



Randomized, double blind, placebo controlled clinical study to assess efficacy and safety of NRL/MW/201901 in subjects suffering from erectile dysfunction

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ABSTRACT

Sex is an integral part of a well-being. Sexual satisfaction is the most important component of the quality of life. In management of ED overall sexual potential and quality of life needs to be taken care of as a holistic approach to management. The aim of the study was to clinically validate effect of NRL/MW/201901 a polyhedral Nutraceutical product in ED. The clinical efficacy of NRL/MW/201901 in patients suffering from erectile dysfunction was evaluated by assessing Quality of Erection Questionnaire and sexual encounter profile with Intra-vaginal ejaculation latency time, serum testosterone and anthropometric analysis etc. NRL/MW/201901 was effective in increasing erection function, orgasmic function, intercourse satisfaction, overall satisfaction and sexual desire. There is marked increase in number of sexual encounters in NRL/MW/201901 treated group. Serum levels of testosterone were increased after treatment of NRL/MW/201901 than in placebo group. It was evident from the anthropometric analysis of the subjects that there was significant increase in resting metabolism and % skeletal muscle content in NRL/MW/201901 treated group. There were no evident adverse events related to drug. Thus it could be concluded that NRL/MW/201901 is safe and effective in the treatment of mild to moderate erectile dysfunction.

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INTRODUCTION

Erectile dysfunction (ED) is a common medical condition that affects approximately 100 million men worldwide and is currently recognized as a major

public health problem (Kapoor and Kapoor, 2016). It is estimated that nearly one half of men older than 40 years have some degree of ED. While in 1995, ED affected over 152 million men worldwide, it is projected that by 2025, more than 320 million patients will be afflicted with the largest projected increases in the developing world (McKinlay, 2000).

Classification

Erectile dysfunction may develop from psychological, neurological, hormonal, and vascular pathologies, or combinations of these factors (Lasker et al., 2010).

Psychological

Psychological factors such as stress, depression, schizophrenia, and a lack of sexual arousal may lead to difficulty in achieving an erection. ED may be

caused by diseases that interfere with libido, and therefore the brain's perception of arousal, such as Alzheimer's, stroke, Parkinson's, or brain trauma. Injury to the spinal cord may interrupt neural pathways to the sacral region, preventing or inhibiting the process of achieving an erection (Steers, 2000).

Hormonal

Hormones such as adrenocorticotropic hormone, oxytocin, prolactin, and androgens, especially testosterone, have been implicated in the modulation of erectile function. Hypogonadism plays a significant role in erectile dysfunction as it is believed that a threshold level of testosterone is necessary for erection to occur, and as men age there is a natural decrease in testosterone production further contributing to ED (Javaroni and Neves, 2012; Shabsigh et al., 2006).

Vascular

Peripheral arterial diseases and endothelial dysfunction seen in diabetes mellitus, atherosclerosis, coronary disease, and hypertension also contribute to the development of ED.

It has also been hypothesized that ED is an early harbinger of cardiovascular disease. Along with these causes, failure to occlude venous outflow from the sinusoids of the corpora can be a contributing factor for ED.

This may develop from degeneration of the tunica albuginea, loss of myogenic venous responses, trauma, or endothelial/smooth muscle dysfunction in the corpora (Gratzke et al., 2010; Jackson et al., 2006).

Nitric Oxide and ED

NO is thought to be the main vasoactive neurotransmitter involved in the erectile response and is released from nonadrenergic, noncholinergic (NANC) neurons as well as from the endothelium. An erection is dependent primarily upon a neurovascular, NANC mechanism peripherally, and on the central nervous system. Nitric oxide synthase is the enzyme responsible for the conversion of L-arginine to NO and L-citrulline.

The hyperpolarization through CGMP mediated pathway leads to blockade of membrane Ca^{2+} channels, decreasing calcium influx and causing smooth muscle cell relaxation.

This relaxation produces dilation of arteries/arterioles resulting in increased blood flow into corporal sinuses in both systolic and diastolic phases. The cavernosal sinuses expand while trapping arterial inflow and thus erection (Burnett et al., 1995; Gonzalez et al., 2002).

Contributing factors of ED

Recognized risk factors for ED include cardiovascular disease (CVD) (hypertension, atherosclerosis, and hyperlipidemia), diabetes, depression, alcohol use, smoking, pelvic/perineal surgery or trauma, neurologic disease, obesity, pelvic radiation, and Peyronie's disease. One study suggested that the relationship between arterial disease and ED is very strong, with 49% (147 of 300) of patients with coronary artery disease noted on cardiac catheterization reporting significant erectile dysfunction. Endothelial dysfunction has been indicated as the pathophysiologic mechanism responsible for both CVD and ED. Some evidence exists to suggest that chronic inflammation associated with metabolic syndrome also plays a role in endothelial dysfunction and erectile function, possibly due to oxidative stress. Hormone deficiency or hypogonadism, whether primary or secondary, has been thought to impact erectile function (Kupelian et al., 2007; Guay, 2005).

Medications

Conventional PDE inhibitors' typical side effects include headache, flushing, dyspepsia, and nasal congestion. Visual abnormalities, back pain and myalgia can occur with sildenafil like molecules. Such conventional drugs are contraindicated in cardiovascular diseases, diabetes and associated risk factors (Bivalacqua et al., 2000).

Need for Herbal Supplements

Historically, ED has been considered an age-dependent disease, with most men developing signs and symptoms of ED after 65 years of age. However, recent studies have demonstrated an increasing incidence of ED in men younger than 40 years, and this trend is likely underestimated because of under-reporting by younger patients.

Indulging in Sex is an integral part of a human being's well-being. ED is an important health concern that significantly affects quality of life and can have a detrimental effect on a man's psychosocial well-being. According to study conducted, the main socio demographic characteristics affecting ED are age, occupation of the patient and of the patient's partner. The main risk factors for developing ED are lifestyle risk factors (smoking and obesity), medical conditions (DM, HTN, heart disease, dyslipidemia, LUTS, hypogonadism), drugs (insulin, psychiatric drugs, and silymarin), and penile and pelvis injury.

Psychogenic factor is present in most cases of ED and hence there is a need to encourage the prevention of ED, including correction of the modifiable risk factors. ED has a significant negative impact on the QoL of both the affected individual and his part-

ner, and hence there is a need to encourage treatment of ED (Mutagaywa *et al.*, 2014; Hatzimouratidis *et al.*, 2010).

ED is no longer managed by only inducing erection but overall sexual potential and quality of life needs to be taken care of as a holistic approach to management. Research on Nutraceutical herbal supplements in management of sexual dysfunction is gaining momentum. The holistic approach offered by herbal supplements in promoting health and well-being can be beneficial in ED management.

In the present study, we evaluated the safety and efficacy of a multi-herb formulation NRL/MW/201901 manufactured by Netsurf Research Lab Pvt. Ltd., for enhancement of sexual health in men. It is consisting of a proprietary blend of L- Citrulline and extracts of *Withania somnifera*, *Mucuna Pruriens*, *Anacyclus pyrethrum*, *Abutilon indicum*, *Trigonella foenum-graecum*, *Ginkgo biloba*, *Myristica fragrans*, *Panax ginseng*, *Tribulus terrestris* and *Szygium aromaticum*. The aim of the present study is to validate effectiveness of NRL/MW/201901 in erectile dysfunction.

MATERIALS AND METHODS

The clinical trial is randomized, double blind and placebo controlled interventional trial. Married male subjects of age between 21 to 50 years of age (both inclusive) attending outpatient department of study site(s) were screened for eligibility criteria. Upon obtaining written informed consent subject's demographic details and clinical examination were collected. Subject's medical, surgical and treatment history was taken. Subject's current medication if any was noted. Subject's vitals (radial pulse, blood pressure, respiratory rate, and axial temperature) were recorded. Subject's clinical examination was done to rule out any organic cause of Sexual Dysfunction.

Assessment of Erectile function was done using Erectile Function (EF) domain score of the International Index of Erectile Function (IIEF) questionnaire. Subjects in an active stable sexual relationship with EF Domain score 11 to 25 i.e. mild to moderate erectile dysfunction were enrolled in the study. Subjects were advised to refrain from antioxidant agents, vitamins, anti-inflammatory drugs, hormones, Nutraceutical, Ayurvedic, Siddha, Unani, herbal/homeopathic medicines for the treatment of erectile dysfunction.

Subject's erectile function, orgasmic function, sexual desire, intercourse satisfaction and overall satisfaction were assessed on International Index of Erec-

tile Function (IIEF). Subject's quality of penile erection was evaluated on quality of erection questionnaire (QEO). Daily diary card was issued to subject to maintain the record of sexual encounter profile and intra-vaginal ejaculation latency time (IELT). Subject's serum testosterone levels were measured as baseline reading. The treatment was adopted for 60 days at 1 capsule BD dose.

On follow up and final follow up visit (i.e. Day 60) subject's serum total testosterone level was checked together with erectile function, orgasmic function, sexual desire, intercourse satisfaction and overall satisfaction, quality of penile erection, sexual encounter profile and intra-vaginal ejaculation latency time (IELT). Any adverse events and tolerability of the product is checked throughout study period. On final follow up visit (i.e. Day 60) and baseline subject's CBC, ESR, Hb%, Liver Function Tests, Lipid Profile, Renal Profile, BSL-F, Urine Routine and Microscopic were done (data is not shown here). Subjects were assessed for anthropometric parameters on every follow up visit.

Inclusion and exclusion criteria

Male subjects aged 21-50 years suffering from ED who scored between 11 to 25 on the Erectile Function (EF) domain of the International Index of Erectile Function (IIEF) at screening visit were selected. Subjects with in an active stable sexual relationship for the entire duration of study, willing to participate in clinical trial, who have read understood and signed informed consent form and willing to make all required study visits were selected for study.

Subjects having anatomical abnormalities of the penis, that have undergone radical prostatectomy, spinal cord injury, or any other surgery of urogenital organs and patients with severe form of sexual dysfunction were excluded. Subjects with prior ineffective treatment with (or non-responder to) any PDE5 Inhibitor or underwent treatment for promoting spermatogenic fertility in last 3 months were excluded. Subjects with any comorbidity in the opinion of the investigators, makes the patient unsuitable for enrolment or could interfere with his participation in, and completion of the protocol and with known hypersensitivity are excluded. Patients receiving hormonal treatment, antidepressants, antipsychotics, or any other psychoactive drugs were excluded from study.

Withdrawal criteria

Subjects were withdrawn from the study (i.e. from any further study medication or study procedure) for the reasons like, 1) at their own request i.e. withdrawal of consent at any time for personal rea-

sons. 2) If, in the investigator's opinion, continuation in the study was detrimental to the subject's well-being. 3) Protocol deviations that could invalidate interpretation of the results (i.e. intake of not permitted concomitant treatments etc.)

Compliance with ethics

All patients provided written and informed consent. The study protocol was approved by the institutional ethics committee of all center. The study was conducted in compliance with the Declaration of Helsinki and the International Conference on Harmonization Guideline for Good Clinical Practice guidelines. Study is registered prospectively on CTRI with registration number CTRI/2019/05/019303 [Registered on: 23/05/2019].

Compliance with treatment

Patients were encouraged not to skip scheduled medication intake or reduce dosages on their own. Lapses observed during visits were documented on the appropriate page of the Case Report Form. Investigators evaluated treatment compliance by measuring unused medication in the subject medication box. If more than 6 doses and 3 doses consecutively were missed during one month, the patient was termed as noncompliant and was excluded from the trial.

Visit Schedules

Screening Visit (up to -14 days), Baseline Visit (Day 0), Visit 1 (Day 30 + 5 days), Visit 2 (Day 60 + 5 days) of treatment

Avoid of bias

The clinical bias was avoided in the study by employing placebo controlled group which were exactly identical capsules that of NRL/MW/201901. Study was double blind about receiving treatment (Test or placebo) to avoid subject's and investigator's bias.

Statistics

Consultant bio-statistician performed the analysis of the data using statistical software SPSS 10.0. Data describing quantitative measures are expressed as median or mean \pm SD. Qualitative variables are presented as frequency and percentage. Data was analyzed by Mann Whitney U test, analysis of variance and Chi Square test.

RESULTS AND DISCUSSION

In the present study, 105 subjects were screened. Out of 105 subjects, 5 lost to follow up in the study after 1 month of treatment. 100 subjects were considered evaluable cases at the end of the study 50

in test and 50 in placebo treated group. Out of 100 completed subjects, the mean age of subjects in test group 35.06 ± 5.57 years and in placebo treated group the mean age of subjects was 36.76 ± 6.11 years. When compared between the age of groups, the difference was statistically insignificant.

Changes in vital parameters

No statistically significant change from baseline to end of therapy values in any of the vital signs (pulse rate, body temperature, and respiratory rate, systolic and diastolic blood pressure) was observed between both the groups.

Efficacy Assessments

Comparison of changes in mean erectile function between the groups

At baseline, mean erectile function was 12.76 among Test group which was comparable to 12.80 among Placebo group and the difference was not significant. After 30 days of treatment, mean erectile function showed a significant increase of 76.50% among Test group and 36.9% among Placebo group from baseline. At the end of 60 days of treatment, mean erectile function showed a significant increase of 94.2% among Test group and 31.8% among Placebo group from baseline. If compared, treatment with NRL/MW/201901 significantly increased erectile function than Placebo group. Data is shown in Table 1 and Figure 1.

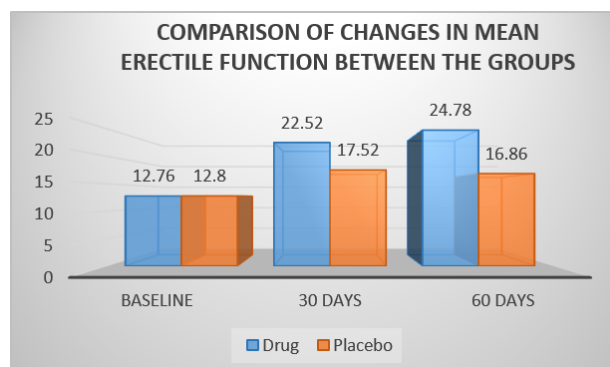


Figure 1: Changes in mean erectile function between the groups

Comparison of changes in mean sexual desire between the groups

Mean sexual desire was 4.14 in Test group which was comparable to 4.18 among Placebo group and the difference was not significant. After 30 days of treatment, mean sexual desire showed a significant increase of 69.1% among Test Group and rise of 29.2% among Placebo group from baseline. At the end of 60 days of treatment, mean sexual desire showed a significant increase of 91.8% among Test

Table 1: Changes in mean erectile function between the groups

Duration (Days)	Mean Erectile Function (mean ± SD)		P value
	Drug (N = 50)	Placebo (N = 50)	
Baseline	12.76 ± 1.78	12.80 ± 1.96	0.49202 (NS)
30	22.52 ± 5.10	17.52 ± 4.75	* < 0.00001
60	24.78 ± 4.25	16.86 ± 2.29	* < 0.00001

NS = Not Significant *Significant
By Mann Whitney U Test (Between Groups)

Group and 33.5% among Placebo group from baseline. If compared, treatment with NRL/MW/201901 significantly increased sexual desire than Placebo group. Data is shown in Table 2 and Figure 2.

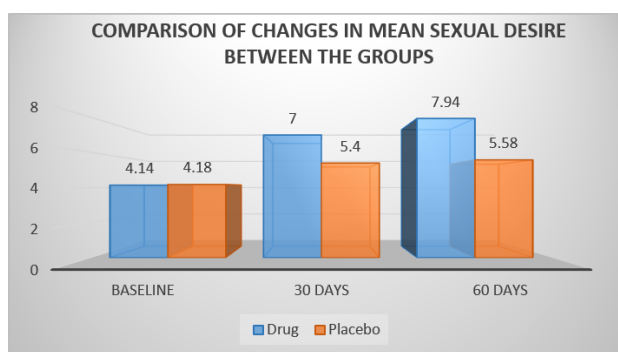


Figure 2: Changes in mean sexual desire between the groups

Comparison of changes in mean orgasmic function between the groups

Mean orgasmic function was 4.22 among Test Group which was comparable to 4.23 among Placebo group and the difference was not significant. After 30 days of treatment, mean orgasmic function showed a significant increase of 75.8% among Drug and increase of 36.2% among Placebo group from baseline. After 60 days of treatment, mean orgasmic function showed a significant increase of 94.8% among Drug and 42.3% among Placebo group from baseline.

If compared, treatment with NRL/MW/201901 significantly increased orgasmic function than Placebo group. Data is shown in Table 3 and Figure 3.

Comparison of changes in mean intercourse satisfaction between the groups

Mean intercourse satisfaction was 6.86 among Test Group which was comparable to 6.68 among Placebo group and the difference was not significant. At the end of 30 days of treatment, mean intercourse satisfaction showed a significant rise of 53.4% among Test Group and rise of 26.9 % among Placebo group from baseline. At the end of 60 days of treatment, mean intercourse satisfaction

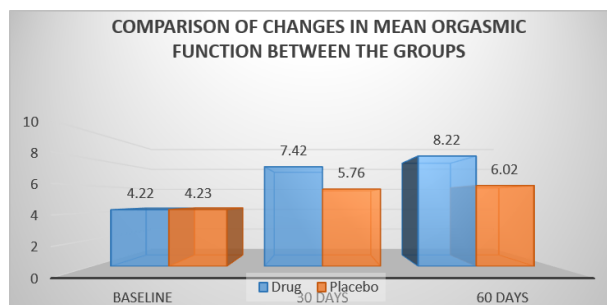


Figure 3: Changes in mean orgasmic function between the groups

showed a significant increase of 71.4% among Test Group and 25.7 % among Placebo group from baseline. If compared, treatment with NRL/MW/201901 significantly increased intercourse satisfaction than Placebo group. Data is shown in Table 4 and Figure 4.

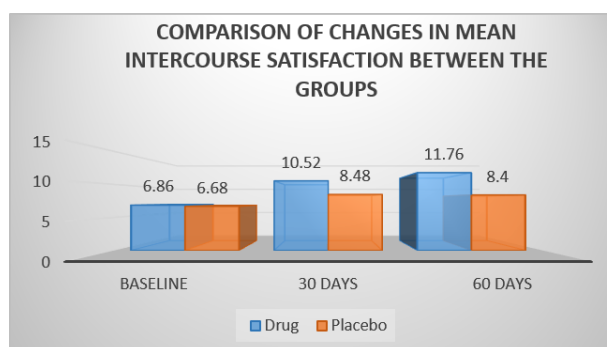


Figure 4: Changes in mean intercourse satisfaction between the groups

Comparison of changes in mean overall satisfaction between the groups

Mean overall satisfaction was 3.78 among Test group which was comparable to 3.82 among Placebo group and the difference was not significant. At the end of 30 days of treatment, mean overall satisfaction showed a significant increase of 75.4% among Test group and 19.7% in Placebo group from baseline. After 60 days of treatment, mean overall satisfaction showed a significant increase of 93.9% among Test group and 31.7% among Placebo group from baseline.

Table 2: Changes in mean sexual desire between the groups

Duration (Days)	Mean Sexual Desire (Mean± SD)		P value
	Drug (N = 50)	Placebo (N = 50)	
Baseline	4.14 ± 0.76	4.18 ± 0.75	0.352 (NS)
30	7.00 ± 1.59*	5.40 ± 1.56	p< .00001
60	7.94 ± 1.02*	5.58 ± 1.07	p< .00001

NS = Not Significant
*Significant By Mann Whitney U Test (Between Groups)

Table 3: Changes in mean orgasmic function between the groups

Duration (Days)	Mean Orgasmic Function (Mean± SD)		P value
	Drug (N = 50)	Placebo (N = 50)	
Baseline	4.22 ± 0.55	4.23 ± 0.53	0.500 (NS)
30	7.42 ± 1.79*	5.76 ± 1.90	p< .00001
60	8.22 ± 1.59*	6.02 ± 1.39	p< .00001

NS = Not Significant
*Significant By Mann Whitney U Test (Between Groups)

Table 4: Changes in mean intercourse satisfaction between the groups

Duration (Days)	Mean Intercourse Satisfaction (Mean± SD)		P value
	Drug (N = 50)	Placebo (N = 50)	
Baseline	6.86 ± 1.09	6.68 ± 1.06	0.400 (NS)
30	10.52 ± 2.90*	8.48 ± 2.17	p< .00001
60	11.76 ± 1.57*	8.40 ± 1.88	p< .00001

NS = Not Significant
*Significant By Mann Whitney U Test (Between Groups)

If compared, treatment with NRL/MW/201901 significantly increased overall satisfaction than Placebo group. Data is shown in Table 5 and Figure 5.

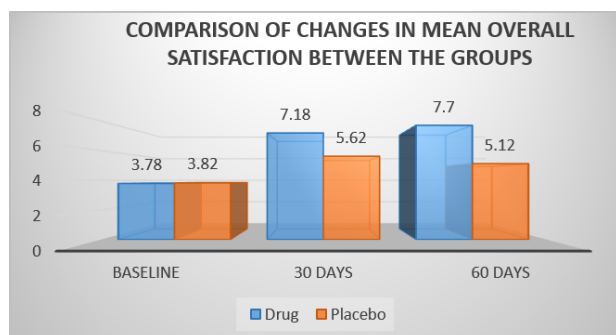


Figure 5: Changes in mean overall satisfaction between the groups

Comparison of changes in mean quality of erection score between the groups

Mean Quality of Erection score was 23.32 among

Test group which was comparable to 23.77 among Placebo group and the difference was not statistically significant. After 30 days of treatment, mean Quality of Erection score showed a significant rise of 178% among Test group and 82.2% among Placebo group from baseline. After 60 days of treatment, mean Quality of Erection score showed a significant increase of 224.4% among Test group and 49.7% among Placebo group from baseline. If compared, treatment with NRL/MW/201901 significantly increased Mean Quality of Erection than Placebo group. Data is shown in Table 6 and Figure 6.

Comparison of changes in mean serum total testosterone between the groups

Mean Serum Total Testosterone was 356.12 among Test group which were comparable to 307.10 among Placebo group but the difference was not statistically significant. After 60 days of treatment, mean Serum Total Testosterone showed a signif-

Table 5: Changes in mean overall satisfaction between the groups

Duration (Days)	Mean Overall Satisfaction (Mean ± SD)		P value
	Drug (N = 50)	Placebo (N = 50)	
	3.78 ± 1.07	3.82 ± 0.72	0.264 (NS)
30	7.18 ± 1.95*	5.620 ± 1.60	p< .00001
60	7.70 ± 1.76*	5.12 ± 1.67	p< .00001

By Wilcoxon Sign Rank Test (Within Group) NS = Not Significant
 *Significant By Mann Whitney U Test (Between Groups)

Table 6: Changes in mean quality of erection score between the groups

Duration (Days)	Mean Quality of Erection Score (Mean ± SD)		P value
	Drug (N = 50)	Placebo (N = 50)	
Baseline	23.32 ± 6.65	23.77 ± 5.39	0.348 NS
30	64.83 ± 23.81*	43.31 ± 18.84	p< .00001
60	75.66 ± 22.08*	35.58 ± 15.57	p< .00001

NS = Not Significant
 *Significant By Mann Whitney U Test (Between Groups)

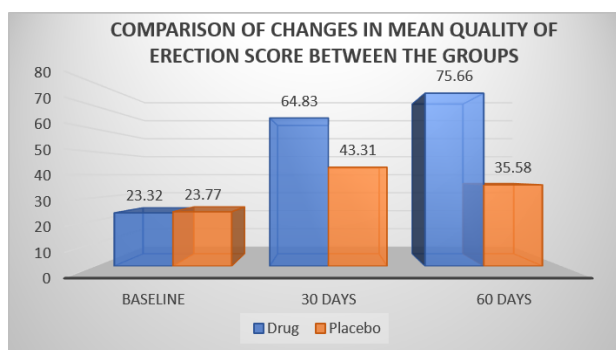


Figure 6: Changes in mean quality of erection score between the groups

icant increase of 41.43% among Test group and 1.44% among Placebo group from baseline. If compared, treatment with NRL/MW/201901 significantly increased Mean testosterone levels than Placebo group. Data is shown in Table 7 and Figure 7.

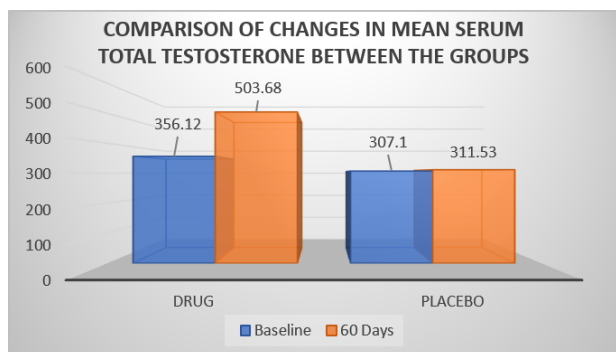


Figure 7: Changes in mean serum total testosterone between the groups

Comparison of mean number of sexual encounters between the groups

Mean number of sexual encounters was 8.12 among Test group which was significantly more than 6.28 among Placebo group. At Day 60, mean number of sexual encounters was 9.02 among Test group which was significantly more as compared to 6.88 among Placebo group. If compared, treatment with NRL/MW/201901 significantly increased sexual encounters than Placebo group. Data is shown in Table 8 and Figure 8.

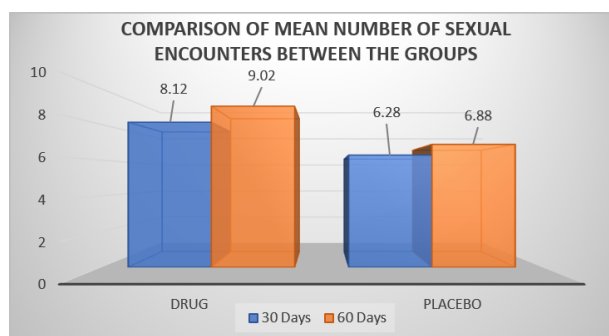


Figure 8: Mean number of sexual encounters between the groups

Comparison of mean intra vaginal ejaculation latency time (IELT) between the groups

At Day 30, mean IELT was 42.20 sec among Test group which was significantly more as compared to 27.64 sec among Placebo group. At Day 60, mean IELT was 53.60 sec among Test group which was significantly more than 29.50 sec among Placebo group. If compared, treatment with NRL/MW/201901 significantly increased IELT than

Table 7: Changes in mean serum total testosterone between the groups

Duration (Days)	Mean Serum Total Testosterone (Mean± SD)		P value
	Drug (N = 50)	Placebo (N = 50)	
Baseline	356.12 ± 104.18	307.10 ± 115.41	0.087 (NS)
60	503.68 ± 106.14*	311.53 ± 91.98	<0.0001

NS = Not Significant

*Significant ByMann Whitney U Test (Between Groups)

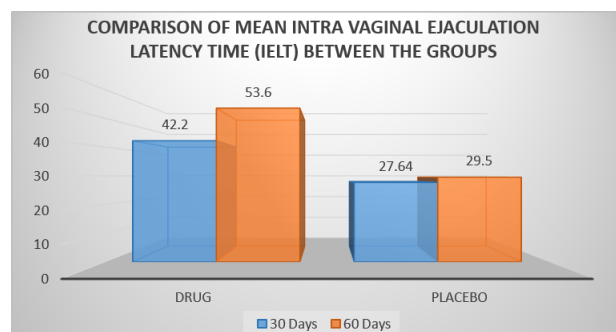
Table 8: Mean number of sexual encounters between the groups

Duration (Days)	Mean No. of Sexual Encounters (Mean± SD)		P value
	Drug (N = 50)	Placebo (N = 50)	
30	8.12 ± 2.13*	6.28 ± 2.25	0.00005
60	9.02 ± 1.53*	6.88 ± 3.27	< 0.00001.

By Mann Whitney U Test

*Significant

Placebo group. Data is shown in Table 9 and Figure 9.

**Figure 9: Mean intra vaginal ejaculation latency time (IELT) between the groups**

Comparison of anthropometric parameters between groups

Mean parameters of anthropometry were comparable at baseline in both the groups and difference was not significant. After treatment at day 60, mean parameters of anthropometry did not show any significant change from baseline in both the Groups except resting metabolism and % of skeletal muscle which was increased significantly till 60 days in NRL/MW/201901 treated group when compared to placebo, as depicted in Table 10.

From the findings of the study, it is evidently demonstrated that NRL/MW/201901 possesses beneficial activity in management of mild to moderate erectile dysfunction. The results depict that NRL/MW/201901 was effective in increasing all domains of IIEF questionnaire i.e. erection function, orgasmic function, intercourse satisfaction, overall satisfaction and sexual desire. There is marked increase in number of sexual encounters

in NRL/MW/201901 treated group compared to placebo.

NRL/MW/201901 is showing increase in Intra vaginal ejaculation latency time (IELT) is the time taken by a man to ejaculate during vaginal penetration. Selective serotonin reuptake inhibitors (SSRIs) tend to improve IELT. There is probable effect of NRL/MW/201901 as an antistress which reduces anxiety and promotes prolonged IELT. It suggests improved stamina in subjects by treatment of NRL/MW/201901.

The available scientific data support that Ashwagandha which is present in NRL/MW/201901 is a real potent regenerative tonic (*Rasayana of Ayurveda*), due to its multiple pharmacological actions like anti-stress, neuroprotective and adaptogenic action. The mechanism on the reproductive system is proposed to be linked to the antioxidative features and ability to improve the hormonal balance of LH, FSH, and testosterone and improve detoxification process. Also, the GABA mimetic feature of this extract is thought to play the main role in inducing gonadotropin releasing hormone secretion and improving hormonal balance.

Improved hardness of penis is responsible for increased erection function the activity could be attributed to the NO like activity of the ingredients present in NRL/MW/201901. Panax ginseng present in product induced NO release as per study conducted in rabbit corpus cavernosum in vitro. It can be postulated that cardiovascular protection may partly induced by the release of NO, a potent antioxidant, especially from perivascular nitric oxidergic nerves in the carvenosa, may partly account for the aphrodisiac effect of *P.ginseng* used

Table 9: Mean intra vaginal ejaculation latency time (IELT) between the groups

Duration (Days)	Mean IELT (Seconds) (Mean± SD)		P value
	Drug (N = 50)	Placebo (N = 50)	
30	42.20 ± 16.48	27.64 ± 15.45	*0.001
60	53.60 ± 17.02	29.50 ± 12.09	*0.001

By Mann Whitney U Test

*Significant

Table 10: Anthropometric examination

Anthropometric Examination	Mean (Mean± SD)				
	Baseline	Drug		Placebo	
		Day 60	Baseline	Day 60	
Height (cm)	166.6± 3.68	166.6± 3.68	166.16 ± 4.58	166.16 ± 4.58	
Weight (kg)	74.604± 6.82	73.48± 5.88	75.86 ± 4.13	74.63 ± 4.02	
Waist Circumference (cm)	99.782± 15.01	98.83± 14.68	102.97 ± 3.55	102.27 ± 3.64	
Hip Circumference (cm)	96.094± 14.31	95.10 ± 13.90	99.63 ± 4.95	99.10 ± 4.92	
Mid upper arm Circumference (cm)	32.28± 2.45	31.64 ± 2.41	32.74 ± 1.86	32.14 ± 1.90	
Triceps skinfold thickness (cm)	17.08± 6.37	16.82 ± 5.99	17.2 ± 6.48	16.68 ± 6.03	
Body Mass index (BMI)	30.83± 2.29	26.46 ± 1.86	27.26 ± 2.60	27.02 ± 1.57	
Waist to Hip ratio	1.0464± 0.05	1.06 ± 0.12	1.03 ± 0.05	15.03 ± 0.04	
Arm Fat Index	33.5± 6.38	32.4 ± 6.20	34.65 ± 5.57	33.76±5.25	
Body Fat %	22.01± 9.38	21.12 ± 3.26	21.48 ± 2.96	21.94 ± 2.58	
Visceral Fat level %	12.866± 3.13	13.02 ± 2.83	13.39 ± 1.74	13.04 ± 1.54	
Skeletal Muscle %	19.09± 3.21	25.46 ± 3.32 *	20.36 ± 2.44	19.64 ± 2.58	
Resting Metabolism (kcal)	1388.1 ± 101.64	1424.52± 104.30*	1343.48 ± 92.75	1317.78 ± 88.33	

By ANOVA Test

P>1.000, Not Significant, P<0.05 Significant

in test drug (Liao *et al.*, 2018). Ginseng has been used as an adaptogen to treat illness, both as a tonic and as a rejuvenator it effectively suppresses stress, which is a major cause of depression (Ali *et al.*, 2013; Lee and Rhee, 2017).

Kapikacchu or Mucuna present in NRL/MW/201901 is famous for its powerful aphrodisiac as it is well known to increase the sperm count and to increase testosterone levels in the body as well. Kapikacchu is an agent that helps the body in building up the mass as well as endurance and also helps the body to increase the muscular strength.

It also significantly increases the sexual desire, penile rigidity, erection and duration of ejaculation with orgasm (Ramdhan *et al.*, 2015). Mucuna pruriens stimulates the secretion of L-Dopa which

converts to the Dopamine. This dopamine stimulates the Pituitary to secrete FSH and LH. With the help of LH, secretion of the Testosterone may occur. Improved level of Testosterone leads to improvement in spermatogenesis and performance. It will be helpful to upgrade the general health. Mucuna pruriens is also found to inhibit the secretion of high Prolactin; which is one of the cause in erectile dysfunction and thus it will help to improve the sexual drive (Praveen *et al.*, 2018).

Serum levels of testosterone were increased after treatment of NRL/MW/201901 and not in placebo group clearly indicated that the desired aphrodisiac effect of NRL/MW/201901 is not only on psychological levels but also acting on hormonal levels to get sustained effect with no evident side effects and adverse events related to drug.

Anacyclus pyrethrum (*A. pyrethrum*) present in NRL/MW/201901 has been used in traditional Indian Ayurvedic medicine to treat male sexual dysfunction, including infertility. Aphrodisiac activity may be due to an increase in the production or effect of androgens. It increases the time of ejaculation and quality of semen. This drug significantly increases body weight, sperm count, motility and viability along with serum testosterone, Luteinizing Hormone and Follicle Stimulating Hormone concentration. So this drug shows androgenic activity. The increased sexual encounters and IELT could be contributed by androgenic activity and improvement in body muscle content by NRL/MW/201901 (data not shared here) (Sharma *et al.*, 2013; Kumar and Chaudhary, 2016; Sharma, 2009).

Trigonella foenum-graecum L. (Fabaceae) seeds extract present in NRL/MW/201901 is reported to be useful in hormonal regulation, particularly for male impotence. Fenugreek extract is reported to enhance endurance capacity and the utilization of fatty acids as an energy source in male mice. These effects are purported to be mediated through an aromatase and 5 α reductase inhibition, thereby increasing total testosterone levels by blocking its conversion to estrogen and dihydrotestosterone, respectively. Increased testosterone levels are known to increase muscle size and strength in men with downstream benefits on body weight, body fat, muscle size, strength, libido, energy, and mood (Bhasin *et al.*, 1996; Wankhede *et al.*, 2016).

Tribulus terrestris commonly known as *Gokharu* present in NRL/MW/201901 contain a variety of chemical constituents which are medicinally important, such as flavonoids, flavonol glycosides, steroidal saponins, and alkaloids. The active extracts and its constituents could improve sexual function through pro-sexual activities and sexual engagement. Its antioxidant, Immuno modulatory and adaptogenic potential holds promise as an aphrodisiac (Chhatre *et al.*, 2014; Sellandi *et al.*, 2012).

Taepongsorat *et al.* (2008) showed that quercetin, one of the main components of ginkgo, and Nutmeg extract present in NRL/MW/201901 presented as anti-stress and antianxiety potential (Moinuddin *et al.*, 2012). Stress is most important precursor to sexual dysfunction and it strongly gets correlated in present study as well that anti-stress ingredients may improve response to arousal and libido (Mackay, 2004).

It was evident from the anthropometric analysis of the subjects that there was significant increase in

resting metabolism and % skeletal muscle content in NRL/MW/201901 treated group as compared to placebo group typically demonstrated the increased muscle activity and activation of metabolism in subjects treated with NRL/MW/201901, though there was no significant fat or body weight gain. No clinically significant post treatment change in any of the lab investigations was observed in both the groups. L-Citrulline present in NRL/MW/201901 is extensively researched product for building cardio metabolic health in men. L-citrulline supplementation has been proved to be safe and psychologically well accepted by patients in erectile dysfunction. Its activity is through modulating blood flow to penis and its nitric oxide synthase like activity which can be contributing to its activity to achieve harder penile erection.

CONCLUSION

The results of the overall study reveals that NRL/MW/201901 hold promising position in management of erectile dysfunction as a result of well conceptualized product supported with highest quality raw material and manufacturing process from Netsurf Research Lab Pvt. Ltd. Thus it could be concluded from the present study that NRL/MW/201901 capsule is safe and effective in the treatment of mild to moderate erectile dysfunction.

Conflict of Interest

None.

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