

# NUTRI NEWS



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## Phytotherapeutic Support of Thyroid Function

by Joseph Collins, ND

### Introduction

The thyroid gland is the small, butterfly-shaped gland found just below the Adam's apple. As the primary endocrine gland responsible for modulating the metabolic rate, optimal thyroid function is required for healthy function of every cell within the human body and plays a critical role in both maintaining the quality of life and decreasing the risks of diseases. Hypothyroidism (underactivity of the thyroid gland) occurs when the thyroid gland produces less than the normal amount of thyroid hormones. The result of not producing enough thyroid hormone is a "slowing down" of many bodily functions. If left untreated, decreased thyroid function can cause elevated cholesterol levels and subsequent heart disease, infertility, muscle weakness, osteoporosis and, in extreme cases, coma or death.

While decreased thyroid function is commonly associated with weight gain, fatigue, cold intolerance and depression, suboptimal thyroid function has also been associated with increased frequency of heart failure, coronary heart disease, dementia, insulin resistance, and dilated cardiomyopathy and increased risk of breast cancer. In addition, hypothyroidism is commonly a co-morbidity factor in cancer, schizophrenia, chronic hepatitis C infection, bipolar disorders, other psychiatric illnesses, and adrenal insufficiency.

### Suboptimal Thyroid Function

Autoimmune hypothyroidism (Hashimoto's disease), is the most common thyroid disease in the United States. It is an inherited condition that affects approximately 14 million Americans and is about 7 times more common in women than in men. Although autoimmune hypothyroidism may be temporary, it usually is a permanent condition.

While autoimmune hypothyroidism is a common condition, recent epidemiological studies demonstrated that

up to 20 percent of certain subjects may display its subclinical form. The prevalence of subclinical hypothyroidism is about 4 to 8.5 percent, and may be as high as 20 percent in women older than 60 years.

Subclinical hypothyroidism is defined as TSH above the upper reference limit with normal levels of free T4. Several investigations have shown that patients with subclinical hypothyroidism have subtle symptoms and signs of mild thyroid failure, that subclinical hypothyroidism can have significant effects on peripheral target organs, and there is a high rate of progression towards overt hypothyroidism. This progressive worsening of thyroid function may be explained in part by the presence of T3 nuclear receptors (TR) in thyroid cells, which demonstrate autocrine actions of thyroid hormones, and suggests that decreased thyroid function propagates further decrease in thyroid function. Even thyroid tissue requires proper function of thyroid hormones

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to perform the act of making those very hormones.

Although suboptimal thyroid function may be sub-classified into hypothyroidism and subclinical hypothyroidism, they both can present with subjective and objective data that indicate deterioration in quality of life and increased risks of diseases.

Even though a Consensus Development Conference held in September of 2002 recommended against population screening for subclinical thyroid disease, clinicians are encouraged to make individual patient assessments when determining the need for testing and treatment.

## Iodine and Iodine Uptake

Proper function of thyroid hormones involves a number of intricate processes, beginning with adequate and consistent intake of dietary iodine. While providing dietary iodine is the first step, the uptake of the iodine by thyroid cells (thyrocytes) requires proper function of sodium-iodide-symporter (NIS) proteins. Thyroid follicular cells transport iodide from blood into the follicular lumen against an iodide gradient by

means of coupled transport of Na<sup>+</sup> ions and I<sup>-</sup> ions via NIS proteins under the influence of TSH. The proinflammatory cytokines, IL-1alpha, IL-1beta, IL-6, and TNF-alpha have each demonstrated the ability to decrease TSH induced expression of NIS proteins. Herein lies the next impedance to optimal thyroid function – inflammation reduces uptake of iodide by thyrocytes.

While phytotherapeutic agents which provide dietary iodine support the first step in hormonogenesis, support of NIS proteins function and control of proinflammatory cytokines are also required to promote optimal thyroid function in these initial steps of thyroid hormonogenesis.

## Iodine and Iodine Uptake Phytotherapeutics

Sea Kelp (*Ascophyllum nodosum*) is an excellent dietary source of iodine. An additional benefit of *Ascophyllum nodosum* is its ability to increase glutathione peroxidase activity, an important antioxidant. Human thyrocytes synthesize and secrete extracellular glutathione peroxidase, which translocates into the intracellular space and prevents peroxidative damage of thyrocytes from diffusion of extracellular H<sub>2</sub>O<sub>2</sub> during stimulation of thyroid-hormone synthesis. *Ascophyllum nodosum* may therefore decrease occurrence of autoimmune thyroid disease, since thyrocytes exposed to locally increased H<sub>2</sub>O<sub>2</sub> increase the risk autoimmune thyroid disease.

Bladderwrack (*Fucus vesiculosus*), another dietary source of natural iodine also demonstrates anti-estrogen properties in both human and animal studies, suggesting that it may contribute protective health to estrogen sensitive tissues.

*Ascophyllum nodosum* and *Fucus vesiculosus* both provide fucoidan a sulfated polysaccharide that has a wide variety of biological activities including antioxidant, anti-thrombotic, anti-inflammatory and anti-autoimmune effects.

*Humulus lupulus* (Hops), contains xanthohumol, a chalcone that enhances uptake of iodine into the thyroid gland by activation of sodium-iodide-symporter (NIS) proteins. Xanthohumol also repressed activation of NF-kappaB, thereby decreasing the expression of proinflammatory cytokines such as TNF-alpha and IL-6, which as noted, can interfere with function of NIS proteins.

*Coleus* (*Coleus forskohlii*) contains forskolin, which is specifically able to mimic the effect of TSH in regard to iodide uptake, organification of iodine, thyroglobulin (TG) production, and promote secretion of T3 & T4, through an increase in the expression of sodium/iodide symporter (NIS) proteins.

Collectively, *Ascophyllum nodosum*, *Fucus vesiculosus*,

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*Humulus lupulus* and *Coleus forskohlii* are able to provide iodine and enhance its uptake into thyrocytes.

### **T3 & T4 Production and Secretion from Thyrocytes**

The next two steps in proper thyroid function involve the production of thyroid hormones by thyrocytes, and the secretion of thyroid hormone from those cells.

The production of thyroid hormones by thyrocytes typically begins with the sulfation of tyrosine residues in thyroglobulin, a process which is under the control of TSH. There is a close correlation between the sulfated tyrosine content of thyroglobulin and the production of thyroid hormones.

The sulfated tyrosine is then acted upon by thyroperoxidase (TPO), an enzyme mainly expressed in the thyroid that binds iodine onto the tyrosine residues on thyroglobulin for the production of thyroxine (T4) or triiodothyronine (T3), a process called "organification of iodine".

### **Phytotherapeutics for T3 & T4 Production and Secretion from Thyrocytes**

As noted, *Coleus* (*Coleus forskohlii*) mimics the effect of TSH in regard to iodide uptake, organification of iodine, thyroglobulin (TG) production, and promotes secretion of T3 & T4. Consequentially, *Coleus* extracts play an important role in this step of thyroid function.

*Bacopa monniera* (also known as Brahmi) exhibits thyroid stimulating abilities through an increase of T4 serum concentrations in animal studies. The increase of T4 by 41% without any notable increase in T3 or hepatic activity suggests that the action of Brahmi has more to do with direct thyroid stimulating activity than it does with hepatic conversion to T3.

Ashwagandha (*Withania somnifera*) is another plant that directly affects production of thyroid hormones. Animal studies during the late 1990s demonstrated its ability to directly act on thyroid tissue to bring about a rise in serum levels of thyroid hormones. A case review in late 2005 presented a 32 year old woman who increased her dosage of ashwagandha to the point where she actually caused an excessive rise of her thyroid hormone levels, though the symptoms resolved spontaneously after discontinuation of the ashwagandha capsules and laboratory values normalized. This case review reveals that serum levels of thyroid hormone can also be raised in humans, though excessive dosages should be avoided.

*Coleus forskohlii*, *Bacopa monniera* and *Withania somnifera* work together to support the optimal function of

thyroid hormone production and secretion by thyrocytes.

### **Optimal Conversion of T4 to T3, with Decreased rT3 Production**

The thyroid hormone thyroxine (T4) is converted to the more active form triiodothyronine (T3) by the 5'-iodothyronine deiodinase (5'DI) enzyme. Inhibition of 5'DI is associated with decreased production of T3, and a relative increase of reverse T3 (rT3), a relatively inactive form of the hormone.

This relative elevation of rT3 levels with suppression of T3 is associated with clinical presentation of hypothyroidism, despite normal to elevated thyroxine (T4), and normal TSH levels. This shift in thyroid hormone metabolism, with increased rT3/T3 ratio, has been associated with inactivation of type I 5'-iodothyronine deiodinase (5'DI) enzyme, by NF-kappa $\beta$ . Activation of NF-kappa $\beta$  also leads to increased expression of proinflammatory cytokines such as TNF-alpha and IL-6 which moderately decrease 5'DI activity.

### **Phytotherapeutics for Optimal Conversion of T4 to T3, with Decreased rT3 Production**

Phytotherapeutic agents targeted to support optimal thyroid hormone metabolism towards T3 and away from rT3, include agents which directly increase iodothyronine deiodinase activity, such as forskolin from *Coleus forskohlii*, and agents which preserve iodothyronine deiodinase activity by decreasing NF-kappa $\beta$  activation, such as xanthohumol from *Humulus lupulus*, guggulsterones from *Commiphora mukul*, Carnosol from *Rosmarinus officinalis*, and withanolides from *Withania somnifera*.

In addition to decreasing NF-kappa $\beta$  activation, guggulsterones also directly stimulate triiodothyronine (T3) production through its action on liver enzymes, while also increasing the activity of endogenous antioxidants.

*Coleus forskohlii*, *Humulus lupulus*, *Commiphora mukul*, *Rosmarinus officinalis* and *Withania somnifera* all support the important step of converting T4 to the more active T3, while opposing the production of the less potent reverse T3.

### **Thyroid Receptor Coupling and Expression in Target Genes**

The final steps in proper thyroid function involve the coupling of membrane receptors to allow thyroid hormones to enter target cells and affect the hormone/receptor complex on target genes.

Thyroid hormone receptor (TR) are nuclear receptors involved in the regulation of cellular response to the thyroid hormone triiodothyronine (T3). Cellular response takes place

after TRs allow T3 binding to T3 response elements (TRE) in target genes within the nuclear DNA. In order for a thyroid hormone receptor (TR) to bind to TREs, the TR must first couple with Retinoid-X-receptors (RXR) in a process called heterodimerization. Heterodimerization is the coupling of two different nuclear receptors to create a heterodimer, such as the RXR/TR heterodimer, which has been proposed to be the principle mediator of target gene regulation on target cells by T3 hormone.

### Phytotherapeutics for Thyroid Receptor Coupling and Expression in Target Genes

Phytotherapeutic agents which support the function of receptor elements and the down regulation of substances that interfere with receptor function have notable clinical application in optimizing thyroid function.

Agents targeted to support optimal thyroid hormone function by promoting the function of RXR receptors include Rosemary (*Rosmarinus officinalis*) and Sage (*Salvia officinalis*) which provide carnosic acid, a polyphenolic diterpene that at low concentrations increases the expression of RXR receptors. As previously noted phytotherapeutic agents that decrease NF-kappaB activation include xanthohumol from *Humulus lupulus*, guggulsterones from *Commiphora mukul*, Carnosol from *Rosmarinus officinalis*, and withanolides from *Withania somnifera*. The improved function of RXR may be another reason why these agents display thyroid supporting actions. Decreased NF-kappaB activation is important for receptor function because NF-kappaB directly interacts with the DNA-binding domain of RXR and may prevent its binding to the targeted DNA sequences nuclear receptor-regulated systems where RXR is a dimerization partner, such as the RXR/TR heterodimer. The RXR/TR initiated gene expression may be enhanced 2.5 to 3-fold by forskolin, the protein kinase A activator that occurs in *Coleus forskohlii*.

### A Final Note on Thyroid Receptors

Proper function of thyroid receptors also requires avoidance of known endocrine disruptors. Gene expression of RXR, a partner heterodimerization of TRs, may be suppressed by bisphenol A (BPA), which is known as an estrogenic and anti-thyroid hormonal endocrine disrupter. Bisphenol A is used in the manufacturing of polycarbonate plastic widely used in water and food containers and epoxy resins that are used for coating the inside of cans used for canning food. A large number of environmental pollutants and other xenobiotics also negatively affect signaling pathways, in which nuclear receptors are involved.

By avoiding endocrine disruptors, and by using phytotherapeutic agents that support both the production of thyroid hormones as well as their utilization by tissues, clinicians play an important role in helping to support optimal thyroid health.

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*For more information on phytocrinology and Dr. Collins' protocols, see <http://www.phytocrine.com>.*

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