Efficacy and Safety of Ashwagandha (*Withania somnifera*) Root Extract in Improving Sexual Function in Women: a double-blind, randomized, placebo-controlled study

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KEYWORDS: Ashwagandha root extract, Female sexual difficulties, Female sexual dysfunction, Female Sexual Function Index (FSFI) Questionnaire, Female Sexual Distress Scale (FSDS).

ABSTRACT

Background: Female sexual function is a complicated and multifactorial function, often combining pathophysiologic, psychological and interpersonal relationship factors. Many otherwise healthy women experience symptoms suggestive of less than full sexual function, orgasm disorders and sexual difficulties. Ashwagandha (Withania somnifera) is classified in Ayurveda as a *'Rasayana'*, which promotes physical and mental health, augments physical energy, increases libido and revitalizes the body in debilitated conditions.

Aim of the Study: To determine the efficacy and safety of a high concentration, full-spectrum Ashwagandha root extract in improving sexual function in healthy women as measured by the Female Sexual Function Index (FSFI) Questionnaire and the Female Sexual Distress Scale (FSDS).

Materials and Methods: This study was a single centre, prospective, double-blind, randomized placebo-controlled trial. A total of 50 subjects were enrolled into the study following a specified screening protocol for determining the baseline values of the parameters to be studied (Day 0). The study subjects were randomized to either (i) Ashwagandha root extract treated group **(Group A;** n=25) or (ii) Placebo-treated group(**Group B**; n=25). The study subjects in Group A were administered one capsule (containing 300 mg of high-concentration full-spectrum root extract of the Ashwagandha plant) orally, twice daily for a period of 8 weeks; in Group B one capsule containing placebo was administered similarly. The Female Sexual Function Index (FSFI), a self-report questionnaire and the Female Sexual Distress Scale (FSDS) were used to assess female sexual function (FSF), and to determine the effect of Ashwagandha root extract in improving FSF. Statistical analysis of the data was done using paired and unpaired 't' test. Data are expressed as mean + SD.

Results: Significant improvement was observed in all the FSFI domain scores in the Ashwagandha root extract-treated group (Group A; n=25) as compared to the baseline values as well as when compared to the Placebo-treated group (Group B; n=25) at 4 weeks and at the end of the study period of 8 weeks. The analysis reveals that supplementation with Ashwagandha root extract results in 122.67% improvement from baseline in difficulties with desire; 62.09% in arousal; 59.30% in lubrication; 82.05% in orgasm; 62.33% in satisfaction; 77.54% in pain and 75.83% in FSFI total scores over 8 weeks of the study period.

Conclusions:

The result of this study demonstrated that oral administration of Ashwagandha root extract significantly improved sexual function in otherwise healthy women as evaluated by the FSFI total and domain scores.

Introduction

Sexuality is an integral part of human expression regardless of age and is a complex process coordinated by the neurological, vascular and endocrine systems [1-5]. Therefore, sexual dysfunction can have a major impact on quality of life in women and men. Sexual satisfaction can be generally defined as '*the degree to which an individual is satisfied or happy with the sexual aspect of his or her relationship'* [6]. Female sexual dysfunction (FSD) affects physical health and emotional well-being and is considered to be a *collective term* for the various disorders of the sexual process in women [7,8] Female sexual difficulties are currently classified as discrete individual disorders in one of the phases of the 'sexual response cycle' – *desire, arousal, orgasm, resolution / satisfaction*, or *pain related to sexual activity*[8]. However, it is to be noted that these individual disorders rarely occur in isolation from each other.

The propagation of the species is a basic aim of nature and is paramount for the survival of the species. Women have a pivotal role to play in the reproduction and multiplication of the human race. Impaired sexual function can have damaging effects on the sense of wholeness, self-esteem and interpersonal relationships of women, which is often emotionally distressing [9,10]. Experiencing problems with the sexual activities is being reported as the strongest and most consistent risk factor for women's sexual distress in a number of studies[9-11].The consequences of compromised and/or disturbed female sexuality might lead to familial discord and divorce, and reproduction is also affected [6,12-14]. While prevalence and risk factors for male sexual dysfunction, in particular erectile dysfunction, have been intensively studied within the past two decades; data regarding FSD are scant [11,15,16]. FSD warrants more attention and the medical health providers need to be aware of the importance of sexuality in this population and its relationship to physical, emotional and social wellbeing of a woman's life.

Problems with sexual desire, arousal, orgasm, and pain are alarmingly common across the world and 32% to 58% of women from US report one or more of these problems[6,7,9,12,13,17-20].Female sexual dysfunction (FSD) is a group of disorders where women could have female sexual arousal disorder (FSAD), female orgasmic disorder (FOD), or hypoactive sexual desire disorder (HSDD). Some women may have combined genital and subjective arousal disorder or isolated genital sexual arousal disorder[21]. These disorders result in decreased libido, vaginal dryness, decreased genital sensation, decreased arousal, difficulty in achieving orgasm, pain and discomfort with intercourse and are majorly due to neuro-vascular, hormonal or psychogenic manifestations [22,23].

Furthermore, chronic stress in modern society leads to all sorts of major health problems. Increasing levels of stress in day-to-day life have a huge impact on both male and female sexual function. Acute and immediate stress results in massive release of cortisol, frequently referred to as the '*stress hormone*'. It has been shown that women with high levels of chronic stress and those exposed to acute stress also show lower levels of sexual arousal [24].

Finally, sexual satisfaction is a broad construct closely intertwined with quality of life, general welfare and happiness [6,14]. It has been observed that women with sexual dysfunction often turn to alternative therapies and herbal adaptogens as a remedy for diminished sexual desire.

Ashwagandha (*Withania somnifera*) also known as Indian Winter Cherry is extensively used in Ayurveda, the traditional health care system in India. This herb is used as a general tonic and 'adaptogen,' helping the body adapt to stress. The root of this plant has been used for thousands of years by Ayurvedic practitioners to treat different health conditions. The role of ashwagandha is seen not only as calming, but as a tonic to replenish lost energy. In addition, it has been shown to possess antioxidant activity as well as an ability to support a healthy immune system [25-29]. It helps the body take care of stress because of its ability to reduce the cortisol levels in chronically stressed individuals, restore healthy adrenal function and normalize the sympathetic nervous system [30-32]. Ashwagandha root extract is used to treat sexual

weakness, erectile dysfunction, performance anxiety in men and diminished sexual desire in women and in all forms of sexual dysfunction [9,28,33,34], particularly where depleted nervous system is playing a role. Ashwagandha is often called *"Indian ginseng"* due to its rejuvenating effects [27,35]. Nonetheless, the specific effects are not similar to ginseng. Rather than providing restless energy as does ginseng, Ashwagandha causes relaxation. Ashwagandha root, both a nervine and 'adaptogen' is known to increase energy through stress reduction [34,35].The root contains antioxidants, iron, amino acids, flavonoids and many active ingredients of the withanolide class. Numerous studies suggest Ashwagandha can directly and indirectly prevent and treat a number of diseases [36,37].

The present study employs the full-spectrum root extract of Ashwagandha which retains and potentiates the synergism in the whole root. It is noteworthy that although various Ashwagandha powders and extracts are available commercially, there are serious shortcomings in standardization and optimization of Ashwagandha extracts. The Ashwagandha root extract used in the present study (KSM-66 Ashwagandha from Ixoreal Biomed in Los Angeles, California) has been extracted with a unique processing technology producing a broad spectrum phyto-pharmaceutical containing the desired quantum of withanolides, that potentiates the action of Ashwagandha manifold, providing pan-therapeutic effects. Earlier studies clearly indicate that the traditional use of Ashwagandha has a logical and scientific basis [27]. Nonetheless, clinical studies are needed to validate the efficacy of this herb in female sexual function and sexual arousal disorders.

Hence, the present study was designed as a prospective, randomized, placebo-controlled trial to assess the efficacy and safety of a high-concentration full-spectrum extract of Ashwagandha roots in improving Female Sexual Dysfunction (FSD) as measured by the Female Sexual Function Index (FSFI) in otherwise healthy women with sexual dysfunction and arousal disorder.

Materials and Methods

This study was a single centre, prospective, randomized, placebo-controlled trial. Fifty female subjects were enrolled in the study following a specified screening protocol for determining the baseline values of the parameters to be studied (Day 0). The study subjects were either assigned to the Ashwagandha root extract-treated group (**Group A**; n=25) or the Placebo-treated group (**Group B**; n=25) in a randomized fashion. Study duration was 8 weeks for each subject.

As indicated earlier, the Ashwagandha root extract used in the present study is KSM-66 Ashwagandha from Ixoreal Biomed in Los Angeles, California). The extract has been standardized to 5% withanolides as ascertained by HPLC. The safety and efficacy of this extract have been assessed in clinical trials already in the literature [30,34]. The analysis of withanolides was performed on a Waters 515 HPLC system, using a Sunfire C18 column of dimension 250 x 4.6 mm, 5µm at a flow rate of 1 ml/min. The solvent system is based on methanol:water (60:40). At the end of the run, the column was flushed with 100% methanol for 30 min. The column temperature was 30 C and the injection volume was 20 µl.

All subjects were enrolled based on their expressed interest in improving their current sexual function and health. Written informed consent with an emphasis on anonymity of interview results was obtained from each subject following a detailed explanation of the objectives and protocol of the study, which was conducted in accordance with the ethical principles stated in the "Declaration of Helsinki" and approved by the institutional ethics committee of Bharati Vidyapeeth Deemed University, Navi Mumbai 400614, India (Date of approval: October 7, 2013). The Ethical Committee notifications followed the Good Clinical Practice (GCP) Guidelines issued by Central Drugs Standard Control Organization and Ethical Guidelines for Biomedical Research on Human Subjects, issued by Indian Council of Medical Research.

Study Subjects:

During the treatment period, the study subjects were required to present themselves at the Trial Centre on specified intervals: **Visit 1**- Day 0, **Visit 2**- Week 4 and **Visit 3**- Week 8. Final safety and efficacy assessments were done at the end of the study (week 8).

Demographic characteristics, including each subject's age were assessed in all women. The women selected for inclusion in the study were available for a 1 hour face-to-face interview by the medical personnel for diagnosis and evaluation of Female Sexual Dysfunction (FSD). The study subjects were enrolled in the study after qualifying the following inclusion and exclusion criteria:

Inclusion criteria:

1. Female subjects between 21 to 50 years of age who have been previously functional and/or experienced in sexual function for several years in the past; having a stable heterosexual relationship with a male partner for at least 1 year.
2. Women who have a male partner with a score of *'not impotent'* or *'minimally impotent'* on the Single-Question, Self-report of Erectile Dysfunction (Massachusetts Male Aging Study).
3. Women who have a baseline total score of <26 on the Female Sexual Function Index (FSFI) and a baseline total score of >11 on the Female Sexual Distress Scale (FSDS).
4. Women who met the diagnostic criteria for Female Sexual Dysfunction (FSD) with any one or more of the following disorders:
    a. Hypoactive sexual desire disorder (HSDD)
    b. Female sexual arousal disorder (FSAD)
    c. Female orgasmic disorder (FOD)
    d. Combined genital and subjective arousal disorder
5. Women who were willing to engage in sexual activities with an intent-to-attain orgasm at least 2 times per week
6. Women who provided a written Informed Consent and were able to understand and comply with all the study requirements.

Exclusion criteria:

1. Women who presented with evidence of unresolved sexual trauma or abuse, with FSD caused by untreated endocrine disease, with chronic dyspareunia which was not attributable to vaginal dryness during the previous 12 months.
2. Women with chronic or severe medical or psychiatric illnesses, drug abuse, infertility, menopause, those who were pregnant or lactating and women with known hypersensitivity to Ashwagandha were excluded from the study

Study and Treatment Protocol

Study Design:

We conducted a single-centre, prospective, randomized, placebo-controlled trial to assess the efficacy and safety of a high-concentration full-spectrum extract of Ashwagandha roots in improving Female Sexual Dysfunction (FSD) as measured by the Female Sexual Function Index (FSFI) in otherwise healthy women with sexual dysfunction and arousal disorder.

Randomization Procedure:

Randomization was done using a Windows operating system based software package (Rando version 1.2©, R. Raveendran 2004). The Study Investigational Product (IP) was packed in a manner that the Study and Placebo (control) medication packs were identical. The packs were coded to conceal the nature of their contents and the label contained the patient serial number (ID of the Study).

Study Drug:

KSM-66 Ashwagandha (High concentration, full spectrum, standardized root extract of *Withania somnifera*) was given in the dose of one

capsule (300 mg) twice per day orally, over a period of 8 weeks. The same protocol was followed for administration of the Placebo capsule.

Study Groups:

1. **Group A**: Ashwagandha root extract-treated Group
2. **Group B**: Placebo-treated Group

Concomitant Medication:

Any other concomitant medication required by the patient was prescribed at the discretion of the investigator and/or the attending clinician in accordance with the routine clinical practice at the study site. It was made certain that, the prescribed medicines did not interfere with the study outcomes.

Efficacy Parameters Evaluated and Measurements

Outcome measures included demographic data, medical and sexual history, quality of life questionnaires: The Female Sexual Function Index (FSFI), the Female Sexual Distress Scale (FSDS), the Sexual activity record (SAR), the Patient's Global Assessment of Response to Therapy (PGART) and the Patients Global Assessment of Tolerability to Therapy (PGATT) were used to evaluate the effectiveness of Ashwagandha root extract in improving female sexual dysfunction (FSD).

Primary Efficacy Outcomes

The Female Sexual Function Index (FSFI)

The FSFI, a self-report questionnaire consists of six domains: desire, arousal, lubrication, orgasm, global satisfaction and pain, assigned with 19 items. Full-scale and individual domain scores were derived from the computational formula described by Rosen et al [8]. Female Sexual Dysfunction (FSD) in the study subjects and its amelioration by Ashwagandha root extract was evaluated by using the FSFI. The FSFI Questionnaire was used at the beginning of the Study (to establish the baseline values), at 4 weeks and at the end of the study period of each group (at 8 weeks).

The FSFI Questionnaire assessed sexual function or problems which had occurred during the previous 4 weeks. In accordance to the FSFI questionnaire, S*exual desire* was assessed as frequency and desire level, by asking 2 questions. *Arousal* was assessed as frequency, level, confidence and satisfaction, by asking 4 questions. *Lubrication* was assessed as frequency, difficulty, frequency of maintaining lubrication and difficulty in maintaining lubrication, by asking 4 questions. *Orgasm* was assessed as frequency, difficulty and satisfaction, by asking 3 questions. *Satisfaction* was assessed as the amount of closeness with partner, sexual relationship and overall sex life, by asking 3 questions. *Pain* was assessed as pain frequency during vaginal penetration and pain frequency following vaginal penetration, by asking 3 questions.

For each of the 6 domains, a score was calculated and the total score was obtained by adding the 6 domain scores. The maximum value score for each domain score is 6 and the maximum value for the FSFI total score is 36 [38]. Interviewers matched respondents on various social attributes in an interview averaging 45 to 60 minutes.

Secondary Efficacy Outcomes

Female Sexual Distress Scale (FSDS)

The FSDS is a self-report questionnaire [39] which measures sexually-related personal distress in women. It lists 12 *feelings* or *problems* and asks the respondent to indicate how often each problem has caused distress in the past 30 days. Response choices are *'never,' 'rarely,' 'occasionally,' 'frequently,'* and *'always'*. The questionnaire is scored by summing the item responses (scaled such that *'never'* equals 0 and *'always'* equals 4).

Sexual Activity Record (SAR)

Assessment of the temporal improvement in sexual activity relative to the baseline values

following administration of the specific therapy was based on the Sexual Activity Record (SAR); which measured the encounter frequency of *'successful and satisfactory sexual events'.*

Patient's Global Assessment of Response to Therapy (PGART)

PGART was assessed by the Study Subjects at the end of therapy on a 5-point scale given below depicting improvement in sexual activity and sexual satisfaction:

Excellent response denoted excellent improvement.

Good response denoted good improvement.

Moderate response denoted some improvement.

Poor response denoted minimal improvement.

Worst response denoted no improvement.

Patients Global Assessment of Tolerability to Therapy (PGATT)

Safety and tolerability of the therapy were assessed at end of the study period. Tolerability of the therapy was assessed by careful recording of adverse events (if any) and judging their causal relationship to the test drug.

PGATT was assessed on a 5-point scale of 'Excellent', 'Good', 'Moderate', 'Poor' and 'Worst' as below:

Excellent tolerability: No adverse effects & patient able to tolerate the drug

Good tolerability: Minimal side effects not interfering with patients daily activities

Moderate tolerability: Some side effects & minimal interference in patients daily activities

Poor tolerability: Significant side effects &Significant interference in patients daily activities

Worst tolerability: Patient not able to tolerate the drug at all due to adverse effects

Compliance:

Subjects were provided "Therapy Kits" containing the medications. At each visit, the investigator/study team noted the number of tablets dispensed and the no. of tablets returned by the subject. Any deviations and dose missed was recorded in the *Case Record Form* and *Drug Accountability Log* for verifications with reasons.

Compliance is a very important aspect of treatment. A patient was considered compliant if ≥ 80% of medication was consumed according to the prescribed regimen.

Data Evaluation and Statistical Analysis:

Analysis Dataset

The recommended for practice for clinical trials is that all analysis is to be done on both the intent-to-treat (ITT) and the per-protocol (PP) datasets. The ITT dataset included all subjects recruited in the study irrespective of their study completion status, whereas the PP dataset included all subjects who completed the study as per the protocol without any protocol violation. In our case, all the subjects completed the study and therefore the ITT dataset and the PP dataset are equivalent.

Data Expression

Categorical data and discrete data are expressed as numbers with percentages (proportions). Changes in the scores from baseline were calculated and expressed as mean change and percent change from baseline. Data are expressed as mean ± standard deviation (SD).

Analysis Methods

Time duration- related changes in each domain score value as compared to the baseline value, as measured at the predetermined time periods in the Ashwagandha root extract-treated Group were compared with the corresponding values in the placebo-treated Group using Kruskall-Wallis test (Non-parametric ANOVA with treatment as the factor). Baseline scores were compared to the post-treatment scores using Friedman test followed by *post-hoc* individual comparisons using Wilcoxon test. All testing was done using two-sided tests at alpha 0.05.

Results and Observations

None of the 50 enrolled women was withdrawn from the study for any reason. The general demographic characters of the subjects are given in Table 1. The study subjects' mean age was 28.12+/-5.12 in the Ashwagandha root extract-treated group (**Group A**; n=25)and 29.44 +/- in the placebo-treated group (**Group B**; n=25).The general demographic characters of both the study groups were comparable (Table 1).

The Female Sexual Function Index (FSFI)

Using the pre-determined cut off scores, and after being screened for inclusion criteria; all the women enrolled in the present study had total FSFI scores suggestive of FSD. Domain scores were suggestive of sexual difficulties related to desire, arousal, lubrication, orgasm, poor satisfaction and pain.

The mean total FSFI scores at week 4 of the study period were found to be 20.25 +/- 1.66 (49.22% change from baseline) in Group A and 17.69 +/- 1.62 (29.79 % change from baseline) in Group B out of a maximum total score of 36.

At week 8 of the study period, the mean total FSFI scores were found to be 23.86 +/- 2.02 in Group A and 20.06 +/- 2.38 in Group B (Figure 1). These data indicate a 75.83% and 47.17% change from baseline in Group A and Group B respectively at week 8; the difference was found to be highly significant ($p<0.001$), evidencing that the full-spectrum, standardized root extract of Ashwagandha (300 mg twice per day orally, over a period of 8 weeks) afforded excellent improvement in FSD in otherwise healthy women as validated by the total FSFI scores.

Desire Domain of FSFI

Figure 2 displays the mean+/- SD score for the desire domain of FSFI; which was comparable between Group A and Group B at week 4 and week 8 respectively. However, a significant ($p<0.01$) increase in the desire domain score was observed in Group A as compared with baseline values (1.80 +/- 0.71) of the same at week 8 (4.01 +/- 0.48).

Arousal and Lubrication Domains of FSFI

Mean FSFI domain scores for arousal and lubrication were significantly ($p<0.001$) higher in Group A than in Group B at week 4 and week 8 of the study period as also when compared to their respective baseline values (Figures 3 and 4) suggesting remarkable improvement in these variables, thus evidencing Ashwagandha root extract's capability in ameliorating sexual difficulties regarding arousal sensation and arousal lubrication.

Orgasm and Satisfaction Domains of FSFI

Mean FSFI domain score for orgasm in Group A showed a steady significant ($p<0.01$) increase from the baseline value up to week 4 of the study period; thereafter, the score value of this parameter of sexual climax maintained its improvement status up till the end of the study period (week 8); which was highly significant ($p<0.001$) as compared to the placebo treatment (Group B) which also showed a similar trend (Figure 5).

Ashwagandha root-extract treatment (Group A) significantly ($p<0.001$) improved the mean FSFI domain score for satisfaction at week 4 and week 8 of the study period as compared to the placebo treatment (Group B) at similar time periods (Figures 6&7). Improvement in the satisfaction domain from the baseline value was remarkable (62.33%) in the intervention group, defining the anti-stress and adaptogenic properties of Ashwagandha.

Pain Domain of FSFI

Ashwagandha root-extract treatment resulted in marked improvement in the mean FSFI domain score for pain at week 8 as compared to Placebo treatment (Group B) at similar time period (Figure 8). However, improvement in the FSFI domain score of this variable was found to be significant ($p<0.01$; 77.54%) in Group A as compared with the baseline value of this parameter.

Female Sexual Distress Scale (FSDS)

The mean total Female Sexual Distress Scale (FSDS) scores depicting sexually related

personal distress in women with FSD showed highly significant improvement with Ashwagandha root-extract treatment (Group A) at week 4 ($p<0.001$) and at week 8 ($p<0.001$) as compared with Group B at the same time periods (Figure 9).

Sexual Activity Record (SAR)

Significant improvement was observed in the total ($p<0.01$) and successful sexual encounters ($p<0.001$) of the trial subjects in Group A at week 8 of the study period as compared to Group B at the same time period (Table 2).

Patient's Global Assessment of Response to Therapy (PGART)

At the end of therapy (week 8) the Study Subjects assessed PGART on a 5-point scale depicting improvement in sexual activity and sexual satisfaction. Of the 25 subjects in Group A, 15 documented an "Excellent**"** response depicting excellent improvement, 9 recorded a "Good" response and 1 subject recorded a "Moderate" response to therapy.

The compliance was excellent for all the patients in both the groups.

Patient's Global Assessment of Response to Therapy (PGART)

No adverse effects of therapy were observed in the Ashwagandha root-extract treatment group (Group A), all the subjects (n=25) showed excellent tolerability of the therapy.

Examination of these data reveals that the full-spectrum Ashwagandha root extract evaluated in this study effectively ameliorated any inadequacies in sexual desire and in the psycho-physiological changes that characterize the female sexual dysfunction and cause marked distress and interpersonal difficulties.

Discussion

Sexual expression is a normal and healthy part of human behaviour. Female sexual dysfunction is a complicated and multifactorial condition combining pathophysiologic, psychological, and interpersonal relationships [40].

Positive sexual experiences are related to health and well-being throughout life; hence, there is a need to think about sexual health as not merely the absence of sexual disorders, but as a key factor affecting the quality of life [41].

Female sexual dysfunction (FSD) is characterized by disturbances in the psycho-physiological changes associated with the 'sexual response cycle' expressed as decreased libido, vaginal dryness, pain and discomfort with intercourse, decreased genital sensation, decreased arousal, and difficulty in achieving orgasm. Among these is hypoactive sexual desire disorder (HSDD), a condition that causes marked distress and interpersonal difficulties [42]. These dysfunctions are due to underlying neuro-vascular, hormonal or psychogenic aetiologies [22]. It has been shown that in female sexual function, neurotransmitter-mediated vascular smooth muscle relaxation results in increased vaginal lubrication, vaginal wall engorgement and vaginal luminal diameter expansion [43].

It is well known that hormonal and metabolic imbalances emerge as our bodies attempt to adapt to chronic stress. Therefore, it is critically important to recognize and respond to the various risk factors for anxiety disorders, chronic stress and depression to prevent and treat metabolic derangements and sex hormone imbalances in FSD. The success of treatment for FSD depends on the underlying cause of the problem. Stress is a multifaceted disorder, and must be addressed as such in order to achieve relief and calm. It is critical to lower cortisol levels, restore healthy adrenal function and normalize the sympathetic nervous system. The sympathetic nervous system is activated in a variety of situations including both sexual arousal and during stress. Furthermore, it has been found that stress related to sexual performance may interfere with sexual arousal [44].

It is distressing that mainstream treatment regimens often fail to address these subtleties, an oversight that majorly contributes to sexual distress in male and female patients. The conventional health care approach typically attempts to alleviate stress with an array of psychoactive drugs that either mimic or manipulate neurotransmitter signalling; however,

psychoactive drugs often fail to address these underlying causes of anxiety and stress.

Although new pharmaceutical agents have been identified for male erectile problems and sexual desire and orgasm disorders in women, individuals with sexual dysfunction often seek alternative therapies. Numerous studies have shown that, in the face of the inevitable stress of contemporary life, one excellent option for health support lies in supplementation using plants called 'adaptogens'.

Ashwagandha (*Withania somnifera*) is proved anxiolytic, antidepressant, and anti-stress adaptogen. It has been found effective in stress-induced sexual dysfunctions in animal models. Ashwagandha has been described in traditional Indian Ayurvedic medicine as an aphrodisiac that can be used to treat male [34] and female sexual dysfunction and infertility. Traditional Indian medicine has used it for centuries to alleviate fatigue and improve general well-being. Ashwagandha can address many of the health and psychological issues that plague today's society. In view of its varied therapeutic potential, it has also been the subject of considerable modern scientific investigations. The major chemical constituents of the Withania genus, the withanolides, are a group of naturally occurring steroidal lactones. In recent years, numerous pharmacological investigations have been carried out into the components of Ashwagandha extracts [36]. Ashwagandha, has long been used by Ayurvedic practitioners as a rejuvenating tonic [27].

As mentioned above, the female sexual response cycle consists of three phases: desire, arousal, and orgasm. During sexual arousal, genital blood flow and sensation are increased. The vaginal canal is moistened (lubrication). During orgasm, there is rhythmical contraction of the uterus and pelvic floor muscles. Within the central nervous system, hypothalamic, limbic-hippocampal structures play a central role for sexual arousal. Sexual arousal largely depends on the sympathetic nervous system. Furthermore, there is a growing body of evidence that women with sexual dysfunction commonly have physiologic abnormalities, such as vasculogenic and neurogenic derangements, contributing to their overall sexual health problems.

Ashwagandha normalizes the body's response to stress triggers and maintains equilibrium within the hypothalamic-pituitary-adrenal axis (HPA). In *Ayurvedic* medicine, Ashwagandha is known as a 'Rasayana', a term used for a group of plants classified as rejuvenative tonics that increase the body's resistance to stress. This traditional Ayurvedic use has been verified by numerous clinical studies and scientific research has validated its role in adrenal gland health; it has been shown to reduce cortisol, stress and anxiety. The standardized extract of Ashwagandha used in the present study has been shown in previous studies to be effective on the negative effects of stress, and to increase energy, reduce fatigue, enhance the sense of well-being, and reduce cortisol levels up to 27.9% [30].

In the present clinical trial situation, the Female Sexual Function Index (FSFI) and the Female Sexual Distress Scale (FSDS) were found to be useful for evaluation of the treatment outcome and the results markedly demonstrated an improvement in female sexual function by supplementing with Ashwagandha. The validation of these self-report questionnaire measures of sexual functioning in women was conducted by medical personnel addressing the protocol of the study.

In the present study, the multidimensional structure of the FSFI and the unidimensional structure of the FSDS were found to be fairly well replicated in the study sample. Internal consistency and stability of the FSFI and its subscales and the FSDS scores were found to be satisfactory to good, and the subscales were reasonably stable across demographic variables. Furthermore, it was observed that the discriminant validity and the ability of the scales to predict the presence or absence of sexual complaints were excellent. The reliability of these measures helped to proactively evaluate and appropriately treat women with FSD.

Our present report is the first clinical study evaluating the effects of a full-spectrum extract of Ashwagandha roots in improving sexual dysfunction in otherwise healthy women. Our findings show that Ashwagandha can

significantly improve the overall female sexual function with no adverse effects.

The profound central nervous system effects, antioxidant activity, anti-inflammatory effects and anti-stress effects of Ashwagandha have been discussed above. These multiple mechanisms of action are associated with the hypothalamic-pituitary-adrenal axis and are postulated as the possible explanations for improvements in sexual arousal and function.

In our study, the baseline (Day 0 of the Study Period of 8 weeks) mean total FSFI scores were 13.57+/-0.90 and 13.63+/-0.95 in the Ashwagandha root extract-treated group and placebo-treated group respectively which were markedly lower than in other reports, compared to their baseline values [1, 11,45-47]. We attribute these lower scores to restrained attitudes towards sex and towards talking about sex in this specific object pool, owing to its Asian Indian cultural norms. However, 8 weeks intake of Ashwagandha root extract significantly improved the status of this parameter, with a mean total score of 23.86+/-2.02; which was significantly ($p<0.001$)higher than the value of the mean total FSFI score in the placebo-treated group (20.06+/-2.38).

Oh et al [1] reported the baseline mean total FSFI score was 21.33, which was slightly lower than in earlier reports. Aslan et al.[45] reported total FSFI score of 24.2 in adult women (mean age 38.6 years) and Nappi et al.[46] reported a total score of 25 (age range 45–65 years). In another study the mean total score on the FSFI was 20.4. [47]. Singh et al [11] reported the mean total FSFI scores of 10.5+/-9.2 in women 40 years of age or above and 22.8+/-8.8 in women below 40 years.

In our data, treatment with Ashwagandha root-extract significantly improved all the individual FSFI domain scores as compared to the baseline values, depicting statistically significant improvement in female sexual dysfunction. Notable improvements were observed in sexual desire and frequency of successful sexual encounters without side effects. Furthermore, treatment with Ashwagandha resulted in significant improvement on the arousal, lubrication, orgasm, satisfaction and pain domains of FSFI at 4 and 8 weeks of the study period, when compared to the control values at similar time periods. These data strongly evidence the favourable effects of the full-spectrum Ashwagandha root extract and the superior effectiveness of this ancient herb in the improvement of the female sexual dysfunction.

A noteworthy observation in the present study was the substantial placebo-effect evident in the functional measures of all the domains of FSFI, in the FSDS scores and in the Event Log Records of successful sexual encounters. This observation confirms previous findings that indicate a marked placebo effect on sexual function of women with sexual difficulties [48, 49]. Several studies have noted major placebo effects; and it is well known that placebo effect adequately manages sexual dysfunction and improves treatment outcomes.

The face-to-face interview by the study subjects while answering the various questions of the FSFI, enabled the women to talk about their sexual problems and concerns. This contributed to the contentment and well-being of the study subjects, resulting in the marked improvement in sexual function in the placebo treated group.

The concept of sexually related personal distress is central to the diagnosis of all female sexual dysfunctions (FSD). Both placebo and Ashwagandha treated subjects showed a decrease in distress by the end of the study; however, the decrease in FSDS score was significantly more in Ashwagandha treated subjects as compared to the placebo treated controls.

Ashwagandha helps in proper nourishment of the tissue, by enhancing circulation [27]; which in the present study (possibly) has resulted in improvements in the vaginal epithelial layer and submucosal microvasculature.[50]. Thus, it is inferred that Ashwagandha root extracts may have an ameliorating effect on sexual function in women with FSD; especially on arousal, lubrication and orgasm.

CONCLUSION

The findings suggest that high-concentration

full-spectrum Ashwagandha root extract could effectively ameliorate the underlying pathologies and improve the variables of female sexual dysfunction. Hence, this full-spectrum Ashwagandha root extract can be used safely as an adaptogen in women to improve sexual function.

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Table 1: General Demographic Characters of the Study Subjects

Parameters	Ashwagandha root-extract treated group (n=25)		Placebo treated group (n=25)	
	Mean	Standard Deviation	Mean	Standard Deviation
Age (years)	28.12	5.12	29.44	6.14
Systolic blood pressure (mm Hg)	122.40	10.12	116.80	14.06
Diastolic blood pressure (mm Hg)	81.60	4.73	76.80	8.02
Pulse Rate (per min.)	72.24	2.11	70.72	2.23
Temperature (°F)	98.18	0.10	98.20	0.16
Respiratory Rate (per min.)	17.12	1.54	17.20	1.53

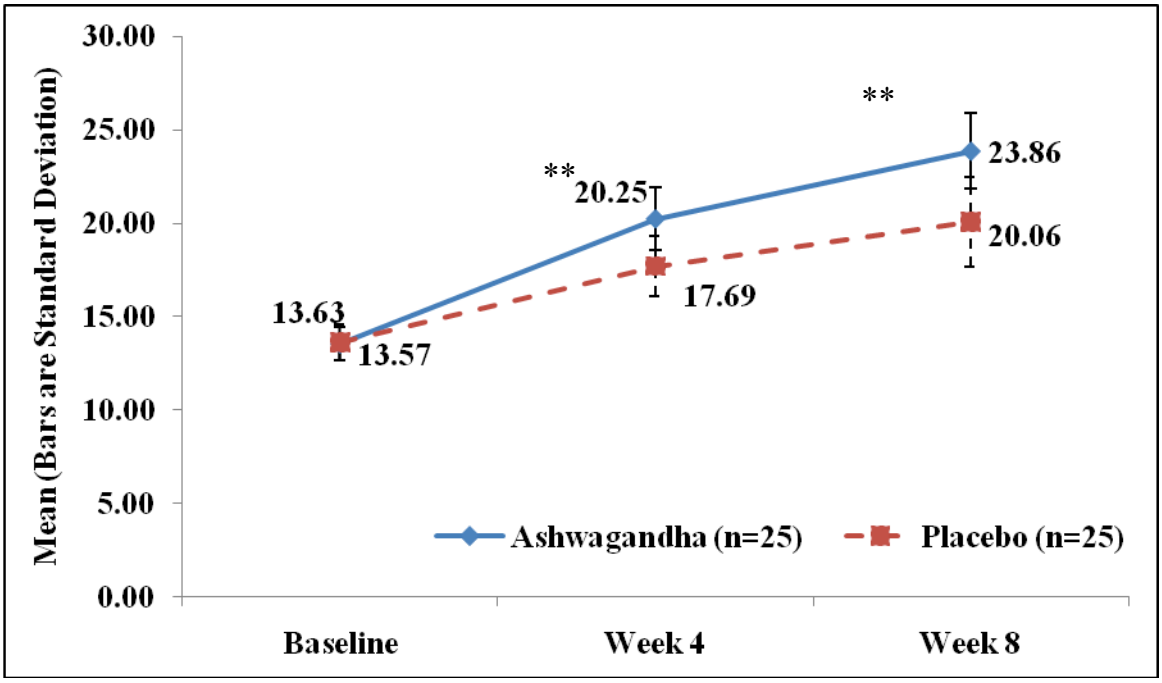

Figure 1: Mean Female Sexual Function Index (FSFI) Total Score in Ashwagandha root-treated group and Placebo treated group. **= p<0.001Ashwagandha root extract-treated group *versus* Placebo-treated group.

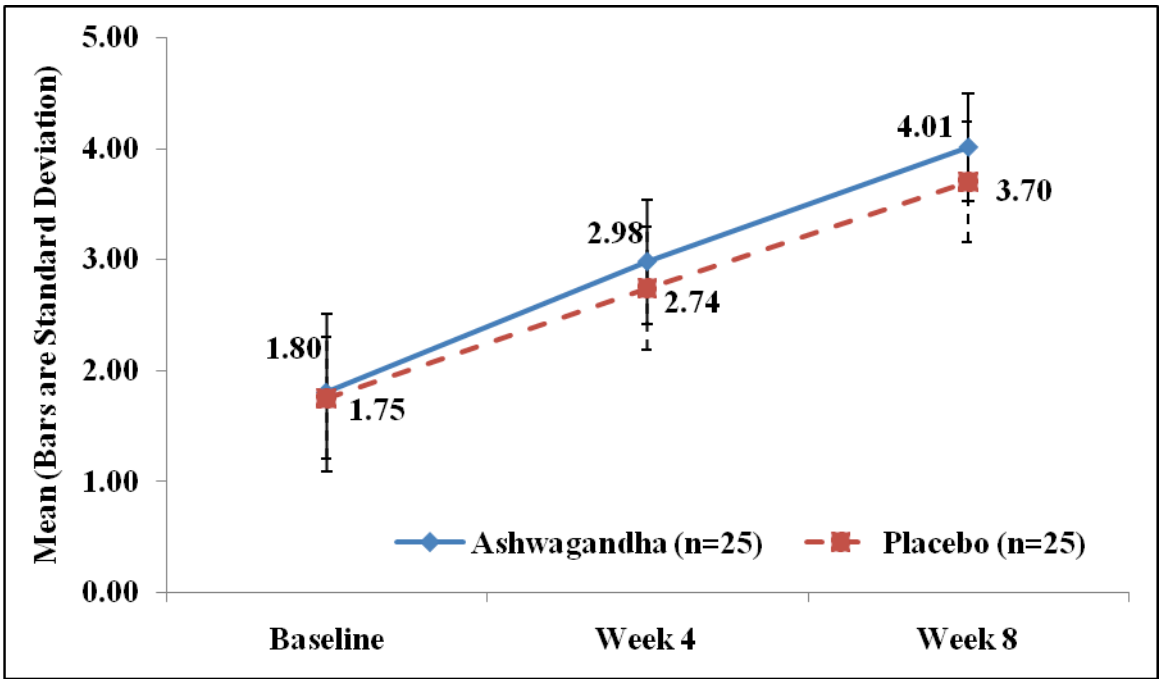

Figure 2: Mean Score for 'Desire' Domain of Female Sexual Function Index (FSFI)in Ashwagandha root-treated group and Placebo treated group.

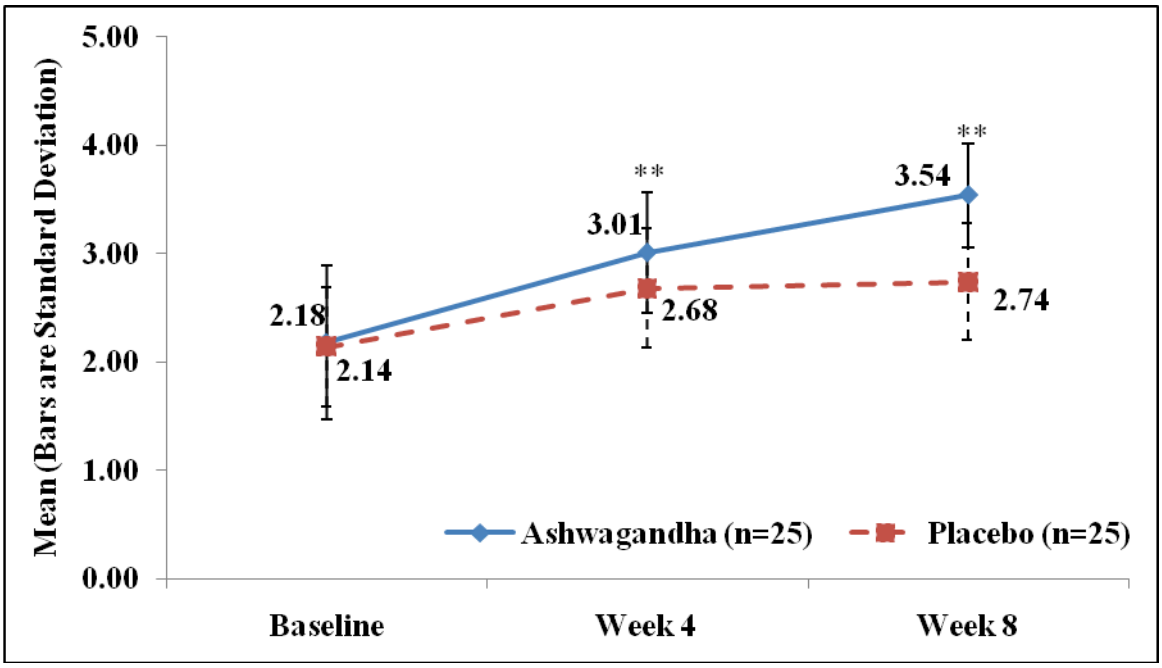

Figure 3: Mean score for 'Arousal' Domain of Female Sexual Function Index (FSFI)in Ashwagandha root-treated group and Placebo treated group.= p<0.001Ashwagandha root extract-treated group *versus* Placebo-treated group.**

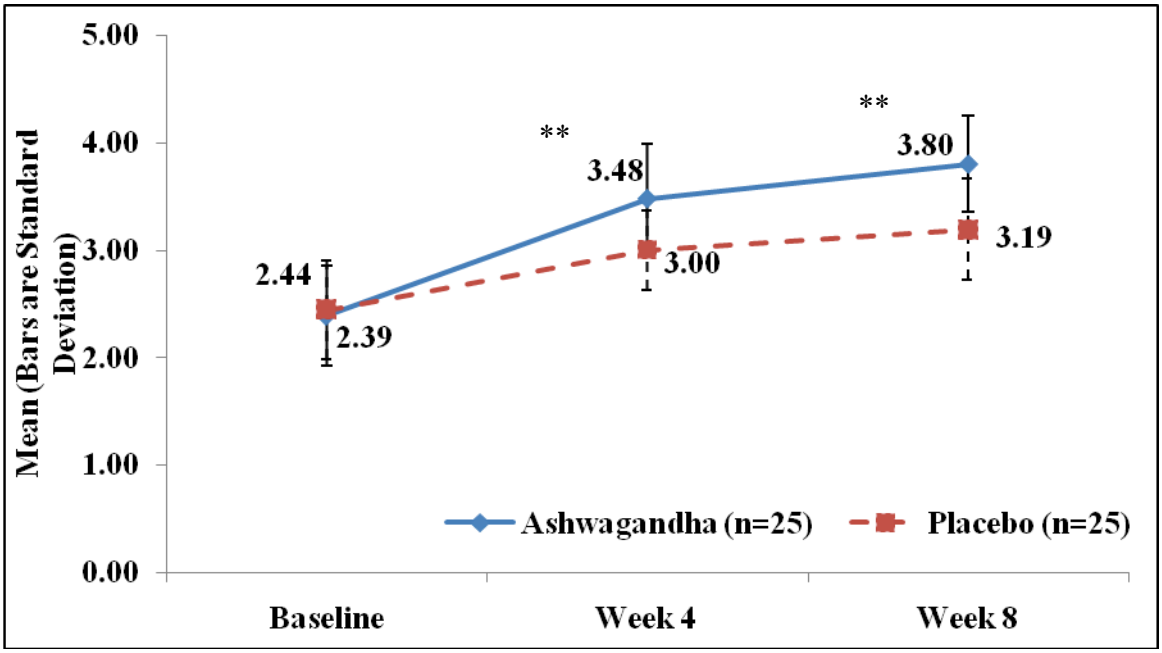

Figure 4: Mean Score for 'Lubrication' Domain of Female Sexual Function Index (FSFI)in Ashwagandha root-treated group and Placebo treated group.= p<0.001Ashwagandha root extract-treated group *versus* Placebo-treated group.**

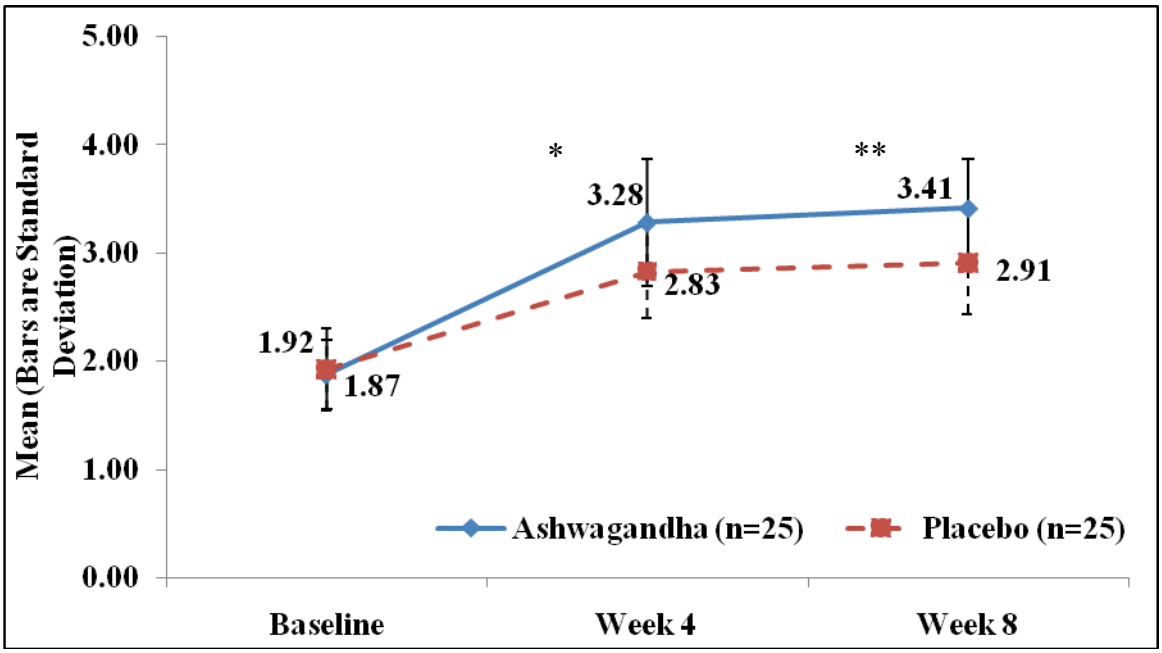

Figure 5: Mean Score for 'Orgasm' Domain of Female Sexual Function Index (FSFI)in Ashwagandha root-treated group and Placebo treated group. *=p<0.01; **= p<0.001Ashwagandha root extract-treated group *versus* Placebo-treated group.

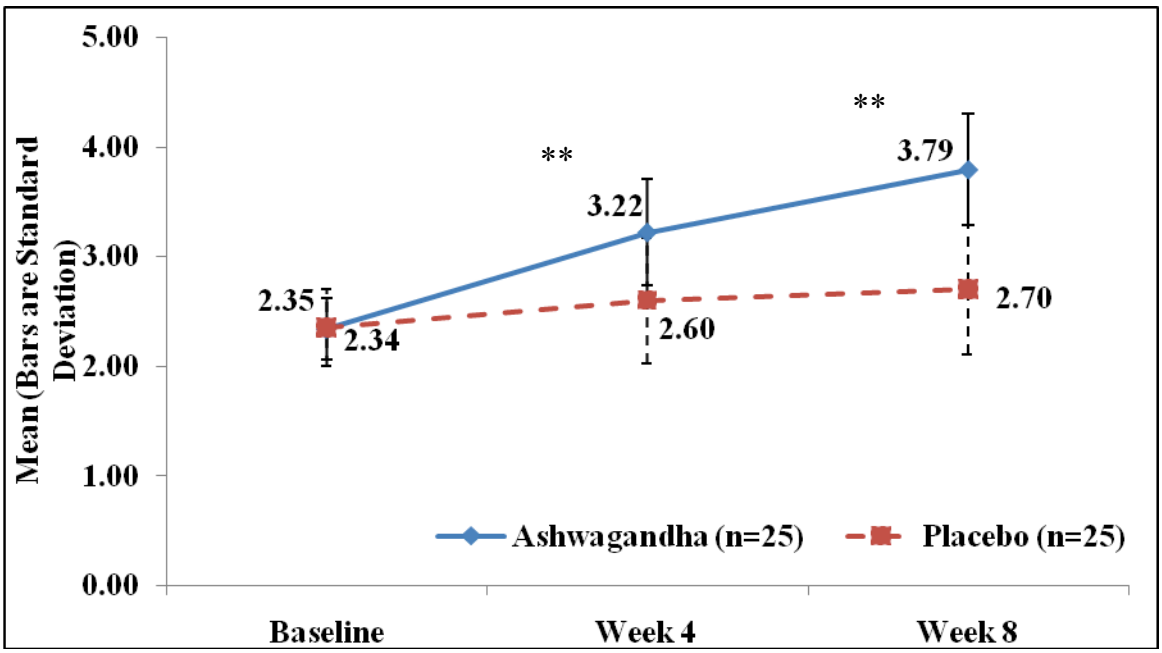

Figure 6: Mean Score for 'Satisfaction' Domain of Female Sexual Function Index (FSFI)in Ashwagandha root-treated group and Placebo treated group.= p<0.001Ashwagandha root extract-treated group *versus* Placebo-treated group.**

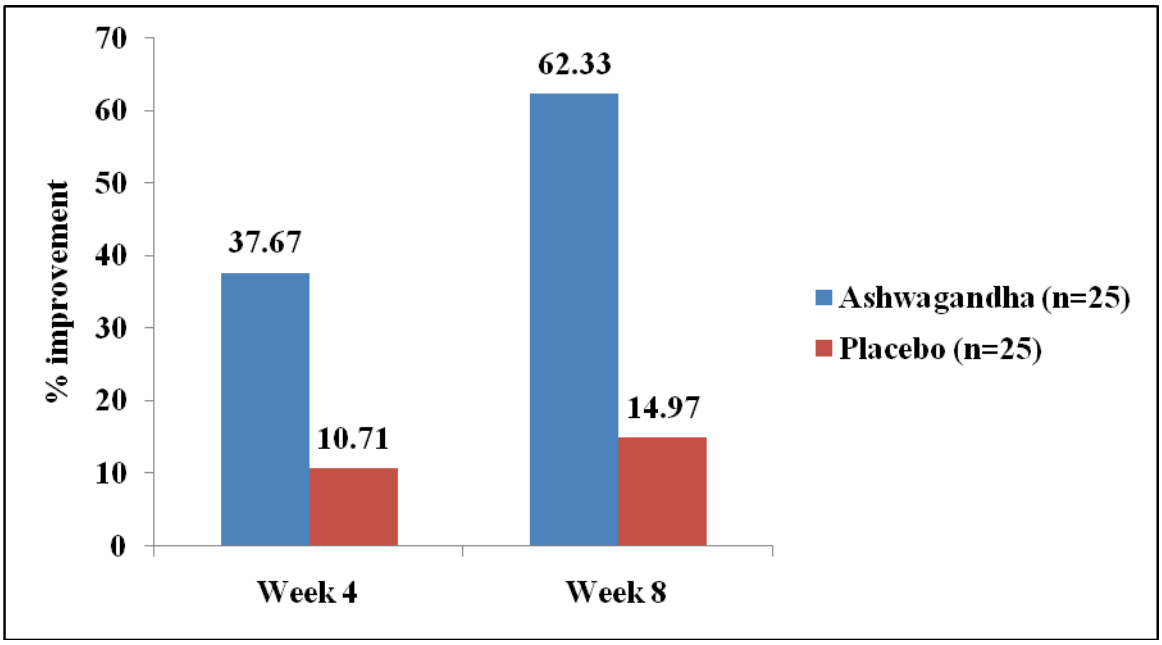

Figure 7: Per cent Improvement in the Mean Female Sexual Function Index (FSFI) Score for 'Satisfaction' Domainin Ashwagandha root-treated group and Placebo treated group.

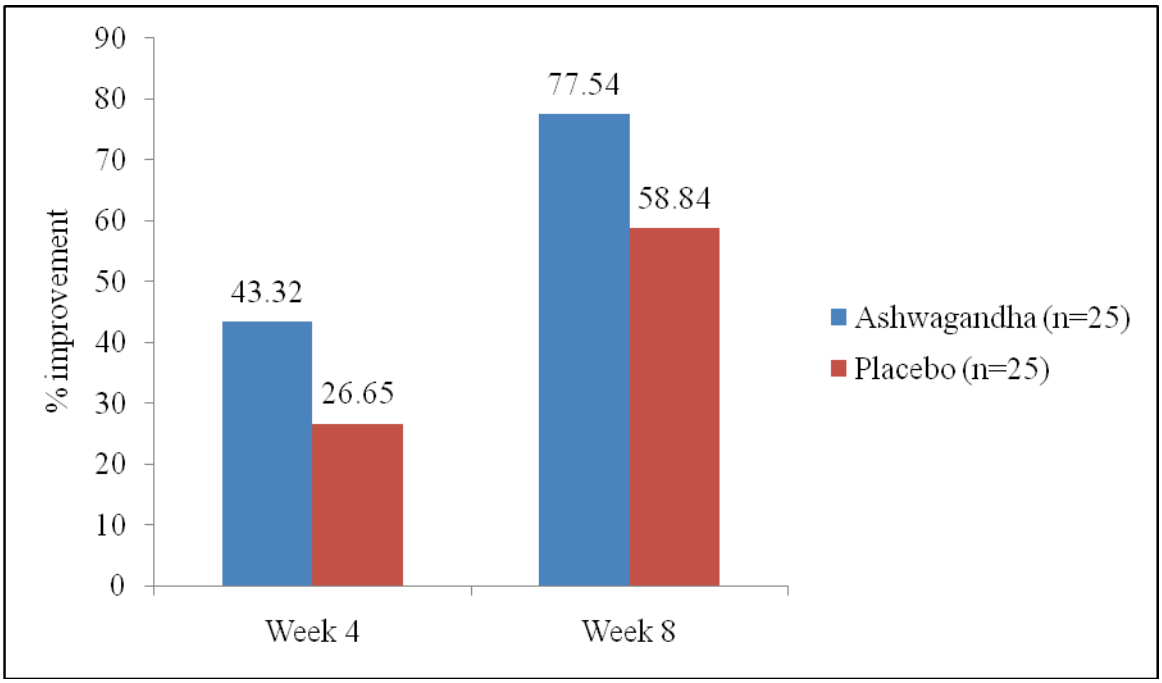

Figure 8: Per cent Improvement in the Mean Female Sexual Function Index (FSFI) Score for 'Pain' Domainin Ashwagandha root-treated group and Placebo treated group.

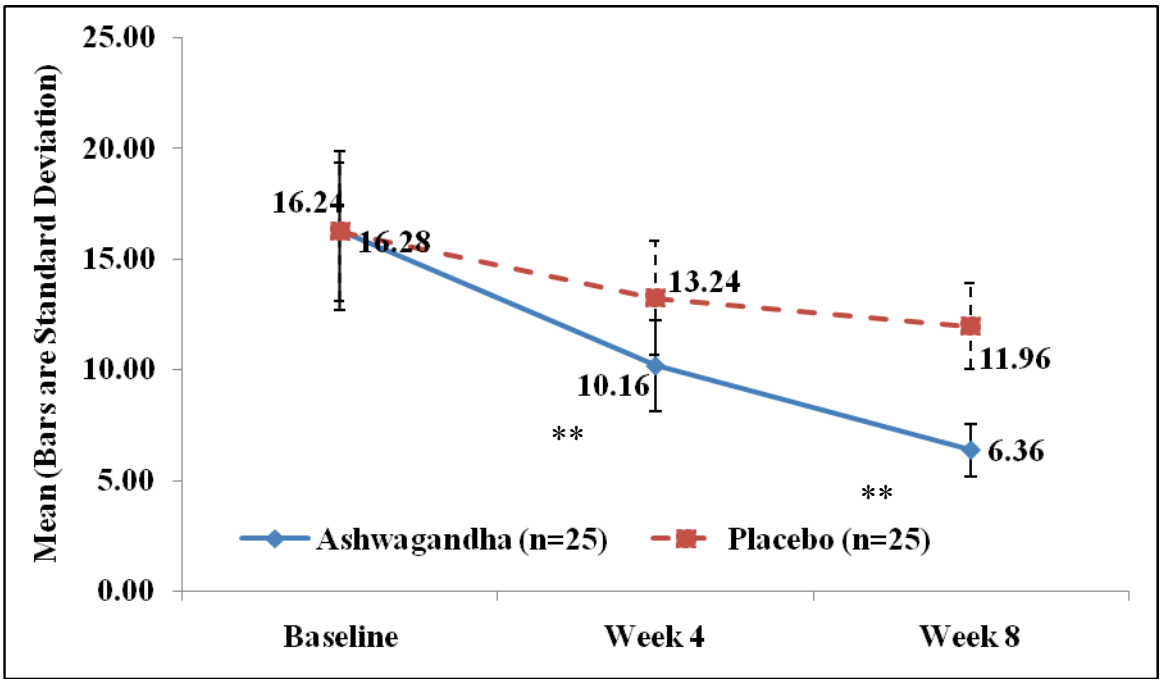

Figure 9: Mean Female Sexual Distress Scale (FSDS) Score in Ashwagandha root extract treated group and Placebo-treated group. **= p<0.001Ashwagandha root extract-treated group *versus* Placebo-treated group.

Table 2: Mean Number of Successful Sexual Encounters in Ashwagandha root extract treated and Placebo-treated groups.

Duration of the Study	Ashwagandha root-extract treated group (n=25)		Placebo treated group (n=25)		Unpaired 't' Test
	Mean	Standard Deviation	Mean	Standard Deviation	'p'
Baseline	1.84	0.80	1.96	1.24	0.687
Week 4	3.60	0.96	3.12	1.42	0.169
Week 8	4.16	0.69	3.16	0.75	<0.001
Change from baseline	**Mean change**	**% change.**	**Mean change**	**% change.**	
Week 4	1.76	95.65	1.16	59.18	0.056
Week 8	2.32	126.09	1.20	61.22	<0.001