

Clinical significance of *Saussurea Costus* in thyroid treatment

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ABSTRACT

ينتمي نبات القسط أو القسط الهندي إلى عائلة Asteraceae وهو أحد النباتات العلاجية المستخدمة على نطاق واسع كعلاج شعبي في المملكة العربية السعودية. قد يتم تطوير مكونات هذا النبات كجزيئات نشطة بيولوجياً. يتراوح معدل انتشار اضطرابات الغدة الدرقية بين العرب من 6.18% إلى 47.34%، وكان قصور الغدة الدرقية الأكثر انتشاراً. على الرغم من عدم وجود علاج طبيعي يمكن أن يحل محل هرمونات الغدة الدرقية، فقد تم بحث دور نبات القسط كعلاج بديل أو كعامل إضافي لعلاج الغدة الدرقية. قد تكون مركبات الفلافونويد والخصائص المضادة للأكسدة الموجودة في نبات القسط لها آلية مهمة تدعم استخدامها العلاجي. البيانات الحالية حول الدور المحتمل لنبات القسط في اضطرابات الغدة الدرقية غير متوفرة والأدلة المتاحة غير حاسمة. تتناول هذه المراجعة الفهم الحالي للاستخدامات العلاجية المتعلقة بهذا النبات في أمراض الغدة الدرقية.

Saussurea costus (*S. costus*) belongs to family of *Asteraceae* and is one of the therapeutic plants extensively used as a traditional medicine in Saudi Arabia. Constituents of this plant have the potential to be developed as bioactive molecules. Among Arabs, the prevalence of thyroid disorders ranges from 6.18 % to 47.34% and hypothyroidism has been reported to be the most prevalent. Although there is no natural treatment that can directly replace thyroid hormones, their role as an alternate treatment or as an add-on to available thyroid treatment has been explored. *Flavonoids* and antioxidant properties of *S. costus* may be an important mechanism involved in supporting its medicinal use. Current data on the possible role of *S. costus* in thyroid disorders is lacking and the available evidence is inconclusive. This review deal with the current understanding of use and myth regarding the use of this medicinal plant in thyroid disease.

Keywords: thyroid, saussurea, treatment, clinical

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Saussurea costus (*S. costus*) synonymous with *Saussurea Slappa*, also known as (نبات القسط أو القسط الهندي) *qust* in Arabic or *Costus root* in English, belongs to family of *Asteraceae*, a species of thistle in the genus *Saussurea* found worldwide mostly in Western Himalayan region of Pakistan and India. The growth of *S. costus* is limited to specific moist Himalayan region at altitude of 2600-4000m.¹ The cultivation of *S. costus* for commercial purpose started in 1920s.² Since ancient times, oils extracted from the root have been used in traditional medicines and perfumes.³ *Saussurea costus* is one of the therapeutic plants extensively used as a traditional medicine in Saudi Arabia.⁴

The medicinal properties of *S. costus* are well recognized in traditional systems of medicine including, Ayurvedic, Chinese, and Tibetan. The roots of *S. costus* are bitter in taste with strong aromatic odor and are believed to have anti-inflammatory, antimicrobial, analgesic, anti-ulcer, anticancer, and hepatoprotective properties in humans. Major constituents of this plant have potential to be developed as bioactive molecules. The *costus* oil (the oil extracted from the roots of *S. costus*) has been used in leprosy.⁵ *Saussurea costus* roots have also been used in many other medical conditions including chronic gastritis, stomach ulcers, rheumatoid arthritis, asthma and bronchitis in traditional medicine and in inflammation-related diseases. *Saussurea costus* is one of the most commercially used herbs in various indigenous systems of medicine.⁶ Data on possible role of *S. costus* in thyroid disorders are lacking. In this article, based on current available evidence, we summarize comprehensive analysis of the role of *S. costus* in thyroid disorders.

Basic details and therapeutic role of *S. costus*.

General pharmacology. *Saussurea costus* is a medicinally important plant and rich in bioactive phytoconstituents. Until now, many compounds of *S. costus* have been identified including *Sesquiterpene terpenes* (ST), anthraquinones, alkaloids and flavanoids. *Sesquiterpene terpenes* are main compounds of *S. costus* root which include dehydrocostus lactone (DCL) (46.8%), costunolide (CS) (9.3%), 8-cedren-13-ol (5.1%) and α -curcumene (4.3%).^{7,8} These constituents have been reported to have medicinal properties and possesses various bioactivities such as antifungal,⁹ antidiabetic,¹⁰ antihelmintic,¹¹ antitumor,¹² antiulcer,¹³ immunomodulator,^{14,15} anti-inflammatory,¹⁴ and anti-hepatotoxic.¹⁴ Identified flavanoids of *S. costus* possess antimicrobial properties.¹⁴

Therapeutic role of *S. costus* in various conditions.

Antitumor effect. Lee et al¹⁶ studied the effect and mechanism of apoptosis in HL-60 human leukemia cells and showed that Costunolide (CS), induces the reactive oxygen species (ROS)-mediated mitochondrial permeability transition and resultant cytochrome c release. This was a very important report on the mechanism of the anticancer effect of costunolide. Dehydrocostus lactone isolated from the hexane extract induced apoptosis in cell lines of DU145 human autonomous androgen prostate cancer and induced cell apoptosis.¹⁴ Ethanolic extract of *S. costus* showed apoptotic effect in a dose and time dependent manner in the treatment of gastric cancer.¹²

Anti-inflammatory effect. Ethanolic extract of *S. costus* showed anti-inflammatory activities through carrageenan induced paw edema and peritonitis animal models.¹⁷ Costunolide also showed anti-inflammatory activity by impeding the protein and mRNA expression of interleukin-1b masking the AP-1 transcription activity.¹⁸

Anti-ulcer effect. The acetone extract from *S. costus* and CS, exhibited both cholagogic effect and inhibitory effect on the formation of gastric ulcer (induced by restraint in water) in mice.¹⁹ In ethanol-induced lesion in rats, amino acid-sesquiterpene adducts, saussureamines A, B and C, isolated from the root of *S. costus* showed anti-ulcer effect. Costunolide and DCL also showed

a gastro protective effect on acidified ethanol-induced gastric mucosal lesions in rats.²⁰

Immunomodulatory effect. Costunolide inhibited the killing activity of cytotoxic T lymphocytes (CTL) through preventing the increasing tyrosine phosphorylation in response to the cross linking of T-cell receptors. Dehydrocostus lactone along with other guaianolides also exhibited inhibitory activity towards the killing function of CTL and the induction of induction of intercellular adhesion molecule-1 (ICAM-1).²⁰ Additionally, extracts of *S. costus* showed hypolipidemic effect when orally administered to rabbits. *Saussurea costus* was found most effective for obese diabetes when a detailed survey and clinical study on potent hypoglycemic plants of different regions from India.^{10,20}

Thyroid disorders and natural treatments. Worldwide, incidence of endocrine diseases including thyroid disorders is increasing. Thyroid disorders are generally classified into hyper and hypothyroidism. Women are more likely to have alteration in thyroid function as compared to men.²¹ In general, patients with thyroid disorders may have decreased circulating thyroid hormones (hypothyroidism) or increased levels of thyroid hormones (hyperthyroidism). Hypothyroidism is one of the most prevalent endocrine disorders characterized by low levels of thyroid hormones (T3 & T4) in the serum and high thyroid stimulating hormone (TSH). The common cause of hypothyroidism is autoimmune thyroiditis.²² The prevalence of hypothyroidism in the general population is variable ranging from 0.3% to 3.7% in the United States to 0.2% to 5.3% in European population.²³⁻²⁵ Approximately, 3% to 8% of world population have subclinical hypothyroidism, a condition with no apparent symptoms of thyroid hormone deficiency. The prevalence of overt hyperthyroidism is approximately 0.5% in both European and American population.^{24,25} In the Arab world, the prevalence of thyroid disorders ranges from 6.18% to 47.34%. The prevalence of goitre in Arabian countries has been reported to be 25% in Egypt and 1.7% in Bahrain.²⁶ In comparison to other populations, the prevalence of thyroid dysfunction among Saudi adults has been reported to be higher. Gaffer et al²⁷ reported an overall prevalence of 43.6% including 40.8% hypothyroidism and 2.8% as hyperthyroidism.²⁷ Like in other countries, among all thyroid disorders, hypothyroidism has been reported to be the most prevalent among Arab population. Among Arabs, a considerably higher prevalence of hypothyroidism has been documented in Saudi population (43.3%) as compared to 6.18%

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in Libya.²⁸ Currently, levothyroxine replacement is the choice of treatment in hypothyroidism. Although, it has been shown that in spite of being euthyroid, patients taking levothyroxine have decreased neurocognitive function and lead a suboptimal quality of life.²⁹ Further, levothyroxine treatment is associated with poor compliance.³⁰

Natural therapies in thyroid dysfunction. Although, there are no natural treatment that can directly replace thyroid hormones, their role as an alternate treatment or as an add-on to available thyroid treatment has been explored. The results of few available studies provided controversial results suggesting significant role of tea in thyroid cancer.³¹ However, later a pooled analysis showed no such role, although the analysis showed heterogeneity in their results.³² Various plants have shown to possess thyrotropic activities (Table 1). All chamomile, sage, and mountain tea have shown association with lower incidence of thyroid diseases both benign and malignant. A study showed that by drinking 2 to 6 cups these teas per week was associated with a reduced incidence of thyroid disease with no clear explanation for this association. Anti-oxidant, anti-inflammatory and anti-cancer activity of polyphenols, flavonoids and catechins present in these teas may have a role in protection from thyroid diseases both benign and malignant. Further research is needed to explain these associations.³³ Ashwagandha, another herb also known *Withania somnifera* or Indian ginseng, is used in traditional medicines and has shown to normalize thyroid abnormalities in subclinical hypothyroidism in humans after 8 week treatment in a recent small study.³⁴ As in hypothyroidism, certain natural treatment has been shown some efficacy in case of hyperthyroidism. In a human study, *Lycopus europaeus*, commonly called bugleweed has shown to reduce the symptoms of mild

hyperthyroidism and autoimmune Graves' disease, which lead to hyperactivity thyroid gland causing hyperthyroidism.³⁵ Possibly, lithospermic acid and other organic acids present in bugleweed decrease thyroid hormones (T4).³⁶ Bugleweed may inhibits antibodies binding to thyroid gland, a cause of graves disease and may thus help alleviate symptoms of mild hyperthyroidism in Graves disease.³⁷ Other natural supplements such as alpha lipoic acid, lemon balm, and motherwort have also been envisaged as therapeutic options.³⁸ Cochrane database does not recommend any specific formulation for clinical use. A meta-analysis showed that Chinese herbal medicines have shown therapeutic efficacy for hyperthyroidism when added to standard treatment but due to inclusion of the studies with sub optimal design, the results cannot be inferred as strong evidence.³⁹

Use of Yingliu mixture, a preparation of various herbs, mustard seed and oyster when used with anti-thyroid medication Methimazole showed symptomatic and biochemical improvement in humans with hyperthyroidism/graves disease probably by reducing TSH receptor autoantibodies (TRAb), TNF- α and IL-10, levels and increasing CD4+ CD25+.⁴⁰ Role of natural treatment in thyroid tumors has also been explored. An animal study showed that a seaweed plant, *Fucus vesiculosus* has shown to inhibit thyroid tumor cell growth in laboratory environment; however, human data in this regard are lacking.⁴¹ Haizao Yuhu Decoction (HYD), a constituent of a Chinese herb, *Thallus Sargassi Pallidi* and *Radix Glycyrrhizae*, has shown to reduce size of thyroid gland (Goitre) by regulating thyroid hormone synthesis in animals.⁴² Various natural treatments have been investigated as an alternative treatment of thyroid diseases but more robust evidence is required before any specific kind of natural therapy can be recommended.

Table 1 - Effect and possible mechanism of various plants preparations on thyroid function.

Plant preparation	Effect on thyroid function	Possible mechanism
Chamomile, Sage and mountain tea	Lower incidence of benign and malignant thyroid disease	Anti-oxidant, anti-inflammatory. Role of polyphenols, flavanoids in anti-cancer effect
Ashwagandha (<i>Withania somnifera</i> Solanaceae)	Increased thyroid hormones levels	Anti-oxidant
Bugleweed (<i>Lycopus europaeus</i>)	Lowers thyroid hormone levels	Inhibition of autoantibody binding receptor activity
Yingliu mixture (mixture of various herbs, mustard seeds and oyster)	Helps in reducing thyroid hormone	TRAb, TNF- α and IL-10, levels and increasing CD4+ CD25+
Haizao Yuhu Decoction (HYD), Constituent of Chinese herb	Reduce thyroid gland (Goitre)	Regulation of thyroid hormones synthesis

TRAb: thyroid stimulating hormone receptor antibodies, TNF- α : tumor necrosis factor

A summary of effects of *S. costus* on thyroid function is shown in **Table 2**.

Role of *S. costus* in thyroid disorders and other human disease and its side effects. The potential role of *S. costus* has been explored in the treatment of various diseases. In an animal study, *S. costus* root extract decreased sodium and calcium ions and reduced renal toxic effects caused by ethephon (2-chloroethylphosphonic acid), a plant growth promoter used to control the plant growth process.⁴³ A study by Abd Eldaim et al⁴⁴ showed protective effect of *S. costus* on ethephon induced reproductive toxicity in rats by ameliorating sperms abnormalities, testicular tissue and DNA damages, P53 protein expressions. Dehydrocostus lactone, a sesquiterpene from *S. costus*, suppresses allergic airway inflammation by binding to dimerized translationally controlled tumor protein, a protein involved in many allergic disorders.⁴⁵ *Sesquiterpene lactones* from *S. costus* root extracts and semi synthetic sesquiterpene analogues play a role in tumor necrosis factor, an inflammatory cytokine inhibition.⁴⁶

In-vitro study has shown that in hepatocellular carcinoma, the volatile oil from *S. costus* inhibits the epithelial growth factor receptor tyrosine kinase-mediated signalling pathway and exerts its antitumor effect.⁴⁷ In a small human study Upadhyay et al⁴⁸ showed that *Aquous extract* of *S. costus* improved clinical and biochemical parameters, coronary circulation and myocardial function in patients suffering from ischemic heart disease.

The role of *S. costus* has been explored in various endocrine diseases. In animal models, the alcoholic extract of the root of *S. costus* improved hypoglycemic

response without increase in plasma insulin with initial accumulation of glycogen in the liver followed by its depletion. Its effect on the histology of thyroid gland was shown to be stimulatory, no toxic effect was observed in liver (on doses up to 400 mg/kg body weight) and no change was observed in adrenal gland and pancreas.⁴⁹

Recently, a study in adult rats evaluated the effect of root extract of *S. costus* on thorium toxicity in brain also assessed the antioxidant effect and modulation activity of thyroid gland. Thorium accumulation caused disturbance in sodium and potassium ions and decrease in monoamines in brain also lead to oxidative stress which was evident by increased lipid peroxidation and decrease glutathione content. Thorium also increased thyroid-stimulating hormone (TSH), triiodothyronine (T3), and thyroxine (T4) levels. These effects of thorium were mitigated with prior oral administration of *S. costus* extract suggesting its protective effect mainly through its antioxidant mechanism.⁴⁵ Antioxidant properties of various plant extracts may be an important mechanism involved in potentiating their medicinal use in various ailments.⁴⁶

Renal, hepatic and lipid abnormalities are seen in thyroid dysfunction.^{50,51} Ethanolic extract of *S. costus* has shown hepatoprotective effect in rats, poisoned with carbon tetrachloride. Liver plays an important role in regulating metabolism of thyroid hormones and similarly thyroid hormones regulate liver function. A study showed that as compared to non-treated mice, treatment with *S. costus* root extract alleviated hyperthyroidism and hypothyroid induced hepatic enzymes derangements. The same study also revealed ameliorating effects of *Costus extract* on altered TSH, T4, sodium, potassium, chloride, albumin, creatinine, urea, calcium ions, cholesterol and triglycerides levels

Table 2 - Summary of effects of *Saussurea costus* (*S. costus*) on thyroid function.

Authors/references	Effect of <i>S. costus</i> on thyroid function
Ansari et al ² 2019	Alleviation of hyper/hypothyroidism induced hepatic enzyme derangements
Bolkiny et al ⁵² 2019	Ameliorating effects on altered thyroid stimulating hormone, thyroxine, sodium, potassium, chloride, albumin, creatinine, urea, calcium ions, cholesterol and triglycerides levels in hypo and hyperthyroidism.
Bolkiny et al ⁵² 2019	Normalized of lipid abnormalities by reducing plasma low-density lipoproteins (LDL) cholesterol, possibly through increased LDL receptor activity
Ahmed et al ⁵⁴ 2018	Amelioration of most signalling pathways and in different tissues in hyperthyroidism through flavanoids reducing thyroid peroxidase activity (may be pronounced during iodine deficiency)
Ahmed et al ⁵⁴ 2018	Chelating effect through bonding with inorganic iodide in amelioration of hyperthyroidism
Alnahadi et al ⁴ 2017	Alleviation of pesticide induced toxic effects on thyroid gland function by improving histomorphological changes in thyroid gland
Alnahadi et al ⁴ 2017	Hypolipidemic effect in hypothyroidism induced hyperlipidemia and favourable modulating impact on the thyroid hormones

in hypo and hyperthyroid mice.⁵² Thyroid hormones may affect renal, electrolytes and mineral metabolism; however, the exact mechanism for these changes is not clear. Some authors have reported altered levels of electrolytes in hypo and hyperthyroidism whereas some contradicts this observation.⁵³ Possibly due to altered metabolic clearance, cholesterol, low density lipoprotein (LDL) levels are increased in hypothyroidism. In a mice study, oral *S. costus* treatment normalized these lipid abnormalities by reducing plasma LDL cholesterol, possibly through increased LDL receptor activity.⁵² A study from Egypt by Sahar et al⁵⁴ showed that a polyherb with *S. costus* “as one of its constituents at low doses” was effective in treating LT₄ induced hyperthyroidism in rats and found it to be safer than anti thyroid drug Carbimazole and ameliorated most signalling pathways and in different tissues. These favorable effects of polyherb on thyroid gland may have been induced by flavonoids such as dillapiole, costunolide and caffeic acid by reducing thyroid peroxidase activity. These effects may be pronounced when iodine is deficient. Other flavonoids, such as kaempferol and quercetin, have also shown irreversible inhibitory effect on thyroid peroxidase activity. Additionally, Tannins like gallic acid and epigallocatechin gallate, which exhibit chelating effect through bonding with inorganic iodide might play a role in ameliorating hyperthyroidism.⁵⁴ Another

animal study by Han et al⁵⁵ in Saudi Arabia assessed the protective effect of aqueous extract of *S. costus* and showed alleviating toxic effects of pesticide on thyroid gland function. Prior treatment by *S. costus* extract in pesticide intoxicated rats improved histomorphological changes in thyroid gland and up modulated thyroid hormones suggesting its protective effect against adverse impact of deltamethrin, a pesticide. This may be related to antioxidant activity of *S. costus*. As hypothyroidism may induce hyperlipidemia, the same study also revealed hypolipidemic effect of the extract of *S. costus* which may be linked to its favorable modulating impact on the thyroid hormones.⁴ Based on such observations, it was proposed that *S. costus* roots can be used as an adjuvant co-therapy to propylthiouracil and thyroxine treatment in hypo- and hyperthyroidism respectively.⁵² A schematic diagram of various biological effects of *S. costus* is shown in **Figure 1**.

Safety and side effects of *S. costus*. Not much information is available about safety and side effect profile of *S. costus*. Generally, *S. costus* root may be safe when taken appropriately by mouth but *S. costus* may contain a contaminant called aristolochic acid which may have nephrotoxic and carcinogenic effects.⁵⁵ Safety of *S. costus* has not been ascertained in pregnant or breast-feeding women. *Saussurea costus* may cause an

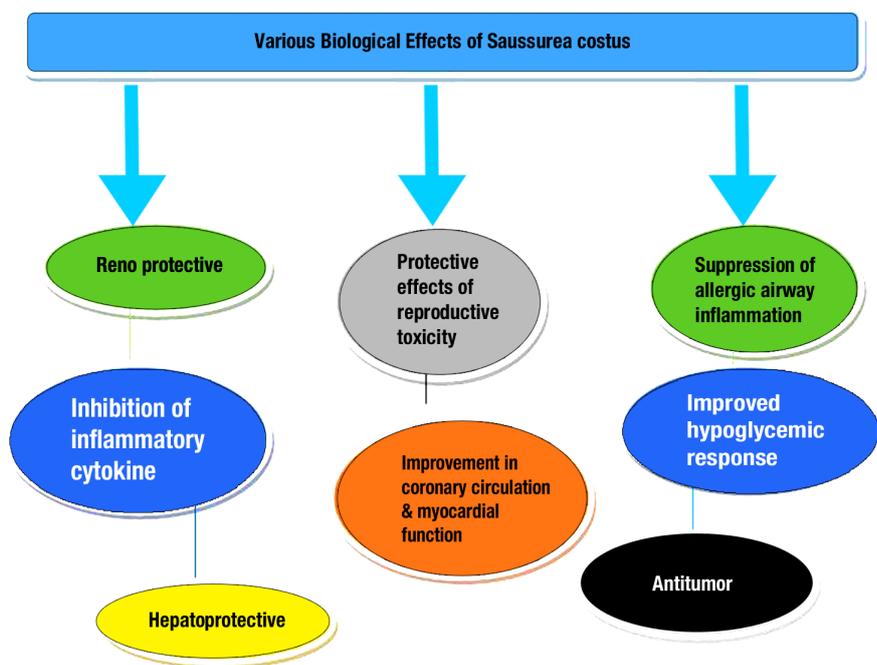


Figure 1 - Schematic diagram of various biological effects of *Saussurea costus*.

allergic reaction in those who are allergic to *Saussurea species*, their constituents including the sesquiterpene lactones (STL). Those exposed to STLs, have been observed to develop contact dermatitis. Concerns have been raised about their concerns regarding the genotoxic embryotoxic potential of these compounds. In vivo and vitro assays have reported mutagenic effect of STLs.⁵⁶

In conclusion, natural therapies are not usually considered a part of standard care modern medicine which is evidence based. It has been envisaged to use natural therapies as a co treatment along with standard treatment speculating absence of side effects of natural treatments and in quest to do more to alleviate ones symptoms and improve health. Available data has shown some role of *S. costus* in the management thyroid disorders in animal models but has not been proven for clinical use. The current available evidence is inconclusive regarding thyrotropic activities of *S. costus* and its potential role in the management of thyroid disorders in humans. More research is needed quantify the effectiveness of *S. costus* for its use in thyroid disorders.

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