

Review article

# Inhibition of endocrine function by botanical agents

## I. BORAGINACEAE AND LABIATAE

Francis Brinker, N.D.

Received 12 July 1989, accepted for publication 1 February 1990

### ANTIGONADOTROPIC ACTIVITY

#### *Lithospermum ruderale*

A recent series of investigations on the influence of medicinal plants on hormones was instigated by a report on the use of *Lithospermum ruderale* (gromwell; stoneseed; puccoon), Fam. Boraginaceae, by the Amerindians of Nevada for contraceptive purposes. It was claimed that "the cold water infusion of the roots, taken as a drink for a period of six months, will insure sterility thereafter".<sup>1</sup> Experiments with mice or rats showed that *L. ruderale* prolonged diestrus,<sup>2</sup> reducing or blocking estrous,<sup>3,7</sup> leading to decreased numbers of births.<sup>2</sup> Females fed a diet with 7-15% *Lithospermum* developed atrophy or atresia of their sex organs without a decrease in body weight or change in the growth of the pituitary or thyroid,<sup>3,4,8</sup> whereas 40% in the diet of immature mice reduced their growth and the weight of their sex organs, as well as the pituitary and thymus.<sup>2</sup> Using injections of extracts also produced retarded growth, atrophied sex or-

gans,<sup>5</sup> and a reduced number of corpora lutea in the ovaries.<sup>7</sup> It was found that the interference of normal function stopped immediately when the *Lithospermum* was withdrawn.<sup>2,4</sup>

*Lithospermum ruderale* does not affect the activity of administered estrogen; the tops even contain some phytoestrogens.<sup>6</sup> The focus of the activity was directly on the pituitary, probably inhibiting the formation of gonadotrophic hormones.<sup>2</sup> Since the gonadotropic potency of the pituitary can be decreased by vitamin B deficient diets,<sup>3</sup> it was shown that *Lithospermum ruderale* is also active in a diet supplemented with excess vitamin B.<sup>8</sup> This study further suggested that the plant's action was due to inhibition of luteinizing hormone (LH) by the anterior pituitary.<sup>8</sup> In the hen *L. ruderale* blocked ovulation and decreased ovarian and oviduct weight, suggesting inhibition of LH action or secretion.<sup>9</sup> Pituitary studies on castrated female mice fed *Lithospermum* showed a marked depression of LH production.<sup>10</sup> The LH activity was inhibited in vitro, as demonstrated by a diminished weight increase in chick testes, and in vivo in cockerels. In addition, tests showed that in vivo inactivation of follicle stimulating hormone (FSH) was pro-

duced using larger amounts of *Lithospermum*.<sup>11</sup>

These results suggest a reduction in sex hormone production secondary to gonadotrophin inhibition by *L. ruderale*. A means of testing this possibility was devised that also had therapeutic implications. Strains of mice that spontaneously develop mammary tumors dependent on stimulation by estrogenic hormones were fed diets with 15-30% *Lithospermum*. Tumor development in one strain was reduced from 58.1% to 2.8% and in the other strain from 96.6% to 21.9%.<sup>12</sup> Using a 10-15% *Lithospermum* diet, the mammary tumor incidence in the former strain was reduced by one half.<sup>13</sup> The potential for application in malignancies dependent upon sex hormones in both males and females is obvious, thus avoiding the conventional castration approach.

While there is some inhibition of FSH, the atrophy of the testes, seminal vesicles, and prostate in males and the ovaries, corpora lutea and uterus in females is due primarily to inactivation of LH.<sup>14,15</sup> Other gonadotropins inhibited by *L. ruderale* in tests include pregnant mare's serum gonadotropin (PMSG) and chorionic gonadotropin.<sup>15-18</sup> Other anterior pituitary hormones similarly affected include prolactin,<sup>16,17</sup> and, more importantly, thyroid stimulating hormone (TSH), leading to a significant reduction in the size of the thyroid.<sup>14-17,19,23</sup> Depending on the dose, *L. ruderale* can inhibit both the release (low dose) and the synthesis (high dose) of pituitary gonadotropins and TSH.<sup>19</sup>

#### *Lithospermum ruderale's* active components

The active principal is extracted in the neutral water fraction. The potency proved greater for the flowers and seeds than the roots, which were more potent than the leaves, while the stems had almost no activity<sup>4</sup>. However, the roots were more active than the entire above-ground plant taken together.<sup>6,11,19</sup> The roots harvested in September were more potent than those in August, which in turn were superior to June roots. Roots stored for 3 years were highly active, and after 4 years were still active. In contrast, ordinary aqueous extracts lose activity rapidly<sup>18</sup>. So, in many of the studies, the *L. ruderale* aqueous extracts were freeze dried to preserve their potency<sup>6,11,14-17,20,22,25</sup> which diminished somewhat

PLANT/ CONSTITUENT	REFERENCE(S)
<b>Boraginaceae</b>	
<i>Anchusa officinalis</i>	
lithospermic acid	30
<i>Echium vulgare</i>	
lithospermic acid	30
<i>Lithospermum officinale</i>	
caffeic acid	28, 33, 44
chlorogenic acid	33
ellagic acid	33
lithospermic acid	30, 42
rosmarinic acid	28, 39, 44
rutin	35
<i>Lithospermum ruderale</i>	
chlorogenic acid	20
D-3-(3,4-dihydroxyphenyl) lactic acid	26, 27
lithospermic acid	21, 22, 23, 27
rosmarinic acid	27
rutin	20
<i>Symphytum officinale</i>	
lithospermic acid	30, 42
<b>Lablatae</b>	
<i>Lycopus europaeus</i>	
caffeic acid	28, 43
chlorogenic acid	43
ellagic acid	43
lithospermic acid	42
luteolin-7-monoglucoside	43
rosmarinic acid	28, 39, 44
<i>Lycopus virginicus</i>	
caffeic acid	28
rosmarinic acid	28, 39, 44
<i>Melissa officinalis</i>	
caffeic acid	32
luteolin-7-glucoside	32
rosmarinic acid	32
<i>Thymus serpyllum</i>	
apigenin	34
caffeic acid	34
luteolin	34
rosmarinic acid	34

TABLE 1. Active oxidized constituents from antigonadotropic and antithyroidal plants.

with time,<sup>14</sup> but went through years of storage without significant change.<sup>25</sup>

Investigations to identify the gonadotropically active constituents of the aqueous *L. ruderale* root extracts were pursued by a variety of techniques. Rutin, chlorogenic acid and succinic acid were identified along with several sugars and amino acids. However, the active substances were determined to be polymeric in nature.<sup>20</sup> Subsequently, lithospermic acid (LA) was iso-

lated from the roots and characterized as a newly discovered polyphenolic carboxylic acid.<sup>21</sup> Crude LA represents 1.4–2.0% of the dried roots. It showed no biological activity unless oxidized by polyphenol oxidase, an enzyme present in the roots which acts rapidly during water extraction. The oxidized polymer of LA inactivated both exogenous and endogenous gonadotropins in rates.<sup>22</sup> A fraction of the water-soluble portion of *L. ruderalis* containing 85% LA inhibited exogenous LH 90.7% in chicks, but FSH inhibition was only 63.5%. No inhibition of exogenous TSH occurred with this fraction.<sup>23</sup>

Since the antigonadotropic activity of LA is small compared to freeze-dried extracts of plants containing it,<sup>24,25</sup> it is not surprising to find other active constituents in *L. ruderalis* as well. New evidence showed the principle polyphenolic constituents of the plant are the salts of D-3-(3,4-dihydroxyphenyl) lactic acid and a family of its oligomeric polyesters. One of these lactic acid salts was shown to inhibit both LH and FSH in chick assays. However, LH was inhibited more completely by lower molecular weight plant compounds and FSH by higher molecular weight compounds.<sup>26</sup> Besides LA and the (dihydroxyphenyl) lactic acid salts, a 7-hydroxycoumaran and rosmarinic acid were also isolated from the roots. Rosmarinic acid appears to be incorporated into LA, existing as a precursor.<sup>27</sup> But it is also one of the most effective plant components when oxidized,<sup>28,44</sup> forming a quinone which reacts with unoxidized phenolics (e.g. caffeic acid) to form quinhydrone that completely suppressed PMSG in very low doses. This synergism is far beyond any additive effect.<sup>29,39</sup>

#### *Lithospermum officinale*, other species, and their components

*L. ruderalis* is not the only Boraginaceae species to exhibit antigonadotropic effects. The plant tops of *Lithospermum officinale*, *L. croceum*, *L. disticum*, *L. latifolium* and *L. arvense* also inhibited PMSG, as did the less potent roots of *L. croceum*, *L. disticum* and *L. latifolium*. *Borago officinalis* (borage) likewise was active against PMSG.<sup>18</sup> Other Boraginaceae plants having antigonadotropic activity as demonstrated in mice include *Symphytum officinale* (comfrey), *Anchusa officinalis*, and *Echium vulgare*. Their

aqueous fractions have many components in common with *L. officinale* including citric, malic, succinic, fumaric, lithospermic and other polyphenolic acids,<sup>30,42</sup> as well as simple and complex carbohydrates.<sup>31</sup>

*L. officinale* has been the most studied of these alternative species. The water-soluble portion of the total herb includes scyllitol, caffeic acid, chlorogenic acid, ellagic acid, catechin tannins, amino acids,<sup>33</sup> rutin,<sup>35</sup> and lithospermic acid.<sup>30</sup> In one study the lithospermic acid oxidized by phenoloxidase in the leaves was shown to be more active in the presence of rutin or chlorogenic acid.<sup>42</sup> *L. officinale* inhibits the activity of the pituitary gonadotropins, PMSG, chorionic gonadotropin and prolactin,<sup>36,39,40</sup> with rapid normalization of activity after treatment ceases.<sup>36</sup> It also inhibited the growth of testes in male rats, but didn't influence testosterone synthesis.<sup>40</sup> The extract acts as a hormone-blocking agent that exhibits no side effects.<sup>36</sup>

A 0.5–1.0 gram herb-equivalent dose of extract daily in mice was sufficient to inhibit estrous and showed no side effects or toxicity. *L. officinale's* long time use in humans as a medicament and beverage has produced no reported ill effects. A single dose of aqueous extract equivalent to 10 grams of dried herb evoked no subjective or objective effects in 3 human subjects. One 34 year old woman consumed an amount of freeze-dried extract equivalent to 20 grams of dry herb per day for 1 week during menstruation and doubled the dose for the remainder of her cycle. No changes in blood picture, urinary findings, pulse-rate or subjective effects were detected. Only a reduction in the rise of ovulatory waking temperature and a lessened progestational development of the endometrium compared to preceding and subsequent cycles were observed, reflecting a diminished luteal secretion.<sup>37</sup>

The active constituents of *L. officinale* are very sensitive to heat before or during extraction (but not thereafter) and are rapidly destroyed in aqueous solutions.<sup>36,37,39</sup> This would imply that freeze-drying the aqueous juice or extract is the superior preservation technique<sup>37,38</sup> and one which was frequently used.<sup>39–41</sup> The *L. officinale* freeze-dried extract can maintain its potency for up to 10 years if not exposed to humidity.<sup>39</sup> A comparison between the extracts of fresh and dried *L. officinale* showed them to be equally

effective against PMSG.<sup>18</sup>

#### *Labiatae species and their components*

Extracts from plants of the Labiatae (mint) family also exhibit antigonadotropic activity. *Lycopus virginicus* and *Melissa officinalis* showed human chorionic gonadotropin (HCG) and PMSG inhibitory activity and a powerful prolactin-depressing effect as well.<sup>39,40,46,47</sup> *Lycopus europaeus* and *Thymus serpyllum* inhibited prolactin also,<sup>40,46</sup> and *L. europaeus* prevented HCG binding.<sup>47</sup> *L. virginicus* had previously been shown to inhibit the growth of testes in rats<sup>40</sup> and to inhibit gonadotropic hormones of the anterior pituitary, pregnant mare's serum and placental origin.<sup>41</sup>

*Melissa officinalis* leaves contain caffeic acid, protocatechuic acid, rosmarinic acid, luteolin-7-glucoside and rhamnazin.<sup>32</sup> *Thymus* contains caffeic, rosmarinic and caffeylquinic acids, and the flavonoids apigenin, luteolin and scutellarin.<sup>34</sup> The leaves of *Lycopus europaeus* have been shown to contain lithospermic acid and the phenoloxidase which activates it.<sup>42</sup> Another analysis revealed that it also contains chlorogenic, caffeic, ursolic, sinapinic and ellagic acids; the flavone glycosides luteolin-7-monoglucoside and apigenin-7-monoglucoside; sugars; ethereal oil; a tannin; a saponin; 12 amino acids and 11 minerals.<sup>43</sup> Rosmarinic acid has also been identified as a constituent of both *Lycopus* species,<sup>28,39,44</sup> along with caffeic acid.<sup>28</sup> Using HCG, LH and FSH in vitro, it was shown that oxidized caffeic acid and rosmarinic acid were both inhibitory. They also reduced endogenous serum LH levels in the rat in vivo.<sup>44</sup>

In studying PMSG inhibition, rosmarinic acid, caffeic acid, chlorogenic acid and lithospermic acid were all shown to be active. Furthermore, the activity of fresh and freeze-dried aqueous extracts clearly exceeds the additive effects of these phenolic ingredients. This is apparently due to the oxidative polymerization of these phenols (which occurs spontaneously in aqueous solution, especially at alkaline pH) catalyzed by manganese, which was found in considerable amounts in the leaves of *Lycopus* species. The same result can be achieved with copper and zinc ions. Added to this is the synergistic effect of oxidized and non-oxidized phenolics, e.g. oxi-

dized rosmarinic acid with caffeic acid. Therefore, the enzymatic oxidation, metal catalytic polymerization and quinone-phenol synergism of components of aqueous extracts of *Lithospermum* and *Lycopus* species, especially when fresh or freeze-dried, offer a reliable means of inhibiting a variety of gonadotropins both in vitro and in vivo.<sup>39</sup> (See tables 1 and 2) This inhibition occurs in females<sup>2-18,22,29,37</sup> and males<sup>5,11,14,15,17,19,23,40</sup> and is particularly applicable to sex hormone dependant conditions.

## ANTITHYROIDAL ACTIVITY

### *Antithyrotropic effects*

Since *Lithospermum ruderale* proved to be antithyrotropic,<sup>14-17,19,23</sup> in addition to being antigonadotropic, it is safe to assume that other antigonadotropic plants would also inhibit thyroid stimulating hormone (TSH). Indeed, this dual activity has been documented for *Lith. officinale*,<sup>36,38</sup> *Lyc. virginicus*,<sup>41</sup> and *Lyc. europaeus*.<sup>45</sup> More recently it has been confirmed that these latter three species, as well as *Melissa officinalis* and *Thymus serpyllum*, cause a decrease in serum and pituitary TSH levels after a single injection.<sup>46</sup> *Lith. officinale* also proved to be antigonadotropic in hypothyroid rats with chronic administration.<sup>46,50</sup>

The anti-TSH activity is apparently due to the inhibition of binding of TSH to the thyroid plasma membrane, thereby preventing stimulation of adenylate cyclase activity.<sup>47,48</sup> Plant constituents found to be active in preventing this TSH binding include caffeic acid, rosmarinic acid (both found in *Melissa* and *Thymus*<sup>32,34</sup>), chlorogenic acid and ellagic acid (all found in *Lithospermum* and *Lycopus* species<sup>27,28,33,43,44</sup>), and norhydroguaiaretic acid (found in *Larrea tridentata*). This is due to their auto-oxygenation to an orthoquinone form that combines with the protein moiety of TSH.<sup>48</sup>

### *Thyroid hormone inhibition*

*Lith. officinale* and *Lyc. virginicus* proved to be more potent than the conventionally used potassium iodide (KI) in blocking thyroid secretion.<sup>40</sup> *Lith. officinale* had a more rapid onset and longer duration than KI. The mode of action was

ACTIVE PLANTS AND OXIDIZED CONSTITUENTS	PLACENTA		ANTERIOR PITUITARY				THYROID					LIVER	REFERENCE(S)	
	PMSG	CG	LH	FSH	PRO	TSH	GIG	IP	AC	T4	T3	ID*		
<b>BORAGINACEAE</b>														
<i>Borago officinalis</i>	■													18
<i>Lithospermum arvense</i>	■													18
<i>Lithospermum croceum</i>	■													18
<i>Lithospermum disticum</i>	■													18
<i>Lithospermum latifolium</i>	■													18
<i>Lithospermum officinale</i>	●	■●	■●	●	●	■●	■	●	■	●	●	■●		18,36-40,44,46,47,49-52
<i>Lithospermum ruderale</i>	■●	■●	■●	■●	■	■●								8-11,15-17,19
<b>LABIATAE</b>														
<i>Lycopus europaeus</i>		■			■	■●	■		■	●	□			45-47,51,54
<i>Lycopus virginicus</i>	■	■	■●	■	■	■●	■		■	□	□	■		39-41,46,47,51,52,54
<i>Melissa officinalis</i>	■	■			■	■●	■		■	□	□	■		39,40,46,47,51,52,54
<i>Thymus serpyllum</i>					■	■				●	●			40,46
<b>CONSTITUENTS</b>														
apigenin												■		53
caffeic acid	■	■	■●	■		■	■					□		29,39,44,48,51,52,54
chlorogenic acid	■					■						□		39,42,48,51,52
D-3-(3,4-dihydroxyphenyl) lactic acid			■	■										26
ellagic acid						■	■					■		48,52,54
lithospermic acid	■		●	●		□								22,23,39,42
luteolin												■		52,53
luteolin-7-glucoside						□						■		48,52
rosmarinic acid	■	■	■●	■		■						■		29,39,44,48,51,52
rutin	■													42

TABLE 2. Endocrine hormones, analogues, actions and enzymes inhibited by borage and mint family plants and their constituents.

Legend: □ does not inhibit; ■ in vitro study; ● in vivo study. Shaded boxes mark studies which were performed on humans.

Abbreviations: PMSG= pregnant mare's serum gonadotropin, CG= chorionic gonadotropin, LH= luteinizing hormone, FSH= follicle stimulating hormone, PRO= prolactin, TSH= thyroid stimulating hormone, GIG= Graves' IgG, IP= iodide pump, AC= adenylate cyclase, T4= thyroxine, T3= triiodothyronine, ID= iodothyronine deiodinase. \* Inhibition improved if constituents have not been oxidized.

apparently different since *Lithospermum* reduced both thyroid hormone secretion and serum TSH levels also.<sup>49,50</sup> A diminished T3 level was induced by *T. serpyllum* and at a 16-fold dose by *Lith. officinale* as well as a decreased serum T4 by both species at a higher dose.<sup>46</sup>

#### Depression of thyroid iodide transport

*Lith. officinale* strongly depresses the iodide pump but does not inhibit the organification process as do the drugs phenylthiouracil and mercaptoimidazole.<sup>50</sup>

#### Iodothyronine deiodinase inhibition

An additional pharmacologic effect of *Lith. officinale*<sup>49,52</sup> and *Lycopus* and *Melissa*<sup>51,52</sup> is the inhibition of peripheral T4-deiodination. This is due to inhibition of iodothyronine deiodinase activity in the liver in a manner comparable to thiouracil, blocking the generation of the calorigenic active T3 and the regulatory active rT3. The constituents found to be active in this regard were the phenolic dimers rosmarinic acid, ellagic acid, and luteolin-7 $\beta$  glucoside. These were concentrated in the most active fraction, an ether extract of the freeze dried extract in aqueous solution. The relative potency of this enzyme inhibition was greatest for *Melissa*, followed by *Lyc. virginicus*, and then *Lith. officinale*.<sup>51,52</sup> Unlike the antigonadotropic and antithyrotropic effect, oxidation of the active constituents of *Lycopus* and *Lithospermum* caused a dramatic decrease in iodothyronine deiodinase inhibition.<sup>52</sup>

The total deiodinase inhibition by the plant extracts cannot be explained by the above three compounds alone. Certain diphenolic flavonoids including luteolin, apigenin and quercetin are also potent inhibitors of iodothyronine deiodinase.<sup>52,53</sup> These may contribute to this effect for *Thymus*,<sup>34</sup> but also possibly in the other plants where they exist as flavone glycosides.<sup>20,22,35,43</sup>

#### Hyperthyroidism

The various mechanisms affected by different plants and constituents offer a multiple approach for inhibiting thyroid function (see Tables 1 and 2). These studies point to the application of the aforementioned botanical agents to the treatment

of hyperthyroidism.<sup>51-53</sup> In fact, *Lycopus* and *Lithospermum* species have long histories of empirical use in hyperthyroidism.<sup>45,54</sup> *Lyc. europaeus* has been found to return the iodine content in serum protein fractions to almost normal values in this condition.<sup>45</sup> The value of its empirical use in Graves' disease was confirmed when it was found that *Lyc. europaeus*, *Lyc. virginicus*, *Lith. officinale* and *Melissa officinalis* and the auto-oxidized constituents caffeic acid and ellagic acid all inhibited Graves' IgG thyroid plasma membrane binding and stimulation of adenylate cyclase activity. Also inhibited by these substances was the long-acting thyroid stimulator (LATS) response.<sup>54</sup>

These findings are especially significant since Graves' disease is the most common form of hyperthyroidism and is not caused by TSH. Other agents commonly used to treat this are propylthiouracil and methimazole, which can cause allergic reactions and in some cases agranulocytosis. Surgery is the other alternative for those of reproductive age or younger, with its attendant risks of vocal cord paralysis and hypoparathyroidism. Radioactive iodine is usually used in patients over 40 years of age due to the risk of birth defects. KI is not used routinely, but in emergency cases only, due to the complications of iodism.<sup>55</sup>

## DOSAGES

#### Freeze-dried extracts

The difficulties of extrapolating experimental results to clinical application are multiple. Most of the studies were performed in vitro. The in vivo studies either use the raw plant material as a major portion of the diet or injected extracts to standardize the dose. The use of freeze-dried aqueous extracts (FDE) was the most favored form utilized in the antithyroidal studies<sup>40,41,46-52,54</sup> as was the case, as previously stated, for the antigonadotropic studies.

In *Lith. ruderalis* the FDE contained about 33% of the total dried tops and 10-40% of the weight of the dried root,<sup>14,23</sup> 70% of which was composed of biologically inactive carbohydrate and 20% a mixture of the polyphenolic carboxylate salts.<sup>23</sup> An ether extract of other FDE has been shown in several studies to be the most effective form

due to an increased concentration of the phenols in this extract. An amount (1-20%) of the FDE was equally active in this form.<sup>51,52</sup> The FDE doses given below, except when noted, are for injections given to laboratory animals, which were found to be more effective than the equivalent oral doses.<sup>6</sup>

#### *FDE doses for different effects*

In testing *Lith. ruderale* FDE for antigonadotropic and antithyrotropic activity, 400mg tops/kg and 364mg roots/kg body weight daily were found to be effective in male and female rats.<sup>14</sup> An equivalent dose in 70 kg humans would be 25-28 grams FDE/day. An ether extract that could reduce this amount by 80% or more would certainly be less burdensome. It must be remembered, however, that Amerindians merely used a cold infusion of the roots, over a period of 6 months, with apparently effective results.<sup>1</sup> *Lith. officinale* FDE was taken orally by 1 human female at a dose (5-13gm) equivalent to 20-40 grams of dry herb/day for 1 month, which produced objective luteinizing hormone inhibitory effects.<sup>37</sup>

Antithyrotropic effects were produced by FDE of *Lith. officinale*, *Lyc. virginicus*, *Lyc. europaeus*, *Melissa officinalis* and *Thymus serpyllum* leaves with a 25 mg/kg body weight dose in rats. The anti-T3 dose of *Thymus* FDE was also 25mg/kg.<sup>46</sup> The 70 kg human equivalent dose would be 1.8 grams FDE. The anti-T3 and anti-T4 doses for *Lith. officinale* and the anti-T4 dose for *Thymus* were 400mg FDE/kg.<sup>46</sup> Considering the empirical use of *Lithospermum* and *Lycopus* extracts for hyperthyroid conditions,<sup>54</sup> reasonable clinical doses are apparently sufficient.

#### FUTURE STUDIES

All of this points to the necessity for controlled clinical trials to evaluate the efficacy and establish the dosage of these agents. Considering this, one should bear in mind the oxidative state of the substances utilized. Since antigonadotropic studies indicate a synergism between oxidized and non-oxidized constituents,<sup>29,39</sup> it would seem useful to employ both forms concurrently. For example, if the plant to be used was freeze-dried fresh, it would prevent auto-oxidation of constituents. This form could then provide a source

of non-oxidized material. If some of the material were then added to water at room temperature 2 hours prior to consumption, an oxidized form of the constituents would then be supplied. Or, the freeze-dried juice or extract could be used for oxidized constituents.

Likewise regarding the antithyroidal effects, oxidized constituents are required for antithyrotropic activity.<sup>48</sup> However, inhibition of the enzyme iodothyronine deiodinase, which transforms thyroxine to active T3, is much greater when the constituents are not oxidized.<sup>52</sup> For optimal efficacy a combination of the two forms would be preferred, as described above.

Another consideration in treating hyperthyroidism or gonadotropin-dependant conditions with FDE is the hormonal effect on the organs not being treated. In other words, if treating the thyroid, sexual function and expression should be monitored since a disruption may possibly occur in normal hormone levels. Administration of testosterone or estrogen/progesterone may be necessary. If the thyroid is not being treated, it may be necessary to supplement some form of thyroid extract and monitor basal body temperature and/or serum thyroxine and T3 levels to insure appropriate metabolic function.

Given these uncertainties about the need for large doses and the potential for undesirable side effects, it would be especially appealing to be able to combine these botanical agents with other bioactive plant substances which could complement their effect through a different physiological mechanism. This would achieve a reduction of dose and risk while improving clinical results. Such a possibility exists in members of another botanical family which will be reviewed in the second part of this paper.

#### ACKNOWLEDGEMENT

*The author acknowledges Eclectic Institute, Inc., Portland, OR for their support.*

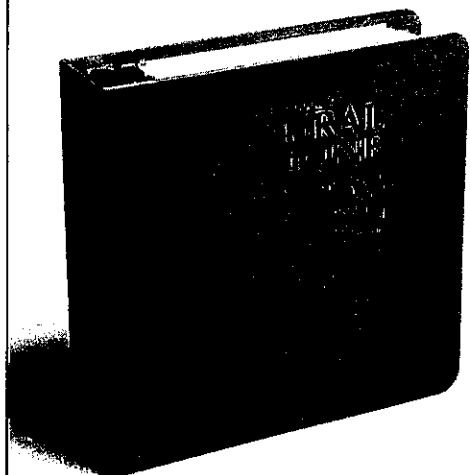
## REFERENCES

1. Train, P., Henrichs, J.R., Archer, W.A. Medicinal Uses of Plants by American Tribes of Nevada, p. 68, Quaterman Publications, Inc., Lawrence, MA, 1982. [First published in 1941 as part of Contributions Towards a Flora of Nevada]
2. Cranston, E.M. The effect of *Lithospermum ruderale* on the estrous cycle of mice. J. Phram. Exp. Ther. 1945; 83:130-42
3. Drasher, M.L., Zahl, P.A. The effect of *Lithospermum* on the mouse estrous cycle. Proc. Soc. Exp. Biol. Med. 1946; 63: 66-70
4. Zahl, P.A. Some characteristics of the anti-estrous factor in *Lithospermum*. Proc. Soc. Exp. Biol. Med. 1948; 67:405-410
5. Skelton, F.R., Grant, G.A. Studies on Action of *Lithospermum ruderale*. Am. J. Physiol. 1951; 161: 379-385
6. Plunkett, E.R., Colpittis, R.V., Noble, R.L. The effect of *Lithospermum ruderale* on Oestrus cycle of the rat. Proc. Soc. Exp. Biol. Med. 1950; 73: 311-13
7. Smith, R.E., Breneman, W.R., Carmack, M. The action of *Lithospermum* in mice. Indiana Acad. Sci. 1957; 67: 312-15
8. Drasher, M.L. The mechanism of action of *Lithospermum ruderale*. Endocrin. 1949; 45: 120-8
9. Zeller, F.J., Breneman, W.R. Carmack, M. The action of *Lithospermum ruderale* on ovulation in the hen. Poultry Sci. 1958; 37: 455-9
10. Drasher, M.L. Further observations on the inhibition of the production of luteinizing hormone by *Lithospermum*. Endocrin. 1950; 47: 399-413
11. Breneman, W.R., Carmack, M. Overack, D.E. Creek, R.O., Shaw, R. Inhibition of anterior pituitary gonadotropins and oxytocin by extracts of *Lithospermum ruderale*. Endocrin. 1960; 67: 583-96
12. Cranston, E.M., Kucera, G.R., Bittner, J.J. *Lithospermum ruderale* and the incidence of mammary tumors in mice. Proc. Soc. Exp. Biol. Med. 1950; 75: 779-81
13. Zahl, P.A., Nowak, A. Incidence of spontaneous mammary tumors in mice with *Lithospermum*-induced diestrus. Proc. Soc. Exp. Biol. Med. 1951; 77: 5-8
14. Plunkett, E.R., Noble, R.L. The effects of injection of *Lithospermum ruderale* on the endocrine organs of the rat. Endocrin. 1951; 49: 1-7
15. Noble, R.L., Plunkett, E.R. Taylor, N.B.G. Factors affecting the control of the pituitary gland. Rec. Prog. Horm. Res. 1950; 5: 263-304
16. Noble, R.L., Plunkett, Graham, R.C. Direct inactivation of gonadotropin, thyrotropin and prolactin by extracts of *Lithospermum ruderale*. Fed. Proc., 1951; 10 [Part I]: 97-98
17. Noble, R.L., Plunkett, E.R., Graham, R.C. Direct hormone inactivation by extracts of *Lithospermum ruderale*. J. Endocrinol. 1954; 10: 212-27
18. Graham, R.C., Noble, R.L. Comparison of the in vitro activity of various species of *Lithospermum* and other plants to inactivate gonadotropin. Endocrin. 1955; 56: 239-47
19. Breneman, W.R., Zeller, F.J. *Lithospermum* inhibition of anterior pituitary hormone. Biochem. Biophys. Res. Comm. 1975; 65: 1047-53
20. Shaw, R.G. A phytochemical investigation of *Lithospermum ruderale*. Dissertation Abstracts, 1961; 21: 2494
21. Johnson, G., Sunderwirth, S.G., Gibian, H. Coulter, A.W. Gassner, F.X. *Lithospermum ruderale*: partial characterization of the principle polyphenol isolated from the roots. Phytochem. 1963; 2: 145-50
22. Gassner, F.X., Hopwood, M.L., Jochle, W., Johnson, G., Sunderwirth, S.G. Antifertility activity of oxidized polyphenolic acid from *Lithospermum ruderale*. Proc. Soc. Exp. Biol. Med. 1963; 114: 20-25
23. Breneman, W.R., Zeller, F.J., Carmack, M., Kelley. In vivo inhibition of gonadotropins and thyrotropin in the chick by extracts of *Lithospermum ruderale*. Gen. Comp. Endocrin. 1976; 28: 24-32
24. Kemper, F.H., Winteroff, H., Sorgens, H., Niehaus, K.D. The antigonadotropic and antithyrotropic activity of plant extracts. Planta Med. 1978; 33: 311
25. Niehaus, K.D., Winteroff, H., Kemper, F.H. Antihormonal effects of plant extracts. Arch. Pharmacol. 1976; 293 Suppl: R39
26. Flexman, E.A. The polyphenolic character of the antigonadotropins from *Lithospermum ruderale* Douglas. Dissert. Abstr. 1968; 28: 2767B- 2768B
27. Kelley, C.J. Mahajan, J.R., Brooks, L.C., Neubert, L.A., Breneman, W.R., Carmack, M. Polyphenolic acids of *Lithospermum ruderale* Doug. ex Lehm (Boraginaceae). 1975; 40: 1804-15
28. Winteroff, H., Gumbinger, H.G., Sourgens, H., Kemper, F.H. Zur Isolierung antigonadotrop wirksamer inhaltsstoffe aus verschiedenen arten der gattungen *Lithosperm* und *Lycopus*. Planta Med. 1980; 39: 245
29. Gumbinger, H.G., Winteroff, H., Sourgens, H., Kemper, F.H., Wylde, R. Formation of compounds with antigonadotropic activity from inactive phenolic precursors. Contraception. 1981; 23: 661-6
30. Kozhina, I.S., Shukhobodskij, B.A., Klyuchnikova, L.A., Dil'man, V.M., Alpatskaya, E.P. Representatives of the Boraginaceae as sources of physiologically active agents. Rast. Resur. 1970; 6: 345-50 C.A. 74: 72812s
31. Boudru, R. Glucide metabolism in the Boraginaceae. Rev. Gen. Botan. 1957; 64: 153-92, 197-260 C.A. 51: 16751g
32. Thieme, H., Kitze, C. Occurrence of flavonoid in *Melissa officinalis*. Pharmazie, 1973; 28: 69-70 C.A. 78:108197
33. Horhammer, L., Wagner, H., Konig, H. Constituents of *Lithospermum ruderale*. Arzneim.-Forsch. 1964; 14: 34-40
34. Litvinenko, V.I., Zoz, I.G. Chemotaxonomic study of the *Thymus* species in the Ukraine. Rast, Resur. 1969; 5: 681-95 C.A. 72:75152s
35. Bech, T.D. Presence of flavonoids in some species of *Lithospermum*. Farm. Zh. 1967; 22: 58-62 C.A. 67: 51033d
36. Kemper, F. Experimental basis for the therapeutic use of *Lithospermum officinale* for blocking of anterior pituitary hormone. Arzneim.-Forsch. 1959; 9: 411-19
37. Wiesner, B.P., Yudkin, J. Inhibition of oestrus by cultivated Gromwell. Nature. 1952; 170: 274-75
38. Kemper, F., Loesner, A. Studies on the preparation of substances with antihormonal action from *Lithospermum officinale*. Arzneim.-Forsch. 1957; 7: 81-2
39. Winteroff, H., Gumbinger, H.G., Sourgens, H. On the antigonadotropic activity of *Lithospermum* and *Lycopus* species and some of their phenolic constituents. Planta Med. 1988; 54: 101-6
40. Sourgens, H., Winteroff, H., Gumbinger, H.G. Mendes, R., Kemper, F.H. Antihormonal effects of plant extracts on hypophyseal hormone in the rat. Acta Endocrin. Suppl. 1980; 234: 49
41. Kemper, F., Loeser, A., Richter, A. Anti-hormone action of *Lycopus*. Arzneim.-Forsch. 1961; 11:92-4
42. Wagner, H., Horhammer L., Frank, U. Lithospermic acid, the antihormonally active principle of *Lycopus europaeus* L. and



## BRINKER REFERENCES CONTINUED

- Symphytum officinale* L. *Arzneim.-Forsch.* 1970; 20: 705-12
43. Horhammer, L., Wagner, H., Schilcher, H. Studies on the ingredients of *Lycopus europaeus*. *Arzneim.-Forsch.* 1962; 12: 1-7
  44. Winteroff, H., Sosa, R., Wylde, R., Winternitz, F. Inhibition of the gonadotropins of different origin by whole plant extracts and some of their constituents. *Naun.-Schmied. Arch. Pharm.* 1981; 316: suppl.:192
  45. Hiller, E., Deglmann, H. The effect of *Lycopus europaeus* extracts on the distribution of iodine in human serum. *Arzneim.-Forsch.* 1955; 5: 465-470
  46. Sourgens, H., Winteroff, H., Gumbinger, H.G., Kemper, F.H. Antihormonal effects of plant extracts: TSH and prolactin-suppressing properties of *Lithospermum officinale* and other plants. *Planta Med.* 1982; 45: 78-86
  47. Auf'mkolk, M., Ingbar, J.C., Amir, S.M., Winteroff, H., Sourgens, H., Hesch, R.D., Ingbar, S.H. Inhibition by certain plant extracts of the binding and adenylate cyclase stimulatory effect of bovine thyrotropin in human thyroid membrane. *Endocrin.* 1984; 116: 1677-86
  48. Auf'mkolk, M., Amir, S.M., Kubota, K., Ingbar, S.H. The active principle of plant extracts with antithyrotropic activity: oxidation products of derivative of 3,4-Dihydroxycinnamic acid. *Endocrin.* 1985; 116: 1677-86
  49. Winteroff, H., Sourgens, H., Kemper, F.H. Antihormonal effects of plant extracts: pharmacodynamic effects of *Lithospermum ruderae* on the thyroid gland of rats. *Horm. Metabol. Res.* 1983; 15: 503-7
  50. Sourgens, H. Further investigations on the mechanism of action of the freeze-dried extracts of *Lithospermum officinale* L. *Naun.-Schmied. Arch. Pharm.* 1981; 301: Suppl: 15
  51. Kohrle, J., Auf'mkolk, M., Winteroff, H., Sourgens, H., Gumbinger, H.G. Iodothyronine deiodinases: inhibition by plant extracts. *Acta. Endocrin. Suppl.* 1981; 16: 188-92
  52. Auf'mkolk, M., Kohrle, J., Gumbinger, H., Winteroff, H., Hesch, R.D. Antihormonal effects of plant extracts and secondary metabolites of plants. *Horm. Metabol. Res.* 1984; 16: 188-92
  53. Auf'mkolk, M., Kohrle, J., Kaminski, T., Jorgensen, E.C. Flavonoids and plant pigments inhibit iodothyronine deiodinases. *Acta Endocrin. Suppl.* 1981; 240: 2-3
  54. Auf'mkolk, M., Ingbar, J.C., Kubota, K., Amir, S.M., Ingbar, S.H. Extracts and auto-oxidized constituents of certain plants inhibit the receptor-binding and biological activity of Graves' disease Immunoglobulins. *Endocrin.* 1985; 116: 1687-93
  55. Berkow, R. Editor-in-chief, *The Merck Manual* 14th ed. pp1001-6, Merck Sharp and Dohme Res. Lab., Rahway, N.J. 1982



“A valuable, well-documented addition to any physician's practice.”

Jonathan Wright, M.D., physician, author and lecturer

“The ultimate book on naturopathic medicine...a classic.”

Leon Chaitow, N.D., D.O., M.B.N.O.A., consulting editor for Journal of Alternative Medicine

The definitive reference on natural medicine. Examines the healing power of nature through empirical clinical medicine and scientific research. Invaluable for students and practitioners in all schools of healing.

by Joseph E. Pizzorno, N.D., leading educator, co-founder and president of Bastyr College, fifteen years of clinical practice, editor of natural medicine journals and Michael T. Murray, N.D., nationally-recognized researcher, educator, lecturer and writer. Contributors include well-known educators and physicians.

- Philosophy and history of natural medicine
- Diagnostic techniques and clinical procedures

- Natural medicine therapeutic modalities
- Syndromes and special topics • Pharmacology, folk use and scientific indications for herbal medicines and nutrients • Specific health problems studied in-depth: diagnostic criteria and pathophysiology reviewed; therapies referenced to scientific literature; key nutritional, life-style, physical, psychological and botanical therapies recommended • High quality loose-leaf, seven-ring format updated quarterly with new research and scientific information.

Free brochure and sample article.  
Bastyr College Publications  
144 N.E. 54th Street Seattle WA 98105  
(206) 523-9585

**BASTYR**  
**COLLEGE**  
NATURAL HEALTH SCIENCES

Send \$150 plus \$8 shipping/handling by check, money order or MasterCard/Visa.  
Quarterly updates at \$75/year. WA residents add 8.1% sales tax.