

REVIEW ARTICLE

PHYTOTHERAPEUTIC APPLICATIONS OF *PIPER LONGUM* FOR THYROID DYSFUNCTION: A REVIEW OF MECHANISMS AND POTENTIALSneh Singh¹ and Shubhra Saraswat^{2*}¹Department of Home Science, Dayalbagh Educational Institute, Agra²Department of Home Science, Dayalbagh Educational Institute, AgraEmail: snehsingh2310664@dei.ac.in

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Abstract: Hypothyroidism is a significant global endocrine disorder resulting from insufficient thyroid hormone production, leading to widespread metabolic dysregulation with symptoms like fatigue, weight gain, and cold intolerance. While synthetic levothyroxine constitutes the primary treatment, there is increasing interest in adjunctive therapies from traditional medicine. This review investigates the potential of *Piper longum* (Pippali), a revered herb in Ayurveda, as a complementary agent for managing hypothyroidism. The therapeutic efficacy of *Piper longum* is primarily attributed to its bioactive alkaloid, piperine, which functions as a bio-enhancer to improve the absorption of selenium a critical cofactor for the deiodinase enzymes that convert thyroxine (T4) to the active triiodothyronine (T3). Furthermore, its documented anti-inflammatory, antioxidant, and metabolic-regulating properties may help alleviate the systemic symptoms and secondary complications associated with the condition. While its long-standing use in traditional systems provides a strong ethnobotanical basis, there is a distinct lack of robust clinical trials to validate these effects in hypothyroid patients. This review highlights the promising, multifactorial role of *Piper longum* in supporting thyroid function while underscoring the urgent need for rigorous scientific investigation to confirm its efficacy and establish its place in modern integrative care.

Keywords: Hypothyroidism, *Piper longum*, Ayurveda, Piperine, Selenium, Bioavailability

INTRODUCTION

Hypothyroidism is a clinical syndrome resulting from the insufficient production of thyroid hormones by the thyroid gland, an endocrine organ situated in the anterior neck. This deficiency impairs the body's capacity to regulate metabolism, cellular function, energy expenditure, and thermogenesis [Chaker L. *et al.*, 2017]. The etiology of hypothyroidism is most commonly attributed to autoimmune processes, such as Hashimoto's thyroiditis, which leads to the progressive destruction of thyroid tissue [Vanderpump M.P.J. 2011]. Other significant causes include iatrogenic factors like surgical thyroidectomy and radiation therapy, pharmacological side effects, and nutritional deficiencies, notably insufficient iodine intake [Taylor P. N. *et al.*, 2018]. Epidemiological data indicate a higher prevalence in females, particularly those over the age of 60 [Hollowell J.G. *et al.*, 2002]. Failure to address hypothyroidism can result in significant morbidity, including cardiovascular complications, reproductive dysfunction, and neurocognitive decline. However, with appropriate therapeutic intervention, the prognosis is generally excellent.

The diagnosis of hypothyroidism is primarily established through biochemical assays of serum

thyroid-stimulating hormone (TSH) and free thyroxine (T4). The standard of care for treatment involves hormone replacement therapy with synthetic levothyroxine, which restores euthyroid status and alleviates clinical manifestations [Graber J.R. *et al.*, 2012, Tomar, 2012].

Function of the Thyroid Gland

The thyroid gland's primary role is the synthesis, storage, and secretion of thyroid hormones: thyroxine (T4) and triiodothyronine (T3). This intricate process is regulated by the hypothalamic-pituitary-thyroid (HPT) axis. The hypothalamus secretes thyrotropin-releasing hormone (TRH), which stimulates the anterior pituitary to release TSH. TSH, in turn, acts on the thyroid gland to promote the uptake of iodine and the production of T4 and T3. These hormones are then released into the bloodstream, where they are transported to target tissues throughout the body. A negative feedback loop exists wherein circulating T4 and T3 levels inhibit the secretion of TRH and TSH, thus maintaining hormonal homeostasis [Chaker L. *et al.*, 2017]. Within the cells, T4 is largely converted to the more biologically active T3, which then binds to nuclear receptors to modulate gene expression and, consequently, a wide array of physiological processes.

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Prevalence of Hypothyroidism

The global prevalence of hypothyroidism demonstrates significant geographic and demographic variability, primarily determined by etiological factors such as regional iodine nutrition and the incidence of autoimmune thyroid disease.

Epidemiological data indicate that overt hypothyroidism affects up to 5% of the general population. An additional 5% to 10% of the population is estimated to have subclinical hypothyroidism. When accounting for undiagnosed cases, the aggregate prevalence of thyroid hormone deficiency may approach 10% [Chiovato L. *et al.*, 2019]. This heterogeneity underscores the necessity for localized epidemiological studies, especially in iodine-deficient regions, to accurately assess disease burden and inform public health strategies.

In India, a large-scale, cross-sectional, multi-center epidemiological study involving a cohort of 5,360 individuals from eight major urban centers revealed a hypothyroidism prevalence of 10.95% (n=587; 95% CI: 10.11%–11.78%). This prevalence comprises 7.48% self-reported cases and a notable 3.47% of previously undiagnosed cases, highlighting a significant disease burden. The investigation identified statistically significant regional and demographic disparities:

- **Geographical Variation:** Prevalence was significantly higher in inland cities (11.73%) compared to coastal regions (9.45%; $P=0.01$).
- **Gender Disparity:** A marked sex-based difference was observed, with a prevalence of 15.86% in females compared to 5.02% in males.

Furthermore, a substantial autoimmune etiology is implicated, as evidenced by a 21.85% seropositivity for anti-thyroid peroxidase (anti-TPO) antibodies within the cohort, indicating that the high prevalence of hypothyroidism constitutes a major public health concern in the region [Unnikrishnan A.G. *et al.*, 2013].

While specific epidemiological data on hypothyroidism prevalence for the state of Uttar Pradesh are not extensively available, the National Family Health Survey (NFHS-5, 2019–2021) provides some insight. According to the survey, the self-reported prevalence of goiter or other thyroid disorders among women in Uttar Pradesh is 1,281 per 100,000, which corresponds to 1.28% [Ministry of Health and Family Welfare 2022].

It is critical to note that this figure is derived from self-reported diagnoses and, therefore, likely represents a significant underestimation of the true disease burden. This is substantiated by findings from a multi-center study in India, which identified that 3.47% of its cohort consisted of previously undiagnosed cases. Given Uttar Pradesh's geographical classification as an inland state, it is plausible that its prevalence rates could be comparable to those observed in other inland urban

centers, such as Delhi, which reported a hypothyroidism prevalence of 11.07%.

However, in the absence of dedicated seroprevalence studies within Uttar Pradesh, such comparisons remain speculative. A definitive assessment of hypothyroidism prevalence in this region necessitates targeted epidemiological research.

Piper Longum

Piper longum Linn., commonly known as long pepper and referred to as "pippali" in Ayurvedic medicine, is a perennial, flowering vine belonging to the Piperaceae family [Chauhan K. *et al.*, 2011]. This slender, aromatic climber is indigenous to the Indo-Malayan region and is widely distributed throughout India, Nepal, Indonesia, Malaysia, and Sri Lanka. For millennia, *P. longum* has been a cornerstone of traditional medical systems, particularly Ayurveda, where it is revered as a potent medicinal herb [Kumar A. *et al.*, 2009].

Botanical Description and Cultivation

P. longum is a dioecious climber, typically reaching a height of 1-2 meters. Morphologically, the plant is characterized by alternate, petiolate, cordate-shaped leaves with entire margins. Its flowers are small, unisexual, and arranged in dense, solitary spikes. The female spikes mature into the medicinally significant fruiting bodies, which are spike-like structures (1-2 cm long) composed of numerous minute, embedded fruits. These fruits are harvested while unripe and subsequently dried for therapeutic use [Kumar S. *et al.*, 2011; Zaveri M. *et al.*, 2010].

The plant flourishes in warm, humid climates with partial shade and requires well-drained, fertile soil for optimal growth. Commercial cultivation is prominent in several Indian states, including the northeastern regions, Kerala, and Tamil Nadu. Propagation is typically achieved vegetatively through stem cuttings or suckers, with the first harvest possible within 6-8 months of planting [Zaveri M. *et al.*, 2010].

Historical Context and Modern Applications

The historical importance of *P. longum* is well-documented in ancient Sanskrit texts, including the *Charaka Samhita* and *Sushruta Samhita*, which date back to approximately 1000 BCE [Zaveri M. *et al.*, 2010]. Traditionally, both the dried unripe fruits and the roots have been utilized for a wide range of therapeutic applications, notably for managing respiratory and digestive disorders [Kumar S. *et al.*, 2011].

In recent decades, extensive scientific investigation has begun to validate these ethnobotanical uses. Research has elucidated the complex phytochemical composition of *P. longum*, identifying compounds responsible for its diverse pharmacological properties [Sunila E.S. *et al.*, 2004]. Furthermore, in classical Ayurvedic practice, it is often a key ingredient in polyherbal formulations. For instance, it is combined with black pepper (*Piper nigrum*) and ginger (*Zingiber officinale*) to create the "Trikatu"

preparation, a synergistic blend designed to enhance the bioavailability and therapeutic efficacy of other active compounds [Chauhan K. *et al.*, 2011].

BOTANICAL DESCRIPTION [Ministry of Health and Family Welfare, Department of AYUSH, 2001]

Table 1: Shows the taxonomical classification of the herb pippali (*Piper longum* Linn.)

Taxonomical Rank	Taxon
Kingdom	Plantae
Division	Magnoliophyta
Class	Magnoliopsida
Order	Piperales
Family	Piperaceae
Genus	Piper
Species	longum
Common name	Pippalimool, long pepper

Phytochemical Properties

Piper longum, commonly known as long pepper, possesses a rich and diverse phytochemical profile

that contributes to its therapeutic efficacy [Choudhary N. *et al.*, 2017].

Table 2: Shows the most bioactive compound in the herb pippali (*Piper longum* Linn.).

Alkaloids	Volatile Oils	Lignans	Other Compounds
Piperine (5-9%): The primary alkaloid, responsible for its pungent taste and many health benefits	Contains components like caryophyllene and eugenol	Compounds like sesamin and sesamol provide antioxidant properties	Also contains steroids, flavonoids, and terpenoids
Others include piperlongumine and piplartine			

Effects of Pippali in Managing Hypothyroidism

Piper longum (Pippali), a phytotherapeutic agent utilized in traditional medicine, is postulated to exert beneficial effects in the management of hypothyroidism, a condition characterized by deficient thyroid hormone production and consequent metabolic dysregulation [Jameson J.L. *et al.*, 2018]. Its potential mechanisms of action are multifaceted and target several pathophysiological aspects of the disorder.

Modulation of Nutrient Bioavailability

The primary bioactive constituent of *P. longum*, piperine, functions as a potent bio-enhancer. It has been shown to improve the gastrointestinal absorption and systemic bioavailability of essential micronutrients, including selenium. Selenium is an indispensable cofactor for the deiodinase enzymes responsible for converting the prohormone thyroxine (T4) into its more biologically active form, triiodothyronine (T3). By optimizing selenium status, piperine may facilitate more efficient T4-to-T3 conversion, a process often impaired in hypothyroid states, thereby supporting overall thyroid hormone economy [Rayman M.P. 2012].

Metabolic Regulation

Hypothyroidism is frequently associated with metabolic sequelae, such as dyslipidemia and impaired glycemic control. Preclinical and clinical evidence suggests that *P. longum* exhibits hypoglycemic and lipid-lowering properties, which

can help mitigate these secondary complications [Kumar S. *et al.*, 2011]. By improving insulin sensitivity and lipid profiles, it may alleviate common symptoms like weight gain and fatigue by optimizing cellular energy utilization [Graber J.R. *et al.*, 2012].

Anti-Inflammatory and Antioxidant Mechanisms

Chronic inflammation and oxidative stress are often implicated in the pathogenesis and symptomatology of hypothyroidism, particularly in cases of autoimmune etiology (e.g., Hashimoto's thyroiditis). The documented anti-inflammatory and antioxidant properties of *P. longum* may help attenuate the inflammatory cascade and reduce oxidative damage. This can lead to the amelioration of systemic symptoms such as arthralgia (joint pain) and fatigue.

Clinical Symptom Amelioration

Clinical observations and trials have indicated that administration of *P. longum* can lead to a reduction in the clinical symptoms of hypothyroidism, such as xeroderma (dry skin) and cold intolerance, sometimes even in the absence of significant alterations in serum thyroid hormone levels [Puri H.S. 2003]. This suggests that its therapeutic effects may not be limited to direct modulation of the thyroid gland but could also involve enhancing peripheral tissue sensitivity to existing thyroid hormones or through other non-thyroidal metabolic pathways [Bianco A.C., *et al.*, 2019].

Mechanism of Action

Pippali's involvement with body metabolism to improve hypothyroidism can be understood through the points as under:

Enhancement of Selenium Absorption:

Pippali contains piperine, an alkaloid known to enhance the bioavailability of various nutrients. Research indicates piperine facilitates the absorption of selenium, a critical mineral for thyroid health. Selenium is essential for the activity of deiodinase enzymes, which convert thyroxine (T₄) to triiodothyronine (T₃), the more biologically active form. In hypothyroidism, this conversion can be impaired, and improved selenium absorption could support better thyroid hormone utilization. For example, studies have shown piperine increases selenium absorption, potentially aiding in maintaining adequate selenium levels, which are vital for thyroid function [Haritha H. *et al.*, 2021].

Regulation of Glucose and Lipid Metabolism:

Pippali exhibits anti-hyperglycemic and anti-hyperlipidemic properties, which are significant for

managing metabolic disturbances in hypothyroidism. Hypothyroid patients often experience insulin resistance and dyslipidemia, contributing to weight gain and cardiovascular risks. A review article highlights pippali's ability to lower blood glucose and lipid levels, suggesting it could mitigate these metabolic issues [Biswas P. *et al.*, 2022]. This could improve energy expenditure and reduce symptoms like fatigue and weight gain.

Anti-inflammatory and Antioxidant Effects:

Hypothyroidism is associated with increased inflammation and oxidative stress, which can exacerbate symptoms. Pippali's anti-inflammatory and antioxidant activities, attributed to compounds like piperine and piperlongumine, may reduce these effects, potentially alleviating symptoms such as joint pain and tiredness. These properties are supported by pharmacological reviews, which note pippali's role in modulating signaling pathways and reducing oxidative damage [Biswas P. *et al.*, 2022].

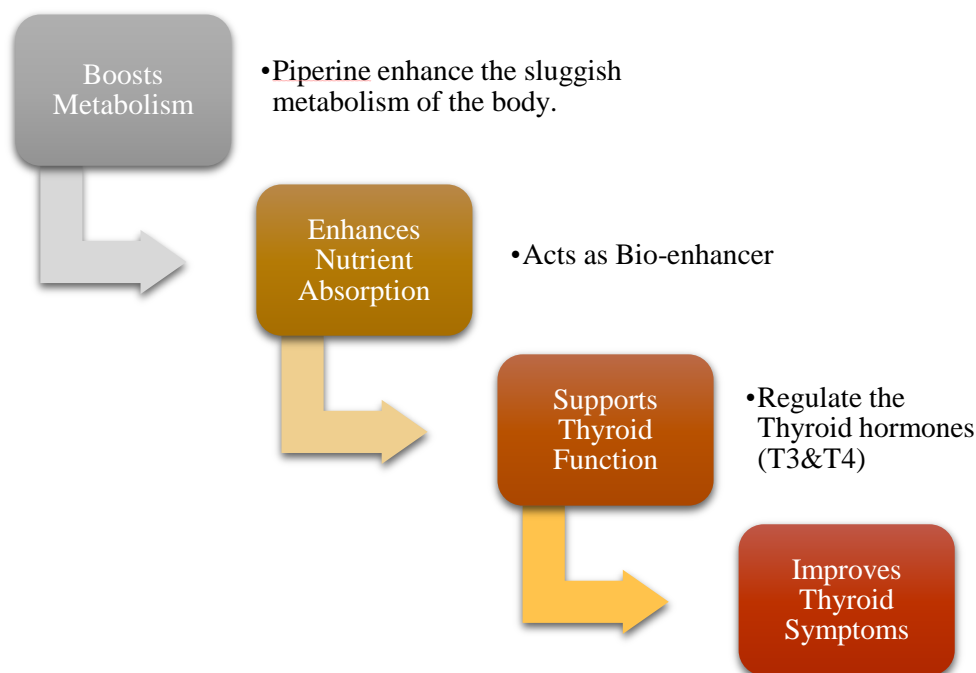


Fig 1. Shows the mechanism of action of pippali.

Dosage

Traditional Ayurvedic Dosage Patterns

Table 3: Description of the dosage pattern of pippali in Ayurveda.

Powder Form [Kumar A. <i>et al.</i> , 2009, Chauhan K. <i>et al.</i> , 2011]	Extract Form [Meghwal M. <i>et al.</i> , 2013, Sunila E.S. <i>et al.</i> , 2004]	Trikatu Formulation [Panda S. <i>et al.</i> , 2009, Keshari P.K. <i>et al.</i> , 2014]	Combination Therapies [Sharma A.K. <i>et al.</i> , 2021, Chandrasekhar K. <i>et al.</i> , 2012, Panda S. <i>et al.</i> , 2009, Keshari P.K. <i>et al.</i> , 2014, Mahapatra A. <i>et al.</i> , 2018]

Morning Dose: 500 mg once daily on an empty stomach	Evening Dose: 500 mg before dinner	Standardized Extract: 250-500 mg twice daily	Combination of Pippali, Ginger, and Black Pepper	With Ashwagandha	With Guggul
Can be mixed with honey or warm water	Suggested to be taken with ghee or warm milk	Morning: After breakfast	1-2 grams daily	Helps improve thyroid hormone levels	Supports thyroid function
Recommended time: Before breakfast		Evening: Before dinner	Helps enhance metabolism and thyroid function	Dosage: 500 mg Pippali + 300 mg Ashwagandha daily	Dosage: 250 mg Pippali + 500 mg Guggul daily

Precautions [Meghwal M. et al., 2013, Kumar A. et al., 2009, Sunila E.S. et al., 2004]

- Consult an endocrinologist before starting
- Regular thyroid function tests
- Monitor for any side effects
- Not a replacement for conventional thyroid medication

Recommended Duration [Chandersekhar K. et al., 2012, Sharma A.K. et al., 2021, Panda S. et al., 2009]

- Initial Phase: 3-6 months
- Maintenance Phase: 1-2 grams weekly
- Continuous monitoring required

Health Benefits

Piper longum (Long Pepper) is a traditional medicinal herb rich in piperine, primarily used for respiratory and digestive health. Modern science confirms it has potent anti-inflammatory, antimicrobial, and antioxidant effects. Its most significant function is as a natural "bio-enhancer," which helps the body better absorb other drugs and nutrients. It is prescribed for various conditions:

Bioavailability Enhancement: A paramount modern application of *P. longum* is its capacity to enhance the bioavailability of other phytochemicals and drugs. Its key compound, piperine, achieves this by inhibiting hepatic and intestinal glucuronidation and interfering with P-glycoprotein-mediated drug efflux. This mechanism effectively boosts the absorption and slows the metabolism of various substances, a property that has spurred the creation of commercial bioavailability enhancers [Meghwal M. et al., 2013].

Anti-inflammatory and Analgesic Activity: *P. longum* demonstrates potent anti-inflammatory and analgesic activity. Piperine and other constituent alkaloids exert these effects by suppressing pro-inflammatory cytokines and enzymes such as cyclooxygenase-2 (COX-2) and lipoxygenase. In animal models, extracts from the plant have successfully reduced edema and pain at levels comparable to standard medications like indomethacin and diclofenac, but with a more

favorable side effect profile [Stohr J.R. et al., 2001; Zaveri M. et al., 2010].

Immunomodulatory Effects: The plant exhibits significant immunomodulatory effects, strengthening both humoral and cellular immune responses. Research shows that its compounds, piperine and piperlongumine, boost the production of interleukins and interferon-gamma while also modulating T-helper cell activity [Sunila E.S. et al., 2004]. These actions make it a valuable agent for autoimmune conditions and as a supportive therapy during infections.

Antimicrobial Properties: A broad-spectrum antimicrobial activity against diverse pathogens is another key property of *P. longum*. *In vitro* investigations have confirmed its efficacy against bacteria, including multidrug-resistant strains like *Staphylococcus aureus* and *Escherichia coli*, as well as fungi (notably *Candida* species) and select viruses [Chauhan K. et al., 2011]. Essential oil components such as eugenol and caryophyllene are major contributors to this antimicrobial action.

Antioxidant Activity: *P. longum* possesses powerful antioxidant activity, primarily due to its lignan and flavonoid content. These compounds demonstrate robust free-radical scavenging capabilities. Scientific studies have verified that its extracts can safeguard lipids, proteins, and DNA from oxidative damage, suggesting potential roles in neuroprotection and anti-aging [Chauhan K. et al., 2011].

Traditional Applications: These scientifically validated properties underpin its extensive traditional applications. It has long been prescribed for:

- **Respiratory Disorders:** Treating conditions such as asthma, bronchitis, and cough, featuring prominently in formulations like "Trikatu" and "Sitopaladi Churna."
- **Digestive Ailments:** Managing dyspepsia, anorexia, flatulence, and various intestinal issues.
- **Metabolic Disorders:** Aiding in the management of obesity and diabetes.
- **Women's Health:** Addressing amenorrhea, dysmenorrhea, and providing post-partum support.

- **General Health Promotion:** Serving as a key component in rejuvenative therapies (Rasayanas) to enhance vitality and promote longevity.

Using Pippali for Everyday Health (Long Pepper) [Sharma L. *et al.*, 2018]

- **For Cough and Congestion:** Create a soothing herbal powder by finely grinding and mixing 10 grams each of holy basil leaves (tulsi), dried ginger (sonth), and long pepper (pippali). Enhance this blend with the powder of 4-6 small cardamoms. To use, mix a small amount of this powder with an equal part of honey to help loosen mucus and relieve coughs.
- **To Help Manage Fever:** Prepare a therapeutic decoction by simmering long pepper root in water. Drinking this twice a day is traditionally believed to help reduce fever, aid in detoxification, and support overall liver function.
- **For Headache Relief:** For a simple, aromatic remedy, gently warm a few long peppers and inhale the vapor. The volatile oils released are thought to help alleviate the symptoms of a tension headache.
- **To Promote Restful Sleep:** For those struggling with sleeplessness, stir approximately 1 gram of long pepper powder into a warm glass of milk. Consuming this before bedtime is considered highly beneficial for promoting sleep.
- **To Ease Breathing Difficulties:** To find relief from respiratory discomfort or shortness of breath (dyspnoea), mix about 2 grams of long pepper powder with a teaspoon of honey. This mixture is traditionally used to help open the airways.
- **For Liver and Spleen Support:** A traditional remedy involves boiling 1-5 grams of long pepper in 200 ml of water until the liquid is reduced. This preparation is often recommended in traditional practices to support the health of the liver and spleen, especially in conditions involving enlargement.

CONCLUSION

Hypothyroidism represents a significant and often underdiagnosed public health concern, particularly in inland regions of India like Uttar Pradesh. The condition's impact on metabolism, energy, and overall well-being necessitates effective management strategies. While conventional hormone replacement therapy remains the standard of care, traditional phytotherapeutic agents like *Piper longum* (Pippali) offer a promising adjunctive approach to support patient health.

The therapeutic potential of Pippali in hypothyroidism is not rooted in direct hormone production but in its multifaceted, supportive mechanisms. Its primary bioactive compound, piperine, acts as a powerful bio-enhancer, notably improving the absorption of selenium a critical

micronutrient for the conversion of T4 to the active T3 hormone. Furthermore, its ability to regulate lipid and glucose metabolism directly addresses the secondary complications often associated with hypothyroidism, such as weight gain and dyslipidemia. By exerting potent anti-inflammatory and antioxidant effects, Pippali also helps mitigate the systemic inflammation and oxidative stress that contribute to symptoms like fatigue and joint pain, especially in autoimmune cases.

In essence, *Piper longum* provides a holistic approach that complements conventional treatment by enhancing nutrient utilization, managing metabolic dysregulation, and alleviating clinical symptoms. However, it's crucial to emphasize that Pippali should be viewed as a supportive therapy rather than a replacement for prescribed medication. A safe and effective approach requires a collaborative strategy, integrating the wisdom of Ayurveda with modern medicine under the guidance of qualified healthcare professionals to optimize patient outcomes and improve their quality of life.

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