POLYHERBAL FORMULATIONS IN THE TREATMENT OF INFERTILITY

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Abstract:

An estimated 5-10 percent of couples are classified as infertile, which means that they have been trying to get pregnant with frequent, unprotected intercourse for at least a year with no success. In about half the cases, male infertility is a factor. Causes of male infertility include abnormal sperm production or function and/or impaired delivery of sperm. In the present work, the polyherbal HG plus tablets were prepared by wet granulation method using different additives. The effects of HG plus tablets over SPEMAN tablets were compared in patients. In Global assessment of therapy by Investigator by 56% by HG Plus tablets vs 42% by SPEMAN tablets. The primary results shows that the HG plus tablets is effective and beneficial over the control tablets.

Key words: Infertility, semen, sperm, Growth hormone,

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INTRODUCTION:

Infertility is recognized as the inability to conceive after 12 months of sexual practice without using contraception. Infertility is one of the problems of human society. Reproductive ability in the male contains the production of semen containing normal spermatozoa (quality) in the adequate number (quantity), together with the desire and ability to mate. Different reasons are involved in the occurrence of male infertility such as genetic disorders, genital duct obstruction, varicocele, decreased sperm production, decreased semen quality parameters, erectile dysfunction and male impotence[1].Different treatment like surgery, chemicals and herbal drugs and laboratory methods are available to help fertility. According to several studies, a number of botanical medicines have a positive effect on sperm parameters. There are many references covering plants with antifertility properties in the literature[2].

Ethnopharmacological surveys have been found to be one of the most reliable tools for the discovery of the natural and semi-synthetic drug. In fact, herbals and other natural products, including their chemical derivatives, represented about 50% of all currently utilized medications worldwide[3]. The usage of plants Kingdom by human beings, as a source of medicines, started from the immemorial time for treatment, protection, and prevention of various illnesses. Till recent time, herbals are considered one of the most important branches of traditional medicine. In fact, this kind of medicine plays until now an important role in health care systems, especially in rural areas in developed and developing countries[4,5]. In fact, traditional medicine is considered a very important branch of pharmacy and medicine and besides that, the used plants in this medicine are considered major sources for the investigation of pharmacologically active drugs in the pharmaceutical industry. In addition, the global public interests are in continuous growing toward the use of this type of medicine. In fact, about 80% of people in rural areas of developing countries utilized traditional medicine, since it is available, cheap and has a variety of health benefits[6].

According to the World Health Organization and the International Committee for Monitoring Assisted Reproductive Technology, infertility is a disorder of the reproductive system which is defined by the failure to achieve a clinical pregnancy after one year or more of regular unprotected sexual intercourse[7].Recently, a huge number of factors caused an increase in infertility levels among males and females, especially in developed countries. These factors include the increased use of contraceptives, rising maternal age, smoking, alcohol, genetic factors, pesticides, narcotics, rates of abortion, and critical economic situations. Besides that, an increase in male impotency could be due to the psychogenic factors, vascular disturbances, neurogenic disorders, endocrine system disturbances and drug treatment[8].

Accordingly, the treatment of infertility has become a large pharmaceutical and medical industries issues, arranging from manufacturing and prescribing fertility hormones and other drugs to in vitro fertilization operations [9]. In 2010, the World Health Organization (WHO) estimated that about 48.5 million couples worldwide were infertile and 1.9% of women aged 20–44 who wanted a child were unable to have their first live birth. In addition, 10.5% of women who had previously given birth were unable to have another baby after five years of trying. This may raise the question about the used measures that caused this high percentage[10].

In the present work, the polyherbal HG plus tablets were prepared by wet granulation method using different additives. The effects of HG plus tablets over SPEMAN tablets were compared in patients. In Global assessment of therapy by Investigator by 56% by HG Plus tablets vs 42% by SPEMAN tablets. The primary results shows that the HG plus tablets is effective and beneficial over the control tablets.

Material and Methods

Composition of Polyherbal Formulation

In the present investigation, **HG PLUS TABLET** was made by combining the Mucuna prurita, Tribulus terrestris, Withania somnifera, Zingiber officinale rhizome ,Piper longum fruit, Piper nigrum fruit (Table 1), to determine the effect of the prepared formulation on oligospermic patients.

Table 1: composition of HG PLUS TABLET Herbal formulation

Sr. No.	Name of constituents	Latin Name	Quantity (mg)
1	Kapikachu Beej (Atmagupta) Ghan	*Mucuna prurita*	500
2	Gokshura Ghan	*Tribulus terrestris*	150
3	Ashwagandha Ghan	*Withania somnifera*	124
4	Trikatu	*Zingiber officinale rhizome* , *Piper longum fruit,* *Piper nigrum fruit*	6
5	*Trikatu*		6
6	Polyvinyl pyrrolidone		10
7	Talc		10
8	magnesium sterate		3

FORMULATION OF HERBAL TABLETS

The tablets were prepared by using by non-aqueous wet granulation method containing drug i.e *Mucuna prurita* 500 mg, *Tribulus terrestris* 150 mg, *Withania somnifera* 124 mg, *Trikatu* 6mg, Polyvinyl pyrrolidone 10 mg, Talc 10 mg, magnesium sterate 3 mg were triturated into fine powder. Then the granules were prepared by adding sufficient quantity of granulating liquid containing Polyvinyl pyrrolidone and Isopropyl alcohol to make a damp mass. This wet mass was passed through sieve no. 16 and dried to get uniform granules. The prepared and evaluated granules were compressed into tablets using a Rotary Tablet Compression machine (Cadmech) with average weight of 645 mg.

Results and Discussion

Composition of Polyherbal Formulation

Recently, polyherbal formulations (PHFs) are gaining importance all over the globe due to their dynamic medicinal and therapeutic claims and demonstrated vast advantages over single herbal formulations (SHFs), in the outlook of aforementioned claims; we have prepared a novel polyherbal formulation (PHF) to recover the male patients from oligospermia, and its composition is described in Table 1.

HG PLUS TABLET

The hypothesis for determination the number of patients needed for the study was derived from data from efficacy trials of drugs for treatment of impotence and male infertility. It was presumed that patients in both the treatment arms would have a relief in symptoms of for reduce impotence and male infertility. a relative decrease in this rate of at least 20-25% is expected in the **'HG PLUS TABLET** arm with a sample size of 100 patients (50 in) **'HG PLUS TABLET** (test arm) and 50 in the **SPEMAN Tablet** as (Control arm) each trial would have a power of 120% to detect a between group difference.

Accordingly, we had planned 100 patient's enrollments at four clinical centers in this trial. Male/Female Patients of 18 to <40 years of age, having impotence and male infertility problems assessed by clinical examination and confirmed through biopsies, were called for participation in this clinical trial. They were included as per the inclusion- exclusion criteria.

Testing of Hypothesis

To test the hypothesis of whether test is more effective than control, we had planned a sample size of 100 patients for this trial in all the four clinical trial centers. Out of the screened one hundred thirtyfive patients, twenty patients did not qualify in the baseline screening parameters and failed to meet inclusion exclusion criteria and fifteen patients did not turn up for the follow up visit. Thus one hundred and twelve patients were found eligible as study patients as per the inclusion-exclusion criteria for this trial. These patients were randomized into either Test or Control treatment for 30 days treatment period.

A clear accounting of the trial patients is given in table 2 overall dispositions of trial patients.

Table 2: Overall dispositions of trial patients

Center No	Screened	Screening Failure	Randomized	Failed to turn up for F/U	Withdrawal	Completed
CTC-001	30	3	27	2	0	25
CTC-002	28	3	25	0	0	25
CTC-003	37	7	30	5	0	25
CTC-004	40	10	30	5	0	25
Total	135	23	112	12	0	100

Tabulation of Demographic of the patients [Screening]

Tabulated depiction of demographic data of patients is being done here. A detailed screening examination was done of all the patients before enrolling them into the clinical trial. Out of all the demographic, following variables were considered critical in terms of having effect on the progress of the trial. The mean baseline demographic and chemical characteristics of Patients enrolled in two study groups are presented in following tables. The total number of one hundred and thirty five (135) eligible patients were enrolled in the study and randomized to test and control group. Out of 135 Patients only 100 Patients completed the study remaining 35 failed to follow up and primary screening.

Laboratory Investigation

Following Laboratory investigations were conducted as a part of general screening at all four centers.

- Physical examination: Determine the swelling or inflammation of muscle.
- Semen analysis.
- X-Ray
- Tunel assay

Efficacy Evaluation

The efficacy of this clinical trial was evaluated by employing two efficacy parameters. The Primary Efficacy Variables of **HG PLUS TABLET** are shown in Table 3 & 4.

Table 3. Clinical Efficacy- 'HG PLUS TABLET

Pt. No	Male Infertility				Male Infertility (Acute)				Male Infertility (Chronic)			
	Days				Days				Days			
	0	6	15	30	0	6	15	30	0	6	15	30
2	4	3	3	0	4	3	2	1	4	4	3	1
4	4	3	3	0	4	3	1	0	4	4	3	1
8	4	3	3	0	4	3	1	0	4	4	3	1
9	4	3	2	0	4	3	1	0	4	3	3	1
11	4	3	3	0	4	2	1	0	4	3	3	1
12	4	3	2	0	4	2	0	0	4	3	3	1
14	4	3	3	0	4	2	0	0	4	4	3	1
16	4	3	2	0	4	2	1	0	4	3	3	1
19	4	3	3	0	4	3	1	0	4	3	3	1
20	4	3	3	0	4	2	0	0	4	4	3	1
21	4	3	3	0	4	2	1	0	4	3	3	1

23	4	3	3	0	4	3	1	1	4	3	3	1
26	4	3	3	0	4	3	1	0	4	3	3	1
27	4	3	3	0	4	3	1	0	4	4	3	1
28	4	3	2	0	4	2	1	0	4	3	3	1
31	4	3	2	0	4	3	1	0	4	3	3	1
33	4	3	2	0	4	3	2	1	4	3	3	1
35	4	3	3	0	4	3	1	0	4	4	3	1
37	4	3	3	0	4	3	2	1	4	3	3	1
39	4	3	3	0	4	3	2	1	4	3	3	1
41	4	3	3	0	4	3	1	0	4	3	3	1
42	4	3	3	0	4	2	1	0	4	4	3	1
43	4	3	2	0	4	2	1	0	4	3	3	1
47	4	3	3	0	4	3	1	1	4	3	3	1
49	4	3	3	0	4	3	1	0	4	3	3	1
52	4	3	3	0	4	2	0	0	4	3	3	1
53	4	3	3	0	4	2	0	0	4	3	3	1
56	4	3	3	0	4	3	1	0	4	4	3	1
58	4	3	2	0	4	3	0	0	4	3	3	1
59	4	3	2	0	4	3	1	0	4	3	3	1
62	4	3	2	0	4	3	2	1	4	3	3	1
63	4	3	3	0	4	2	0	0	4	3	3	1
66	4	3	3	0	4	3	2	1	4	4	3	1
67	4	3	3	0	4	3	1	0	4	3	3	1
70	4	3	3	0	4	3	0	0	4	3	3	1

74	4	3	3	0	4	2	0	0	4	3	3	1
75	4	3	3	0	4	2	0	0	4	3	3	1
78	4	3	3	0	4	3	1	0	4	4	3	1
79	4	3	2	0	4	3	0	0	4	3	3	1
83	4	3	2	0	4	3	1	0	4	3	3	1
84	4	3	2	0	4	3	2	1	4	3	3	1
85	4	3	3	0	4	2	0	0	4	3	3	1
88	4	3	3	0	4	3	2	1	4	4	3	1
89	4	3	3	1	4	4	2	3	4	4	2	3
93	4	4	3	1	4	3	3	2	4	3	3	2
96	4	3	3	1	4	4	2	3	4	4	2	3
97	4	3	3	1	4	3	3	3	4	3	3	3
100	4	3	3	1	4	3	4	3	4	3	4	3
The grading according to LFT **Extreme severe=4, Severe=3, Moderate=2, Mild=1,None=0**												

Table 4 : Clinical Efficacy- 'HG PLUS TABLET

Pt. No	**MALE INFERTILITY**				**MALE INFERTILITY (Acute)**				**MALE INFERTILITY(Chronic)**			
	Da				**Days**				**Days**			
	0	**6**	**15**	**30**	**0**	**6**	**15**	**30**	**0**	**6**	**15**	**30**
1	4	4	3	1	4	3	3	2	4	3	3	3
3	4	4	3	1	4	3	3	2	4	3	3	3
5	4	4	3	1	4	4	3	2	4	4	4	3
6	4	3	3	1	4	3	3	2	4	3	3	3
7	4	3	3	1	4	3	3	2	4	4	4	3
10	4	3	3	1	4	4	3	2	4	4	3	3
13	4	4	3	1	4	3	3	2	4	3	4	2

15	4	3	3	1	4	3	3	2	4	4	3	3
17	4	3	3	1	4	3	3	2	4	3	3	3
18	4	4	3	1	4	4	3	2	4	3	4	3
22	4	3	3	1	4	3	3	2	4	3	3	3
24	4	3	3	1	4	4	2	2	4	4	3	2
25	4	3	3	1	4	4	2	2	4	4	2	3
29	4	4	3	1	4	3	3	2	4	3	3	3
30	4	3	3	1	4	3	2	2	4	3	2	2
32	4	3	3	1	4	3	4	2	4	3	4	3
34	4	3	3	1	4	4	3	2	4	4	3	3
36	4	4	3	1	4	3	3	2	4	3	3	3
38	4	3	3	1	4	3	3	2	4	3	3	3
40	4	3	3	1	4	4	2	2	4	4	2	2
44	4	3	3	1	4	4	4	2	4	4	4	3
45	4	4	3	1	4	3	3	2	4	3	3	3
46	4	3	3	1	4	3	2	2	4	3	2	3
48	4	3	3	1	4	4	2	2	4	4	2	3
50	4	3	3	1	4	3	3	2	4	3	3	3
51	4	3	3	1	4	3	4	2	4	3	4	3
54	4	3	3	1	4	3	3	2	4	3	3	2
55	4	4	3	1	4	3	2	2	4	3	3	2
57	4	3	3	1	4	3	2	2	4	3	3	2
60	4	3	3	1	4	3	3	2	4	4	3	2
61	4	3	3	1	4	3	2	2	4	3	3	2
64	4	3	3	1	4	4	4	2	4	3	3	2
65	4	4	3	1	4	4	3	2	4	4	3	2
68	4	3	3	1	4	4	3	2	4	3	3	2
69	4	3	3	1	4	3	3	2	4	3	3	2
72	4	3	3	1	4	3	2	2	4	3	3	2
73	4	4	3	1	4	4	4	2	4	4	3	2
76	4	3	3	1	4	4	2	2	4	3	3	2
77	4	3	3	1	4	3	3	2	4	3	3	3
80	4	3	3	1	4	4	3	2	4	4	3	3

81	4	3	3	1	4	3	3	2	4	3	3	2
82	4	4	3	1	4	3	2	3	4	3	2	3
86	4	3	3	1	4	3	4	3	4	3	4	3
87	4	3	3	1	4	4	2	3	4	4	2	3
90	4	4	3	1	4	3	3	2	4	3	3	2
91	4	3	3	1	4	4	2	3	4	4	2	3
94	4	3	3	1	4	3	3	3	4	3	3	3
95	4	3	3	1	4	3	4	3	4	3	4	3
98	4	4	3	1	4	3	3	3	4	3	3	3
99	4	3	3	1	4	3	3	3	4	3	3	3
The grading according to LFT Extreme severe=4,Severe=3,Moderate=2,Mild=1,None =0												

Summary of primary efficacy evaluation

It is evident from table 3 and 4 that the test drug i.e. was more efficacious than the control drug. The baseline mean score for reduction in impotence and male infertility problems in the control arm was 4, which showed reduction within 15 days of treatment, whereas in the same period the test arm, which had baseline mean score for male infertility problems.

Statistically, the test arm showed near to the control arm in terms of significant improvement in the baseline on 15 days and at end of 30days. [p<0.001]

Evaluation of secondary Efficacy Variable:

Overall tolerability of study medications was assessed by physicians at the end of the study 89% rated the tolerability of 'HG PLUS TABLET excellent to good versus 52% of SPEMAN Tablets.

Number of 'HG PLUS TABLET taken to SPEMAN TABLET to reduce IMPOTENCE and MALE INFERTILITY. Problems during the 30 days study Table 5.

Table 5: Number of 'HG PLUS TABLET taken to SPEMAN TABLET

Number of tablets taken in 30 days study period			
Center No	Test Arm	Control Arm	Statistical Significance
1	28	27	0.021[S]
2	24	25	0.008[S]
3	21	23	0.011[S]
4	27	25	0.009[S]
Total	**100**	**100**	**0.008[S]**

Total Score

Effect of 'HG PLUS TABLET in increasing Quality of Life Questionnaire of the European Foundation to reduce Hepatotoxicity (QUALEFFW-41) scores from baseline to end of treatment (at Day 30) was statistically significant shown in Table 6

Table 6: Clinical Efficacy Effect on QUALEFFW-41 Total scores

	Baseline	Day- 06	Day- 15	Day 30
QUALEFFW-41 TOTAL				
'HG PLUS TABLET	0.82 ± 0.24	1.93 ± 0.12	4.01 ± 0.24	6.14 ± 0.13
SPEMAN TABLET	0.82 ± 0.24	1.59 ± 0.13	3.85 ± 0.20	4.96 ± 0.10
QUALEFFW-41 scores are expressed as mean ± SD				

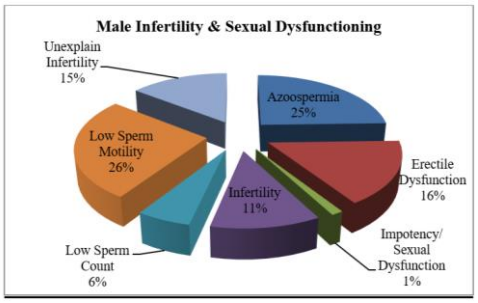

Figure 1: Global assessment of therapy by Investigator

Global Assessment of Therapy by Investigator

Global assessment of therapy by investigator (Figure 1) on Day 30 shows an increase of 'HG PLUS TABLET therepy over SPEMAN TABLET when compared but a considerable percentage increment also supports 'HG TABLET TABLET in terms of its safety profile over SPEMAN TABLET in. treating impotence and male infertility is shown inTable 7. The semen profile analysis before and after treatment is shown in Figure 2 & 3. The comparison of Patients Global Response of 'HG PLUS TABLET and SPEMAN Tablets is shown in Table 8.

Table 7: results of Global assessment of therapy by Investigator

Global assessment of therapy	'HG PLUS TABLET	SPEMAN Tablets
Excellent	56%	42%
Very Good	18%	23%
Good	12%	19%
Fair	14%	16%
Poor	0%	0%

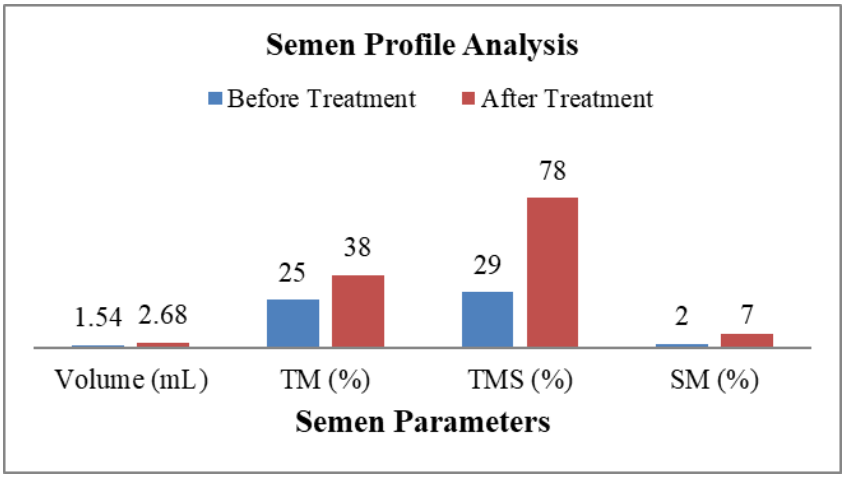

Figure 3: Semen profile analysis

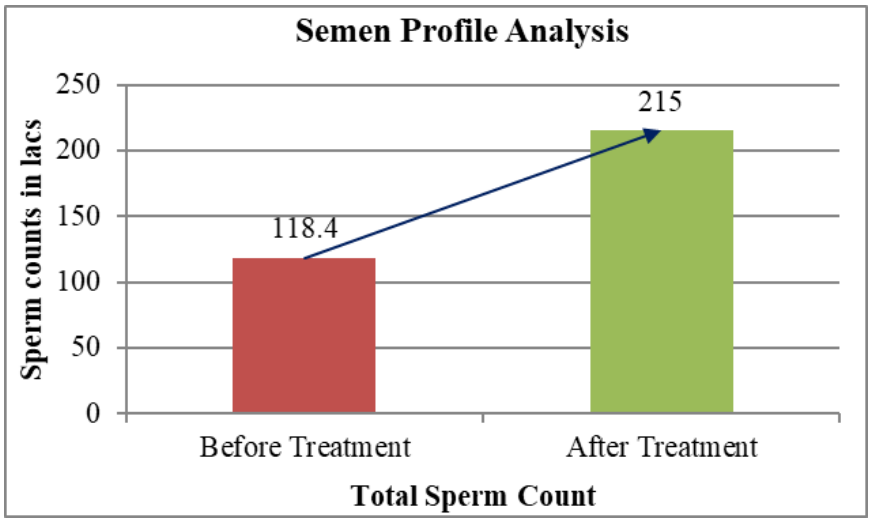

Figure 4: Semen profile analysis and total sperm count

Table 8: Comparison of Patients Global Response of 'HG PLUS TABLET and SPEMAN Tablets

Attribute	'HG PLUS TABLET	SPEMAN Tablets
Excellent	76%	62%
Very Good	14%	12%
Good	11%	19%
Fair	3%	11%
Poor	0%	0%

Conclusion

At the end of treatment (Day 30), the proportion of subjects in 'HG PLUS TABLET group who wished to continue receiving the trial medication, was higher as per subjects' opinion. The Safety Evaluation shows that no adverse clinical symptoms were reported during the study. All the patients were given the contact number of the investigators and asked to call the investigator or the reporting authority to notify about the adverse events. Anybody who participated and took one dose was evaluated for adverse events and safety measures were carried out whenever necessary following is a representation of adverse events during the study. Out of a total of zero adverse events occurring in the study, There were no serious adverse events throughout in the trial. There were no serious adverse events throughout in the trial.

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