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Piper Longum and Primary Hypothyroidism: A Review of Potential Therapeutic Application

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Abstract

Hypothyroidism, a widespread endocrine disorder marked by inadequate thyroid hormone production, affects millions globally, manifesting symptoms such as fatigue, weight gain, and joint pain. While levothyroxine is the core of treatment, interest in complementary therapies rooted in traditional medicine is also on the rise. This review evaluates the potential therapeutic role of Piper Longum, a revered herb in Ayurveda known as long pepper, in managing primary hypothyroidism. Rich in phytochemicals, Piper Longum contains piperine (an alkaloid), which enhances selenium bioavailability, a critical factor in converting thyroxine (T4) to the active triiodothyronine (T3). Additionally, its anti-inflammatory, antioxidant, and metabolic-regulating properties may alleviate common hypothyroid symptoms. Drawing from its extensive use in traditional practices and supported by preliminary scientific studies, Piper Longum shows promise as a complementary approach. However, the lack of robust clinical trials necessitates further research to confirm its efficacy and safety. This review underscores Piper Longum's potential to enhance hypothyroidism management while highlighting the need for evidence-based integration into modern therapeutic strategies.

Keywords: *hypothyroidism, piper longum, Ayurveda, treatment, anti-inflammatory, bioavailability, phytochemicals, thyroxine, triiodothyronine, clinical trial, therapeutic, weight gain.*

INTRODUCTION

Hypothyroidism is a common endocrine disorder characterized by the thyroid gland's inability to produce sufficient thyroid hormones to meet the body's metabolic needs [1]. The thyroid, a butterfly-shaped gland located in the neck, is crucial in regulating numerous bodily functions, including metabolism,energy production, body temperature, and overall cellular function [2].The condition typically develops when the thyroid gland is damaged or fails to produce adequate hormones, most commonly due to autoimmune diseases like Hashimoto's thyroiditis [3]. Other causes include surgical thyroid removal, radiation treatment, certain medications, and iodine deficiency followed by the ayurvedic concoctions. Women, particularly those over 60, are more likely to develop hypothyroidism compared to men.If left untreated, hypothyroidism can lead to more serious complications, including heart problems, infertility, and cognitive impairments [4]. However, with proper medical management, most individuals can lead normal, healthy lives [5].

Diagnosis involves blood tests measuring thyroid-stimulating hormone (TSH) and thyroxine (T4) levels [6]. Most patients are treated with synthetic thyroid hormone replacement therapy, typically levothyroxine, which effectively manages symptoms and restores normal metabolic function [7].

PREVALENCE OF HYPOTHYROIDISM

Worldwide: The prevalence of hypothyroidism varies globally, influenced by factors like iodine nutrition and autoimmune disease prevalence. Research suggests overt hypothyroidism affects up to 5% of the general population, with subclinical hypothyroidism adding another 5-10%, depending on the region and diagnostic criteria. For example, a review article notes hypothyroidism affects up to 5% of the population, with a further estimated 5% being undiagnosed, suggesting a total prevalence of around 10% [8]. This variation highlights the need for region-specific studies, especially in iodine-deficient areas.

India: In India, a cross-sectional, multi-center epidemiological study conducted in eight major cities (Bangalore, Chennai, Delhi, Goa, Mumbai, Hyderabad, Ahmedabad, and Kolkata) reported a hypothyroidism prevalence of 10.95% (n = 587, 95% CI, 10.11-11.78) among 5360 participants. This included 7.48% self-reported cases and 3.47% previously undetected cases. The study found higher prevalence in inland cities (11.73%) compared to coastal cities (9.45%, P = 0.01), with significant demographic associations, such as 15.86% in females versus 5.02% in males [9]. This high prevalence poses a public health concern, particularly given the autoimmune involvement indicated by 21.85% anti-TPO antibody positivity.

UttarPradesh: Specific data on hypothyroidism prevalence in Uttar Pradesh is limited.

However, the National Family Health Survey (NFHS-5, 2019-2021) reports that 1281 women per 100,000 (1.281%) in Uttar Pradesh have been diagnosed with goitre or thyroid disorders, which may include hypothyroidism (Ministry of Health and Family Welfare 2022). This figure is based on self-reported diagnosed cases and likely underestimates the true prevalence due to undiagnosed hypothyroidism, as evidenced by the eight cities study where 3.47% were undetected. Given Uttar Pradesh's inland location, it may align with higher prevalence rates seen in similar regions like Delhi (11.07% in the eight cities study), but dedicated studies are needed for confirmation.

PIPER LONGUM

Piper longum Linn., commonly known as long pepper or "pippali," is a flowering vine belonging to the family Piperaceae [10]. This slender aromatic climber is native to the Indo-Malayan region, with significant distribution across India, Nepal, Indonesia, Malaysia, and Sri Lanka. For millennia, P. longum has held an esteemed position in traditional medicine systems, particularly in Ayurveda where it is considered one of the most important medicinal plants [11].

The dried unripe fruits, which resemble catkins with numerous minute fruits embedded in a spike-like structure, along with its roots, have been used extensively for treating various ailments ranging from respiratory disorders to digestive issues [12].

The historical significance of P. longum is evidenced by its mention in ancient texts like the Charaka Samhita and Sushruta Samhita, dating back to 1000 BCE [13]. In recent decades, modern scientific research has validated many traditional uses and revealed the complex phytochemical composition that underpins its diverse pharmacological properties [14].

P. longum is a perennial, dioecious climber that grows to a height of 1-2 meters. The plant features alternate, petiolate leaves that are cordate in shape with entire margins. The flowers are small, unisexual, and arranged in solitary, dense spikes. The female spikes develop into the characteristic fruiting spikes (1-2 cm long) that are harvested before ripening, dried, and used medicinally. The plant thrives in warm, humid conditions with partial shade and well-drained, fertile soil [15].

Fig. 1: The figure shows the pippali ripe fruit and the leaf of the plant.

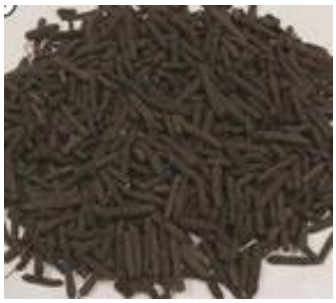

Fig. 2: The figure shows dried pippali fruit.

It is cultivated commercially in various parts of India, particularly in the northeast regions, Kerala, and Tamil Nadu [16]. Propagation is typically done through cuttings or suckers, with harvesting occurring approximately 6-8 months after planting.

In traditional practice, P. longum is frequently combined with other herbs like ginger and black pepper (forming the classical "Trikatu" preparation) to enhance bioavailability and therapeutic efficacy of various formulations [17].

BOTANICAL DESCRIPTION [18]

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 [19].The most significant bioactive compounds include:

1. Alkaloids: Piperine (5-9%) is the primary alkaloid and is responsible for the pungent taste. Other alkaloids include piperlongumine, piperlonguminine, piplartine, and pipernonaline.

2. Volatile oils: The essential oil contains components such as caryophyllene, piperidine, piperonal, and eugenol.

3. Lignans: Sesamin, pulvuatilol, fargesin, and sesamol contribute to the plant's antioxidant properties.

4. Esters: Primarily terpene esters such as terpinyl acetate and ethyl cinnamate.

5. Other compounds: Various steroids, glycosides, terpenoids, and flavonoids are also present in significant amounts.

ROLE OF PIPPALI IN MANAGING HYPOTHYROIDISM

Pippali, also known as long pepper, is an herb used in traditional medicine that might help with hypothyroidism by boosting body metabolism. Hypothyroidism means your thyroid gland doesn't make enough hormones, which can slow down your metabolism, leading to symptoms like fatigue and weight gain [20]. Here's how pippali could help:

- **Enhancing Nutrient Absorption**: Pippali contains piperine, which can improve the absorption of selenium, a mineral crucial for converting T4 (thyroxine) to T3 (triiodothyronine), the more active thyroid hormone [21].

Better selenium levels might support thyroid function, especially in hypothyroidism where this conversion can be impaired [22].

- **Improving Metabolic Health**: Studies suggest pippali can lower blood sugar and cholesterol levels, which are often high in hypothyroidism [23]. This could help with symptoms like weight gain and fatigue by improving how your body uses energy [24].

- **Reducing Inflammation and Oxidative Stress:** Pippali's anti-inflammatory and antioxidant properties might reduce symptoms like joint pain and tiredness, which are common in hypothyroidism and can be worsened by inflammation [25].

- **Symptom Relief:** Clinical trials show pippali can reduce hypothyroidism symptoms, like dry skin and cold intolerance, even if thyroid hormone levels don't always increase significantly [26]. This suggests it might work by improving how your body uses existing hormones or by other metabolic effects [33].

MECHANISM OF ACTION

Pippali's involvement with body metabolism to improve hypothyroidism can be understood through several key mechanisms:

1. 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 [32].

2. 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 [27]. This could improve energy expenditure and reduce symptoms like fatigue and weight gain.

3. 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 [34].

DOSAGE

Traditional Ayurvedic Dosage Patterns

Powder Form [28]

1. Morning Dosage:

- 500 mg once daily on an empty stomach
- Can be mixed with honey or warm water
- Recommended time: Before breakfast

2. Evening Dosage:

- 500 mg before dinner
- Suggested to be taken with ghee or warm milk

Extract Form[35], [36]

1. Standardized Extract:

- 250-500 mg twice daily
- Morning: After breakfast
- Evening: Before dinner

Trikatu Formulation [19], [11]

- Combination of Pippali, Ginger, and Black Pepper
- 1-2 grams daily
- Helps enhance metabolism and thyroid function

Precautions [13],[18],[27]

- Consult an endocrinologist before starting
- Regular thyroid function tests

- Monitor for any side effects
- Not a replacement for conventional thyroid medication

Recommended Duration[3], [9], [12]
- Initial Phase: 3-6 months
- Maintenance Phase: 1-2 grams weekly
- Continuous monitoring required

COMBINATION THERAPIES

1. With Ashwagandha [8], [9]
- Helps improve thyroid hormone levels
- Dosage: 500 mg Pippali + 300 mg Ashwagandha daily

2. With [15], [28], [36]
- Supports thyroid function
- Dosage: 250 mg Pippali + 500 mg Guggul daily

OTHER HEALTH BENEFITS

The phytochemical composition varies depending on geographical location, climatic conditions, and the part of the plant being analyzed. The fruits typically contain higher concentrations of piperine and volatile oils compared to the roots or stems.

P. longum has been a cornerstone in traditional medicine systems, particularly Ayurveda, Unani, and Siddha, where it is prescribed for various conditions:

1. Respiratory disorders: Used for treating bronchitis, asthma, cough, and common cold. It is a key ingredient in formulations like "Trikatu" and "SitopaladiChurna."

2. Digestive ailments: Prescribed for dyspepsia, anorexia, flatulence, abdominal pain, and intestinal disorders.

3. Metabolic disorders: Used in the management of diabetes and obesity.

4. Neurological conditions: Applied in the treatment of paralysis, epilepsy, and certain types of headaches.

5. Women's health: Utilized for amenorrhea, dysmenorrhea, and post-partum care.

6. General health promotion: Often included in rejuvenative formulations (Rasayanas) for improving vitality, immunity, and longevity.

7. Anti-inflammatory and Analgesic Activity: Multiple studies have demonstrated that piperine and other alkaloids from P. longum exhibit significant anti-inflammatory effects by inhibiting pro-inflammatory cytokines and enzymes like cyclooxygenase-2 (COX-2) and lipoxygenase. Animal models have shown that P. longum extracts reduce edema and pain comparable to standard drugs like diclofenac and indomethacin but with fewer side effects [31].

8. Antimicrobial Properties: P. longum exhibits broad-spectrum antimicrobial activity against various pathogens. In vitro studies have shown efficacy against bacteria (including multi-drug resistant strains of Staphylococcus aureus and Escherichia coli), fungi (particularly Candida species), and certain viruses [24]. The essential oil components, particularly eugenol and caryophyllene, contribute significantly to these properties.

9. Immunomodulatory Effects: Research indicates that P. longum strengthens both cellular and humoral immune responses. Piperine and piperlongumine have been shown to enhance the production of interleukins and interferon-gamma while modulating T-helper cell responses (Sunila and Kuttan 2004). These properties make it valuable in autoimmune conditions and as an adjuvant during infections.

10. Antioxidant Activity: The lignans and flavonoids in P. longum exhibit potent free radical scavenging activity. Studies have demonstrated that P. longum extracts protect against oxidative damage to lipids, proteins, and DNA, potentially contributing to its anti-aging and neuroprotective effects [3].

11. Hepatoprotective Effects: P. longum extracts show significant liver-protective properties against various hepatotoxins, including alcohol, carbon tetrachloride, and certain medications. This activity is attributed to its antioxidant properties and ability to enhance liver detoxification enzymes [30].

12. Anticancer Potential: Several in vitro and animal studies suggest that piperine, piperlongumine, and other alkaloids from P. longum possess anticancer activities through multiple mechanisms, including inhibition of cell proliferation, induction of apoptosis, and suppression of angiogenesis. Particularly promising results have been observed in models of breast, colon, and lung cancers [29].

13. Bioavailability Enhancement: Perhaps one of the most significant modern applications of P. longum is its ability to enhance the bioavailability of other drugs and phytochemicals.

Piperine inhibits hepatic and intestinal glucuronidation and interferes with P-glycoprotein-mediated drug efflux, thereby increasing the absorption and reducing the metabolism of various compounds [32]. This property has led to the development of commercial bioavailability enhancers containing piperine.

PIPPALI AS HOME REMEDY(Long Pepper)[9]

- **Cough Treatment:** Prepare a fine powder by mixing 10 grams each of holy basil leaves, dried ginger, and long pepper. Add a powder of 4-6 small cardamoms. Take this powder with an equal amount of honey to relieve mucus accumulation.
- **Fever Management:** Prepare a decoction of long pepper root in water and drink twice daily. This decoction helps treat fever, eliminates toxins, and supports liver regeneration.
- **Headache Relief:** Inhale the aroma of hot long pepper to alleviate headache symptoms.
- **Insomnia Treatment:** Consume 1 gram of long pepper powder with milk, which is highly beneficial for addressing sleeplessness.
- **Respiratory Distress (Dyspnoea):** Take 2 grams of long pepper powder mixed with honey to ease breathing difficulties.
- **Enlarged Spleen and Liver:** Boil 1 gram of long pepper and 5 grams of long pepper powder in 200 grams of water. This preparation is particularly useful for treating enlarged hepatic and splenic conditions.

CONCLUSION

Hypothyroidism is a prevalent condition that requires effective management to prevent serious health complications. While conventional treatments like levothyroxine are standard, there is growing interest in complementary approaches, particularly from traditional medicine. Piper Longum, with its rich phytochemical profile and historical use in Ayurveda, presents a promising avenue for supporting thyroid health. Research suggests that Piper Longum may enhance selenium absorption, crucial for thyroid hormone conversion, and improve metabolic parameters often disrupted in hypothyroidism. Its anti-inflammatory and antioxidant properties could also alleviate associated symptoms. However, while traditional use and preliminary studies are encouraging, more rigorous clinical trials are needed to establish the efficacy and safety of Piper Longum for hypothyroidism management. It is important to note that Piper Longum should not replace prescribed thyroid medications but could be considered as a complementary therapy under medical supervision. The exploration of Piper Longum for hypothyroidism not only highlights the potential of traditional herbs in modern healthcare but also underscores the importance of integrating evidence-based natural remedies into comprehensive treatment plans.

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