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The Pharma Innovation

ISSN (E): 2277- 7695
ISSN (P): 2349-8242
NAAS Rating: 5.03
TPI 2020; 9(8): 61-67

www.thepharmajournal.com
Received: 12-06-2020
Accepted: 21-07-2020

Dr. Waseem Ahmed HM
PG Scholar, Department of Molajat, National Institute of Unani Medicine, Bangalore, Karnataka, India

MA Siddiqui
Director and HOD, Department of Molajat, National Institute of Unani Medicine, Bangalore, Karnataka, India

MA Quamri
Reader, Department of Molajat, National Institute of Unani Medicine, Bangalore, Karnataka, India

Anzar Alam
Ph.D., Scholar, Department of Molajat, National Institute of Unani Medicine, Bangalore, Karnataka, India

Shahid M
PG Scholar, Department of Molajat, National Institute of Unani Medicine, Bangalore, Karnataka, India

Corresponding Author:
Dr. Waseem Ahmed HM
PG Scholar, Department of Molajat, National Institute of Unani Medicine, Bangalore, Karnataka, India

Efficacy of *Dawa-ul-Khasak* in treatment of erectile Dysfunction: An exploratory, single arm pre and post clinical trial

Dr. Waseem Ahmed HM, MA Siddiqui, MA Quamri, Anzar Alam and Shahid M

DOI: https://doi.org/10.22271/tpi.2020.v9.i8a.6836

Abstract
Background and Objectives: Erectile Dysfunction or Impotence is defined as inability to achieve or maintain an erection sufficient for satisfactory sexual performance. ED is well-defined under the heading of *Zoaf-e-bah* with the synonyms such as *Nuqs-e-Nauoz, Zoaf-e-Inaaz, Isterqa-e-Qazeeb*.
Methods: 30 eligible patients of Erectile Dysfunction with IIEF-15 Score < 24 were enrolled in an open, single arm, pre and post, exploratory clinical trial with 4 weeks treatment duration. The test drug *Dawa-ul-Khasak*, with a dose of 7gms twice a day given. The effect of the study was assessed subjective and objectively in different follow ups. Patients were assessed for improvement in erectile function and sexual quality of life by using IIEF-15 Score and SQoL-M Scales respectively every 14th and 28th day of treatment. Patients were also assessed for subjective parameter on 7th, 14th, 21st and 28th day of study.
Results: The Mean ± SD of variable Erectile Function (EF), Orgasmic Function (OF), Sexual Desire (SD), Intercourse Satisfaction (IS) and Overall Satisfaction (OS) at 0 day were 14.43±3.65, 5.57±2.13, 5.43±1.33, 6.90±1.99 and 4.50±1.25 respectively; while it was increases to 23.37±3.47, 7.67±1.65, 6.97±1.56, 10.33±2.56 and 7.27±1.05 respectively; at 28th day of the study with highly significant 'p' value of <0.001. The Mean ± SD of the Sexual Quality of Life-Male Questionnaire at 0 day was 33.27±12.41 while it was 48.98±12.32 at 14th day and 57.87±11.40 at 28th day. Significant statistical difference in IIEF-15 Score and SQol-M Questionnaire was observed in improving erectile function at 14th and 28th day (p< 0.001).
Interpretation and Conclusion: Based on the observation of the results of the study, it can be concluded that *Dawa-ul-khasak* is effective in the management of ED.

Keywords: Erectile Dysfunction; Impotency; *Khar-e-Khasak; Ghokru; Zoaf-e-Bah*

1. Introduction
Contribution of Unani medicine in the field of sexual medicine and impotency is dated back as early as in 4th century BC, where Buqrat (Hippocrates) devoted his considerable time to the subject of impotence; he discusses the etiology of impotence and later it was named as erectile dysfunction [2].
Jalinus (Galen), was the first to postulate accumulation of air is responsible for the penile erection. His idea so dominated throughout medieval medicine that nearly everyone then alive was a Galenist [2].
According to the WHO, sexual health is a state of physical, emotional, mental and social well-being in relation to sexuality and not merely the absence of disease, infirmity, or dysfunction [3]. Erectile Dysfunction (ED) is defined as the persistent inability to attain and maintain an erection sufficient to permit satisfactory sexual performance. Erection is a complex phenomenon which implies a delicate and coordinated equilibrium among the neurological, vascular and the tissue compartments. It includes arterial dilation, trabecular smooth muscle relaxation, and activation of the corporeal veno-occlusive mechanism [4].
It is a multidimensional but common male sexual dysfunction that involves an alteration in any of the components of the erectile response, including organic, relational and psychological [5] with significant impacts on sexual function and overall quality of life [6]. It's also sometimes referred to as impotence [7]. It may be common among men with diabetes [8]. And is considered as one of the most diffuse sexual disorders [9]. It is estimated that more than 320 million

patients will be affected in 2025 [10]. The prevalence of erectile dysfunction in the Indian population is pegged merely at the global average (10 % of men <40, and up to 52 % of men > 40) [11]. Its incidence increases drastically from about 6% in the age group 20-29 years and 50-70% in the age group 40-79 years [12]. Age is a strong determinant of occurrence of ED, and epidemiological studies indicate a strong relationship between ED and advancing age [8].

ED leads to depression, anxiety and can contribute to marital breakdowns where as men are reluctant to seek help for fear embarrassment and become isolated within their relationship [13]. It also has damaging repercussions on the couple's quality of life and life satisfaction of the patient (and his partner), resulting in fear, loss of self-image and self-confidence [14].

In Unani literature, *inteshaar-e-zakar* (Penile Erection) is termed as *Nauoz* or *Inaaz* (plural) [15] which is described under the caption of *Amraz-e-Gurda* in the name of *Zauf-e-Bah*. The concept of *Zauf-e-Bah* due to *Nuqs-e-Nauoz* has been mentioned in Unani literatures. Eminent hakims like Ibne Sina in *Al Qanoon Fit Tibb* [16], Ali Bin Abbas Majoosi in *Kamil Al-San't* [17], states that *Nuqs-e-Nauoz* as one of the causes of *Zauf-e-Bah*.

Unani system defines erectile dysfunction as *Isterkha e Ala-e-Qazeeb* (Weakness of Penis). For normal Erection *Qazeeb's Asba-e-Majufa* (Smooth Musculature) gets dilated by *Reeh and Rooh-e-Haiwani* (which is associated with arterial blood). When nerves and muscles of this organ get involved (Paralyzed – *Isterq'a*) then it neither dilates nor attains erection. The possible causes of ED are *Zaufe Badan*, Avoidance of sex, *Sue mizaj*, Paralysis of nerves, Specific disease like syphilis cystitis, cystic stones, intestinal worms, rectal disease, or any injury, riding of horses or over indulging in sexual acts / Masturbation [18].

Razi says: Excessive prevention from coition leads to either erectile dysfunction or oligospermia. Weakness of erectile function, reduction in duration of erection, lack of stimulation and reduction in penile size indicates paralysis of that organ [19].

According to *Ibn-e-Sina*, the causes of *Zoaf-e-Bah* (Impotence) are broadly divided into 5 categories [16].

1. The cause of ED is within the penis itself like either *Su-e-Mizaj* (malady of temperament) or lining of the penis.
2. The cause of ED lies in the surrounding organs like, testes, *Awiya-e-Mani* (seminiferous tubule) and this cause is due to *Su-e-Mizaj* of one or more temperament along with *Yaboosat* (dryness) or even by only *Yaboosat* (dryness) itself.
3. The cause lies either in vital organs, or in muscles surrounding or attached to them. It may be between the muscles of organs of coition and vital organs.

a. One of the common cause is due to involvement of the heart, due to which there is a lack of *Nafaq or Reeh* (gases material) required for the penile erection,
b. In case of liver involvement, the probable cause of ED is the *madda* of sperm production doesn't reach from the liver to the genital organs,
c. In case of involvement of the brain, there occurs cessation of *madda* (material) that provides the power of sensitivity.
d. If the cause is in kidneys e.g. weakness, sliming *(lagiri)* or *Su-e-Mizaj barid* of kidney or some other kidney diseases which leads to ED,
e. Or the cause may be *Su-e-Hazam (*Malady of digestion).

4. Sometimes the cause of ED is in lower part of the body, which may be due to single / multiple *Su-e-Mizaj* of either cold, hot or dryness, which leads to cessation of production of *Nafaq or Reeh* (gases material), which is necessary for erection.
5. The cause is either in the passages of sexual intercourse or in their nearby organs, e.g. in case of surgical removal of hemorrhoids, if the nerve innervates the anus and the penis (pudendal nerve) [20] gets trapped, can cause erectile dysfunction [21].

The treatment of ED comprises psychosexual therapy, lifestyle modifications, medical and surgical management [6]. There are many treatment options for ED currently being used such as; Non-PDE5-i oral agents (*Dopaminergic agents, Melanocortin receptor agonists, Soluble guanylate cyclase stimulators & activators, Rho-kinase inhibitors), topical therapy*, low-intensity shockwave therapy, Stem cell therapy & Gene therapy [22].

Presently Phosphodiesterase-5 inhibitors (PDE5-i) are considered the most popular treatment and are currently the first line monotherapy for ED [23]. However, it should be taken into account that some patients with complex ED may not be responders to PDE5-i monotherapy and also it is not depicted from side effects. The most common reported side effects are headache, muscular pains, hot flushes, tearing, painful erection and Priapism (particularly in case of intracavernosal injection with prostaglandin E1 (PGE1; alprostadil)) [24]. All have serious side effects and higher cost, search of natural supplement from medicinal plants as an aphrodisiac substance is significantly desired.

Several researchers claimed on the basis of preclinical and clinical data, that most of the traditional medicine (plant derivatives, minerals and animal sources) showed beneficial effects in Erectile Dysfunction [25-27].

There is no evidence of any study carried out in Unani System of medicine for erectile dysfunction, till date. Further, there are various RCT's carried out on *Tribulus terrestris* and *Anacyclus pyrethrum* proving effective in managing Erectile Dysfunction [28].

Therefore, a poly herbal formulation *Dawa-ul-Khasak* containing Ghokru Khurd / Khare Khask (*Tribulus terrestris)*, Aqarqarha (*Anacyclus pyrethrum)* and Sonth *(Zingeber officinal)* [29-31] is taken from classical unani text to evaluate its efficacy scientifically in Erectile Dysfunction patients.

2. Methodology

2.1. Ethical clearance

The protocol was approved by the Institutional Ethics Committee of National Institute of Unani Medicine Bangalore, India (IEC Number: NIUM/IEC/2015-16/005/Moal/05) and CTRI registration No: CTRI/2018/01/011271. It was implemented in accordance with provisions of the Declaration of Helsinki, and ICMR Good Clinical Practice guidelines.

2.2. Study population and participant eligibility

2.2.1. Inclusion criteria

- ED with IIEF-15 Score < 24
- ED between the groups of 25 to 60 years.
- ED of broad-spectrum etiology
- Patients should be in a stable relationship at least for the past 3 months and sexually active by one of the following: Intercourse / Caressing / Foreplay / Masturbation

2.2.2. Exclusion criteria

- ED with IIEF-15 Score ≥ 24
- ED below and above the age of 25 and 60 years respectively
- Patients with an active urinary tract infection (UTI) or Prostatitis
- Patients who had a previous prostate surgery / who had a prostate biopsy
- ED with known concomitant Pathological status such as cardiovascular diseases / cerebrovascular / Severe Renal or Hepatic Insufficiency / Hypogonadism / Genital anomaly / Obesity
- ED with addiction of Chronic Alcoholism / Drug abuse / history of medications like PDE5-i and PGE1

2.3. Informed Consent

Patients, who fulfilled the prior declared inclusion criteria, were invited to receive detailed written information about the procedure of clinical trial before obtaining their written informed consent.

2.4. Method of Collection of Data

Through clinical study of patients visiting Moalajat OPD, NIUM, Bangalore.

a. Subjective parameters:
- Difficulty in achieving penile erection.
- Difficulty in maintaining penile erection during penetration.

b. Objective parameters:
- International Index of Erectile Function (IIEF-15) Questionnaire.
- Sexual Quality of Life- Men (SQoL-M).
- Serum Testosterone level.

2.5. Study design

A single armed, open, pre and post, exploratory clinical trial was performed on 30 patients of erectile dysfunction in the year March 2017 to February 2018 at Moalajat OPD of NIUM, Bangalore. Study personnel and participants were aware of the drugs given for the duration of the intervention. The study consisted of a weekly screening for 4 weeks (baseline, 7th, 14th, 21st and 28th day) and post study follow up for 2 weeks after enrollment.

2.6. Sample size: Sample size was fixed as 30 patients. (Consort diagram, figure 1)

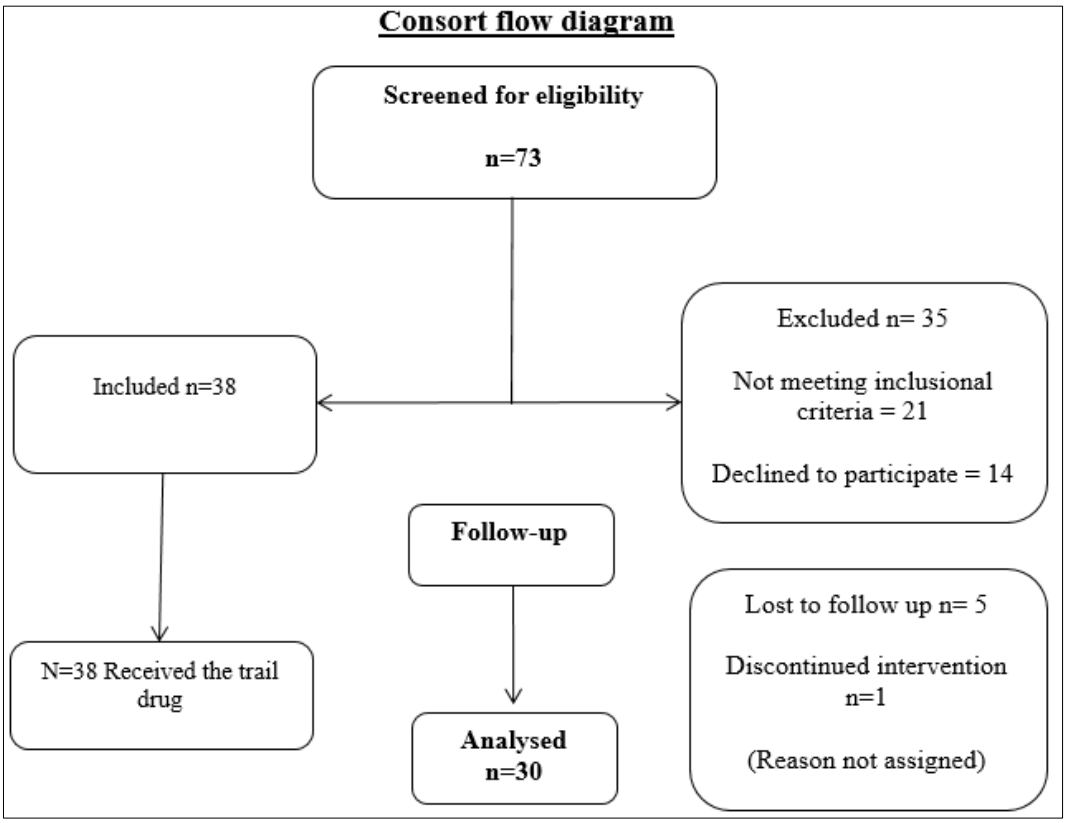

Fig 1: Sample size Consort flow chart

2.7. Test Intervention

All patients were given a powdered Unani herbal formulation *Dawa-ul-Khasak* orally orally 2 hours after food with Milk twice a day for 4 weeks. The ingredients of *Dawa-ul-Khasak* are mentioned in the Table 1. Each 14gm of the powder contains

Table 1: Test drug ingredients [29]

S. No.	Unani Name	Scientific Name	Weight
1	*Khar-e-Khasak*	Tribulus terrestris Linn.	4.5 gm
2	*Aqarqarha*	Anacyclus pyrethrum DC.	1.25 gm
3	*Sonth*	Zingiber officinale Rosc.	1.25gm
4	Sugar	Saccharum officinarum	7gm

2.8. Method of Preparation with Dosage

All the ingredients of *Dawa-ul-Khasak*, were powdered separately in pulverizer and later sieve with No. 80 (BSS) for obtaining fine powder [32]. *Khar-e-Khasak is then Mudabbar as described in Al Qarabadeen. Fresh Khar-e-Khasak were collected personally and its juice is obtained.* This juice was poured over powdered Khar-e-Khasak and dried under the sun. This process is repeated three times [33]. This mass is again passed through standard sieve of no.80. After this Aqarqarha, Sonth and sugar were powdered and passed through sieve of size no. 80. All the above ingredients were mixed well and stored in air tight containers. The drugs are taken in the ratio as described in the table no.*1*. 7 gm of *Safoof* (Powder) will be given orally 2 hours after food with Milk twice a day for 4 weeks.

2.9. Outcome measures

Before the start of the treatment, subjective as well as objective parameters were assessed. Subjective parameters include difficulty or inability to either achieve or maintain penile erection. Objective parameters include pre and post analysis of IIEF-15 Questionnaire Score [34], SQoL-M Questionnaire Score [35] and Serum Testosterone level [36]. The assessment of the efficacy of subjective parameters in this study was based on arbitrary grading system as follows

Table 2: IIEF-15 questionnaire grading [34]

S. No.	Nature	Erectile function	Orgasmic Function	Sexual Desire	Intercourse Satisfaction	Overall Satisfaction
1	No ED	25 – 30	9 – 10	9 – 10	13 – 15	9 – 10
2	Mild	19 – 24	7 – 8	7 – 8	10 – 12	7 – 8
3	Mild to Moderate	13 – 18	5 – 6	5 – 6	7 – 9	5 – 6
4	Moderate	7 – 12	3 – 4	3 – 4	4 – 6	3 – 4
5	Severe	0 – 6	0 – 2	0 – 2	0 – 3	0 – 2

IIEF-15 Questionnaire Score is a Multidimensional scale for assessment of erectile function analysed on 0, 14th and 28th day of trail which was rated on a 5 areas - Erectile Function, Orgasmic Function, Sexual Desire, Intercourse Satisfaction and overall Satisfaction. SQoL-M Questionnaire is an arbitrary grading scale analysed on 0, 14th and 28th day of trail. Serum Testosterone level was taking on baseline and at the end of the study. Following investigations were done to exclude the patients of other co-morbidities as well as to assess safety of the test drug: Hb%, TLC, DLC, ESR, Random Blood Sugar. After the completion of treatment, the pre and post treatment values or scores of different parameters (subjective and objective) were assessed and subjected to comparison and statistical analysis to evaluate the efficacy of the test drug.

2.10 Statistical analysis

Descriptive and inferential statistical analysis has been carried out in the present study. Student t test (two tailed, dependent) has been used to find the significance of study parameters on continuous scale with in each group. Paired Proportion test has been used to find the significance of proportion in paired data. The Statistical software namely SPSS 18.0, and R environment ver.3.2.2 were used for the analysis of the data and MS Word and Excel have been used to generate graphs, tables etc. Results on continuous measurements are presented on Mean ± SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance of the study is assessed at 5% level of significance.

Significant figures
+ Suggestive significance (P value: $0.05<P< 0.10$)
* Moderately significant (P value: $0.01<P\leq 0.05$)
** Strongly significant (P value: $P\leq 0.01$)

3. Results

a) As shown in table no. 03, the Means± SDs of IIEF-15 Questionnaire are as follows. In Domain, Erectile Function, the Means ± SDs were 14.43 ± 3.65, 20.20 ± 3.51 and 23.37 ± 3.47 at baseline, 14th day and 28th day, respectively. In Domain, Orgasmic Function (OF), the Means ± SDs were 5.57 ± 2.13, 7.33 ± 1.75 and 7.67 ± 1.65 at baseline, 14th day and 28th day, respectively. In Domain, Sexual Desire (SD), the Means ± SDs were 5.43 ± 1.33, 7.03 ± 1.38 and6.97 ± 1.56 at baseline, 14th day and 28th day, respectively. In Domain, Intercourse Satisfaction (IS), the Means ± SDs were 6.90 ± 1.99, 9.57 ± 2.34 and 10.33 ± 2.56 at baseline, 14th day and 28th day, respectively. In Domain, Overall Satisfaction (OS), the Means ± SDs were 4.50 ± 1.25, 7.10 ± 1.12 and 7.27 ± 1.05 at baseline, 14th day and 28th day, respectively.

Table 3: Means± SDs of IIEF-15 Questionnaire

Domains	Baseline	Follow up 2	Follow up 4	difference		P value	
				Baseline-Follow up 2	Baseline-Follow up 4	Baseline-Follow up 2	Baseline-Follow up 4
EF	14.43 ± 3.65	20.20 ± 3.51	23.37 ± 3.47	-5.767	-8.933	<0.001**	<0.001**
OF	5.57 ± 2.13	7.33 ± 1.75	7.67 ± 1.65	-1.767	-2.100	<0.001**	<0.001**
SD	5.43 ± 1.33	7.03 ± 1.38	6.97 ± 1.56	-1.600	-1.533	<0.001**	<0.001**
IS	6.90 ± 1.99	9.57 ± 2.34	10.33 ± 2.56	-2.667	-3.433	<0.001**	<0.001**
OS	4.50 ± 1.25	7.10 ± 1.12	7.27 ± 1.05	-2.600	-2.767	<0.001**	<0.001**

b) As shown in table no. 04, the Mean ± SD of Serum Testosterone of enrolled patients was 308.01 ± 120.13 at baseline which improved to 434.07±136.10 at the end of the study (P<0.001 when compared to baseline).

Table 4: Means ± SD of Serum Testosterone Level (ng/dl)

Objective parametres	Before Treatment	After Treatment	difference	t value	P value
Sr.Testosterone	308.01±120.13	434.07±136.10	-126.060	-4.505	<0.001**

Student t test (Two tailed, Dependent)

c) As shown in table no. 05, the Mean ± SD of SQoL-M Questionaire score of enrolled patients was 33.27±12.41at baseline which improved to 48.98±12.32 at 14th day (p<0.001 when compared to baseline) and further upgraded to 57.87±11.40 at 28th day (P< 0.001 When compared to 14th day).

Table 5: Means ± SD of SQoL-M Questionaire score

SQoL-M	Min-Max	Mean ± SD	difference	t value	P value
Baseline	12.12-65.15	33.27±12.41	-	-	-
Follow up 2	16.66-69.69	48.98±12.32	15.75	8.491	<0.001**
Follow up 4	16.66-74.24	57.87±11.40	24.65	12.915	<0.001**

Student t test (Two tailed, Dependent)

d) As depicted in table 06, the changes in safety parameters were not statistically significant.

Table 6: Effect on safety parameters

Domains	Before Treatment	After Treatment	difference	t value	P value
Hemoglobin (g/dl)	14.06±1.38	14.58 ±1.47	-0.523	-1.902	0.067+
TLC (c/cumm)	6246.67 ± 2019.51	6213.33±1641.85	33.333	0.095	0.925
ESR mm/hr	12.20±10.79	13.73±10.78	-1.533	-0.871	0.391
AST (IU/L)	24.50±8.88	24.60±10.90	-0.100	-0.056	0.956
ALT (IU/L)	30.03±15.59	31.33±18.66	-1.300	-0.464	0.646
Blood Urea (mg/dl)	27.73±6.04	26.32±3.72	1.410	1.307	0.202
Serum Creatinine (mg/dl)	0.82±0.14	0.83±0.12	-0.011	-0.491	0.627

4. Discussion

The present study evaluated efficacy and treatment satisfaction of *Dawa-ul-Khasak* in men with erectile dysfunction (ED) who's IIEF-15 Score is less than 24 score. This is the first trail to assess the efficacy a Unani drug *Dawa-ul-Khasak* on men with erectile dysfunction. Additionally, the study is also novel by being the first, using the IIEF-15 Questionnaire with all domains, that provides data on patient satisfaction.

The IIEF addresses the relevant domains of male sexual function (that is, erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction), is psychometrically sound, and has been linguistically validated in 10 languages. This questionnaire is readily self-administered in research or clinical settings. The IIEF demonstrates the sensitivity and specificity for detecting treatment-related changes in patients with erectile dysfunction [34].

International Index of Erectile Function (IIEF-15) Questionnaire were assessed through arbitrary score as No ED (≤25), mild ED (19-24), mild to moderate ED (13-18), moderate ED (7-12) and severe ED (≥6) respectively.

Since time immemorial, Unani medicine has been adopted by many cultures and is widely practiced all over the world. The causes of Erectile Dysfunction are four [21]. They are

1. Low sperm count or low motality
2. Weakness of the *Aaza-e-Raisa wa Shareefa* (Vital organs): e.g. weakness of Heart, Brain, Stomach, Liver, Kidneys or their *Su-e-Mizaj*.
3. Dropping or Lining of the penis, may be due to weakness or slimming of the body: Further weakness / sliming of the body is due to
   a. Long term termination of sexual activity.
   b. Excessive *Su-e-Mizaj* of cold, heat or dryness,
   c. Reduced production of *Riyah* in the spongy body of penis,
   d. Weakness of the nerves supplying penis, which may be either due to excessive absorption of morbid phlegm *(khaam balgam)*, excessive standing in cold water, sitting over the ice bar for long time or due to masturbation.
4. Psychogenic causes like fear of not with standing the act of copulation or thought of remorse, which leads to reduction in libido and *Zoaf-e-Inteshar* [21].

The above said causes either individually or in combination, reduces the penile tumescence and rigidity causing erectile dysfunction. Unani medicine treats and eliminates the root cause, correcting the underlying issues and helps in improving penile rigidity so as to achieve / maintain proper erection.

The process of improving erectile function is done through the test drug, *Dawa-ul-Khasak* 7gm twice a day. The aphrodisiac effect of *Dawa-ul-Khasak* is also described in various texts. The effect of *Dawa-ul-Khasak* in the improvement of erection and rigidity may be because of its *Mubahi, mulaziz, Muharik-e-Asaab etc.* properties. It is a compound comprising of 3 drugs, viz. *Khar-e-Khasak, Aqarqarha and Sonth* said to possess *Mubahi, mulaziz, mumsik, Muharik-e-Asaab, Mugaliz-e-Mani, Muqtimaat-e-Qazeeb and Musallib* [21, 29-32, 37].

A total of 30 patients of erectile dysfunction were enrolled and treated with a Unani formulation (*Dawa-ul-Khasak*) in a 4 week single armed exploratory clinical trial which shows clinically and statistically highly significant improvement in IIEF-15 Score (p<0.001). Almost all patients experienced improvement in their erectile function, Orgasmic function and also in their Sexual Quality of life. The discussion on the data showing efficacy of treatment based on subjective and objective parameters along with demographic data is being presented below to draw inferences.

A maximum of 83.4% (25) patients were observed in the age group of 21-40 years. Although the observed value in this study is quiet higher than any previous study conducted, the probable cause would be due to the reason that that young

men are much worried about their sexual life, anxiety around sexual performance, embarrassment or low self-esteem due to inability to perform, relationship problems and the emotional effects over quality of life. For these, they prefer to seek treatment at the early stage of the disease [38]. The possible cause of ED in young men nowadays may be due to changes in their lifestyle, like obesity, sedentary life, reduction in the hours of sleep, which correlates with the concept of *Asbab-e-Sit-e-Zarooriya* which is not maintained in its equilibrium and in some lifestyle disease diseases like cholesterol, blood pressure and diabetes. Also due to the fact that younger generations are more addicted towards smoking, drinking alcohol and using recreational drugs etc.

On the basis of *Mizaj*, 66.7% (20) of the patients were associated with *Balghami*. This data is in conformity with the description of *Hasan Qureshi* who mentioned that *Zoaf-e-Bah* is more prevalent in those persons who have *Barid Ratab Mizaj* [39].

The Subjective Parameters are assessed weekly with the help of paired proportion test. The data showed revealed highly significant improvement in subjective parameters with *P*<0.001. The objective parameters such as International Index of Erectile Function (IIEF-15) Questionnaire, Sexual Quality of Life-Men (SQoL-M) are assessed fortnightly, whereas Serum testosterone level were assessed pre and post study with the help of Student t test (Two tailed, Dependent). As a result of 4 weeks of treatment with *Dawa-ul-Khasak* 14 gm / day significantly improved erectile function and produced superior treatment satisfaction in men with mild to moderate ED. (Table No. 3, 4, 5)

In domain of Erectile Function, Mean ± SD improvement with *Dawa-ul-Khasak* was reflected by a greater than 8-point change (IIEF-EF score 23.37±3.47 to 14.43±3.65) with highly significant 'p' value ($p< 0.001$). (Table No. 3)

This represents a notable change from baseline, despite the relatively mild to moderate ED population that was enrolled (IIEF- EF Score between 13-18); a significant variation from baseline might have been estimated. These findings are consistent with previous study of Brock GB, *et al.* where tadalafil improves erectile function when compared to placebo [40].

In domain of Orgasmic Function, Mean ± SD improvement was reflected by a greater than 2-point change (IIEF-OF score 5.57±2.13 to 7.67±1.65) with highly significant 'p' value ($p< 0.001$). (Table No. 3)

The results found in orgasm function score may be due to its *Mubahi, mulaziz, mumsik* properties. Also because of good performance due to improvement in erection and ejaculation followed by psychological counseling.

For the other domains of IIEF, including Intercourse Satisfaction, Sexual Desire, and Overall Satisfaction, patients had a significantly higher endpoint and a greater change from baseline across all domains compared to baseline with $p< 0.001$. (Table No.3) The probable cause for the improvement in these may be due to the psychotherapy provided by the counseling also plays an important role in the satisfaction.

In Sexual Quality of life (SQoL-M Score) significant change from baseline is observed. The total score improved after treatment from baseline (33.27±12.4) to the end of the study (57.87±11.40) with a mean difference of 24.65. ($p< 0.001$) (Table No. 5)

Improvement on self and partner's satisfaction after intercourse may be because of improvement in erection, rigidity and the time of ejaculation. In specific, in class 2 "When I think about my sexual life, I feel Depressed" the improvement from baseline to end point is much greater with raw score improving from 2 to 6. Similarly in class 11: "When I think about my sexual life, I feel like I have lost something" the raw score is improved from the baseline significantly, from 5 to 2. i.e. from Almost always or always to a few times (much less than half the time).

In objective parameter, Serum Testosterone the Mean ± SD value increases from 308.01±120.13 to 434.07±136.10, over a period of 4 weeks. The mean difference is noted at the end of the study which is -126.060, and 'P' value is <0.001, making it highly significant for the study. (Table-4). The improvement in serum testosterone level from the baseline is due to the protodioscin (in *Khar-e-Khasak)* has an androgen-mimetic action, binding and activating the receptor of testosterone. So this substance is able to increase the endogenous production of testosterone, dihydrotestosterone, a hormone luteinizing hormone (LH), dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEA-S) as documented by Gauthman K Adaikan PG and Prasad RN [41-42].

It also may be attributed to *Muqawi-e-Bah, Muharrik* and *Tauleed-e-Reeh* properties of *Khar-e-Khasak, Aqarqarha and Sonth*, present in this formulation. This finding is in accordance with the description of the drugs mentioned in *Firdous Al Hikmat, Aljame-ul-mufradat al-advia wa al-aghziya, Bayaz-e-Khaas* and Unani Pharmacopoeia of India [29-32, 37].

As evident from the Table-6, the parameters relating to toxicity of drugs are assessed pre and post study. No Significant improvement noted. This indicates that the oral administration of drug formulation is safe for therapeutic use.

The overall effect of *Dawa-ul-Khasak* was found highly significant in managing erectile dysfunction with $p< 0.001$ in both subjective and objective parameters as well. The effect of *Dawa-ul-Khasak* in the improvement of erection and rigidity may be because of its *Mubahi* and *Musallib* property by the virtue of *Firdous Al Hikmat* and *Al-Akseer*. In *Al-Akseer* it has been mentioned as one of the best remedy for *Zoaf-e-Baa* due to *Zoaf-e-Inteshar*. No side effect was reported and compliance to the treatment was found good. No study limit has been confined.

Further studies with similar variables may be recommended for Randomized Control Study and with larger sample size.

5. Conclusion

Though, the present clinical trial is a single arm prospective trial but it includes some important methodological strength, notably a treatment protocol that is a foundation of Unani line of treatment.

It reveals that the drug *Dawa-ul-Khasak* is effective on subjective as well as in objective parameter. As diabetes is considered as an important risk factors for ED, and the test drug doesn't show any raise in RBS and also there were no sign of any toxicity or side effect. Thus, it may be inferred that the *Dawa-ul-Khasak* is effective in management of ED. Also in conventional medicine, presently PDE5-i are the most popular treatment but they are not depicted from side effects. In such cases, *Dawa-ul-Khasak* can be safely used for the same purpose.

Limitations of the study were small sample size and shorter duration of clinical trial and without control. Despite these limitations, our data reflect substantial effectiveness. However, it is suggested to carry out randomized controlled clinical trial on large patient populations to elucidate their

further effectiveness in erectile dysfunction patients and improvement in Sexual quality of life. As diverse mechanisms are involved in development of erectile dysfunction, elaborate studies are recommended to ascertain pharmacological actions of test formulation for longer duration in future studies.

6. **Acknowledgements**
The authors gratefully thank to the participants enrolled in the study.

7. **Conflict of Interest:** All the authors have no conflict of interest.

8. **Sources of Support:** This clinical trial was supported by National Institute of Unani Medicine, Ministry of AYUSH, Govt. of India.

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