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*ORIGINAL ARTICLE*

# Efficacy and Safety of Ashwagandha Root Extract in Subclinical Hypothyroid Patients: A Double-Blind, Randomized Placebo-Controlled Trial

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**Abstract**

***Background:*** Subclinical hypothyroidism, a thyroid disorder without obvious symptoms of thyroid deficiency, occurs in 3%–8% of the global population. Ashwagandha [*Withania somnifera (L.) Dunal]*, a traditional medicine in Ayurveda, is often prescribed for thyroid dysfunctions.

***Objective:*** This pilot study was designed to evaluate the efficacy and safety of ashwagandha root extract in subclinical hypothyroid patients.

***Design, Setting, and Participants:*** A prospective, randomized, double-blind, single-center placebo-controlled study was performed at Sudbhawana Hospital, Varanasi, India between May 2016 and September 2016. Fifty subjects with elevated serum thyroid stimulating hormone (TSH) levels (4.5–10 μIU/L) aged between 18 and 50 were randomized in either treatment ($n=25$) or placebo ($n=25$) groups for an 8-week treatment period.

***Interventions:*** Ashwagandha root extract (600 mg daily) or starch as placebo.

***Efficacy Variables:*** Serum TSH, serum triiodothyronine (T3), and thyroxine (T4) levels.

***Results:*** A total of four subjects (two from each group) withdrew their consent before the second visit. Eight weeks of treatment with ashwagandha improved serum TSH ($p<0.001$), T3 ($p=0.0031$), and T4 ($p=0.0096$) levels significantly compared to placebo. Ashwagandha treatment effectively normalized the serum thyroid indices during the 8-week treatment period in a significant manner (time-effects: TSH [$p<0.001$], T3 [$p<0.001$], and T4 [$p<0.001$]). Four subjects (8%) (ashwagandha: 1[4%]; Placebo: 3[12%]) out of 50 reported few mild and temporary adverse effects during this study.

***Conclusion:*** Treatment with ashwagandha may be beneficial for normalizing thyroid indices in subclinical hypothyroid patients.

**Keywords:** ashwagandha, *Withania somnifera (L.) Dunal,* subclinical hypothyroidism, efficacy, safety

## Introduction

SUBCLINICAL HYPOTHYROIDISM (SCH), alternatively termed mild thyroid failure, often arises due to its precursor Hashimoto's thyroiditis, a chronic autoimmune disorder. Elevated serum thyroid stimulating hormone (TSH) despite normal serum thyroxine (T4) levels typically suggests SCH.[1] SCH occurs in 3%–8% of the total population, affecting 6%–10% of females and 2.4%–3% of males.[2,3] The prevalence of SCH increases with aging and affects 10% of hexagenerians.[2] Clinical manifestation of SCH may or may not include symptoms of hypothyroidism and the disorder can typically be diagnosed through an amplified level of TSH (4.5–10 μIU/L), as well as presence of antithyroid antibody clusters, including microsomal antithyroperoxidase (TPO) and antithyroglobulin in the blood.[1,4] Presence of TPO may catalyze the progression of SCH to clinically overt hypothyroidism by 4.3% per year compared to 2.6% for TPO undiagnosed patients.[5] SCH may exacerbate other critical ailments like dyslipidemia, type 2 diabetes mellitus, aortic calcification, impaired vascular function, atherosclerosis, and myocardial and neuromuscular dysfunction.[1]

Physicians consider levothyroxine therapy as the only available treatment for SCH and recommend this therapy when TSH level exceeds 10.0 μIU/L.[6,7] However, the utility of levothyroxine treatment for patients diagnosed with TSH

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levels between 4.5 and 10 μIU/L remains controversial considering the overall risks versus benefits of the therapy.[8] A recently published Cochrane review concluded that thyroid hormone therapy for SCH has neither improved survival nor decreased cardiovascular morbidity, and the data on health-related quality of life and symptoms did not reveal any significant differences between placebo and treatment.[9]

Absence of reliable treatment options for SCH inspired scientists to investigate the field of complementary and alternative medicines for a better alternative. Ashwagandha *[Withania somnifera (L.) Dunal]* is recommended by traditional healers for various hormonal disorders, including thyroid imbalances and goiter. Ashwagandha acts as an adaptogen to stabilize the physiologic processes, promote homeostasis, and revitalize the body. Other scientific studies reported sedative hypnotic, anxiolytic, hypotensive, immunomodulatory, anti-inflammatory, and antioxidant activities of ashwagandha.[10] In addition, ashwagandha can potentially ameliorate hypothyroidism as this phytomedicine reduced serum thyroxine (T4) and triiodothyronine (T3) concentrations in experimental animals.[11,12] In a solitary randomized clinical trial conducted among persons with bipolar disorder, ashwagandha improved laboratory thyroid indices (TSH, T4, and T3) as an ancillary outcome.[13]

This prospective, randomized, double-blind, placebo-controlled clinical pilot study was aimed at evaluating the efficacy and safety of ashwagandha root extract in subclinical hypothyroid patients.

## Materials and Methods

### Study design and protocol

This 8-week single-center study was conducted in a prospective, randomized, double-blind, parallel-group, and placebo-controlled design between May and September 2016 at Sudbhawana Hospital, Varanasi, India. The protocol of the study was not altered during the study.

General health camps were conducted at the study center between May and July 2016, where ~150–175 patients participated. Ninety participants in these health camps were diagnosed with elevated TSH levels (4.5–10 μIU/L) with normal T3 and T4 levels. Fifty subjects were selected among the participants based on the following inclusion criteria: age between 18 and 50 years without significant medical history, ability to provide written informed consent and understand the risks and benefits of the protocol, serum TSH level between 4.5 and 10 μIU/L, and serum T3 and T4 levels within normal range.

Exclusion criteria included the following: history of smoking within past year; hypersensitivity to ashwagandha and related herbal products; under treatment with any thyroid medications, nutritional/energy supplements, hypotensives, beta-blockers, inhaled beta agonists, hormonal contraceptives, corticosteroids within prior 3 months or psychotropics within prior 8 weeks, or diagnosed with heart disease, diabetes, stroke, depression, or other neurologic/psychiatric disorders; psychiatric hospitalization within past year; or a body–mass index less than 30 $kg/m^2$.

At the screening visit, a brief medical history was acquired from each subject, and general physical and vital parameters, hematologic profiles, and body weight were recorded. Baseline serum TSH, T3, and T4 levels were evaluated. A qualified psychiatrist performed a clinical psychiatric examination on each subject to identify any psychiatric disorder that would warrant exclusion from the study. Study visits were scheduled at 4 and 8 weeks after the screening visit.

### Ethical consideration

The study was conducted as per the Declaration of Helsinki (1989) and Guidelines for Clinical Trials on Pharmaceutical Products in India—GCP Guidelines issued by the Central Drugs Standard Control Organization, Ministry of Health, Government of India. Institutional Review Board approval was obtained from the study center at Sudbhawana Hospital, Varanasi, India. The ethics committee approval number was ECR/667/Inst/UP/2014. Informed consent was obtained from each patient before study enrollment.

### Investigational products

The authors received the investigational product, KSM-66 Ashwagandha (a 100% aqueous extract of *Withania somnifera* roots, containing 5% withanolides as estimated by HPLC; Batch# KSM/16/568) as a gift sample from its manufacturer, Ixoreal Biomed, Los Angeles, California.

### Randomization and blinding

After screening, research coordinators randomized the eligible subjects through a computer-based predetermined randomization (SAS version 9.1.2) in a 1:1 ratio and assigned them to either the ashwagandha or placebo group. As a double-blind study, the randomization and group assignment process were concealed from doctors and subjects. Both the investigational product (ashwagandha) and placebo (starch as inner filler) were formulated as hard gelatin capsules and packed in identical and tamper-proof containers. The labels of the medication packs were coded to conceal their contents. Research coordinators, study investigators, and attending care personnel were prohibited from accessing the randomization codes and allocations.

### Interventions and efficacy variables

The treatment group received 300 mg of ashwagandha root extract in capsule form, twice daily with water for 8 weeks. The control group received an identical dose of placebo capsules. The efficacy variables, that is, serum TSH, T3, and T4 levels of the subjects, were evaluated at baseline and during subsequent visits (fourth and eighth week).

### Safety evaluation and adverse events

Physical, hematologic, and vital parameters of each subject were monitored at each visit. Physical parameters included detailed monitoring of the cardiovascular, respiratory, musculoskeletal, genitourinary, and nervous system of each subject, while hematologic parameters included assessment of hemoglobin, hematocrit, platelet count, RBC, and WBC count. Vital parameters like systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature were observed throughout the study period.

### Statistical analysis

Quantitative data are expressed as means with standard deviations; categorical and discrete data were expressed as numbers with percentages. Missing data were managed by

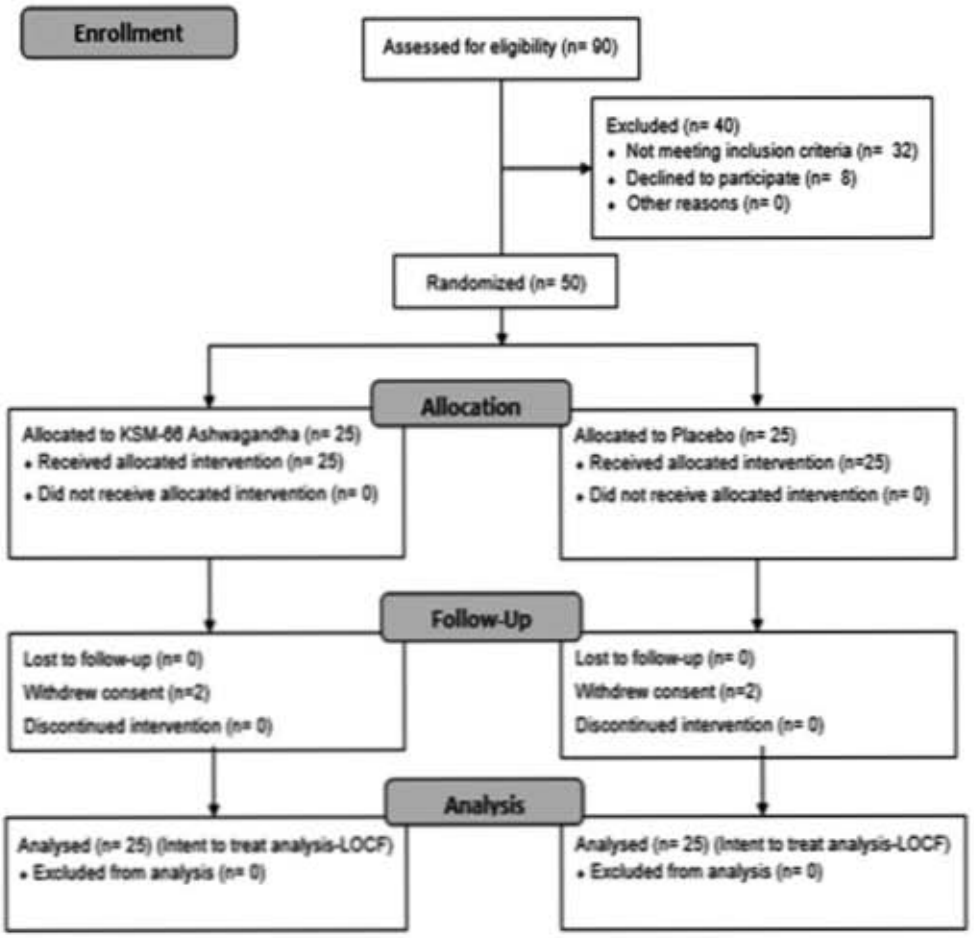


**FIG. 1.** CONSORT flow diagram: patient distribution and study design.

last observation carried forward (LOCF) method. All analyses were performed using SPSS 19.0. Changes in the efficacy variables over time were compared using one-way repeated-measures ANOVA followed by Bonferroni's *post hoc* test to assess within-group differences. The two groups were compared for between-group differences using an unpaired *t*-test at 95% CI. All testing was done using two-sided tests at alpha 0.05.

## Results

Between May and September 2016, 50 subjects were recruited and 25 each were randomized to the experimental and control arm, as evident in the CONSORT diagram (Fig. 1). Most of the recruited subjects [total, 27/50, 54%; treatment group, 13/25 (52%); control group, 14/25 (56%)] were males (Table 1). At baseline, demographic, physical, hematologic, and vital parameters were similar in both groups. Of the 50 participants, 4 (8%) subjects, 2 from each intervention and placebo group, withdrew their consent. The final per-protocol analysis included 46 participants out of 50 (92%), with 23 in each group.

Mean scores at baseline and 4 and 8 weeks for thyroid indices for both ITT (LOCF) and per protocol (PP) analysis are shown in Table 2. Data and outcome of both ITT (LOCF) and PP analysis were similar with minor differences. Hence, the authors have explained only ITT (LOCF) data in this section.

### *Serum T3 levels*

As per ITT (LOCF) analysis, a significant time effect was observed for the ashwagandha treatment group on serum $T_3$ levels ($F\ [2, 23] = 14.063$, $p < 0.001$, $\eta p^2 = 0.550$). The treatment with ashwagandha for 4 and 8 weeks resulted in significant increase in serum $T_3$ levels from baseline values by 18.6% ($p = 0.0121$) and 41.5% ($p < 0.0001$), respectively. Interestingly, in absence of a therapeutically active agent, serum $T_3$ levels in the placebo group significantly reduced over time ($F\ [2, 23] = 6.259$, $p = 0.007$, $\eta p^2 = 0.352$). Following a significant fall of −15.9% ($p = 0.0067$) at fourth week, serum T3 levels increased to register a −0.03% ($p = 0.7387$) change from baseline at eighth week.

TABLE 1. DEMOGRAPHIC CHARACTERISTICS

| | *Ashwagandha (n = 25) mean (SD)* | *Placebo (n = 25) mean (SD)* |
|---|---|---|
| Age (years) | 35.56 (7.95) | 35.08 (9.56) |
| Weight (kg.) | 67.52 (9.57) | 67.8 (7.71) |
| Height (cm) | 162.12 (8.85) | 163 (9.17) |
| Gender (%) | | |
| Male | 13 (52.00) | 14 (56.00) |
| Female | 12 (48.00) | 11 (44.00) |

SD, standard deviation.

TABLE 2. T3, T4, AND THYROID STIMULATING HORMONE LEVELS: MEAN VALUES AT THE END OF 4 AND 8 WEEKS

| Parameters | *Ashwagandha* | | *Placebo* | | *Difference between the groups* | | p-*values*[a] (*Ashwagandha vs. placebo*) |
|---|---|---|---|---|---|---|---|
| | *Mean (SD)* | *95% CI* | *Mean (SD)* | *95% CI* | *Mean* | *95% CI* | |
| T3: ITT (LOCF) (nmol/L) | | | | | | | |
| *n* | 25 | | 25 | | — | — | — |
| Visit 1 (baseline) | 1.18 (0.27) | 1.07–1.28 | 1.26 (0.30) | 1.15–1.38 | −0.09 | −0.24 to 0.07 | 0.2893 |
| Visit 2 (4 week) | 1.40 (0.32) | 1.27–1.53 | 1.06 (0.18) | 0.99–1.09 | 0.34 | 0.19–0.48 | <0.0001 |
| Visit 3 (8 week) | 1.67 (0.51) | 1.47–1.87 | 1.22 (0.50) | 1.00–1.42 | 0.45 | 0.17–5.41 | 0.0031 |
| *p*-values[b] (time effect) | <0.001 | | 0.007 | | — | | — |
| T3: PP (nmol/L) | | | | | | | |
| *n* | 23 | | 23 | | — | — | — |
| Visit 1 (baseline) | 1.19 (0.27) | 1.08–1.31 | 1.25 (0.28) | 1.13–1.37 | −0.06 | −0.23 to 0.10 | 0.4459 |
| Visit 2 (4 week) | 1.44 (0.31) | 1.30–1.56 | 1.04 (0.12) | 0.99–1.09 | 0.40 | 0.26–0.53 | <0.0001 |
| Visit 3 (8 week) | 1.73 (0.49) | 1.53–1.93 | 1.21 (0.51) | 1.00–1.42 | 0.51 | 0.23–0.80 | 0.0011 |
| *p*-values[b] (time effect) | <0.001 | | 0.006 | | — | | — |
| T4: ITT (LOCF) (nmol/L) | | | | | | | |
| *n* | 25 | | 25 | | — | — | — |
| Visit 1 (baseline) | 93.53 (12.88) | 66–110.22 | 91.80 (13.45) | 63.61–111.5 | 1.73 | −5.58 to 9.03 | 0.645 |
| Visit 2 (4 week) | 102.20 (12.33) | 70.97–118.5 | 88.79 (14.53) | 62.4–123 | 13.41 | 5.94–20.88 | 0.001 |
| Visit 3 (8 week) | 111.84 (14.01) | 70.97–133 | 95.84 (30.82) | 65.7–199 | 16.00 | 2.384–29.64 | 0.022 |
| *p*-values[b] (time effect) | <0.001 | | 0.466 | | — | | — |
| T4: PP (nmol/L) | | | | | | | |
| *n* | 23 | | 23 | | — | — | — |
| Visit 1 (baseline) | 95.32 (11.78) | 90.50–100.14 | 92.47 (12.75) | 87.26–97.68 | 2.85 | −4.24 to 9.95 | 0.4356 |
| Visit 2 (4 week) | 104.74 (8.99) | 101.07–108.42 | 89.20 (14.11) | 83.43–94.97 | 15.50 | 8.71–22.39 | <0.0001 |
| Visit 3 (8 week) | 115.22 (8.01) | 111.95–118.50 | 96.85 (31.52) | 83.97–109.74 | 18.37 | 5.08–31.66 | 0.0096 |
| *p*-values[b] (time effect) | <0.001 | | 0.467 | | — | | — |
| TSH: ITT (LOCF) (μIU/mL) | | | | | | | |
| *n* | 25 | | 25 | | — | — | — |
| Visit 1 (baseline) | 6.48 (0.85) | 6.15–6.82 | 6.72 (0.93) | 6.36–7.09 | −0.24 | −0.74 to 0.26 | 0.3067 |
| Visit 2 (4 week) | 5.67 (1.04) | 5.27–6.08 | 6.85 (1.29) | 6.34–7.36 | −1.17 | −1.83 to −0.52 | 0.0006 |
| Visit 3 (8 week) | 5.35 (1.08) | 4.93–5.78 | 7.05 (1.93) | 6.28–7.80 | −1.69 | −2.56 to −0.82 | 0.0002 |
| *p*-values[b] (time effect) | <0.001 | | 0.725 | | — | | — |
| TSH: PP (μIU/mL) | | | | | | | |
| *N* | 23 | | 23 | | — | — | — |
| Visit 1 (baseline) | 6.51 (0.89) | 6.15–6.88 | 6.79 (0.91) | 6.41–7.16 | −0.27 | −0.79 to 0.25 | 0.3488 |
| Visit 2 (4 week) | 5.62 (1.06) | 5.19–6.07 | 6.91 (1.29) | 6.38–7.44 | −1.29 | −1.98 to −0.60 | 0.0009 |
| Visit 3 (8 week) | 5.28 (1.09) | 4.83–5.73 | 7.13 (1.97) | 6.32–7.93 | −1.85 | −2.77 to −0.93 | 0.0004 |
| *p*-values[b] (time effect) | <0.001 | | 0.727 | | — | | — |

[a]*p*-value was obtained by unpaired *t*-test comparing the mean between treatment and placebo group (two tailed, $\alpha = 0.05$).
[b]*p*-value was obtained by repeated measured ANOVA (time effect).
CI, confidence interval; T3, triiodothyronine; T4, thyroxine; TSH, thyroid stimulating hormone; ITT, intent to treatment; LOCF, last observation carried forward; PP, per protocol.

For the between-group comparison, T3 levels for ashwagandha and placebo groups were similar at baseline ($p=0.2893$). However, serum T3 levels increased significantly in the ashwagandha group over placebo at fourth week ($p<0.0001$) and eighth week ($p=0.0031$). In addition, change in T3 levels from the baseline was statistically significant in the ashwagandha group compared to placebo at fourth week ($p=0.0002$) and eighth week ($p=0.0011$).

### *Serum T4 levels*

The treatment with ashwagandha produced a significant time effect on serum T4 levels [F (2, 23)=21.803, $p<0.001$, $\eta p^2=0.655$], which resulted in significant increase in serum T4 levels from baseline values by 9.3% ($p=0.0027$) and 19.6% ($p<0.0001$) at fourth and eighth weeks, respectively. However, serum $T_4$ levels in the placebo groups did not change significantly over time [F (2, 23)=0.790, $p=0.466$, $\eta p2=0.064$].

From similar baseline values ($p=0.6451$), serum T4 levels increased significantly in the ashwagandha group over placebo at fourth week ($p=0.0010$) and eighth week ($p=0.0221$). The change in T4 levels from the baseline was statistically significant in the ashwagandha group compared to placebo at fourth week ($p=0.0110$) and eighth week ($p=0.0394$).

### *Serum TSH levels*

A significant time effect was noted in the ashwagandha group on serum T4 levels [F (2, 23)=12.256, $p<0.001$, $\eta p^2=0.516$], along with a significant fall in serum T4 levels from baseline values at fourth and eighth weeks by −12.5% ($p=0.0002$) and −17.4% ($p<0.0001$), respectively. However, serum $T_4$ levels in the placebo group did not change significantly over time [F (2, 23)=0.326, $p=0.725$, $\eta p^2=0.028$].

Both groups had similar values for serum TSH levels at baseline ($p=0.3067$). However, serum TSH levels decreased significantly in the ashwagandha group compared to placebo at fourth week ($p=0.0006$) and eighth week ($p=0.0002$). In addition, the change in TSH levels from the baseline was statistically significant in the ashwagandha group compared to placebo at fourth ($p=0.0019$) and eighth week ($p=0.0026$).

### *Safety analysis and adverse events*

Ashwagandha treatment was found safe based on evaluated physical, hematologic, and vital parameters. No significant changes in any of these parameters were observed for both groups during the study. As per ITT analysis, four subjects (8%) (ashwagandha: 1[4%]; Placebo: 3[12%]) out of 50 reported effects such as fever, asthenia, cough, and headache. The severity of these adverse events was mild and temporary.

## Discussions

In this prospective, randomized, placebo-controlled pilot study, the authors determined the efficacy of ashwagandha root extract in subclinical hypothyroid patients. A detailed analysis revealed that daily treatment with ashwagandha for a period of 8 weeks produced a significant decrease in serum TSH level ($p<0.01$) and an increase in serum T3 ($p<0.01$) and T4 ($p<0.01$) levels compared to placebo. Ashwagandha treatment effectively normalized the thyroid indices during the eight-week treatment period in a significant manner (time effects: TSH [$p<0.001$], T3 [$p<0.001$], T4 [$p<0.001$]). Treatment with ashwagandha was found safe and tolerable, with few mild and temporary adverse events.

The results of the present study are in accordance with previous studies.[11–13] The results indicate a possible role for ashwagandha in regulating HPT axis. The antistress and cortisol lowering effect of ashwagandha may provide a suitable explanation for the current outcome.[10] An inverse relationship exists for regulation of HPT and HPA axis.[14] Chronic stress activates HPA axis by increasing cortisol levels, which in turn inhibits HPT axis and reduces serum T3 and T4 levels.[14] Treatment with ashwagandha lowers serum cortisol levels by downregulation of HPA axis, which in turn upregulates HPT axis to normalize the levels of the thyroid indices. Other factors like inflammation and dopamine levels also upregulate HPA axis and downregulate HPT axis.[15,16] The anti-inflammatory and antidopaminergic properties of ashwagandha may contribute to the thyroid modulating effect of the plant extract.[17,18]

### *Limitations*

This prospective study contains some significant limitations due to the study's status as a pilot study, which comprises a small sample size and study duration. A future study with a larger population and longer duration is required to monitor T4 levels for avoiding any associated risk of thyrotoxicosis, as a previous case study mentioned that a 32-year-old healthy woman developed thyrotoxicosis while taking ashwagandha capsules.[19]

## Conclusion

The outcome of the present study highlights the beneficial role of ashwagandha root extract for normalizing thyroid hormone levels in subclinical hypothyroid patients; however, further studies are required to elucidate the underlying mechanisms of ashwagandha.

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## Author Disclosure Statement

No competing financial interests exist.

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