International Journal of Herbal Medicine
Available online at www.florajournal.com

E-ISSN: 2321-2187
P-ISSN: 2394-0514
www.florajournal.com
IJHM 2024; 12(4): 14-23
Received: 21-05-2024
Accepted: 28-06-2024

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A clinical study on subclinical hypothyroidism and its management with an extract of Jawarish e Bisbasa formulation: A randomized double-blind placebo-controlled clinical trial

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DOI: https://doi.org/10.22271/flora.2024.v12.i4a.938

Abstract
Subclinical Hypothyroidism is defined as a condition in which the serum thyroid stimulating hormone level is above the normal reference range, but serum thyroxine T_4 and tri iodo thyronine T_3 levels (free and total) are within the normal range. The majority of patients with Subclinical Hypothyroidism show no clinical features of thyroid dysfunction. In a large screening population, the overall percentage of SCH ranges from 5 to 10%. In this clinical study, a polyherbal Unani formulation Jawarish e Bisbasa consisting of *bisbasa (Myristica fragrans), zanjabeel (Zingiber officinalis), asarun (Valeriana wallichii), taj qalmi (Cinnamomum cassia), darchini (Cinnamomum zeylanicum), filfil siyah (Piper nigrum), qaranfal (Szygium aromaticum), filfil daraz (Piper longum), heel khurd (Elettaria cardamomum), heel kalan (Amomum subulatum)* in the form of extract, was tested and found highly significant in terms of efficacy as well as safety. The test formulation (hydroalcoholic extract) was well tolerated and no adverse/ side effects were observed during the entire period of protocol therapy in any patient in the test group. The dosing load was also reduced to one-tenth of its semisolid form.

Keywords: Jawarish e Bisbasa, Placebo, Polyherbal, Subclinical Hypothyroidism

1. Introduction
Subclinical Hypothyroidism is defined as a condition in which the serum thyroid stimulating hormone level is above the normal reference range, but serum thyroxin T_4 and tri iodo thyronine T_3 levels (free and total) are within the normal range. The majority of patients with Subclinical Hypothyroidism show no clinical features of thyroid dysfunction [1-2]. In a large screening population, the overall percentage of SCH ranges from 5 to 10%. In a study of the elderly population, the prevalence of SCH ranges from 7 to 20 percent. Since the levels of T_3 and T_4 hormones in SCH are within the normal range, the distinction between compensated hypothyroidism and euthyroid is obscured but the diagnosis of SCH is based on the raised level of TSH i.e., <15mIU/L [4].

Women are more likely to have Subclinical Hypothyroidism than men. TSH level of less than 10 mIU/l but more than 5 mIU/l is found in 80 percent of patients with Subclinical Hypothyroidism. The most notable complication of Subclinical Hypothyroidism is its high proclivity to progress to true hypothyroidism. It is also linked with dyslipidaemia and an increased risk of cardiovascular diseases. The most recent practical approach for treating clinical hypothyroidism with levothyroxine is when serum TSH level exceeds more than 20mIU/L. In pregnant women or women who wish to conceive, levothyroxine therapy may be started if their TSH level is less than 10 but more than 5mIU/l [2, 29].

Subclinical Hypothyroidism is a common endocrine disorder that affects 3 to 8% of the general population. Antithyroid antibodies are present in 80% of SCH patients. Prior radioiodine therapy and external neck and head irradiation may result in mild thyroid dysfunction [2, 29]. TSH values may be temporarily elevated following episodes of postpartum thyroiditis.

Because of the recent rise in the prevalence of SCH and metabolic risk factors such as poor cardiac function and dyslipidaemia involved, the American Thyroid Association has advocated for screening using serum TSH levels above the age of 35, followed by a 5-year follow-up.

As a consequence of the high likelihood of SCH causing complications during pregnancy and fetal brain development, expecting women should be carefully screened for Subclinical Hypothyroidism [2, 29].

"According to the findings of the Whickham survey, the risk of developing hypothyroidism in women was 4.3 percent per year if both serum TSH levels and anti-thyroid antibodies were elevated, 2.6 percent chance in patients with elevated TSH alone, and 2.1 percent chance per year with positive anti-thyroid antibodies alone". A recent prospective study by Gerald Huber and colleagues concluded that baseline TSH >12uIU/mL, reduced thyroid reserve, and positive for thyroid peroxidase antibodies were high-risk factors for progression to overt hypothyroidism. Thus, treatment of Subclinical Hypothyroidism is an effective effort in preventing the progression to frank hypothyroidism [4].

According to Casey *et al*., Allan *et al*., Vaidya *et al*., and Mannisto *et al*. researches, Subclinical Hypothyroidism is common during early pregnancy, affecting about 2.5 percent of pregnant women [8-12]. In a study conducted by Sahu *et al*. in India on 633 pregnant women, it has been observed that 4.15 percent of pregnant females have Subclinical Hypothyroidism [7]. The prevalence of Subclinical Hypothyroidism in children and adolescents seems to be distinctly lower, i.e., < 2% due to limited studies addressing SCH in the paediatric population [5-6]. In another study on children aged 0.5-16.0 years, it was found that the prevalence of mild SCH was 2.9 percent when thyroid function tests were performed during routine assessments [13].

Baseline TSH level, old age, female sex, and the presence of thyroid autoantibodies are all well-known risk factors for Subclinical Hypothyroidism and its progression to frank hypothyroidism. Smoking addiction, environmental temperature, and ethnicity are some of the risk factors for the development of overt hypothyroidism from the subclinical stage [14-18].

Subtle clinical features of Subclinical Hypothyroidism may manifest as weakness, dry skin, lethargy, cold intolerance, hair loss, pallor of the skin, constipation, hypomotility, puffy face, anorexia, unexplained weight gain, etc. [19-23].

Unani and Arab physicians have made significant contributions to every field of medical science. When we survey the classical Unani literature, we find that Unani physicians such as *Buqrat, Ibn Sina, Jalinoos, Abu Bakr Zakaria Razi, Ali Ibn Abbas Majoosi, Ismail Jurjani, Ibn Hubal Baghdadi, Ibn Zohar,* and others were not very much familiar with the endocrine glands but had a fair idea about the pathological conditions and diseases produced due to malfunctioning of these glands.

Hypothyroidism treatment is usually with levothyroxine but its use in Subclinical Hypothyroidism is controversial [20,22,24]. Over-treatment and under-treatment are common in patients on levothyroxine (especially in Subclinical hypothyroidism). Over-treatment can increase the risk of atrial fibrillation, myalgia, osteoporosis, etc. While no treatment in SCH can lead to Coronary artery disease, Cerebrovascular accident, or heart failure due to cardiomyopathy, there is no evidence of levothyroxine to prevent cardiovascular and cerebrovascular adverse effects [25]. Small number of hypothyroidism patients has residual symptoms even after adequate levothyroxine replacement [24].

Based on the above *Usool-e-ilaaj*, a pharmacopeial compound polyherbal formulation known as *Jawarish e Bisbasa* consisting of ten single herbal drugs has been selected from the Unani classical literature [26-27, 30-32]. All the single drugs of this polyherbal formulation are hot and dry in temperament and have the properties of *Musakhkhin* (calorific) and *Mujaffif* (desiccant). They are also used for the treatment of the diseases produced by *Sue Mizaj Balghami*.

1.1 Hypothyroidism in Unani medicine

The concept of Subclinical Hypothyroidism is not available as such in Unani Classical literature but its symptomatology can be related *to Sue Mizaj Barid Maddi,* especially *Sue Mizaj Balghami*. A number of Unani drugs which have hot and dry temperaments & properties of *Musakhkhin* (calorific) and *Mujaffif* (desiccant) can be used in the treatment of Subclinical Hypothyroidism. A large no of single drugs e.g.; *Bisbasa, Filfil siyah, Filfil daraz, Zanjabeel, Darchini, Taj qalmi, Qaranfal, Heel Khurd, Heel kalan, Asarun* [28] and compound formulations such as *Jawarish e bisbasa, Jawarish falafali, Jawarish kamooni, Jawarish jalinoos, Majoon Zanjabeel, Majoon Chobchini* are available in Unani classical literature which can be used to treat the symptoms of SCH.

1.2 Study justification

Subclinical Hypothyroidism is becoming more common, particularly among women and pregnant women. It is also closely related to metabolic syndrome. The two most serious consequences of failing to treat Subclinical Hypothyroidism are dyslipidemia and impaired cardiac function. The individuals affected with Subclinical Hypothyroidism are at increased risk of Clinical Hypothyroidism and thus are at increased risk of infertility, amnesia, cardiac disorders, peripheral neuropathy, birth defects, myxoedema, goiter, etc., and in children, mental and physical retardation as well, so, it has become a distressing problem for which treatment is not recommended in modern system of medicine. Therefore, searching for a safe and effective drug is the need of the hour especially from herbal sources for Subclinical Hypothyroidism.

In view of the above, *Jawarish-e-Bisbasa* has been selected from the Unani classical literature to treat Subclinical Hypothyroidism in this study. In Unani classical literature, the *Jawarish-e-Bisbasa* is prescribed for the management of *sue mizaj balghami* with clinical features like central obesity, fatty liver, amnesia, puffy face, loss of appetite, somnolence, etc. The above symptoms are also presented in SCH. *Jawarish-e-Bisbasa* of Unani medicine is available in paste form so, it is difficult to be consumed the patient. Hence, we have decided to change its dosage from *jawarish* (paste) to capsule. This formulation contains *bisbasa (Myristica fragrans), zanjabeel (Zingiber officinalis), asarun (Valeriana wallichii), taj qalmi (Cinnamomum cassia), darchini (Cinnamomum zeylanicum), filfil siyah (Piper nigrum), qaranfal (Szygium aromaticum), filfil daraz (Piper longum), heel khurd (Elettaria cardamomum), heel kalan (Amomum subulatum)* and all of the ingredients are having metabolic rate enhancer activity. Moreover, *ilaichi khurd, taj qalmi,* and *bisbasa* have the property to increase the secretion of thyroid hormones but, *zingiber officinalis* has TSH-lowering activity.

Hence, the 50% hydroalcoholic extract of *Jawarish-e-Bisbasa* in the form of a capsule has been taken to evaluate its effect in the treatment of Subclinical Hypothyroidism.

2. Material Methods

2.1 Study Design: The present study was designed as a randomized Double-Blind Placebo-controlled clinical trial.

2.2 Randomization: Randomization was done by the block randomization method. 40 patients were allocated by using the block randomization method into two groups, comprising

20 patients in each of the test group and control group respectively.

2.3 Sample size: 40 Patients were included in the study. 20 Patients in each test and control group.

2.4 Criteria for the selection of patients: Both male and female patients aged between 18-65 years with clinical signs and symptoms were enrolled from the outpatient Department of Moalejat, Ayurvedic & Unani Tibbia College Hospital, Karol Bagh, New Delhi.

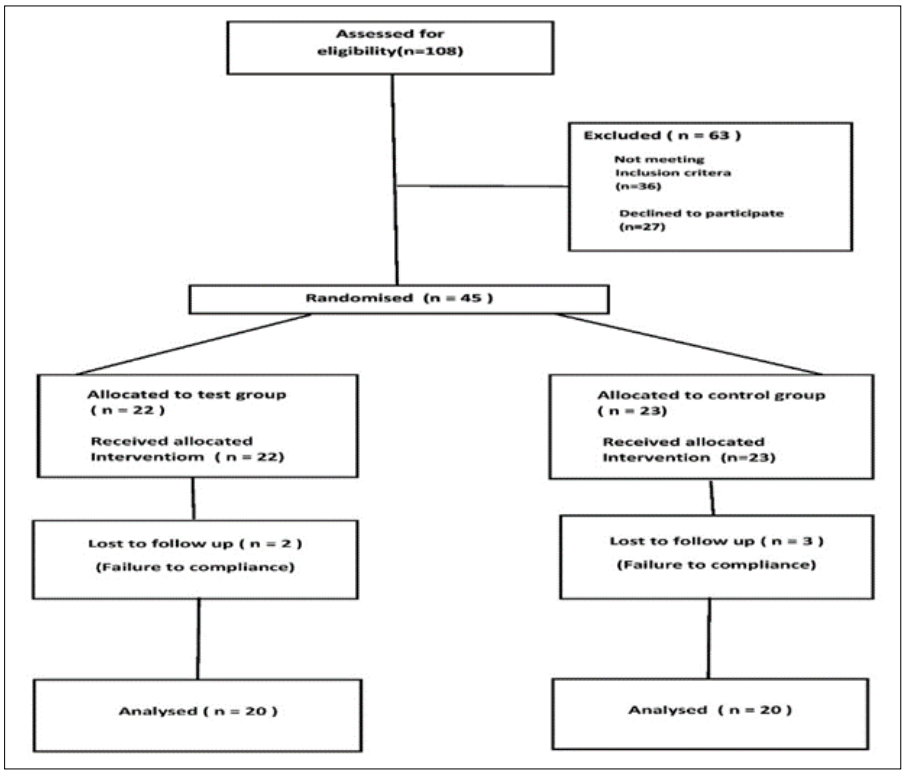


Fig 1: Flow chart of participation of patients in the present clinical trial

2.4.1 Inclusion criteria
- Patients between the age of 18-65 years of either sex.
- Diagnosed cases of Subclinical Hypothyroidism.
- Patients willing to participate and sign the understood and informed consent form.

2.4.2 Exclusion criteria:
- Pregnancy and lactating women.
- Renal and hepatic insufficiency and malignancy.
- Patient unwilling to sign the consent form.
- Patient taking hormonal therapy.

2.4.3 Withdrawal criteria
- Failure to follow the protocol therapy
- Non-compliance with therapy.
- The cases in which adverse drug reaction is noticed

2.5 Duration of study
- One and a half years.

2.5.1 Duration of protocol therapy: The treatment period in both test and control groups was fixed as 42 days (6 weeks).

2.6 Clinical evaluation of disease: The clinical evaluation of the patients for Subclinical Hypothyroidism was done on the following basis as per the designed Case Record Form (CRF).
- History taking
- General physical examination
- Investigations

2.7 Ethical consideration: The proposed study was started after obtaining the approval from Institutional Ethics Committee. Written informed consent to participate in the study was obtained from each patient and the study was conducted as per Good Clinical Practice (G.C.P.) Guidelines.

2.7.1 CTRI: CTRI No-CTRI/2021/06/034158. After getting approval from the Institutional Ethics Committee, the trial was registered in the Clinical Trial Registry of India.

2.8 Criteria for Diagnosis of Subclinical Hypothyroidism
- Serum TSH level >5 and <15mIU/L [2,4,6].

2.9 Criteria for selection of the Unani formulation: In Unani classical literature, Subclinical Hypothyroidism is not mentioned, but Subclinical Hypothyroidism's manifestations resemble the *sue mizaj balghami*. therefore, the line of treatment of *sue mizaj balghami* as described in classical Unani text-the drugs having hot and dry temperament, *Musakkhin* (calorific) and *Mujaffif* (desiccant) and anti-phlegmatic properties may be used in the treatment of this condition.
Based on the above *usool-e-ilaaj*, a polyherbal Unani formulation known as *Jawarish e Bisbasa* containing ten Unani herbal drugs in the form of an extract was selected for the treatment of Subclinical Hypothyroidism.

2.10 Procedure: After a thorough screening, diagnosed patients of Subclinical Hypothyroidism who fulfilled inclusion/ exclusion criteria, were enrolled in the study. Patients were randomly allocated into two groups after making them understand the study and taking their voluntary informed written consent. The test group had 20 patients and

the control group too had the same number of patients. Those falling under the test group were given the 50% hydro-alcoholic extract of Jawarish-e-bisbasa polyherbal Unani formulation in the form of the capsule (500mg) one capsule twice a day orally with water after meals and the control group was given placebo capsules containing corn flour with identical appearance capsule (500mg each) twice in a day orally with water after meals. Patients were advised to visit for follow-up on a weekly basis. The data for both groups were statistically analysed and compared with each other using appropriate statistical tests. Subjective parameters were assessed by Friedman and Mann Whitney U statistical tests and objective parameters and safety parameters were analysed with the help of ANOVA, paired t-test, and unpaired t-test. The safety of both groups was ensured by monitoring the kidney & and liver functions and haematological parameters. Any unwanted effect of the drug during the study was also noted down carefully.

2.11 Study drug

2.11.1 Test drug: Test group, 50% Hydro-alcoholic extract of *Jawarish e bisbasa* formulation containing ten herbs namely *Bisbasa* (*Myristica fragrans*), *Zanjabeel* (*Zingiber officinalis*), *Asarun* (*Valeriana wallichii*), *Taj qalmi* (*Cinnamomum cassia*), *Dalchini* (*Cinnamomum zeylanicum*), *Filfil siyah (Piper nigrum), Qaranfal (Szygium aromaticum), Filfil daraz (Piper longum), Heel khurd (Elettaria cardamomum), Heel kalan (Amomum subulatum)* in the form of a capsule. Each capsule contained 500mg of 50% hydroalcoholic extract of the above-said formulation.

2.11.2 Control drug: Control group, identical capsules containing 500mg of corn flour (placebo).

2.11.3 Preparation of test drug: The ingredients of the test drug i.e., 50% hydro-alcoholic extracts of *Bisbasa (Myristica fragrans), Zanjabeel (Zingiber officinalis), Asarun (Valeriana wallichii), Taj qalmi (Cinnamomum cassia), Dar chini (Cinnamomum zeylanicum), Filfil siyah (Piper nigrum), Qaranfal (Szygium aromaticum), Filfil daraz (Piper longum), Heel khurd (Elettaria cardamomum), Heel kalan (Amomum subulatum)* were procured from Vital Herbs, Uttam Nagar, Delhi-110059 along with their certificate of analysis (C.O.A). All the above-mentioned extracts as per the below-given ratio were mixed and filled up in capsules with a capacity of 500mg.

Table 1: Composition and quantity of herbal ingredients used in the test drug (Jawarish-e-Bisbasa) for the treatment of Subclinical Hypothyroidism

S. No	Test drug (Extract)	Part used	Quantity
1.	*Bisbasa (Myristica fragrans)*	Arillus	32.25mg
2.	*Zanjabeel (Zingiber officinalis)*	Rhizome	32.25mg
3.	*Asarun (Valeriana wallichii)*	Rhizome	40.3mg
4.	*Taj qalmi (Cinnamomum cassia)*	Stem bark	40.3mg
5.	*Dar chini (Cinnamomum zeylanicum)*	Stem bark	32.25mg
6.	*Filfil siyah (Piper nigrum)*	Fruit	64.5mg
7.	*Qaranfal (Szygium aromaticum)*	Flower bud	24mg
8.	*Filfil daraz (Piper longum)*	Fruit	40.3mg
9.	*Heel kalan (Amomum subulatum)*	Fruit	162.5mg
10.	*Heel Khurd (Elettaria cardamomum)*	Fruit	32.25mg

2.12.4 Preparation of Control Group: The ingredient of the placebo group (corn flour) along with the certificate of Authentication/Analysis (C.O.A) was procured from vital herbs Uttam Nagar, Delhi-110059. The corn flour was filled in identical capsules weighing 500 mg each.

2.13 Dosage schedule: The test group (group A) received the test drug in the dose of 1 capsule (500mg) twice daily after meals with plain water for 42 days.
The control group (group B) was given a placebo in the form of capsules of 500mg each, 1 capsule twice daily after meals with plain water for 42 days.

2.14 Follow up: The clinical and laboratory evaluation of all patients was performed and recorded during follow-up visits at the baseline, week 1, week 2, week 4, and week 6.

2.15 Drug compliance: Compliance with the test drug/ placebo capsules was monitored at each follow-up visit by counting their numbers.

2.16 Assessment of Temperament (Mizaj): The temperament of each patient was assessed before and after the completion of treatment based on ten classical parameters (*Ajnas-e-Ashra*) as prescribed in Unani Classical literature.

2.17 Criteria for assessment of efficacy: To assess the efficacy of treatment of Subclinical Hypothyroidism in both groups, the following subjective and objective parameters were used.

2.17.1 Subjective parameters
- Tiredness
- Cold intolerance
- Constipation
- Appetite

2.17.2 Objective parameters
- TSH
- Weight with respect to BMI

2.18 Assessment of safety: To establish the safety of drugs, the following investigations were carried out at baseline, on the 7th day, and just after termination of treatment.
- **Hemogram:** Hb%, TLC, DLC & ESR
- **Liver function test:** S.G.O.T, S.G.P.T and Alkaline phosphatase
- **Kidney function test:** Blood urea and Serum creatinine

2.19 Adverse event documentation: Any side effect/ unwanted effect or adverse reaction during the study was noticed and recorded carefully.

2.20 Statistical analysis: After six weeks of the treatment, pre-treatment and post-treatment values of subjective and objective parameters in each group were analysed and

compared to evaluate the efficacy of the treatment by applying appropriate statistical tests. Subjective parameters were assessed by the Friedmann (F) test for intragroup comparison and the Mann-Whitney U test for intergroup comparison. Objective parameters were analysed with the help of repeated measures ANOVA for intragroup comparison, paired t-test for intragroup comparison, and unpaired t-test for intergroup comparison.

2.21 Confidentiality: The Confidentiality of the patient's identity was truly maintained. The patient will not be identified by name or photograph in any study-related publications.

3. Observation and Results

3.1 Efficacy

3.1.1 Effect of trial drugs on serum TSH: As shown in Table 2 & Figure 2, in the test group, the mean values of TSH decreased highly significantly from 8.74±2.98 at the baseline to 6.88±3.49 on the 7th day and 4.76±3.08 at the termination of the study (P=0.0001). While in the control group, the mean values of TSH increased significantly from 7.17+2.68 on 0 days to 7.04±3.30 on the 7th day and 10.09±6.67 at the end of therapy (P=0.003).

Table 2: Effect of the test drug on serum TSH levels over 42 days of treatment

TSH	Day 0 Mean ± SD	Day 7 Mean ± SD	Day 42 Mean ± SD	Mean difference (Before and after)	P-Value (Within the group)
Test	8.74±2.98	6.88±3.49	4.76±3.08	3.98	0.0001
Control	7.17±2.68	7.04±3.30	10.09±6.67	-2.92	0.003
Mean difference	-1.56	0.16	5.34		
P-value (Between the group	0.09	0.88	0.002		

*Values with plus/minus signs are expressed as Means + S.D

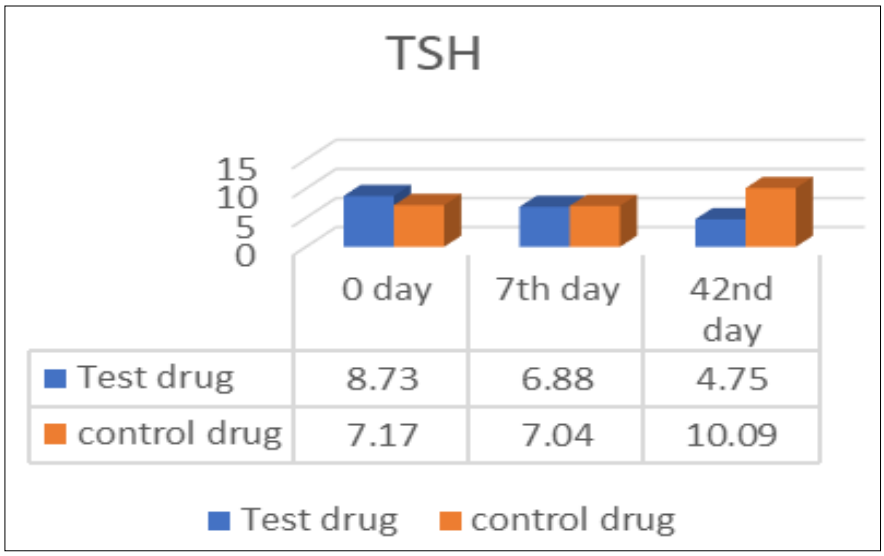
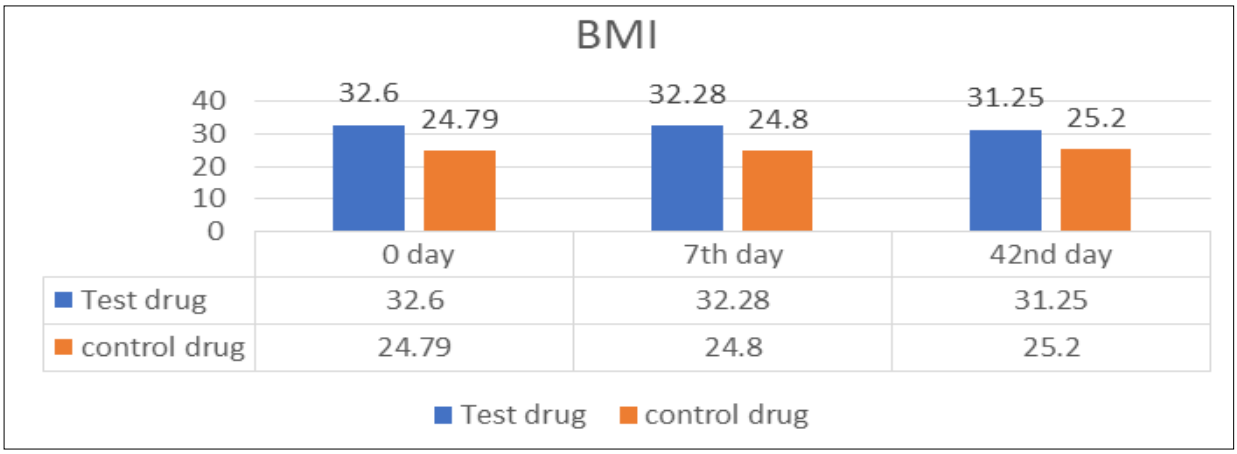


Fig 2: Graph showing the effect of the test drug on serum TSH levels in the test and control groups over the 42-day treatment period

3.1.2 Effects of trial drugs on BMI

The mean BMI values observed in the test group were 32.60+6.80 at the baseline, 32.28±6.90 on the 7th day, and 31.25±6.83 on the 42nd day, the difference is highly significant (P=0.0001). On the other hand, in the control group the mean BMI also underwent a significant increase from 24.79+4.86 on 0 days to 24.80±4.88 on the 7th day and 25.20±5.05 at the end of the trial (P=0.007). On applying an unpaired t-test, the inter-group difference was statistically significant (p< 0.05).



*Values with plus/minus signs are expressed as Means + S.D

Fig 3: Graph depicting the changes in Body Mass Index (BMI) in the test and control groups throughout the study

Table 3: Changes in Body Mass Index (BMI) in the test and control groups during the study period

BMI (Kg/m2)	Day 0 Mean ± SD	Day 7 Mean ± SD	Day 42 Mean ± SD	Mean difference (Before and after)	P-Value (Within the group)
Test	32.60±6.80	32.28±6.90	31.27±6.83	1.33	0.0001
Control	24.79±4.86	24.80±4.88	25.20±5.05	-0.41	0.007
Mean difference	-7.81	-7.47	-6.07		
P-value (Between the group	0.0002	0.0003	0.003		

3.1.4 Effect of trial drugs on tiredness

In test group 0(0%), 4(20%), 12 (60%), and 4(20%) patients belongs to grade 0 to grade 3 respectively on the baseline of the treatment, 0 (0%), 12(60%), 8 (40%) and 0(0%) belongs to grade 0 to grade 3 on 7th day, 2 (10%), 14(70%), 4 (20%) and 0 (0%) belongs to grade 0 to grade 3 at 14th day, 9(45%), 10(50%), 1(5%) and 0(0%) patients belongs to grade 0 to grade 3 at 28th day and 14 (70%), 5(25%), 1(5%) and 0(0%) patients belongs to grade 0 to grade 3 at the termination of the study.

In the control group: 2 (10%), 7(35%), 11(55%), and 0(0%) patients belong to grade 0 to grade 3 respectively on the baseline of the treatment, 3 (15%), 7(35%), 10(50%) and 0(0%) patients belong to grade 0 to grade 3 at the 7th day, 3(15%), 6(30%), 11(55%) and 0(0%) patients belongs to grade 0 to grade 3 at 14th day, 4(20%), 3(15%) and 3 (15%) patients belongs to grade 0 to grade 3 at 28th day and 3(15%), 4(20%), 9 (45%) and 4 (20%) patients belongs to grade 0 to grade 3 at the termination of the study.

When the scores of tiredness in both Groups, Test, and control, were compared statistically by using 'Friedman' test for intragroup comparisons and MANN WHITNEY 'U' test for intergroup comparison, it was found that tiredness reduced in the subjects of the Test group highly significantly ($p<0.001$) at 42nd day with respect to baseline and in case of control group, statistically, result is significant ($p<0.05$) at 42nd day with respect to baseline. Intergroup comparison on the 42nd day showed the better efficacy of the test drug and that was also significant statistically ($p<0.001$).

Table 4: Impact of the test drug on the severity of tiredness over the course of the treatment

Tiredness	0 Day		7th Day		14th Day		28th Day		42nd day		P-Value (Within the group)
	Test	Control	Test	Control	Test	Control	Test	Control	Test	Control	
0	0	2	0	3	2	3	9	4	14	3	Test group
1	4	7	12	7	14	6	10	3	5	4	0.0001
2	12	11	8	10	4	11	1	10	1	9	Control group
3	4	0	0	0	0	0	0	3	0	4	0.023
Total	20	20	20	20	20	20	20	20	20	20	
p-value (Between the group)	0.04		0.97		0.14		0.002		0.0001		

3.1.5 Effect of trial drug on cold intolerance

In the assessment of cold intolerance, in the test group: 12(60%), 5(25%), 3 (15%), and 0(0%) patients belong to grade 0 to grade 3 respectively on the baseline of the treatment. 14(70%), 6(30%), 0 (0%), and 0(0%) patients belong to grade 0 to grade 3 respectively on the 7th day, 17(85%), 3(15%), 0 (0%) and 0(0%) patients according to grade 0 to grade 3 on 14th day, 19(95%), 1(5%), 0 (0%) and 0(00%) patients according to grade 0 to grade 3 at 28th day and 19(95%), 1(5%), 0(0%) and 0(0%) patients according to grade 0 to grade 3 at the termination of the study.

In the control group: 14(70%), 5(25%), 1 (5%), and 0(0%) patients belong to grade 0 to grade 3 respectively on the baseline of the treatment. 13(65%), 6(30%), 1(5%), and 0(0%) patients belong to grade 0 to grade 3 respectively on the 7th day, 12(60%), 5(15%), 3 (15%) and 0(0%) patients according to grade 0 to grade 3 on 14th day, 9(45%), 7(35%), 4 (20%) and 0(0%) patients according to grade 0 to grade 3 at 28th day and 8(40%), 8(40%), 4(20%) and 0(0%) patients according to grade 0 to grade 3 at the termination of the study.

When the score of cold intolerance in both Groups, A, and B, were compared statistically by using the Friedman test for intragroup comparison and Mann-Whitney test for intergroup comparison, it was found that the Test group was highly significant (P=0.004) on the 42nd day with respect to baseline and in case of the control group, significant (P=0.0001) at 42nd day with respect to baseline. Intergroup comparison on the 42nd day was also significant (P=0.001).

Table 5: Effectiveness of the test drug in reducing cold intolerance among participants

Cold intolerance	0 Day		7th Day		14th Day		28th Day		42nd Day		P-Value (Within the group)
	Test	Control	Test	Control	Test	Control	Test	Control	Test	Control	
0	12	14	14	13	17	12	19	9	19	8	Test group
1	5	5	6	6	3	5	1	7	1	8	0.0004
2	3	1	0	1	0	3	0	4	0	4	Control group
3	0	0	0	0	0	0	0	0	0	0	0.0001
Total	20	20	20	20	20	20	20	20	20	20	
P-Value (Between the group)	0.5		0.73		0.0001		0.005		0.0001		

3.1.6 Effect of trial drugs on constipation

In the assessment of constipation, in the test group: 3(15%), 17(85%), 0(0%), and 0(0%) patients belong to grade 0 to grade 3 respectively on the baseline of the treatment. 17(85%), 3(15%), 0(0%), and 0(0%) patients belong to grade 0 to grade 3 respectively on the 7th day, 19(95%), 1(5%), 0 (0%) and 0(0%) patients according to grade 0 to grade 3 on 14th day, 19(95%), 1(5%), 0 (0%) and 0(0%) patients according to grade 0 to grade 3 at 28th day and 19(95%), 1(5%), 0(0%) and 0(0%) patients according to grade 0 to grade 3 at the termination of the study.

In the control group: 8(40%), 12(60%), 0 (0%), and 0(0%) patients belong to grade 0 to grade 3 respectively on the baseline of the treatment. 11(55%), 9(45%), 0(0%), and 0(0%) patients belong to grade 0 to grade 3 respectively on the 7th day, 7(35%), 13(65%), 0(0%) and 0(0%) patients according to grade 0 to grade 3 on 14th day, 7(35%), 13(35%), 0 (20%) and 0(0%) patients according to grade 0 to grade 3 at 28th day and 6(40%), 13(40%), 1(20%) and 0(0%) patients according to grade 0 to grade 3 at the termination of the study.

When the score of cold intolerance in both groups, a and b, were compared statistically by using the Friedman test for intragroup comparisons and Mann-Whitney test for intergroup comparison, it was found that the test group was highly significant (P=0.0001) on the 42nd day with respect to baseline and in case of the control group, significant (P=0.0001) at 42nd day with respect to baseline. Intergroup comparison on 42nd day was also significant (P=0.0004).

Table 6: Reduction in constipation severity in patients treated with the test drug compared to the control group

Constipation	0 Day		7th day		14th day		28th day		42nd day		P-Value (Within the group)
	Test	Control	Test	Control	Test	Control	Test	Control	Test	Control	
0	3	8	17	11	19	7	19	7	19	6	Test Group
1	17	12	3	9	1	13	1	13	1	13	0.0001
2	0	0	0	0	0	0	0	0	0	1	Control group
3	0	0	0	0	0	0	0	0	0	0	0.0001
Total	20	20	20	20	20	20	20	20	20	20	
P-Value (Between the group)	0.17		0.1		0.001		0.001		0.0004		

3.1.7 Effect of trial drugs on Appetite

In the assessment of appetite, in the test group: 5(25%), 12(60%), 3(15%), and 0(0%) patients belong to grade 0 to grade 3 respectively on the baseline of the treatment. 8(40%), 11(55%), 1(5%), and 0(0%) patients belong to grade 0 to grade 3 respectively on the 7th day, 16(80%), 4(20%), 0 (0%) and 0(0%) patients according to grade 0 to grade 3 on 14th day, 18(90%), 2(10%), 0(0%) and 0(00%) patients according to grade 0 to grade 3 at 28th day and 18(90%), 2(10%), 0(0%) and 0(0%) patients according to grade 0 to grade 3 at the termination of the study.

In the control group: 9(45%), 11(55%), 0 (0%), and 0(0%) patients belong to grade 0 to grade 3 respectively on the baseline of the treatment. 10(50%), 10(50%), 0(0%), and 0(0%) patients belong to grade 0 to grade 3 respectively on the 7th day, 10(50%), 9(45%), 1(5%) and 0(0%) patients according to grade 0 to grade 3 on 14th day, 7(35%), 9(45%), 4 (20%) and 0(0%) patients according to grade 0 to grade 3 at 28th day and 7(35%), 9(45%), 4(20%) and 0(0%) patients according to grade 0 to grade 3 at the termination of the study.

When the score of appetite in both groups, TEST, and CONTROL, were compared statistically by using the Friedman test for intragroup comparisons and Mann-Whitney test for intergroup comparison, it was found that the test group was highly significant (P=0.0001) on the 42nd day with respect to the baseline and in case of the control group, significant (P=0.002) at 42nd day with respect to baseline. Intergroup comparison on 42nd day was also significant (P=0.002).

Table 7: Improvement in appetite observed in patients receiving the test drug during the study

Appetite	0 day		7th day		14th day		28th day		42nd day		P-Value (Within the group)
	Test	Control	Test	Control	Test	Control	Test	Control	Test	Control	
0	5	9	8	10	16	10	18	7	18	7	Test Group
1	12	11	11	10	4	9	2	9	2	9	0.0001
2	3	0	1	0	0	1	0	4	0	4	Control group
3	0	0	0	0	0	0	0	0	0	0	0.002
Total	20	20	20	20	20	20	20	20	20	20	
P-Value (Between the group)	0.12		0.5		0.09		0.002		0.002		

3.2 Safety assessment in test group (N=20)

Table 8(a): Hematological and biochemical safety assessment in the test group over the study duration.

Parameters		Assessments		
		0 Day	7th Day	42nd Day
Hemoglobin		10.92 ± 1.12	11.14 ± 1.11	11.3 ± 0.89
TLC		9460.2 ± 1613.92	9920 ± 1090.91	9585 ± 1133.82
DLC	Neutrophils	67.21 ± 7.90	70.15 ± 4.70	69.95 ± 4.85
	Eosinophils	4.30 ± 1.58	4.45 ± 1.50	4.5 ± 2.11
	Basophils	0.06 ± 0.15	0 ± 0	0 ± 0
	Lymphocytes	26.65 ± 7	24.75 ± 4.63	25.95 ± 5.19
	Monocytes	1.59 ± 1.97	0.55 ± 1.05	0.4 ± 0.5
	ESR	29.3 ± 6.86	27.15 ± 7.37	27 ± 5.94
LFT	SGOT	32.26 ± 10.15	30.1 ± 5.98	27.9 ± 6.34
	SGPT	39.33 ± 8.71	36.37 ± 4.37	37.34 ± 5.41
	S. Alk. Phos.	163.54 ± 56.84	195.75 ± 30.98	166.75 ± 30.84
KFT	B. Urea	29.07 ± 6.41	31.6 ± 4.60	29.23 ± 4.67
	S. Creatinine	0.91 ± 0.17	0.91 ± 0.13	0.95 ± 0.13

*Values with plus/minus signs are expressed as Means + S.D.

3.3 Safety assessment in the control group (N=20)

Table 8(b): Hematological and biochemical safety assessment in the control group over the study duration.

Parameters		Assessments		
		0 Day	7th Day	42nd Day
Hemoglobin		10.69+1.65	10.89+1.19	11.01+1.01
TLC		8027.9+1748.86	9665+806.07	9115+1274.55
DLC	Neutrophils	61.37+9.30	70.15+4.68	68.35+5.13
	Eosinophils	5.17±2.03	4.45+1.19	4.5+1.19
	Basophils	0.37+0.65	0.05+0.22	0+0
	Lymphocytes	30.08+6.06	24.5+4.55	26.7±4.95
	Monocytes	3.08+5.06	0.85+0.93	0.35+0.67
	ESR	31+12.59	28.95+12.37	27.5+9.83
LFT	SGOT	34.81+21.58	33.69+11.90	31+4.88
	SGPT	37.40+26.09	38.66+11.17	37.18+5.00
	S. Alk. Phos.	153.22+61.15	173.32+40.04	166.1+30.25
KFT	B. Urea	26.84+5.28	29.56+6.09	27.3+4.00
	S. Creatinine	0.84+0.15	0.90+0.14	0.88+0.11

*Values with plus/minus signs are expressed as Means + S.D.

4. Discussion

The present clinical study was conducted in the Department of Moalejat in Ayurvedic and Unani Tibbia College and Hospital, Karol Bagh, New Delhi to evaluate the efficacy of a test formulation for the management of Subclinical Hypothyroidism. A total of 108 patients were observed for the study. During screening 63 patients did not fulfil inclusion criteria and were excluded from the study, the remaining 45 patients were allocated to test (Group A) and control (Group B) groups with the help of the block randomization method respectively. However, 2 patients from the test group and 3 patients from the control group did not complete the full course of treatment leaving behind 20 patients in the test and 20 patients in the control group who completed the course of treatment completely. Statistical analysis was done only for those patients who completed the course of treatment.

The results indicate that the test group is more effective in reducing tiredness, cold intolerance, decreasing constipation, and increase in appetite.

The improvement in tiredness may be due to the *Muqawwi-i-aam*, *Muharrik*, and *Muqawwi-i-asab* effect of *bisbasa (myristica fragrans), Filfil siyah (Piper nigrum), Darchini (Cinnamomum zeylanicum), Taj qalmi (Cinnamomum cassia), Asarun (Valerina wallichii)* ingredients of the test formulation.

The effect may be in cold intolerance, because all ingredients of the test formulation have *Haar Mizaj* and possess *Musakhkhin* (calorific) properties like *Filfil siyah (Piper nigrum), Filfil daraz (piper longum), Darchini (Cinnamomum zeylanicum), Taj qalmi (Cinnamomum cassia),* etc.

The effect may be in constipation, because most ingredients of test formulation have *Haar Mizaj* and possess increased *istehala* (metabolism) of the body, mulayyan and mushil properties like *Filfil siyah (Piper nigrum), filfil daraz (piper longum), Darchini (Cinnamomum zeylanicum), taj qalmi (Cinnamomum cassia),* etc.

The effect may be in appetite because most ingredients of test formulation have metabolism enhancer, *hazim*, and *mushtahi* properties like *Filfil siyah (Piper nigrum), Filfil siyah (Piper nigrum), filfil daraz (piper longum), Darchini (Cinnamomum zeylanicum), taj qalmi (Cinnamomum cassia),* etc.

In the present study, the test drug has been found efficacious in reducing the level of TSH i.e., from 8.74(before treatment) to 4.76 after 6 weeks of treatment. This significant result of the test drug can be attributed to thyroid stimulating properties of *Bisbasa, Heel khurd, Filfil siyah,* and *Taj qalmi.*

In another experimental study, *Zanjabeel* has also been found directly effective for the reduction of TSH.

This improvement in BMI might be due to *Musakkhin*, Hypolipidemic, *Mudir, Muhallil, Mushile balgham*, and *Muarriq* properties of most of the ingredients of test drug i.e., *bisbasa, zanjabeel, asarun, taj qalmi, darchini, filfil siyah, qaranfal, filfil daraz, heel khurd,* and *heel kalan.*

Individual drugs that constitute the composition of test formulation have been reported to possess some interesting pharmacological effects that directly or indirectly support our hypothesis regarding the efficacy of the trial formulation. The *Musakhkhin* (calorific) and *Muharrik* (stimulant) properties of *Bisbasa, Filfil siyah, Filfil daraz, Asarun,* and *Taj qalmi* enhance the metabolism and increase *Hararate Tabaiya* that brings back the normal temperature in test group. The *Muhallil* and *Mujaffif* properties of *Bisbasa, Filfil daraz, Heel khurd*, and *Asarun* metabolize/oxidize the morbid matter thus reducing BMI and Body Weight. Furthermore, the *Mudir* (diuretic) and *muarrik* (diaphoretic) effects of the drugs viz *Filfil siyah, Asarun, Darchini, Zanzabeel*, and *Taj qalmi* help in the excretion of morbid material through diuresis and perspiration.

4.1 Adverse effects

- No significant adverse effects were observed in the test group.
- On the contrary, 1 case (5%) in the test group developed palpitation after 3 weeks of administration of the capsule form of the trial drug. This side effect could be because of the hot and dry temperament possessing drugs like *bisbasa, long, zanzabeel, asarun,* etc.

5. Conclusion

The results of this study can be concluded as follows:

- It may be concluded that the test formulation used in this study was found to be statistically effective in the management of Subclinical Hypothyroidism as it has reduced TSH levels below 5mIU/L in 75% of the cases.
- The test drug subsided the clinical features of Subclinical Hypothyroidism and improved the general condition of the patients.
- The test formulation was well tolerated and no adverse/ side effects were observed during the entire period of protocol therapy. However, only one patient complained

of palpitation in the test group. This side effect could be because of the hot and dry temperament possessing drugs *like bisbasa, long, zanzabeel, asarun*, etc.

In view of the above observations and discussion, it may be concluded that the test formulation has been found safe, efficacious, and cost-effective in the management of SCH. The test formulation produced a significant positive effect on various subjective parameters such as tiredness, cold intolerance, constipation, and appetite and objective parameters such as TSH, and BMI without demonstrating any significant side effect. However, a long-term multicentric study with a larger sample size may be conducted to generate comprehensive data in terms of the safety and efficacy of the drug in the management of Subclinical Hypothyroidism.

6. Acknowledgment
This article is taken from the MD thesis of Dr. Irshad under the supervision of Professor Rais Ur Rahman Head, Dept of Moalejat A. & U. Tibbia College New Delhi, India.

7. Conflict of interest
There is no conflict of interest.

8. Funding
No funding was received from any organization for conducting the study or the preparation of this manuscript.

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