# We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

**4,800**
Open access books available

**122,000**
International authors and editors

**135M**
Downloads

Our authors are among the

**154**
Countries delivered to

**TOP 1%**
most cited scientists

**12.2%**
Contributors from top 500 universities

CLARIVATE ANALYTICS BOOK CITATION INDEX INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

## Interested in publishing with us?
## Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

15

# Synthetic and Plant Derived Thyroid Hormone Analogs

Suzana T. Cunha Lima[1], Travis L. Merrigan[2] and Edson D. Rodrigues[3]
[1]*Federal University of Bahia*
[2]*Community Colleges of Spokane*
[3]*Centro Universitário Estácio da Bahia*
[1,3]*Brazil*
[2]*USA*

## 1. Introduction

Nuclear receptors (NRs) are transcription factors that regulate gene expression in response to small signaling molecules. The NR family includes receptors for thyroid hormone (TH) (Yen, 2001), retinoids, vitamin D, steroid hormones, fatty acids, bile acids and cholesterol derivatives, a variety of xenobiotics and other ligands. Additionally, other members are called orphans and could either bind to ligands that have not yet been identified or modulate gene expression in a ligand independent fashion (Webb et al., 2002).

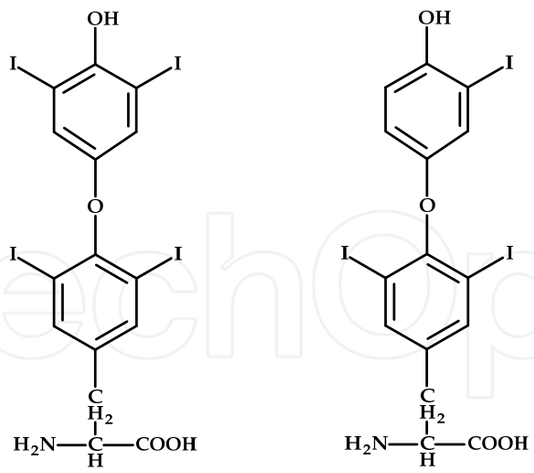
Since NR play important roles in development and disease, they are important candidates for pharmaceuticals. This family of proteins can be modulated by natural and synthetic ligands and are therefore promising targets for drug discovery. The natural ligands may include different kinds of plant molecules or even a combination of compounds present in raw extracts of medicinal plants.

### 1.1 Compounds that bind NR

Ligands that target NRs include TH, glucocorticoids, estrogens for hormone replacement therapy (HRT), the diabetes drug thiazolidinedione, synthetic retinoids, and many others. Though the list of possible targets is extensive, it is restricted by the fact that NR ligands have both beneficial and deleterious effects. For instance, TH improves overall lipid balance and promotes weight loss by increasing metabolism, but causes tachycardia that can be severe enough to lead to heart failure, muscle wasting and osteoporosis (Felig & Baxter, 1995; Braverman et al. 2000). Likewise, estrogen use in HRT alleviates symptoms of hot flashes and reverses bone loss, but increases the risk of breast and uterine cancers, and stroke (Gustafsson, 1998; McKenna & O´Mally, 2000; McDonnel & Norris, 2002).

### 1.2 Thyroid hormone receptor (TR) isoforms

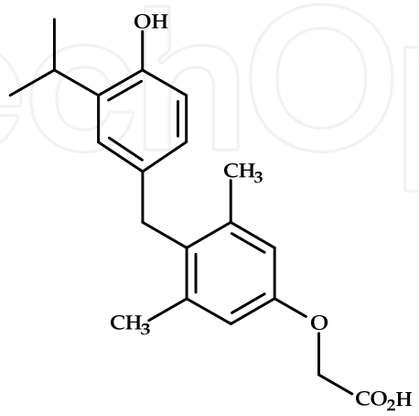
Thyroid hormone signals are transduced by two related thyroid receptor subtypes, TR α and TR β (Figure 01.) which are encoded by different genes (Gauthier et al., 1999).




**Thyroxine** **Triiodothyronine**

Fig. 1. Chemical structures of thyroid hormones thyroxine (α) and triiodothyronine (β).

Studies of TR isoform-specific knockout mice and patients with resistance to thyroid hormone syndrome suggest that TR α mediates the effects of thyroid hormone on heart rate, whereas analogs that exclusively stimulate TR beta might have desirable effects without causing cardiac distress. Indeed, animal studies using thyroid receptor agonists with modest TR beta selectivity have validated this hypothesis (Taylor et al. 1997; Baxter et al., 2001; Grover et al., 2003). However, structure-based approaches to develop ligands with further improvements in isoform specificity are limited by the fact that the LBDs of TR alfa and TR beta are ~75% identical in amino acid sequence, and that the internal hydrophobic cavities that hold the hormone, called the pocket of the receptor, differ by just one amino acid (Ser-277 in TR alfa versus Asn-331 in TR beta). Therefore, it would be interesting to develop selective TR agonists that increase metabolism and improve lipid balance, but do not cause side effects on the heart. The first compound to show this property was GC-1 (Figure 02), an analog of T3 (Chiellini et al., 2002).



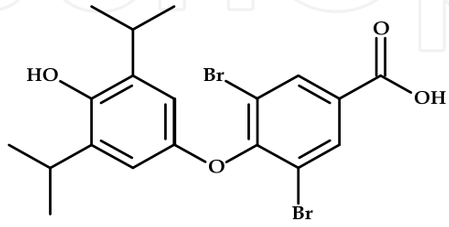

**GC-1**

Fig. 2. Chemical structure of the β-specific thyroid hormone receptor agonist GC1.

## 2. TR antagonists

### 2.1 First generation of synthetic ligands

TR antagonists would be useful for short-term relief from the symptoms of hyperthyroidism, and might even be used on a long term basis. The first generation of T3 antagonists, which include DIBRT, HY-4, and GC-14, used the "extension hypothesis" as a general guideline in hormone antagonist design (Baxter et al., 2002; Yashihara et al., 2001; Chiellini et al., 2002). This extension in the ligand structure blocks normal receptor function by occupying the pocket region where the hormone normally binds.




**Thyroid hormone receptor antagonist DIBRT**

Fig. 3. Chemical structure of thyroid hormone receptor antagonist DIBRT.

### 2.2 Novel series of antagonist compounds

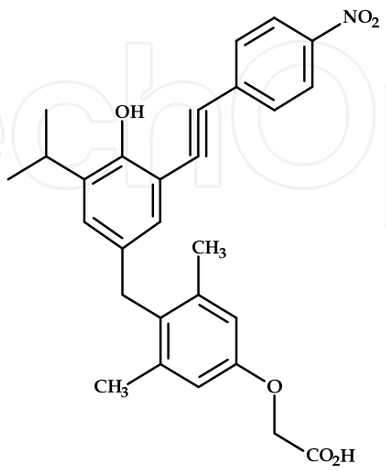
Although the "extension hypothesis" is applicable to the design of nuclear receptor antagonists, the nature of chemical groups that convert agonist ligands to antagonists will likely depend on specific interactions between residues of the receptor and the ligand extension, to help stabilize the antagonist conformation. Following the first designed TR antagonists it was reported the design and synthesis of a novel series of compounds sharing the GC-1 halogen-free thyronine scaffold (second generation). One of them (NH-3) is a T3 antagonist with improved TR binding affinity and potency that allow for further characterization of its observed activity. One mechanism for antagonism appears to be the ability of NH-3 to block TR-coactivator interactions (Ngoc-Ha et al., 2002). NH-3 (Figure 04.) is the first T3 antagonist to exhibit potent antagonism in vivo and therefore may prove to be a generally useful tool for studying the effects of TR inactivation in a variety of animal models. Until now, such studies have been done primarily using TR-knockout mice because a pharmacological tool for inducing TR inactivation has not been available. TR inactivation was limited under previous ligands because they have only a modest affinity and potency for the thyroid hormone receptor (TR), which limits studies of their actions. T3 antagonists such as NH-3 may be useful therapeutic agents in the treatment of hyperthyroidism and other metabolic disorders.

## 3. Plant ligands of nuclear receptors

### 3.1 Estrogen analogs

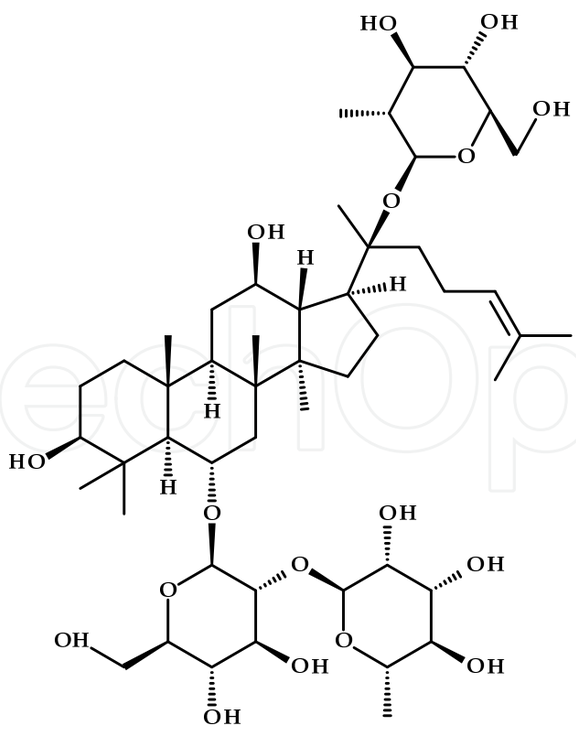
Although modern research on drug discovery involves the design of hormone analogs based on the structure of the receptor, natural ligands can also be found in nature. Estrogen analogs are most common and have been discovered in a variety of plants. Ginsenosides (Figure 05.)

for instance, found in *Ginko biloba*, have demonstrated pharmacological effects on the central nervous, cardiovascular, and endocrine systems. Although no direct interaction of the compound with estrogen receptor seems to be necessary for estrogenic action, the author classified this plant ligand as a novel class of potent phytoestrogen (Chan et al., 2002).




**NH-3**

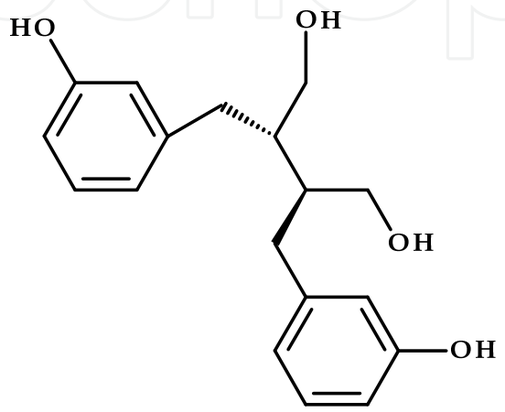
Fig. 4. Chemical structure of the thyroid hormone receptor antagonist NH-3 (Lim et al. 2002), designed by the extension hypothesis from GC-1 compound.




**Ginsenoside**

Fig. 5. Chemical structure of a ginsenoside.

Recently, *Tephrosia candida* (native to the tropical foothills of the Himalayas in India and introduced in South America) was reported to contain estrogenically active chemical constituents, which acted by binding to estrogen receptor ERα. Results were interpreted via virtual docking of isolated compounds to an ERα crystal structure (Hegazy et al., 2011). Also sesame ligands, from *Sesamum indicum* (flowering plant, native to Africa and widely naturalized in tropical regions around the world), and their metabolites have been evaluated for estrogenic activities (Pianjing et al., 2011). Two of them, enterodiol (Figure 06.) and enterolactone, have been indicated to have estrogenic/antiestrogenic properties on human breast cancer cells.




**Enterodiol**

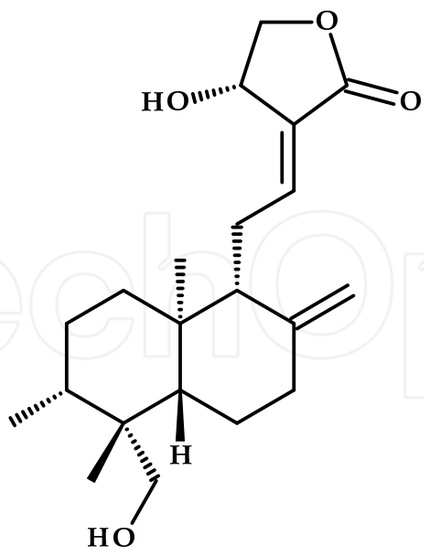
Fig. 6. Chemical structure of an enterodiol

### 3.2 Androgen analogs

As compared to estrogen analogs, androgen-like compounds in the flora are less frequently referred in scientific literature. But a few chemicals have shown androgen-like activity. Andrographolide (Figure 07.), an herbal medicine, inhibits interleukin-6 expression and suppresses prostate cancer cell growth (Chun et al., 2010). According to the author, this phytochemical could be developed as a therapeutic agent to treat both androgen-stimulated and castration-resistant prostate cancer. Another compound, Isoangustone A, present in hexane/ethanol extract of *Glycyrrhiza uralensis*, induces apoptosis in DU145 human prostate cancer (Seon et al., 2010). This species, also known as Chinese liquorice, is a flowering plant native to Asia, which is used in traditional Chinese medicine.

#### 3.2.1 Androgen ligands in the diet

Some studies have specifically demonstrated that consuming one or more portions of broccoli per week can reduce the incidence of prostate cancer, and also induce the progression from localized to aggressive forms of prostate cancer (Trakka, et al. 2008). The reduction in risk may be modulated by glutathione S-transferase mu 1 (GSTM1) genotype, with individuals who possess at least one GSTM1 allele (i.e. approximately 50% of the population) gaining more benefit than those who have a homozygous deletion of GSTM1, according to the author.




**Andrographolide**

Fig. 7. Chemical structure of an andrographolide.

From these studies, we can conclude that diet has a significant influence on the activity of the androgen receptors and possibly other types of nuclear receptor. If so, a wide range of diseases may be avoided by increasing intake of food that contains hormone analogs or other nuclear receptor modulators.

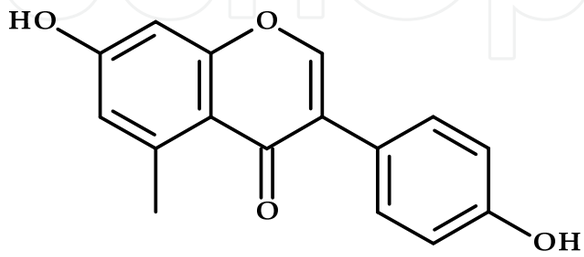
### 3.3 Plant thyroid hormone analogs

Concerning the thyroid hormone receptor, we find even fewer studies about thyroid hormone ($T_3$ and $T_4$) analogs in plants. In a work about patients where thyroid have been removed partially or totally due to thyroid cancer, the plant *R. rosea* was seen as a viable alternative treatment for the symptoms of short-term hypothyroidism in patients who require hormone withdrawal (Zubeldia et al., 2010). Some compounds of natural origin have also shown to affect the thyroid hormone feedback system by interfering with different components of this homeostatically regulated system: biosynthesis, secretion and metabolism, transport, distribution, and action of thyroid hormones, including the feedback mechanism.

Genistein (Figure 07.) and daidzein, the major components of soy, influence thyroid hormone synthesis by inhibition of the iodide oxidizing enzyme thyroperoxidase. This interferes with thyroid hormone transport proteins and 5′-deiodinase type I activities in peripheral tissues, leading to altered thyroid hormone action at the cellular level. Synthetic flavonoids, such as F21388, which is structurally similar to thyroxine, cross the placenta and also reach the fetal brain of animal models (Hamann et al. 2008).

The cruciferous family was also referred when we consider thyroid modulators in plant. In a study that examined the effects of both soy-foods and specific phytoestrogenic molecules on the development of thyroid cancer in humans it was demonstrated that intake of plants from that family decreases the risk of this kind of cancer (Horn-Ross et al., 2002). The

compounds that may be associated with this effect are, according to the author, isoflavones, lignans and 2-hydroxyestrogens. Although anti-carcinogenic response was linked to those molecules, it was not explained how they may affect metabolism in humans or their physiological mechanism of action. Another compound, indole-3-carbinol, the most studied component of cruciferous vegetables, has been demonstrated to have chemopreventive activity in several different animal models of carcinogenesis, including mammary gland, but in another hand, the same compound has also been reported to exhibit adverse promoting effects, including liver and thyroid gland tumorigenesis (Murilo & Mehta, 2001).




**Genistein**

Fig. 8. Chemical structure of a Genistein.

It seems to have a cross talk between the thyroid hormone receptor and the estrogen receptor. Our recent results (Cunha Lima et al, not published) have shown that ligands originally referred for thyroid diseases have activated estrogen receptor in transient transfection assays. This could explain why phytoestrogens have caused responses in thyroid cancer and thyroid hormone analogs have also effect in breast cancer, for example.

### 3.4 Toxicity of thyroid hormone analogs

Considering medications used for thyroid hormone replacement, as sodic levothyroxine, a$T_4$ analog, the side effects referred (Cunha Lima , 2008) may include headache, chest pain, rapid or irregular heartbeat, shortness of breath, trembling, sweating, diarrhea and weight loss. The most severe responses are those related to the heart, which can lead to serious cardiopathies and are due to the α isoform of the receptor, as cited previously. A single base difference in the pocket of the protein can lead to these harmful responses. This means that we have a two step work on the search for new agonists and antagonists: they should mimesis the response caused by the thyroid hormone (or antagonize it, depending on the disease) and second, they should have a β specificity to avoid tachycardia and more serious heart problems.

In the other hand, some compounds that modulate TR may not be specific for this receptor, as it is very common with estrogen ligands. Since women hormone analogs may interfere with the function of the thyroid, as referred before with some flavonoids, they may have beneficial effects in cases of thyroid cancer. Nevertheless those compounds may influence thyroid actions at the cellular level and could cause side effects harmful for healthy individuals.

### 3.5 Ethnobotanical search for TR plant ligands

Since thyroid hormone analogs have much fewer discovered natural ligands, and most of those nuclear receptor ligands are found from plant sources, ethnobotanical surveys can be a good strategy to discover hormone analogs in nature. This approach has an increased probability of success in locations with higher biodiversity; because they contain a privileged number of candidate species. Along with botanical diversity, ethnobotanical surveys are likely to succeed where the population has an in depth knowledge of medicinal plants and systematically uses those plants to treat a range of metabolic disorders.

In a recent work (Cunha Lima et al., 2008) we investigated the medicinal flora used for the treatment of metabolic disorders in Salvador, Bahia, in Northeastern Brazil. The city has hot, tropical weather, with average daily highs reaching $17^0$C in the winter and $38^0$C in the summer. Northeastern Brazil is the economically poorest region of the country, 60% of the active population has an income under $100 per month, (Brazilian Institute of Statistics and Geography, 2003) and many residents depend on medicinal plants to treat multiple ailments and diseases.

The referred study analyzed the knowledge of the urban population of Bahia city on the use of potentially therapeutic plants for the treatment of Diabetes mellitus type 2 (DM2), thyroid diseases, obesity and cardiopathies. Questionnaires were applied to traditional healers as well as to patients of the thyroid disease and diabetes ambulatory in the Hospital from Federal University of Bahia (UFBA). Thirty-one cited species were collected, taxonomically classified, and stored in Alexandre Leal Costa Herbarium (ALCB) from UFBA. Leaves were most commonly used in preparations (87%), followed by the whole plant (10%), and fruits and seeds (3%). The majority of the preparation (88%) required decoction (boiling the plant tea for at least 5 minutes); the rest includes infusion (liquid preparation without boiling) and ingestion of the fresh plant. Among the plant parts used the leaves were more frequent (87%), followed by the whole plant (10%), seeds and fruits (3%). The families Asteraceae (17%), Lamiaceae (15%) and Myrtaceae (12%) were the most cited among plants referred.

This survey identified botanical families frequently cited in other surveys of medicinal plant use in Brazil. In two studies conducted in the state of Rio de Janeiro, one in Rio city (Azevedo & Silva) and one in the reservation of Mangaratiba (Medeiros et al., 2005), the Asteraceae and Lamiaceae family of plants were the most frequently cited, the same happening in Conceição Açú-MT (Pasa et al., 2005). Species from the Asteraceae family were also the most frequently noted for medicinal use in a survey done in Ingaí-MG (Botrel et al., 2006) and by a "quilombola"(community of people descended from former Brazilian slaves), among the plants with possible action in the central nervous system (Rodrigues & Carlini, 2004). These data suggest that the Asteraceae and Lamiaceae family have excellent pharmacological potential on different kinds of diseases and they are currently being investigate in many clinical studies.

In the survey performed by our group in Salvador (Cunha Lima, 2008), the plant most used for the treatment of DM2 belongs to the genus Bauhinia (pata-de-vaca). The most commonly cited species in this work, *B. forficate*, has the flavonoid Kaempferitrina, Kaempferol-3-O-α-Diraminoside and the steroid Sitosterol as the hypoglycemic active principle (da Silva & Cechinel Filho, 2002). *Terminalia catappa* was the second most cited species for the treatment

of DM2. Ahmed et al. (2005) demonstrated that the extract from this plant also has hypoglycemic activity and improves general clinical conditions.

Among the plants used for obesity control, with probable effect on the metabolism, *Borreria verticillata* (carqueija or vassorinha-de-botão) was the species with the highest number of references in our survey. This plant, also used for the treatment of diabetes type 2, is found across Brazil. Phytochemical studies have demonstrated the presence of alcaloids and iridoids (Vieira et al., 1999) associated with their antipyretic and analgesic properties, although no active principle linked to obesity was confirmed. The leaves of *Bauhinia forficata*, *Costus spiralis* and *Theobroma cacao*, were used as teas in combination with the commercial medical prescriptions sibutramine (an oral anorexiant used for weight control) and niphedipine (a dihydropyridine calcium channel blocker used for high blood pressure) indicated by the physicians from the Diabetes Ambulatory of the Federal University of Bahia Hospital (HUPES). The teas of *Tragia volubilis* leaves and the seeds of *Ocimum gratissimum* were also used in combination with niphedipine and aspirin.

The problems related to the thyroid attended at the Hospital of Federal University of Bahia include throat itch, tachycardia, arm pain, chokings, dizziness and fainting. The most extreme side effects symptoms are associated with the T4 hormone replacement for patients whose thyroid was partially or completely removed. The doses used vary from 50 to 200mcg/day of sodic levotiroxine. In addition to the plants cited for treatment of thyroid problems, watercress (*Nasturtium officinale* R.Br.) and spring-green (*Brassica oleraceae* L.) were eaten as iodine source. Although the majority of the patients did not tell their doctors they were using those teas, there are no reported adverse side effects due to the combination of the plant products and the medications indicated, nor any reference in the literature about harmful effect of such interaction.

Ethnobotanical surveys are good source of information for drug candidates and offer a less expensive way of finding hormone analogs than the design of synthetic compounds. The cited information represents an important source of regional knowledge on plants with pharmacological potential and presents 31 candidates (Table 1) that might contain triiodothyronine (T3) and thyroxin (T4) analogs, including agonists, antagonists and other compounds able to modulate thyroid receptor that may act against metabolic disorders.

Brazil has more than 55.000 species of cataloged plants (Simões & Schenkel, 2002), a significant portion of which has some phytotherapic activity known by the local population. However, the number of patents on plant-based pharmaceuticals is very small. In particular, the capital of Bahia has numerous plants used by inhabitants to treat diseases and this use is part of the local culture, based in the Candomblé (religion of African origin which uses many plants in rituals and treatments). Traditionally, information about medicinal plants is shared orally. Therefore, it is necessary to scientifically systematize and analyze this phytotherapic knowledge so that those species can be identified and their pharmacological properties tested.

Table 2 lists the species referred in this survey that had their active principles identified and/or properties confirmed, and the bibliographic references where the data was obtained. These works include results from clinical and experimental studies aiming the confirmation of therapeutic properties.

| | Vernacular Name | ALCB | Family | Species |
|---|---|---|---|---|
| 1. | aroeira | 76103 | Anacardiaceae | *Schinus terebinthifolius* Raddi |
| 2. | graviola | 76101 | Annonaceae | *Annona muricata* L. |
| 3. | jaca-de-pobre | 76154 | Annonaceae | *Annona montana* Macfad |
| 4. | carrapixo-de-agulha | 76135 | Asteraceae | *Bidens bipinnata* L. |
| 5. | carrapixo-preto | 76111 | Asteraceae | *Bidens pilosa* L. |
| 6. | chapéu-de-couro | 76138 | Asteraceae | *Zinnia elegans* Jacq. |
| 7. | urucum | 76100 | Bixaceae | *Bixa orellana* L. |
| 8. | cactus | 78152 | Cactaceae | *Cereus sp.* L. |
| 9. | pata-de-vaca | 76159 | Caesalpiniaceae | *Bauhinia forficata* Link |
| 10. | amendoeira | 76096 | Combretaceae | *Terminalia catappa* L. |
| 11. | cana-de-macaco | 76122 | Costaceae | *Costus spiralis* (Jacq,) Roscoe |
| 12. | mamona | 76141 | Euphorbiaceae | *Ricinus communis* (L.) Müll. Arg. |
| 13. | urtiga | 76108 | Euphorbiaceae | *Tragia volubilis* (L.) Müll. Arg. |
| 14. | alecrim ou alecrim-do-reino | 76128 | Lamiaceae | *Rosmarinus officinalis* L. |
| 15. | hortelã-grosso | 76110 | Lamiaceae | *Plectranthus amboinicus* (Lour.) Spreng |
| 16. | quiôiô | 76112 | Lamiaceae | *Ocimum gratissimum* L. |
| 17. | canela | 76099 | Lauraceae | *Cinnamomum zeylanicum* Breyn |
| 18. | erva-de-passarinho | 76107 | Loranthaceae | *Struthanthus flexicaulis* Mart. |
| 19. | Murici | 78150 | Malpighiaceae | *Byrsonima sericea* DC. |
| 20. | barbatimão | 76158 | Leguminosae | *Abarema cochliocarpum* (Gomez) Barnbey |
| 21. | jamelão | 76156 | Myrtaceae | *Syzygium cumini* (L.) Skeels |
| 22. | pitangueira | 76163 | Myrtaceae | *Eugenia uniflora* L. |
| 23. | capim- cidreira ou capim-santo | 75150 | Poaceae | *Cymbopogon citratus* Stapf. |
| 24. | roma | 76162 | Punicaceae | *Punica granatum* L. |
| 25. | carqueija ou vassourinha-de-botão | 76132 | Rubiaceae | *Borreria verticillata* (l.) G.Mey |
| 26. | laranjeira | 76097 | Rutaceae | *Citrus aurantium* L. |
| 27. | vassourinha | 76114 | Scrophulariacea | *Scoparia dulcis* L. |
| 28. | cacau | 78148 | Sterculiaceae | *Theobroma cacao* L. |
| 29. | erva cidreira | 76105 | Verbenaceae | *Lippia alba* N.E.Brown |
| 30. | melissa | 76120 | Verbenaceae | *Lippia alba* L.. |
| 31. | levante | 76123 | Zingiberaceae | *Alpinia nutans* Roscoe |

Table 1. Medicinal plants candidates for thyroid hormone analogs according to ethnobotanical research in Salvador-Bahia, Brazil (Cunha Lima, 2008).

| Species | Properties associated to the referred use | Reference |
|---|---|---|
| *Bauhinia forficata* | The flavonoids Kaempferitrin and Kaempferol-3-*O*-α-Diraminoside and the steroid Sitosterol found in the extract own hypoglycemic properties. | da Silva & Cechinel Filho (2002) |
| *Terminalia catappa* | Leaf extract prepared in different ways produced antidiabetic response with 1/5 of the lethal dose revealed by the lipid, creatine and urea profile as also serum alkaline phosphatase. The same dose caused anti-diabetic effects with fruit extracts. | Ahmed et al (2005)<br>Nagappa et al (2003) |
| *Rosmarinus officinalis* | The anti-oxidants impair the mechanism of oxidation that occurs in cancer, heart disease , atherosclerosis and aging. | Ibanez et al (2000) |
| *Cymbopogon citratus* | Intense anti-oxidant activity due to the phenolic composition. The essential oil extracted from the leaf causes depression of the CNS in rats. | Prakash et al (2007); Negrelle (2007) |
| *Bidens pilosa* | Deposits of opaline silica in the leaves and extracts of the whole plant obtained with n- hexane demonstrated significant anti-cancer activity. | Parry (1986); Sundararajan et al (2006) |
| *Lippia alba* | Flavonoids found in this plant are active against different kinds of cancer including thyroid cancers. | Ren et al (2003) |
| *Annona muricata* | Graviola, a Brazilian fruit from the plant *Annona muricata* demonstrated anti-diabetic effect greater than the medication Clorpropamide, oral hypoglycemic from the sulphonilurea class. | Carvalho (2005) |
| *Annona montana* | The plant has kinase protein inhibitors that act creating obesity resistance and increasing insulin production. | Bialy et al (2005) |
| *Syzygium cumini* | The species presents anti-diabetic action in clinical and animal studies. Stem extracts stimulate the development of cells positive for insulin in the pancreatic epithelial duct. | Mentreddy (2007); Teixeira et al (2004); Schossler et al (2004) |
| *Citrus aurantium* | The combination of *C. aurantium* extract, caffeine and Saint John´s Herb (*Hypericum perforatum)* is safe and effective for weight lost and improvement of lipid levels in obese adults. | Colker et al (1999) |
| *Alpinia nutans* | The hidroalcoolic extract induces a dose-dependent decrease in artery pressure in rats and dogs. | Mendonça et al (1991) |
| *Lippia alba* | The aqueous extract of leaves from this plant, associated to the ones from *Melissa officinalis* and *Cymbopogon citratus* caused significant reduction in cardiac rhythm in rats, without changing the contractile strength. | Gazola et al (2004) |

| Species | Properties associated to the referred use | Reference |
|---|---|---|
| *Bauhinia forficata* | The rats treated with decoction of the plant leaves demonstrated significant reduction in serum and urine glucose. The results obtained with the purified extracts confirmed the therapeutic use for treatment of diabetes in clinical studies. | Pepato et al (2002); da Silva & Cechinel Filho (2002) |
| *Eugenia uniflora* | The empiric use of this plant is due to the hypotensive effect, mediated by vessel dilatation and weak diuretic effect that may be related to increased renal blood flow. | Consolini et al (1999) |
| *Punica granatum* | Flavonoid rich fractions obtained from fruit extracts demonstrated antiperoxidative effect. Malondialdehyde, hydroperoxide, and conjugated dienes were significantly decreased in the liver, while enzymatic activity of catalase, superoxide dismutase and glutathione reductase have shown significant increase. | Sudheesh (2005) |
| *Scoparia dulcis* | Plant extracts were effective on decreasing hyperglycemia and the susceptibility to free oxygen radicals in rats. | Latha & Pari (2004) |

Table 2. Plant species referred in the survey that have their therapeutic properties confirmed or active principles isolated according to scientific publications.

## 4. Conclusion

Studying medicinal plants can be a less expensive way of finding treatments for hundreds of diseases. This can be an important factor in areas where a great part of the population lacks financial conditions of buying allopathic medication and, in the other hand, have a big incidence of metabolic disorders.

The search for hormone analogs in medicinal plants is extremely promising. Over 100 existing nuclear receptors have been identified, not counting the orphan NRs that lack known ligands. Since those transcription factors modulate almost all genetic activity and human physiology, they are important targets for drug discovery. Besides the ligands, usually hormones, other molecules can also modulate nuclear receptors, including cofactors (co-activators and co-repressors), responsive elements, and other ligands (not exclusively the hormone that naturally binds this receptor). According to that, the molecules found in plants do not have to be only analogs of hormones, but also compounds similar to all other complementary modulators of NRs.

Countries with higher biodiversity are good targets for discovery of plant molecules that can control the activity of thyroid receptor. Unfortunately there is not enough scientific knowledge about their medicinal plants or about patent procedures that would guarantee intellectual property of discoveries made by local scientists. In addition to that, the forests are being devastated very fast before important plant compounds can be found. Therefore, additional research needs to be done to identify new ligands and other

molecules in the flora that can modulate TR and may be used in the treatment of diseases related to thyroid malfunction.

## 5. References


Ahmed, S.M., Vrushabendra, B.M., Dhanapal, P.G. & Chandrashekara, V.M. (2005). Anti-Diabetic activity of *Terminalia catappa* Linn. Leaf extracts in alloxan-induced diabetic rats. *Iranian Journal of Pharmacology & Therapeutics*, Vol. 4, No. 1, pp. 36-39. ISSN: 1735-2657.

Azevedo, S.K.S. & Silva, I.M. (2006). Plantas medicinais e de uso religioso comercializadas em mercados e feiras livres no Rio de Janeiro, RJ, Brasil. *Acta Botanica Brasílica*, Vol. 20, No. 1, pp.185-194. ISSN 0102-3306.

Baxter, J. D., Dillmann, W. H., West, B. L., Huber, R., Furlow, J. D., Fletterick, R. J., Webb, P., Apriletti, J. W. & Scanlan, T. S. (2001). Selective modulation of thyroid hormone receptor action. *Journal of Steroid Biochemistry and Molecular Biology,* Vol. 76, No.1-5, pp. 31–42. ISSN: 0960-0760.

Baxter, J.D., Goede, P., Apriletti, J.W., West, B.L. & Feng, W. (2002). Structure-Based Design and Synthesis of a Thyroid Hormone Receptor (TR) Antagonist. *Endocrinology*, Vol. 143, No. 2, pp. 517-524. ISSN: 1945-7170.

Botrel, R. T., Rodrigues, L. A., Gomes, L. J., Carvalho, D.A., & Fontes, M.A.L. (2006). Uso da vegetação nativa pela população local no município de Ingaí, MG, Brasil. *Acta Botanica Brasílica*, Vol. 20, No. 1, pp. 143-156. ISSN: 0102-3306.

Bialy, L., Waldmann, H., Chemie, A. (2005). Review. Inhibitors of protein tyrosine phosphatases: Next-generation drugs? *Angewandte Chemie International Edition*, Vol. 44, No. 25, pp. 3814-3839. ISSN: 1521-3773.

Braverman, E., Utiger, R.D. (2000). *Ingbar, S.H. & Werner, S.C. The Thyroid: A Fundamental and Clinical Text* (9th Edition), Lippincott Williams & Wilkins, Philadelphia. ISBN-10: 0781750474.

Carvalho, A.C.B., Diniz, M.F.F.M., Mukherjee, R. (2005). Hypoglycemic activity studies of some plants used in diabetes treatment in Brazilian traditional medicine. *Revista Brasileira de Farmácia,* Vol. 86, No. 1, pp.11-16. ISSN: 2176-0667.

Chan, R.Y., Chen , W.F., Dong, A., Guo, D. & Wong, M.S. (2002). Estrogen-like activity of ginsenoside Rg1 derived from *Panax notoginseng*. *The Journal of Clinical Endocrinology & Metabolism,* Vol. 87, No. 8, pp. 3691-3695. ISSN: 1945-7197.

Chiellini, G., Nguyen, N. H., Apriletti, J.W., Baxter, J.D. & Scanlan, T.S. (2002). Synthesis and biological activity of novel thyroid hormone analogues: 5'-aryl substituted GC-1 derivatives. *Bioorganic & Medicinal Chemistry Letters,* Vol. 10, No. 2, pp. 333-346. ISSN: 0960-894X.

Chiellini, G., Nguyen, N., Apriletti, J. W., Baxter, J.D., Scanlan, T. S., Laudet V. & Gronemeyer, H. (2002). *The Nuclear Receptor Facts Book. Factsbook Series*, 1st ed., Academic Press, London. ISBN 10: 0124377356.

Chun , J.Y. , Tummala , R., Nadiminty, N., Lou, W., Liu, C., Yang, J., Evans, C.P., Zhou, Q. & Gao, A.C. (2010). Andrographolide, an herbal medicine, inhibits interleukin-6 expression and suppresses prostate cancer cell growth. *Genes Cancer*. Vol. 1, No. 8, pp. 868-876. ISSN: 1947-6019.

Colker, C.M., Kalman, D.S., Torina, G.C., Perlis, T., Street, C. (1999). Effects of *Citrus aurantium* extract, caffeine, and St. John's Wort on body fat loss, lipid levels, and

mood states in overweight healthy adults. *Current Therapeutic Research*, Vol. 60, No. 3, pp.145-153. ISSN: 0011-393X.

Consolini, A.E., Baldini, O.A., Amat, A.G. (1999). Pharmacological basis for the empirical use of *Eugenia uniflora* L. (Myrtaceae) as antihypertensive. *Journal of Ethnopharmacology*, Vol. 66, No. 1, pp.33-39. ISSN: 0378-8741.

Cunha Lima, S.T., Rodrigues, E.D., Melo, T., Nascimento, A.F. Guedes, M.L.S., Cruz, T., Alves, C., Meyer, R., & Toralles, M.B (2008). Levantamento da flora medicinal usada no tratamento de doenças metabólicas em Salvador, BA- Brasil. *Revista Brasileira de Plantas Medicinais,* Vol. 10, No. 4, pp. 83-89. ISSN: 1516-0572.

da Silva, K.L. & Cechinel Filho, V. (2002). Plants of the genus Bauhinia: chemical composition and pharmacological potential. *Química Nova*, Vol. 25, No. 3, pp. 449-454.

Felig, P.F. & Baxter J.D. (1995). *The thyroid: physiology, thyrotoxicosis, hypothyroidism, and the painful thyroid*. Frohman (Eds.), *Endocrinology and Metabolism*, McGraw-Hill, New York. ISBN: 0070204489 / 0-07-020448-9.

Gauthier, K., Chassande, O., Plateroti., M., Roux, J.P., Legrand, C., Pain, B., Rousset, B., Weiss, R., Trouillas, J., Samarut, J. (1999). Different functions for the thyroid hormone receptors TRα and TRβ in the control of thyroid hormone production and post-natal development. *EMBO Journal*, Vol. 18, No. 3, 623 – 631. ISSN: 0261-4189.

Gazola, R., Machado, D., Ruggiero, C., Singi, G., Macedo Alexandre, M. (2004). *Lippia alba*, *Melissa officinalis* and *Cymbopogon citratus*: effects of the aqueous extracts on the isolated hearts of rats. *Pharmacological Research*, Vol. 50, No. 5, pp. 477-480. ISSN: 1096-1186.

Grover, G. J., Mellström, K., Ye, L., Malm, J., Li, Y. L., Bladh, L. G., Sleph, P. G., Smith, M. A., George, R. & Vennström, B., Mookhtiar, K., Horvath, R., Speelman, J., Egan, D. & Baxter, J.D. (2003). Selective thyroid hormone receptor-β activation: A strategy for reduction of weight, cholesterol, and lipoprotein (a) with reduced cardiovascular liability. *Proceedings of the National Academy of Science of the United States of America*, Vol. 100, No. 17, pp. 10067–10072. ISSN: 0027-8424.

Gustafsson, J.A. (1998). Therapeutic potential of selective estrogen receptor modulators. *Current Opinion in Chemical Biology*, Vol. 2, No. 4, pp. 508–511. ISSN: 1367-5931.

Hamann, I., Seidlova-Wuttke, D., Wuttke, W. & Köhrle, J. (2008). Environment and endocrinology: The case of thyroidology. *Annales d'Endocrinologie*, Vol. 69, No. 2, pp. 116-122. ISSN: 0003-4266.

Hegazy, M.E., Mohamed, A.E., El-Halawany, A.M., Djemgou, P.C., Shahat, A.A. & Pare´, P.W. (2011). Estrogenic Activity of Chemical Constituents from *Tephrosia candida*. *Journal of Natural Products*, Vol. 74, No. 5, pp 937–942. ISSN: 0163-3864.

Horn-Ross, P.L., Hoggatt, K.J. & Lee, M.M. (2002). Phytoestrogens and Thyroid Cancer Risk: The San Francisco Bay Area Thyroid Cancer Study. *Cancer Epidemiology Biomarkers Prevention,* Vol. 11, pp.42-49. ISSN: 1055-9965.

Ibañez , E., Cifuentes, A., Crego, A.L., Señoráns, F.J., Cavero, S. & Reglero, G. (2000). Combined use of supercritical fluid extraction, micellar electrokinetic chromatography, and reverse phase high performance liquid chromatography for the analysis of antioxidants from rosemary (*Rosmarinus officinalis* L.). *Journal of Agricultural and Food Chemistry*, Vol. 48, No. 9, pp. 4060-4065. ISSN: 0021-8561.

Latha, M. and PARI, L. (2004). Effect of an aqueous extract of *Scoparia dulcis* on blood glucose, plasma insulin and some polyol pathway enzymes in experimental rat

diabetes. *Brazilian Journal of Medical and Biological Research*, Vol. 37, No. 4, pp. 577-586. ISSN: 1678-4510.

Lim ,W., Nguyen, N., Ha, Y. Y., Scanlan, T. S. & Furlow, J. D. (2002). A Thyroid Hormone Antagonist That Inhibits Thyroid Hormone Action *in Vivo. Journal of Biological Chemistry,* Vol. 277, No. 38, pp. 35664–35670. ISSN: 1083-351X.

McDonnell, D.P. & Norris, J.D. (2002). Connections and regulation of the human estrogen receptor, *Science*, Vol. 296, No. 5573, pp. 1642–1644. ISSN: 1095-9203.

McKenna, N.J. & O'Malley, B.W. (2000). An issue of tissues: divining the split personalities of selective estrogen receptor modulators. *Nature Medicine,* Vol. 6, pp. 960–962. ISSN: 1546-170X.

Medeiros, M.F.T., Fonseca, V.S. & Andreata, R.H.P. (2004). Plantas medicinais e seus usos pelos sitiantes da reserva do Rio das Pedras, Mangaratiba, RJ, Brasil. *Acta Botanica Brasílica*, Vol. 18, No. 2, pp. 391-399. ISSN: 0102-3306.

Mendonça, V.L.M., Oliveira, C.L.A., Craveiro, A.A., Rao, V.S., Fonteles, M.C. (1991). Pharmacological and toxicological evaluation of *Alpinia speciosa*. *Memórias do Instituto Oswaldo Cruz*, Vol. 86, No. 2, pp. 93-97. ISSN: 0074-0276.

Mentreddy, S.R. (2007). Medicinal plant species with potential antidiabetic properties. *Journal of the Science of Food and Agriculture*, Vol. 87, No. 5, pp.743-750. ISSN: 1097-0010.

Murillo, G. & Mehta, R.G. (2001). Cruciferous Vegetable and Cancer Prevention. *Nutrition and Cancer,* Vol. 41 (1-2), pp. 17-28. ISSN: 0163-5581.

Nagappa, A.N. , Thakurdesai, P.A. , Rao, N.V. & Singh, J. (2003). Antidiabetic activity of *Terminalia catappa* Linn fruits. *Journal of Ethnopharmacology*, Vol. 88, No. 1, pp. 45-50. ISSN: 0378-8741.

Negrelle, R.R.B. & Gomes, E.C. (2007). *Cymbopogon citrates* (DC.) Stapf.: chemical composition and biological activities. *Revista Brasileira de Plantas Medicinais*, Vol. 9, No. 1, pp. 80-92. ISSN: 1516-0572.

Ngoc-Ha, N., Apriletti, J.W., Cunha Lima, S.T., Webb, P., Baxter, J.D. & Scanlan, T. S. (2002). Rational Design and Synthesis of a Novel Thyroid Hormone Antagonist That Blocks Coactivator Recruitment. *Journal of Medicinal Chemistry,* Vol. 45, No. 15, pp. 3310-3320. ISSN: 0022-2623.

Parry, D.W., O'neill C. H., Hodson, M.J. (1986). Opaline silica deposits in the leaves of *Bidens pilosa* L. and their possible significance in cancer. *Annals of Botany*, Vol. 58, No. 5, pp. 641-647. ISSN: 1095-8290.

Pasa, M.C., Soares, J.J. & Germano, G.N. (2005). Estudo etnobotânico na comunidade de Conceição-Açú. *Acta Botanica Brasílica*, Vol. 19, No. 2, pp. 195-207. ISSN: 0102-3306.

Pepato, M.T., Keller, E.H., Baviera, A.M., Kettelhut, I.C., Vendramini, R.C., Brunetti, I.L. (2002). Anti-diabetic activity of *Bauhinia forficata* decoction in streptozotocin-diabetic rats. *Journal of Ethnopharmacology*, Vol. 81, No. 2, pp. 191-197. ISSN: 0378-8741.

Pianjing , P., Thiantanawat, A., Rangkadilok, N., Watcharasit, P., Mahidol, C.& Satayavivad J. (2011). Estrogenic activities of sesame lignans and their metabolites on human breast cancer cells. *The Journal of Agricultural and Food Chemistry*, Vol. 12, No. 1, pp. 212-221. ISSN: 0021-8561.

Prakash, D., Suri, S., Upadhyay, G. & Singh, B.N. (2007). Total phenol, antioxidant and free radical scavenging activities of some medicinal plants. *International Journal of Food Sciences and Nutrition*, Vol. 58, No. 1, pp. 18-28. ISSN: 0963-7486.

Ren, W., Qiao, Z., Wang, H., Zhu, L., Zhang, L. (2003). Flavonoids: Promising anticancer agents. *Medicinal Research Reviews,* Vol. 23, No. 4, pp. 519-534. ISSN: 0198-6325.

Rodrigues, E. & Carlini, E.A (2004). Plants used by a Quilombola group in Brazil with potential central nervous system effects. *Phytotherapy Research*, Vol. 18, No. 9, pp. 748- 53. ISSN: 0951-418X.

Schossler, D.R.C., Mazzanti, C.M., da Luz, S.C.A, Filappi, A., Prestes, D., da Silveira, A.F., Cecim, M. (2004). Syzygium cumini and the regeneration of insulin positive cells from the pancreatic duct. *Brazilian Journal of Veterinary Research and Animal Science*, Vol. 41, No. 4, pp. 236-239. ISSN: 1413-9596.

Seon , M.R., Lim , S.S., Choi, H.J., Park, S.Y., Cho, H.J., Kim, J.K., Kim, J., Kwon, D.Y. & Park, J.H. (2010). Isoangustone A present in hexane/ethanol extract of *Glycyrrhiza uralensis* induces apoptosis in DU145 human prostate cancer cells via the activation of DR4 and intrinsic apoptosis pathway. *Molecular Nutrition & Food Research,* Vol. 54, No. 9, pp. 1329-39. ISSN: 1613-4133.

Simões, C. M. O. & Schenkel, E. P. (2002). A pesquisa e a produção brasileira de medicamentos a partir de plantas medicinais: a necessária interação da indústria com a academia. *Revista Brasileira de Farmacognosia.* Vol. 2. No.1, PP. 35-40. ISSN 0102-695X.

Sudheesh, S., Vijayalakshmi, N.R. (2005). Flavonoids from *Punica granatum* - potential antiperoxidative agents. *Fitoterapia*, Vol. 76, No. 2, pp.181-186. ISSN: 0367-326X.

Sundararajan, P., Dey, A., Smith, A., Doss, A.G., Rajappan, M. & Natarajan, S. (2006). Studies of anticancer and antipyretic activity of *Bidens pilosa* whole plant (2006). *African Health Sciences*, Vol. 6, No. 1, pp. 27-30. ISSN: 1680-6905.

Taylor, A. H., Stephan, Z. F., Steele, R. E. & Wong, N. C. (1997). Beneficial Effects of a Novel Thyromimetic on Lipoprotein Metabolism. *Molecular Pharmacology,* Vol. 52, No. 3, pp. 542–547. ISSN: 0026-895X.

Teixeira, C.C., Weinert, L.S., Barbosa, D.C., Ricken, C., Esteves, J.F. & Fuchs F.D. (2004). *Syzygium cumini* (L.) Skeels in the treatment of type 2 diabetes: results of a randomized, double-blind, double-dummy, controlled trial. *Diabetes Care*, Vol. 27, No. 12, pp. 3019-3020. ISSN: 0149-5992.

Traka, M., Gasper, A.V., Melchini, A., Bacon, J.R., Needs, P.W., Frost, V., Chantry, A., Jones, A.M.E., Ortori, C.A., Barrett, D.A., Ball, R.Y., Mills, R.D., Mithen, R.F. (2008). Broccoli Consumption Interacts with GSTM1 to Perturb Oncogenic Signalling Pathways in the Prostate. *PLoS One*, Vol. 3, No. 7, pp. 1-14. ISSN: 1932-6203.

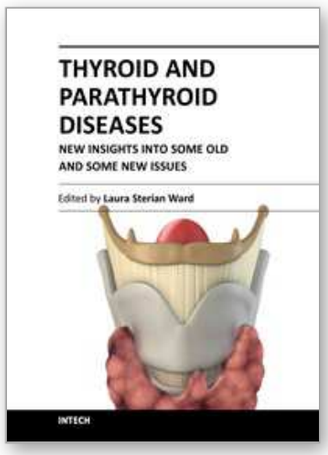
Vieira, I. J. C. , Mathias, L., Braz-Filho, R. & Schripsema, J.. (1999). .Iridoids from Borreria verticillata.*Organic Letters*, Vol.1, No.8, pp.1169-71. ISSN: 1523-7052.

Webb, P., Nguyen , N.H., Chiellini , G., Yoshihara, H.A., Cunha Lima, S.T., Apriletti, J.W., Ribeiro, R.C., Marimuthu, A., West, B.L., Goede, P., Mellstrom, K., Nilsson, S., Kushner, P.J., Fletterick, R.J., Scanlan, T.S. & Baxter, J.D. (2002). Design of thyroid hormone receptor antagonists from first principles. *Journal of Steroid Biochemistry and Molecular Biology,* Vol. 83, No. 1–5, pp. 59–73. ISSN: 0960-0760.

Yen, P.M. (2001). Physiological and molecular basis of thyroid hormone action. *Physiological Reviews*, Vol. 81, No. 3, pp. 1097–1142. ISSN: 0031-9333.

Yoshihara, H.A., Apriletti, J.W., Baxter, J.D. & Scanlan, T.S. (2001). A designed antagonist of the thyroid hormone receptor. *Bioorganic & Medicinal Chemistry Letters,* Vol. 11, No. 21, pp. 2821-2825. ISSN: 0960-894X.

Zubeldia, J.M., Nabi, H.A., Jiménez, D.R.M, & Genovese, J. (2010). Exploring new applications for *Rhodiola rosea*: can we improve the quality of life of patients with short-term hypothyroidism induced by hormone withdrawal? *Journal of Medicinal Food,* Vol. 13, No. 6, pp. 1287-1292. ISSN: 1096-620X.




**Thyroid and Parathyroid Diseases - New Insights into Some Old and Some New Issues**

Edited by Dr. Laura Ward

ISBN 978-953-51-0221-2
Hard cover, 318 pages
**Publisher** InTech
**Published online** 07, March, 2012
**Published in print edition** March, 2012

This book was designed to meet the requirements of all who wish to acquire profound knowledge of basic, clinical, psychiatric and laboratory concepts as well as surgical techniques regarding thyroid and parathyroid glands. It was divided into three main sections: 1. Evaluating the Thyroid Gland and its Diseases includes basic and clinical information on the most novel and quivering issues in the area. 2. Psychiatric Disturbances Associated to Thyroid Diseases addresses common psychiatric disturbances commonly encountered in the clinical practice. 3. Treatment of Thyroid and Parathyroid Diseases discusses the management of thyroid and parathyroid diseases including new technologies.



INTECH
open science | open minds

**InTech Europe**
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

**InTech China**
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

IntechOpen