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# Efficacy of Ayurvedic herbal formulation and Ayurvedic herbo-mineral formulation in hypothyroidism patients

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## ABSTRACT

**Background:** Hypothyroidism is one of the major endrocrine disorders seen in general population worldwide. Although modern drugs are quite effective in managing hypothyroidism, it is subject to sustaining certain side effects. So, we aim to evaluate the efficacy of Ayurvedic herbal formulation and Ayurvedic herbo-mineral formulation in managing hypothyroidism in Nepalese population. **Methods and analysis:** This study was a randomized, double-blind, and controlled trial. A total of 50 participants with the diagnosis of hypothyroidism was randomly assigned to the intervention group or control group in a ratio of 1:1 for 4 weeks. The primary outcome measure was the thyroid-stimulating hormone level, and secondary outcome measures was the change in body mass index, waist-hip ratio, blood glucose level, lipid profile, liver function tests and renal function tests between the baseline and at 4 weeks after intervention. Statistical analysis was done by comparing categorical variables using chi-square test and Fisher's exact test and comparing continuous variables using paired and unpaired student's *t* test. **Results:** There was a decrease in TSH levels of the participants by 12.5% and 7.9%, after intervention with AHF and AHMF, respectively. There were a small statistical significant difference only in waist-hip ratio ( p= 0.04) when compared before and after treatment with AHF and AHMF whereas there was no significant changes observed in other clinical variables after intervention with AHF and AHMF. **Conclusion:** This study may provide new evidence for the effectiveness of Ayurvedic herbal formulation and Ayurvedic herbo-mineral formulation in hypothyroidism in context of Nepal.

**Keywords:** Ayurvedic herbal formulation, Ayurvedic herbo-mineral formulation, Hypothyroidism, Nepal.

## INTRODUCTION

Hypothyroidism is one of the major endocrine disorders seen in general population worldwide. It occurs due to the deficiency of thyroid hormones and leads to the reduction of basal metabolic rate, affect physical and mental growth during infancy or childhood [1]. The prevalence of hypothyroidism in the developed world and Nepal is 4.6% and 13%, respectively [2-4].

Thyroxine (T4) and tri-iodothyronine (T3) are the two hormones secreted by the thyroid gland for maintenance of body homeostasis. Disorders of the thyroid gland can stimulate the overproduction of thyroid hormones or cause glandular destruction and hormone deficiency. Hypothyroidism is defined as reduced production of thyroid hormones [5]. The causes of hypothyroidism are usually divided primary, secondary and tertiary hypothyroidism. The permanent loss or destruction of the thyroid by autoimmune diseases, irradiation injury etc. is called peripheral or primary hypothyroidism, which is the cause of approximately 99% of cases of hypothyroidism. Insufficient stimulation of the normal thyroid gland as a result of hypothalamic and pituitary defects in the thyroid stimulating hormone (TSH) molecule is described as central or secondary and tertiary hypothyroidism, respectively and is accounted for less than 1% of all cases throughout the world [6-8]. The common signs and symptoms of hypothyroidism are fatigue, lethargy, constipation, cold intolerance, weight gain, hoarse voice, pale and dry skin, brittle fingernails and hair, a puffy face, an elevated blood cholesterol level, muscle aches, tenderness, stiffness and weakness, pain, stiffness of swelling in the joints, heavier than normal menstrual periods, and depression. Hypothyroidism in infants and teenagers may result in poor growth and mental development as well as delayed development of permanent teeth and puberty [7]. Diagnosis of categories of hypothyroidism is based on an appropriate laboratory evaluation. TSH assays is preferred as the primary test to establish the diagnosis of primary hypothyroidism whereas free thyroxine (fT4) or total thyroxine are more important measures for the diagnosis of secondary or tertiary hypothyroidism. In addition to these tests, thyroid peroxidase (TPO) antibodies (TPOAbs), thyroglobulin antibodies, thyroid scans, and ultrasonography may be included to diagnosis the cause of hypothyroidism. In primary abnormality of thyroid function, serum TSH is elevated with normal serum fT4. Autoimmune thyroid disease is detected mostly by measuring circulating antibodies against TPO. Autoimmune process gradually reduces the thyroid function, and there is a compensation phase when the normal thyroid hormone levels are maintained

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by a rise in TSH levels. Subclinical hypothyroidism is defined as thyroid hormone deficiency with fewer or no apparent clinical features of hypothyroidism in patients and is characterized biochemically by elevation of TSH levels with normal fT4 concentrations [7]. Later, fT4 levels fall and TSH levels rise further; symptoms become more readily apparent at this stage with TSH levels >10 mIU/L and is described as clinical hypothyroidism or overt hypothyroidism. Once clinical or subclinical hypothyroidism is known, further diagnosis is confirmed by evaluating the presence of TPO antibodies, which are present in >90% of patients with autoimmune hypothyroidism [5].

In the management of hypothyroidism, the firm form of hormone replacement therapy was the natural thyroid preparations i.e. thyroid extract, desiccated thyroid, or thyroglobulin, which contained both T3 and T4 [6]. Two major findings in hormone replacement therapy improvised towards a more appropriate approach in 1970s [9]. The discovery of peripheral deiodinase-mediated T4 to T3 provided a physiologic justification for L-thyroxine (LT4) monotherapy in treating hypothyroidism [10]. However, 10-15% of the L-thyroxine monotherapy treated hypothyroidism patients did not get the normal levels of T3 in serum and may lead to neurocognitive impairment in the patients as a consequence [8, 11]. Recently, recipients of both T3 and LT4 patients showed more clinical beneficial than LT4 monotherapy recipients patients in some studies [12, 13]. Excessive thyroid hormone replacement carries the potential for serious long-term metabolic complications (e.g. accelerated osteoporosis, drug intolerance, hypersensitivity) [14, 15]. Although modern drugs are quite effective in getting TSH level down, it is subject to sustaining certain side effects. Hence, the primary aim should be to utilize the available resources around us, which are cost-effective and environment-friendly. As a result, an attempt of alternative approach to LT4 in the treatment of hypothyroidism is needed and one such approach is Ayurveda treatment modality to manage hypothyroidism.

There are no direct references in Ayurvedic classical texts in terms of hypothyroidism. However, the physiological and biochemical functions of the thyroid hormone can be compared with the term "Agni" (digestive power maintaining body metabolism) [6]. According to principles of Ayurvedic pathogenesis, the main factor responsible is hypofunctioning of Agni (Agnimandya). Agnimandya of Dhatus (element tissues of the body) also occurs in pathogenesis of the disease and all these features are similar to the decreased basal metabolic rate [7]. In authentic textbook of Ayurveda i.e. Charaka Samhita and Sushruta Samhita, a disease called Galaganda and Gandmala are mentioned as a solitary swelling in the neck among 20 varieties of Kaphaja diseases and encapsulated swelling in the anterior angle of the neck, respectively [16, 17]. It can be correlated to goiter or tumor where thyroid functions may or may not be affected [6]. Galaganda is due to vitiation of the Kapha dosha mainly along with Vata and Medas [7]. Vata-Kapha increment and decreased Agni reveal various symptoms which are manifested in hypothyroidism. The Vata symptoms like fatigue, loss of energy, cold intolerance, dry skin, hair loss, muscle pain, joint pain, weakness in the extremities, mental impairment, forgetfulness, impaired memory, inability to concentrate, blurred vision, decreased hearing, constipation, menstrual disturbances, impaired fertility, decreased perspiration whereas the Kapha symptoms like lethargy, sleepiness, weight gain, decreased appetite, cold intolerance, fullness in the throat, hoarseness etc. are similar to symptoms of hypothyroidism [18]. In other words, the clinical manifestation of hypothyroidism can be related to symptoms of Kaphaavrata Samana Vata, a condition where movement and functioning of Samana Vata is obstructed by Kapha causing metabolic derangements in the form of Agnisada (diminished digestive fire) [7]. Hence, selection of drugs for management of hypothyroidism in Ayurveda is mainly based on herbs that pacifies Vata-Kapha Dosha and increases Agni. In Ayurvedic perspective, these are Deepana (digestive) herbs which increase metabolism and Pachana herbs which clear the Ama (toxic buildup in the body). Sunthi (*Zingiber officinale*), Maricha (*Piper nigrum*), Pippali (*Piper longum*), Guduchi (*Tinospora cordifolia)* and Abhrak Bhasma (calcined mica purified ash), which have pacifying Kapha-Vata Dosha and Agni-Deepana property, have proven effective on scientific grounds can be used to manage hypothyroidism [19-26].

Some animal model studies revealed that *Zingiber officinale* has a beneficial effect in hypothyroidism [27-29] and restored thyroid health in hypothyroidism [30]. Piperine is the main alkaloid found in the fruit *Piper nigrum*. Chavarria *et al*. showed that piperine enhances the bioavailability of several drugs and nutraceuticals and possesses anti-inflammatory activity. Although there is no evidence for the effects of piperine in humans, studies conducted in rodents point to a thyroid-disrupting effect of pepper and isolated piperine [31]. A water extract of *Piper nigrum* induced a reduction in serum T3 and T4 levels after 15 days of treatment. An ethanolic extract of *Piper nigrum* had the opposite effect and induced an elevation in thyroid hormone levels [32]. Another study found suppressed hepatic D1 activity in the groups receiving high or low doses of piperine, with the former showing reduced serum T3 and T4 levels and the latter only showing reduced serum T3 levels [33]. This suggested that piperine has a direct suppressive effect on the thyroid at higher doses, but at lower doses, it directly inhibits the peripheral metabolism of thyroid hormones mediated by the D1 in the liver. *Piper longum* increases the absorption of selenium, whose deficiency can impair thyroid function because conversion of T4 into T3 is catalysed by specific selenoproteins [34]. *Tinospora cordifolia* is an immunomodulatory drug which may be proved beneficial in autoimmune hypothyroidism [35, 36]. Abhrak Bhasma is also regarded as an immunomodulatory drug and can be used in treating autoimmune hypothyroidism [37-39].

So, we aim to evaluate and compare the efficacy of Ayurvedic herbo formulation consisting of Sunthi, Maricha, Pippali and Guduchi and Ayurvedic herbo-mineral formulation consisting of Sunthi, Maricha, Pippali, Guduchi and Abhrak Bhasma in patients with hypothyroidism in Nepalese population.

**MATERIALS AND METHODS**

This clinical trial is a double-blind, randomized, and controlled trial to evaluate the clinical efficacy of AHMF compared with that of the AHF and to justify for a large-scale multicenter clinical trial for hypothyroidism patients in the future. The study was conducted at National Ayurveda Research and Training Center (NARTC), Kirtipur, Nepal. Patients with hypothyroidism underwent a standardized baseline evaluation before treatment including detailed history taking, physical examination and laboratory testing. Included participants were randomly divided into two groups, an AHMF group and the other that received AHF group. The efficacy of AHMF group was assessed after 4 weeks' treatment.

**Diagnosis criteria**

The diagnostic criteria for hypothryoidism was based on the criteria set by the American Association of Clinical Endocrinologists and the American Thyroid Association in 2012 [40].

**Inclusion criteria**

The inclusion and exclusion criteria were adopted from the study by Bai l *et al*. [41].

1. Diagnosis based on persistently elevated TSH levels (> 4.6 mU/L), irrespective of fT4 range.
2. Age of minimum of 18 years to a maximum of 70 years.
3. Capability of complete compliance and completion of follow-up.
4. Willingness to provide written informed consent.

**Exclusion criteria**

1. Current prescription of levothyroxine, antithyroid drugs, amiodarone, or lithium.
2. Recent thyroid surgery or radioiodine therapy within 1-year of the study's start date.
3. History or presence of clinically relevant cardiovascular, renal, metabolic, hematological, neurological, psychiatric, systemic, or infectious disease or malignant tumor.
4. Severe mental disorder.
5. Recent hospitalization for major illness or elective surgery within 1-year of the study's start date.
6. Pregnancy or lactation, intention to become pregnant, and/or not using appropriate contraceptive methods.
7. Allergy to components of the agents used in the study.
8. Terminal illness.
9. History of alcoholism or substance abuse.
10. Recent participation in other clinical trials.

**MATERIALS**

The ingredients of the herbo-mineral formulation are stems of guduchi (*Tinospora cordifolia*), rhizomes of sunthi (*Zingiber officinale*), fruits of maricha (*Piper nigrum)* and fruits of pippali (*Piper longum)* and Abhrak Bhasma (Calcined Mica purified ash).

Initially, available samples of the ingredients was collected from local markets. The five samples was further selected from organoleptic observation and physico-chemical parameters and microbial limits was tested at NARTC. Those samples detected with higher level of physical parameters or any microbial parameters was excluded. The final sample was selected based on merely free of microbial contamination and was processed for manufacture of the medicines. A total of selected 10 part stem of guduchi, 1/3 part rhizomes of sunthi, 1/3 part fruit of marich and 1/3 part fruit of pippali were carefully washed with sterile water, dried under the sunlight with a transparent sterile cover and stored in the well closed cellophane bags separately. In context of Abhrak bhasma, it was selected on the basis of meeting standard and Ayurveda parameters and its toxicity study suggesting non-toxic effect when taken orally.

**Preparation of the medicine**

Trikatu Churna (sunthi, maricha and pippali each in equal proportions) was prepared in laboratory using method described in Ayurvedic Formulary. All the ingredients mixed together in equal proportion were finely powdered by automatic herbs grinder available in NARTC's laboratory. The dried Trikatu powdered was stored into a sterilized container and labeled with an expiration date. For the preparation of the herbo-mineral formulation, 10 part of guduchi stems was cut into small parts and kept in 4 times its volume of water for few hours to prepare the decoction. After few hours, the decoction was filtered and again heated on flame to get the pure guduchi extract. When the extract was thickened and reached a gel like consistency, the equal amount of Trikatu Churna previously prepared was added and mixed thoroughly. Here, we had estimated that 1 part of guduchi extract will be obtained from 10 part of guduchi stem. Then, 1/4 part of Abhrak bhasma was mixed into the above prepared medicine and grinded in the mortar and pestle steadily until Abhrak Bhasma was homogenously mixed.

The medicines was rolled in palms to make the pill of 375 mg in weight. The pills was dried under direct sunlight for few days until there was no moisture left in it. According to Ayurveda Bhavaprakash, minimum dosages of guduchi extract and trikatu churna are 500 mg and 1 gm/day in adult are recommended. Similarly, according to Rasa Ratna Samuchahya, standard dosage of abhrak bhasma is 250 mg/day. Each pills of Ayurvedic herbo-mineral medicine weighs 375 mg and consists of: aqueous extract of guduchi (*Tinospora cordifolia*): 166.67 mg, Abhrak Bhasma (Calcined Mica ash/Mica nanoparticles): 41.67 mg, powdered form of sunthi (*Zingiber officinale*) rhizome: 55.56 mg, powdered form of pippali (*Piper longum*) fruit: 55.56 mg and powdered form of marich (*Piper nigrum*) fruit: 55.56 mg.

For the control group, the above mentioned preparation was the same without mixing Abhrak Bhasma. Each pills of Ayurvedic herbo-mineral medicine weighs 375 mg and consists of: aqueous extract of guduchi (*Tinospora cordifolia*): 187.5 mg, powdered form of sunthi (*Zingiber officinale*) rhizome: 62.5 mg, powdered form of pippali (*Piper longum*) fruit: 62.5 mg and powdered form of marich (*Piper nigrum*) fruit: 62.5 mg. The preparation of the medicine was conducted under instruction and supervision of specialists.

All investigators were Ayurveda consultants and received standardized training for the diagnostic interview before the start of the research. Two clinicians diagnosed the hypothyroidism. Participants in the intervention group took Ayurvedic herbo-mineral formulation orally thrice a day for 4 weeks, whereas participants in the control group took polyherbal formulation orally thrice a day for 4 weeks. Patients visited at 0, 2 and 4 weeks.

**Outcome Measures**

**Primary outcomes**

The primary outcome was the change in TSH from baseline to week 4. Biochemical measurements of TSH levels were performed in the laboratory of each center at 2 weeks' interval.

**Secondary outcomes**

The change in BGL, LFT, RFT and lipid profile (total cholesterol, triglyceride, high-density lipoprotein and low-density lipidprotein) were secondary outcomes.

**Statistics**

This study is a trial of a new therapeutic regimen of Ayurvedic polyherbal formulation and Ayurvedic herbo-mineral formulation. So, we aim to analyze in small sample size recruiting 25 participants in each groups. Statistical Package for the Social Sciences (SPSS) version 17.0 (SPSS, Inc., Chicago, IL) software was used for data analysis. Continuous data with normal distribution was presented as mean (standard deviation), and those without normal distribution as median (interquartile range). Differences between groups were evaluated using the $\chi^2$ test or Fisher's exact test and paired or unpaired *t*-test. All statistical tests were 2-sided tests, and *p*-value of < .05 was considered statistically significant.

The trial was approved by the Ethics Committee of NARTC. After the clinicians provided a complete explanation to the participants, written informed consent was obtained from the participants before treatment intervention.

**RESULTS**

Out of 50 participants, 9 (18%) and 41 (82%) participants were male and female, respectively. Among the participants, 47 (94%) participants were married whereas only 3 (6%) participants were unmarried. According to ethnicity categorization, more participants belonged to indigenous ethnicity (32%) followed by Chhetri (22%), Madhesi (20%), Brahman (18%) and others (8%). Participants with graduate and above (42%) were more predominant than other education category. In context of occupation, 40% of the participants were houseworkers, 36% were private employees and 24% were businesspersons. The frequency of participants with current physical activity is slightly higher than frequency of participants with no physical activity (54% vs. 46%). In the study participants, non-alcohol consumers (76%), non-tobacco users (92%) and vegetarians (60%) were more frequent than alcohol consumers (24%), tobacco users (8%) and non-vegetarians (40%), respectively (Table 1). When compared between AHF and AHMF groups, no significant differences were observed except for meat consumers variable 76% vs. 4% in AHF and AHMF group, respectively (Table 1).

**Table 1:** Demographic and lifestyle characteristics of the patients in AHF and AHMF group

| Demographic and lifestyle characteristics | AHF group n (%) | AHMF group n (%) | Total patients n |
|---|---|---|---|
| **Sex** | | | |
| Male | 6 (24) | 3 (12) | 9 |
| Female | 19 (76) | 22 (88) | 41 |
| **Marital Status** | | | |
| Married | 24 (96) | 23 (92) | 47 |
| Unmarried | 1 (4) | 2 (8) | 3 |
| **Ethnicity** | | | |
| Brahman | 5 (20) | 4 (16) | 9 |
| Chhetri | 4 (16) | 7 (28) | 11 |
| Indigenous | 9 (36) | 7 (28) | 16 |
| Madhesi | 6 (24) | 4 (16) | 10 |
| Others | 1 (4) | 3 (12) | 4 |
| **Education** | | | |
| Primary | 1 (4) | 5 (20) | 6 |
| Lower secondary | 4 (16) | 3 (12) | 7 |
| Higher secondary | 7 (28) | 3 (12) | 10 |
| Graduate and above | 13 (52) | 8 (32) | 21 |
| None | 0 (0) | 6 (24) | 6 |
| **Occupation** | | | |
| House work | 8 (32) | 12 (48) | 20 |
| Business | 7 (28) | 5 (20) | 12 |
| Private employee | 10 (40) | 8 (32) | 18 |
| **Exercise** | | | |
| Current physical activity | 13 (52) | 14 (56) | 27 |
| No physical activity | 12 (48) | 11 (44) | 23 |

| | | | |
|---|---|---|---|
| **Alcohol** | | | |
| Alcohol consumers | 4 (16) | 8 (32) | 12 |
| Non-alcohol consumers | 21 (84) | 17 (68) | 38 |
| **Tobacco** | | | |
| Tobacco users | 2 (8) | 2 (8) | 4 |
| Non tobacco users | 23 (92) | 23 (92) | 46 |
| **Meat** | | | |
| Non-vegetarian | 19 (76) | 1 (4) | 20 |
| Vegetarian | 6 (24) | 24 (96) | 30 |

Table 2 shows the comparison of baseline symptoms between AHF group and AHMF group. There was no significant differences between the symptoms except for hoarseness of voice ($p$ = 0.004).

**Table 2:** Baseline frequency of symptoms between AHF and AHMF group

| Symptoms | AHF group n (%) | AHMF group n (%) | $p$ – value[a] |
|---|---|---|---|
| **Cold intolerance** | 9 (36) | 11 (44) | 0.56 |
| **Hoarseness of Voice** | 0 (0) | 7 (28) | 0.01[b] |
| **Fatigue** | 18 (72) | 19 (76) | 0.75 |
| **Dryness of skin** | 9 (36) | 10 (40) | 0.77 |
| **Weight gain** | 11 (44) | 11 (44) | 1.00 |
| **Constipation** | 8 (32) | 7 (28) | 0.76 |
| **Others** | 7 (28) | 11 ( 44) | 0.24 |

[a]Analyzed by chi-square test.

[b]Analyzed by Fisher's exact test.

The baseline characteristics of the study participants between AHF group and AHMF group are shown in Table 3. There were no significant differences in other variables except for age, waist circumference, hip circumference, bilirubin direct and alkaline phosphatase. The mean age of AHF group and AHMF group were 41.5 (9.1) years and 48.8 (10.2) years, respectively. AHF group tends to have more waist and hip circumferences than AHMF group. Although, mean values of bilirubin direct and alkaline phosphatase were more in AHF group than AHMF group, the laboratory values of the variables were within the normal range.

**Table 3:** Baseline characteristics differences between AHF and AHMF group

| Variables | AHF group (n = 25)[a] | AHMF group (n = 25)[a] | $p$ – value[b] |
|---|---|---|---|
| **Age (years)** | 41.5 (9.1) | 48.8 (10.2) | 0.01 |
| **Body weight (kg)** | 70.7 (10.3) | 70.4 (13.1) | 0.93 |
| **Body height (m)** | 1.55 (0.06) | 1.56 (0.08) | 0.62 |
| **Body mass index (kg/m$^2$)** | 29.4 (4.3) | 28.8 (4.6) | 0.64 |
| **Waist circumference (cm)** | 101.0 (6.6) | 95.4 (9.5) | 0.02 |
| **Hip circumference (cm)** | 106.2 (7.3) | 100.9 (7.8) | 0.02 |
| **Waist-hip ratio** | 0.95 ( 0.06) | 0.93 (0.07) | 0.28 |
| **Systolic blood pressure (mm Hg)** | 124.8 (14.8) | 127.9 (13.9) | 0.45 |
| **Diastolic blood pressure (mm Hg)** | 83.4 (7.9) | 85.0 (10.4) | 0.54 |
| **TSH (uIU/mL)** | 5.6 (1.1) | 6.3 (2.6) | 0.22 |
| **T3 (pmol/L)** | 4.2 (0.7) | 4.5 (0.5) | 0.09 |
| **T4 (pmol/L)** | 14.4 (2.3) | 14.9 (2.2) | 0.44 |
| **RBS mg/dL)** | 97.0 (20.4) | 101.8 (21.2) | 0.42 |
| **Blood urea ( mg/dL)** | 27.9 (4.4) | 25.7 (5.8) | 0.14 |
| **Serum creatinine (mg/dL)** | 0.8 (0.3) | 0.7 (0.2) | 0.17 |
| **Bilirubin Total ( mg/dL)** | 0.8 (0.3) | 0.8 (0.2) | 1.00 |
| **Bilirubin Direct ( mg/dL)** | 0.2 (0.2) | 0.1 (0.0) | 0.02 |
| **AST (IU/L)** | 27.7 (6.5) | 25.0 (6.5) | 0.12 |

| | | | |
|---|---|---|---|
| **ALT (IU/L)** | 26.9 (4.3) | 27.1 (5.0) | 0.88 |
| **Alkaline Phosphatase (IU/L)** | 114.2 (33.7) | 86.2 ( 22.0) | 0.001 |
| **Total cholesterol (mg/dL)** | 153.6 (43.5) | 174.2 (40.2) | 0.09 |
| **HDL cholesterol (mg/dL)** | 51.8 (12.9) | 47.6 (11.2) | 0.23 |
| **LDL cholesterol (mg/dL)** | 78.2 (29.7) | 86.9 (21.1) | 0.29 |
| **Triglycerides (mg/dL)** | 124.9 (59.4) | 139.0 (56.3) | 0.39 |

[a]Variables are expressed as mean (standard deviation).

[b]Analyzed by unpaired *t*-test.

There was no statistically differences in symptoms before and after intervention of AHF in AHF group (Table 4).

**Table 4:** Comparison of symptoms before and after intervention in AHF group

| Symptoms | Before intervention n (%) | After intervention n (%) | *p* – value[a] |
|---|---|---|---|
| **Cold intolerance** | 9 (36) | 7 (28) | 0.54 |
| **Fatigue** | 18 (72) | 12 (48) | 0.08 |
| **Dryness of skin** | 9 (36) | 6 (24) | 0.35 |
| **Weight gain** | 11 (44) | 10 (40) | 0.77 |
| **Constipation** | 8 (32) | 6 (24) | 0.53 |
| **Others** | 7 (28) | 7 (28) | 1.00 |

[a]Analyzed by chi-square test.

There was a slightly statistically significant decrease in waist-hip ratio ($p$ = 0.04), diastolic blood pressure ($p$ = 0.04) and alkaline phosphatase ($p$ = 0.02) when before and after intervention of AHF were compared (Table 5). Similarly, when TSH levels were compared before and after intervention, there was a significant decrease of 12.5% in TSH levels ($p$ = 0.00) after intervention of AHF (Table 5). Unlikely, T3 levels showed a significant increase of 14.3% ($p$ = 0.00) after intervention of AHF (Table 5).

**Table 5:** Comparison of variables before and after intervention in AHF group

| Variables | Before intervention (n = 25)[a] | After intervention (n = 25)[a] | *p* – value[b] |
|---|---|---|---|
| **Body weight (kg)** | 70.7 (10.3) | 70.2 (9.9) | 0.05 |
| **Body mass index (kg/m$^2$)** | 29.4 (4.3) | 29.2 (4.3) | 0.05 |
| **Waist circumference (cm)** | 101.0 (6.6) | 100.2 (6.2) | 0.16 |
| **Waist-hip ratio** | 0.95 ( 0.06) | 0.93 (0.05) | 0.04 |
| **Systolic blood pressure (mm Hg)** | 124.8 (14.8) | 123.2 (13.3) | 0.42 |
| **Diastolic blood pressure (mm Hg)** | 83.4 (7.9) | 81.4 (8.6) | 0.04 |
| **TSH (uIU/mL)** | 5.6 (1.1) | 4.9 (1.0) | 0.00 |
| **T3 (pmol/L)** | 4.2 (0.7) | 4.8 (0.7) | 0.00 |
| **T4 (pmol/L)** | 14.4 (2.3) | 14.2 (2.6) | 0.70 |
| **RBS mg/dL)** | 97.0 (20.4) | 96.9 (18.6) | 0.96 |
| **Blood urea ( mg/dL)** | 27.9 (4.4) | 26.1 (6.0) | 0.09 |
| **Serum creatinine (mg/dL)** | 0.8 (0.3) | 0.7 (0.2) | 0.70 |
| **Bilirubin Total ( mg/dL)** | 0.76 (0.26) | 0.76 (0.17) | 0.05 |
| **Bilirubin Direct ( mg/dL)** | 0.18 (0.16) | 0.13 (0.06) | 0.19 |
| **AST (IU/L)** | 27.7 (6.5) | 27.6 (6.4) | 0.94 |
| **ALT (IU/L)** | 26.9 (4.3) | 27.3 (3.6) | 0.56 |
| **Alkaline Phosphatase (IU/L)** | 114.2 (33.7) | 101.0 ( 25.2) | 0.02 |
| **Total cholesterol (mg/dL)** | 153.6 (43.5) | 154.9 (37.6) | 0.84 |
| **HDL cholesterol (mg/dL)** | 51.8 (12.9) | 53.3 (13.6) | 0.58 |
| **LDL cholesterol (mg/dL)** | 78.2 (29.7) | 79.7 (23.5) | 0.66 |
| **Triglycerides (mg/dL)** | 124.9 (59.4) | 129.7 (50.0) | 0.50 |

[a]Variables are expressed as mean (standard deviation).

[b]Analyzed by paired *t*-test.

Table 6 showed no significant differences in symptoms before and after intervention in AHMF group.

**Table 6:** Comparison of symptoms before and after intervention in AHMF group

| Symptoms | Before intervention n (%) | After intervention n (%) | *p* – value[a] |
|---|---|---|---|
| **Cold intolerance** | 11 (44) | 7 (28) | 0.24 |
| **Hoarseness of Voice** | 7 (28) | 6 (24) | 0.75 |
| **Fatigue** | 19 (76) | 16 (64) | 0.35 |
| **Dryness of skin** | 10 (40) | 6 (24) | 0.23 |
| **Weight gain** | 11 (44) | 8 (32) | 0.38 |
| **Constipation** | 7 (28) | 4 (16) | 0.31 |
| **Others** | 11 ( 44) | 8 (32) | 0.38 |

[a]Analyzed by chi-square test.

Among the variables, statistically significant decrease was only observed in waist-hip ratio ($p$ = 0.04) and TSH ($p$ = 0.001) before and after intervention of AHMF (Table 7). There is a decrease of 2.1% and 7.9% in waist-hip ratio and TSH level after intervention of AHMF, respectively.

**Table 7:** Comparison of variables before and after intervention in AHMF group

| Variables | Before intervention (n = 25)[a] | After intervention (n = 25)[a] | *p* – value[b] |
|---|---|---|---|
| **Body weight (kg)** | 70.4 (13.1) | 70.3 (12.7) | 0.67 |
| **Body mass index (kg/m$^2$)** | 28.8 (4.6) | 29.2 (5.1) | 0.26 |
| **Waist circumference (cm)** | 95.4 (9.5) | 94.8 (8.1) | 0.26 |
| **Hip circumference (cm)** | 100.9 (7.8) | 101.8 (6.8) | 0.27 |
| **Waist-hip ratio** | 0.95 (0.08) | 0.93 (0.07) | 0.04 |
| **Systolic blood pressure (mm Hg)** | 127.9 (13.9) | 128.4 (12.0) | 0.72 |
| **Diastolic blood pressure (mm Hg)** | 85.0 (10.4) | 86.5 (9.8) | 0.24 |
| **TSH (uIU/mL)** | 6.3 (2.6) | 5.8 (2.5) | 0.001 |
| **T3 (pmol/L)** | 4.5 (0.5) | 4.6 (0.6) | 0.21 |
| **T4 (pmol/L)** | 14.9 (2.2) | 14.6 (1.7) | 0.29 |
| **RBS mg/dL)** | 101.8 (21.2) | 104.1 (21.3) | 0.28 |
| **Blood urea ( mg/dL)** | 25.7 (5.8) | 24.3 (5.1) | 0.34 |
| **Serum creatinine (mg/dL)** | 0.7 (0.2) | 0.7 (0.1) | 0.88 |
| **Bilirubin Total ( mg/dL)** | 0.8 (0.2) | 0.8 (0.2) | 0.71 |
| **Bilirubin Direct ( mg/dL)** | 0.1 (0.0) | 0.1 (0.0) | 0.19 |
| **AST (IU/L)** | 25.0 (6.5) | 25.2 (5.7) | 0.91 |
| **ALT (IU/L)** | 27.1 (5.0) | 28.4 (5.7) | 0.43 |
| **Alkaline Phosphatase (IU/L)** | 86.2 ( 22.0) | 98.4 ( 34.7) | 0.07 |
| **Total cholesterol (mg/dL)** | 174.2 (40.2) | 178.5 (37.6) | 0.49 |
| **HDL cholesterol (mg/dL)** | 47.6 (11.2) | 50.1 (12.3) | 0.37 |
| **LDL cholesterol (mg/dL)** | 86.9 (27.4) | 81.5 (18.2) | 0.20 |
| **Triglycerides (mg/dL)** | 139.0 (56.3) | 134.9 (47.7) | 0.57 |

[a]Variables are expressed as mean (standard deviation).

[b]Analyzed by paired *t*-test.

Symptoms between AHF and AHMF group after intervention are compared in Table 8 and only hoarseness of voice showed a statistical significant difference between AHF and AHMF group.

**Table 8:** Comparison of symptoms between AHF and AHMF groups after intervention

| Symptoms | AHF group n (%) | AHMF group n(%) | *p* – value[a] |
|---|---|---|---|
| **Cold intolerance** | 7 (28) | 7 (28) | 1.00 |
| **Hoarseness of Voice** | 0 (0) | 6 (24) | 0.02** |
| **Fatigue** | 12 (48) | 16 (64) | 0.25 |
| **Dryness of skin** | 6 (24) | 6 (24) | 1.00 |
| **Weight gain** | 10 (40) | 8 (32) | 0.56 |
| **Constipation** | 6 (24) | 4 (16) | 0.48 |
| **Others** | 7 (28) | 9 (36) | 0.76 |

[a]Analyzed by chi-square test.

[b]Analyzed by Fisher's exact test.

Table 9 shows the comparison of variables between AMF and AHMF groups after intervention. There was no statistical significant difference in variables except for waist circumference ((*p* = 0.01) and hip circumference (*p* = 0.03) between AMF and AHMF group (Table 9).

**Table 9:** Comparison of variables between AMF and AHMF groups after intervention

| Variables | AHF group (n = 25)[a] | AHMF group (n = 25)[a] | *p* – value[b] |
|---|---|---|---|
| **Body weight (kg)** | 70.2 (9.9) | 70.3 (12.7) | 0.98 |
| **Body mass index (kg/m²)** | 29.2 (4.3) | 29.2 (5.1) | 1.00 |
| **Waist circumference (cm)** | 100.2 (6.2) | 94.8 (8.1) | 0.01 |
| **Hip circumference (cm)** | 106.2 (7.3) | 101.8 (6.8) | 0.03 |
| **Waist-hip ratio** | 0.93 (0.05) | 0.93 (0.07) | 1.00 |
| **Systolic blood pressure (mm Hg)** | 123.2 (13.3) | 128.4 (12.0) | 0.15 |
| **Diastolic blood pressure (mm Hg)** | 81.4 (8.6) | 86.5 (9.8) | 0.06 |
| **TSH (uIU/mL)** | 4.9 (1.0) | 5.8 (2.5) | 0.10 |
| **T3 (pmol/L)** | 4.8 (0.7) | 4.6 (0.6) | 0.28 |
| **T4 (pmol/L)** | 14.2 (2.6) | 14.6 (1.7) | 0.52 |
| **RBS mg/dL)** | 96.9 (18.6) | 104.1 (21.3) | 0.21 |
| **Blood urea ( mg/dL)** | 26.1 (6.0) | 24.3 (5.1) | 0.26 |
| **Serum creatinine (mg/dL)** | 0.7 (0.2) | 0.7 (0.1) | 1.00 |
| **Bilirubin Total ( mg/dL)** | 0.76 (0.17) | 0.80 (0.19) | 0.44 |
| **Bilirubin Direct ( mg/dL)** | 0.13 (0.06) | 0.11 (0.04) | 0.17 |
| **AST (IU/L)** | 27.6 (6.4) | 25.2 (5.7) | 0.17 |
| **ALT (IU/L)** | 27.3 (3.6) | 28.4 (5.7) | 0.42 |
| **Alkaline Phosphatase (IU/L)** | 101.0 ( 25.2) | 98.4 ( 34.7) | 0.76 |
| **Total cholesterol (mg/dL)** | 154.9 (37.6) | 178.5 (37.6) | 0.03 |
| **HDL cholesterol (mg/dL)** | 53.3 (13.6) | 50.1 (12.3) | 0.39 |
| **LDL cholesterol (mg/dL)** | 79.7 (23.5) | 81.5 (18.2) | 0.76 |
| **Triglycerides (mg/dL)** | 129.7 (50.0) | 134.9 (47.7) | 0.71 |

[a]Variables are expressed as mean (standard deviation).

[b]Analyzed by unpaired *t*-test.

## DISCUSSION

In the present study, most of the study participants were female, non-alcohol consumers and non-tobacco users. The present study showed that there is a statistically significant decrease of 12.5% and 7.9% in TSH levels after intervention of AHF and AHMF, respectively. There was also a small statistically significant decrease in waist-hip ratio after intervention in AHF and AHMF group.

A significantly higher proportion of females than male in the present study is consistent with the previous studies [1-4, 8]. The mean age of the study participants was similar to the study by Unnikrishan A.G et.al (45.1 ± 10.3 and 46 ± 14.7 years) [1]. The higher proportion of non-alcohol consumers and non-tobacco users may be probably associated with the higher proportion of female in our study as in Nepalese population female tends to consume less alcohol and tobacco.

The common symptoms presented in the study participants were fatigue (74%), weight gain (44%), cold intolerance (40%), dryness of skin (38%), constipation (30%) and hoarseness of voice (14%). The other symptoms puffiness of the face and eyelids, peripheral oedema, breathlessness, weakness, lethargy, muscle ache, hair loss and irregular menstrual cycle (only in pre-menopausal women) were also presented at the time of recruitment but in relatively less participants (data not shown). The common symptoms were also presented in another study by Singh K *et al*., [42].

The study participants had higher BMI (29.1 ± 4.4) and WHR (0.94 ± 0.07). Hence, our study also suggested the association between obesity and hypothyroidism like the previous studies [43-46].

There was a significant reduction of 12.5% after intervention of AHF for 4 weeks. The ingredients used in AHF intervention Each pills of Ayurvedic herbo-mineral medicine consists of aqueous extract of guduchi (*Tinospora cordifolia*), powdered form of sunthi (*Zingiber officinale*) rhizome, powdered form of pippali (*Piper longum*) fruit and powdered form of marich (*Piper nigrum*) fruit. To our knowledge, this is the first study to evaluate the efficacy of AHF in hypothyroidism. However, the ingredients of sunthi, marich and pippali were found to be common in other study evaluating ayurvedic medicines in the management of hypothyroidism [47]. Similarly, there was a significant decrease of 7.9% after intervention of AHMF for weeks. The ingredients used were similar to AHF except for addition of abhrak bhasma. Abhrak Bhasma has the property of Granthivishahar [48] and we hypothesized the addition of Abhrak bhasma in polyherbal formulation may have more beneficial aspect in hypothyroidism than use of only polyherbal formulation. But, in our study there was no significant difference between AHF and AHMF intervention in management of hypothyroidism.

There are several limitations in our study, Although, the gold standard of clinical trial is double blinded, randomized, placebo controlled clinical trial, but we used Ayurvedic polyherbal formulation in control group. This might have not postulated the true efficacy of AHMF when compared with AHF. The reason behind this is the ethical committee did not approve the study to use placebo controlled, double blinded, randomized clinical trial. The sample size of the present study was limited and was not withdrawn through the methodology of sample size calculation. We did not categorize the study participants by gender. Hypothyroidism is more prevalent in female population and since the sample size is small the study participants were not adjusted for gender. We can also not elucidate the possible biological mechanism to explain the decreasing trend of TSH levels both in AHF and AHMF group after intervention. It may be due to chance finding as the sample size is small. The duration of the study period was limited for 4 weeks, thus, we could not predict the duration of intervention intake to normalize the TSH levels. The participants recruited as hypothyroidism was only based on increase TSH levels than its normal range and we did not further evaluate the categorization of hypothyroidism. We could not explain whether all the study participants belonged to sub-clinical hypothyroidism or clinical hypothyroidism.

To our knowledge, this is the first study to evaluate the efficacy of Ayurvedic herbal formulation and Ayurvedic herbo-mineral formulation in management of hypothyroidism in Nepalese population. Ayurvedic medicines could be a better alternative to better understanding and managing hypothyroidism, thereby reducing complications in the long run. Nonetheless,more randomized placebo controlled trials are required to confirm the efficacy of AHF and AHMF intervention in managing hypothyroidism.

## CONCLUSION

This study suggested that the use of Ayurvedic herbal formulation and Ayurvedic herbo-mineral formulation has beneficial aspect in managing hypothyroidism in context of Nepalese population. But, the present study did not show any beneficial effects in obesity. However, further studies are needed to confirm the beneficial effect of Ayurvedic herbal formulation and Ayurvedic herbo-mineral formulation in hypothyroidism.


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### Authors' contributions

Joshi AM and Yadav RA conceived and designed the study. Shrestha S and Joshi AM carried out literature search, interpretation of data and drafted the manuscript. Shrestha S, Shrestha J and Joshi AM participated in study design and edited the manuscript. All authors have seen and approved the final manuscript.

### Conflict of Interest

None declared.

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