranted in several conditions (notably depression and anxiety) where co-existing forms of MSD often masquerade each other posing a daunting challenge to the physician to determine which dysfunction developed first.

In addition to the normal functioning of the essential components of the sexual response cycle, an important aspect of sexual satisfaction in a man is his partner's sexual satisfaction. It has been well recognized that sexual dysfunction is a ''couple's problem,'' and not just the identified patient's problem.[13] Greater treatment satisfaction scores of EDITS (patient and partner version) corroborated by positive results of subjects and investigators assessments only ascertain the beneficial effect of E-MA-H and E-MA-HP.

One of the study objectives left unsatisfactorily achieved was the determination of a therapeutic dose facilitating patient compliance. Of the 3 actives, E-MA-H (low dose) produced the most consistent results across all efficacy parameters. Inexplicably responses to high dose of E-MA-H were not significantly different than those to low dose. This could possibly be explained by the threshold effect due to which a higher dose was unable to elicit any greater response than the lower dose. This requires confirmation in further dose determination studies.

Despite the overall improvement of sexual function, treatment with E-MA-H and E-MA-HP had no significant impact on the testosterone levels of men in this study. Any contribution of a testosterone like action to enhancement of libido or erectile function is thus ruled out. Nevertheless the finding is consistent with the fact that ED was only occasionally improved by testosterone therapy.[14] Further, it is postulated that the antistress[15,16] properties of a few ingredients (Asparagus and *Shilajeeet*) and the ability of others[17] (Withania and Tribulus) to increase nitric oxide production may have resulted in the improved libido and erectile function, respectively.

Subject age is one of the most strongly associated factors of MSD. The Massachusetts male aging study found that more than 50% of men aged 40–70 have a minimal, moderate, or severe degree of erectile dysfunction.[18] After age, a higher probability of impotence was directly correlated with heart disease, hypertension, diabetes, associated medications, and indices of anger and depression. It was noteworthy that the beneficial results of E-MA-H and E-MA-HP were observed in older adults (average age of subjects was 40 years); however, all other risk factors including uncontrolled diabetes were excluded in the present study. Thus the efficacy of E-MA-H and E-MA-HP in sexual dysfunction with common comorbid conditions remains to be determined in future studies.

The AE profile of E-MA-H and E-MA-HP as demonstrated in this study is of special relevance in view of currently available drugs, which have reported considerable safety and tolerability concerns.[19] This leads to a possible application in patients in whom use of Sildenafil is contraindicated due to concomitant use of nitrates and α blockers.

## CONCLUSION

The study has adopted a comprehensive approach to assessment of sexual function in men; different from examination of individual components or aspects. E-MA-HP and both doses of E-MA-H in this study were effective and well tolerated in the management of multiple aspects of MSD. Further studies should aim at confirming the optimum dose and mechanism of action.

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