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Effects of natural products and nutraceuticals on steroid hormone-regulated gene expression

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Abstract

Background: There is an increasing trend in the use of complementary and alternative therapies to treat or prevent hormonally dependent pathologies. Methods determined whether several of these natural products and nutraceuticals, commonly taken for hormone-related effects, possess steroid hormone activity. The agonist and antagonist estrogenic, androgenic, and progestational activities of 20 natural products and nutraceuticals were assessed using an in vitro tissue culture indicator system. Two steroid-regulated proteins (pS2 and prostate-specific antigen [PSA]) were quantified, using ELISA-type immunoassays, as markers of agonist and antagonist activity. *Results*: Four of the products tested, two isoflavone preparations, Promensil™ and Estro-Logic™, chamomile, and grapeseed extracts, were found to have weak estrogenic agonist activity, with the latter two also demonstrating weak progestational activity. Several of the products tested exhibited antagonistic (blocking) activity, including antiestrogenic activity by Prostate-Ease, wild yam root, and dong quai, and antiandrogenic activity by dong quai, Promensil™, and rosehips. *Conclusions*: Several of these natural products demonstrate weak steroid hormone activity.

Keywords: Phytoestrogens; Natural estrogens; Steroid hormone activity; Cancer preventions; Nutraceuticals

1. Introduction

Recently, there is a trend for healthy individuals and cancer patients to use complementary and/or alternative medicines [1]. These are largely unproven therapies [2] that, at present, have no government regulations. Self-prescribed herbal and natural products represent one of the most popular alternative therapies used by the North American public [1,3]. Moreover, the majority of households from the National Health and Nutrition Examination Survey III study [4] admit taking herbal supplements, many without reporting such practices to physicians or other healthcare workers [3–5].

Healthy men and women, and prostate and breast cancer patients report several hormonally related reasons for taking herbal remedies. Saw palmetto (*Serenoa serrulata*), an extract from the saw palmetto berries, is commonly used for treating benign prostatic hypertrophy (BPH) and accompanying uri-

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nary tract problems [6–8], and is now being extended, through self-medication, to prostate cancer management [2]. Pumpkin extract is also being used for BPH [9]. Dong quai (*Angelica sinesis*) and Mexican wild yam root (*Dioscorea villosa*) are being used by menopausal and postmenopausal women as phytoestrogens and/or phytoprogestins [10–12]. Isoflavone preparations are being sold in the market (e.g. Promensil™ by Novogen and Estro-Logic™ by Quest) to reduce risk of cardiovascular disease [13–16], osteoporosis [15,16], and to combat menopausal symptoms such as hot flushes [17,18].

Other nutraceuticals being widely used by the public include echinacea (*Echinacea purpurea* and *E. angustifolia*) to boost immune function [19,20], St. John's wort (*Hypericum perforatum*) as an antidepressant [21,22], cranberry extract for antibacterial and antioxidant activity [23,24], and grapeseed extract, for its antioxidant activity [25,26]. Many of these natural products have been hypothesized to have anticarcinogenic activity [25–27], and are being used ad libitum by breast and prostate cancer patients [28,29].

Because many of these natural products presumably have hormonal activity, and others are being used by individuals with, or at risk of developing hormone-dependent cancers, we evaluated steroid hormone agonist and antagonist activities of these preparations, using an in vitro tissue culture system. The BT-474 human breast cancer cell line, which is positive for estrogen (ER), androgen (AR), and progesterone (PR) receptors, was used. For assessing biological activity, we utilized secreted proteins, namely pS2, which is ER regulated, and prostate-specific antigen (PSA), which is under the control of ARs and progestins.

2. Materials and methods

2.1. Materials

The BT-474 human breast cancer cell line was purchased from the American Type Culture Collection (Rockville, MD). The levels of ER and PR, as quantified by commercial ELISA assays (Abbot Diagnostics, Abbot Park, Chicago, IL) were 29 and 389 fmol/mg protein, respectively. Although the AR content was not quantified, Northern blot studies indicated that this cell line contains AR [30]. All steroids used were from Sigma (St. Louis, MO). Stock, 10^{-2} mol/l solutions of steroids were prepared in absolute ethanol. Natural products and nutraceuticals were purchased from pharmacies and health food stores (Table 1), with the exception of Estro-Logic™, which was a gift from Bruce Chapman, Boehringer Ingelheim Self Medication. ICI 182,780 was purchased from Tocris Cookson, Ballwin, MO, and RU-486 (mifepristone), and RU 56187 (nilutamide) were gifts from Roussel-UCLAF (Romainville, France). Stock, 10^{-2} mol/l solutions of antagonists were prepared in absolute ethanol.

2.2. Methods

2.2.1. Preparations of natural products and nutraceuticals

All liquid extracts were diluted 1:10 in anhydrous ethanol. Contents of capsules were mixed with 2 ml ethanol and incubated overnight. The liquid phase was then separated by centrifugation. Gelcaps were broken and the liquid contents were diluted with 1 ml ethanol. Tablets were crushed and incubated with 2 ml ethanol overnight. The liquid layer was then separated by centrifugation. Syrups were diluted 1:10 in distilled water. More dilute solutions were further prepared in ethanol.

2.2.2. Definition of biological activity

In this study, we have used the breast carcinoma cell line BT-474 as a biological testing system and the steroid hormone-regulated proteins pS2 (ER regulated) and PSA (AR and progestin regulated) as indicators of hormone action. Natural products that stimulated pS2 production were defined as having estrogenic agonist activity, whereas those that stimulated PSA production were defined as having progestational/androgenic agonist activity. Discrimination between progestational and androgenic activity was made by blocking experiments with either mifepristone (antiprogestin) or nilutamide (anti-AR). Blocking (antagonist) activity of the natural products was defined as their ability to block production of pS2 (stimulated by estradiol) or PSA (stimulated by ei-

Table 1
Natural products and nutraceuticals tested

Name	Active component/claim	Form	Source
Black tea	Theaflavins	tea	Natural food store
Canadian ginseng	Ginsenosides	capsule	Natural food store
Carob syrup	B vitamins	syrup	Natural food store
Chamomile	Apigenin	gel-tab	Jamieson Natural Sources
Cran-Max	Procyanidins	tablet	Swiss Natural Sources
Dong quai	Phyto-progestin	extract	Swiss Natural Sources
Echinacea	Immune function, anti-inflammatory	extract	Swiss Natural Sources
Estro-Logic™	Soy isoflavones	capsule	Quest
Evening primrose oil	γ-Linolenic acid	gel-tab	Jamieson Natural Sources
Garlic	Allium extract	gel-tab	Swiss Natural Sources
Grapeseed	Procyanidins	capsule	Swiss Natural Sources
Green tea	Cathecins	tea	Natural food store
Promensil™	Red clover isoflavones	tablet	Novogen
Prostate-Ease	Saw palmetto, flaxseed, pumpkin seed extracts	gel-tab	Swiss Natural Sources
Rosehips	Vitamin C	tablet	Swiss Natural Sources
Saw palmetto	Alleviate BPH symptoms	extract	Herbs Etc.
Siberian ginseng	Ginsenosides	capsule	Natural food store
St. John's wort	Antidepressant	capsule	Swiss Natural Sources
Watermelon juice	Prostate health	juice	Natural food store
Wild yam root	Diosgenin	extract	Gaia Herbs

ther dihydrotestosterone [DHT] or norgestrel). These definitions are descriptive of the final effect but do not imply any mechanistic aspects of this up- or down-regulation of the indicator genes.

2.2.3. Cell culture

BT-474 cells were grown to confluency in phenol-free RPMI media (Gibco BRL, Gaithersburg, MD) supplemented with 10% fetal calf serum, 10 mg/ml insulin, and 200 mmol/l glutamine at 37 °C, 5% CO_2. Once confluent, they were subcultured in 24-well microtiter plates using the same media, but with substitution of charcoal-stripped fetal calf serum for the regular fetal calf serum.

2.2.4. Agonist activity study

The cells were stimulated with natural product at full strength (stock solution), and 10-, 100-, and 1000-fold dilutions. Estradiol, norgestrel, and DHT at 10^{-8} mol/l were used as positive controls and ethanol (solvent) as a negative control. The cells were incubated with the stimulant for 7 days. The tissue culture supernatants were then harvested and quantified for pS2 and PSA proteins. Preparations that were found to stimulate PSA production were subsequently tested using mifepristone (RU-486, an antiprogestin) or nilutamide (an anti-AR) to determine whether the effect was progestational or androgenic.

2.2.5. Antagonist activity study

The BT-474 cells were incubated with natural product at full strength, or at 10-, 100-, or 1000-fold dilutions for 1 h, after which time the cells were stimulated with either estradiol, norgestrel, or DHT at 10^{-9} mol/l. The cells were then incubated for 7 days at the same conditions as above. Steroid was also tested alone (no candidate blocker added) to determine maximum production of pS2 and PSA. The blocking activity of faslodex (ICI 182,780, an antiestrogen), mifepristone, and nilutamide used at 10^{-7} mol/l, served as positive controls for antagonist activity, and ethanol (solvent) was a negative control. After 7 days, the tissue culture supernatants were harvested and analyzed for pS2 and PSA. Percentage blocking was calculated by quantifying

the concentration of pS2 or PSA produced by natural product plus steroid, divided by the concentration of pS2 or PSA produced by steroid alone, and multiplying by 100. Products were defined as having antagonist activity if their blocking activity was $\geq 50\%$.

2.3. Assays

2.3.1. pS2 assay

We used an ELISA-type competitive immunoassay for pS2 which was developed in house. The details of this assay are described elsewhere [31]. The detection limit of this assay is ~ 20 ng/ml.

2.3.2. PSA assay

PSA was quantified using an ELISA-type immunofluorometric procedure described elsewhere [32]. The detection limit of this assay is ~ 1 ng/l.

3. Results

The structure of some active ingredients of the tested preparations is shown in Fig. 1. Of the 24 products tested (Table 1), 4 demonstrated significant estrogenic activity at the highest concentration. These included the red clover isoflavone preparation, Promensil™, the soy isoflavone preparation Estro-Logic™, grapeseed extract, and chamomile extract. Data with the first two preparations are presented in Fig. 1. Promensil™ exhibited cytotoxic activity in the undiluted form, similar to that observed with genistein at high concentrations [33]. At lower concentrations, there was a dose–response relationship and the estrogenic agonist activity was detectable up to 1000-fold dilution (Fig. 1). Estro-Logic™ did not have any cytotoxic effect at the dilutions tested, and also demonstrated a dose–response relationship down to 100-fold dilution (Fig. 1). Promensil's activity was about seven times higher than Estro-Logic's at their most potent dilutions. This activity was equivalent to estradiol's estrogenic activity at 10^{-8} mol/l.

Grapeseed and chamomile extracts exhibited both weak estrogenic and weak progestational activity but only at the highest concentrations tested (~ 200 ng/ml pS2 concentration in tissue culture supernatant). None of the natural products tested exhibited androgenic activity (as assessed by PSA production

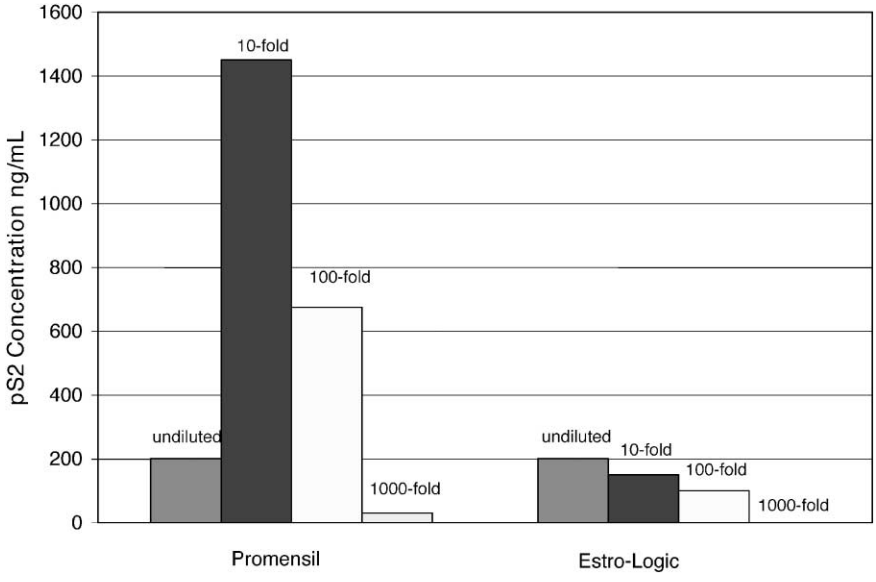

Fig. 1. Dose–response of ER-like activity of Promensil™ and Estro-Logic™. Dose–response activity was demonstrated for both isoflavone preparations: red clover isoflavones and soy isoflavones, respectively. The products were tested undiluted, and at 10-, 100-, and 1000-fold dilutions in anhydrous ethanol. The maximal activity seen with Promensil™ (10-fold dilution) was equivalent to the activity of 10^{-8} mol/l estradiol (data not shown).

Table 2
Biological activity of natural products as detected by our tissue culture screening procedure

Product	Activity					
	Agonist[a]			Antagonist[b]		
	Estrogen	Progestin	Androgen	Estrogen	Progestin	Androgen
Promensil™	×					× (63%)
Estro-Logic™	×					
Grapeseed extract	×	×				
Chamomile extract	×	×				
Prostate-Ease				× (77%)		
Wild yam root				× (70%)		
Dong quai				× (50%)		× (71%)
Rosehips						× (75%)

[a] For dose–response curves, see Fig. 1.
[b] We present percentage blocking in parentheses, under the specified experimental conditions.

by the cell line BT-474). On the other hand, several products exhibited antiestrogenic and antiandrogenic activity at the highest concentration tested (Table 2). These included Prostate-Ease, wild yam root, and dong quai (anti-ERs) and rosehips, dong quai, and Promensil™ (anti-ARs). Table 2 summarizes the activities of the products that have been tested positive with our screening method.

4. Discussion

The use of alternative and complementary products is rapidly expanding [1–5]. As the North American population ages, hormonal events such as menopause and andropause are coming to the forefront of medical issues [34,35], and the incidences of steroid hormone-dependent cancers are continuing to increase [36]. Many menopausal women are turning to natural alternatives such as soy isoflavones, wild yam root, and dong quai. Similarly, many men, are looking towards complementary or alternative therapies to treat BPH, or prevent prostate cancer [28,37,38]. Saw palmetto and PC-SPES are among many appealing alternatives [9,10,37,38].

Promensil™ contains 40 mg isoflavones per tablet, primarily genistein, biochanin A, daidzein, and formononetin, which is approximately equivalent to the isoflavone content of a cup of soy milk and five cups of chickpeas. Isoflavones have been found to increase arterial compliance in postmenopausal women [39], thus, presumably reducing heart disease risk. Recently, it has also been clinically shown to maintain bone density. Our findings suggest a mechanism for these physiological effects. This isoflavone preparation showed significant estrogenic activity, equivalent to 10^{-8} mol/l estradiol. This product also demonstrated anti-AR activity, similar to that demonstrated for the soy isoflavones genistein and biochanin A in previous studies (Ref. [40] and our unpublished data).

Grapeseed extract, which contains procyanidins, compounds structurally similar to flavonoids, and chamomile, which contains apigenin, a flavone, showed both estrogenic and progestational activity at the highest concentration tested. Procyanidins present in polyphenolic fractions of grapeseeds are strong antioxidants, and have been demonstrated to have antiproliferative and anticarcinogenic activities in cell culture and animal studies, respectively [41–43]. Apigenin has been shown in our previous studies to have weak estrogenic, and relatively strong progestational activities [44,45]. This flavonoid is present in chamomile extract, and the activity of this natural product (Table 2) is likely due to apigenin.

Positive results were not found for all natural products tested. Dong quai, which has been made into tonics by Chinese women for centuries [13], and wild yam root, both used as sources of phytoestrogens and phytoprogestins, were found not to have significant estrogenic or progestational activity, but rather to have weak antiestrogenic and/or antiandrogenic activities. A study conducted by Zava et al.

[46] looking at Mexican wild yam products containing diosgenin, found that this product did not bind to either ER or PR, and, moreover, this steroid precursor is not metabolized to a progestational form in the human body. Whether any true steroid hormone-related physiological benefit can be derived from either of these products has yet to be ascertained. At present, the one double-blinded clinical study looking at the effects of dong quai in postmenopausal women has found no benefit over placebo in alleviating menopausal symptoms [47].

Saw palmetto and Prostate-Ease, both used for prostatic pathologies, including BPH and prostate cancer, did not show androgenic nor antiandrogenic activity. Prostate-Ease did show weak antiestrogen activity. For saw palmetto, these results suggest that its effects are likely not mediated by the steroid hormone receptor system. One suggested mechanism is anti-inflammatory, through α_1-adrenoreceptors [48].

In conclusion, we have demonstrated, by using an in vitro system, that several natural products and nutraceuticals exhibit weak steroid hormone agonist and antagonist activity, while many others do not. These data may be useful to explain some of the in vitro biological activities or the lack of biological activity of these preparations. Moreover, the eventual precise definition of the biological activities of these compounds may help in the more rational use of these as natural therapeutic or chemopreventive agents.

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