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Steroid hormone activity of flavonoids and related compounds

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Key words: cancer prevention, cancer risk, diet and cancer, estrogen-like compounds, flavonoids, phytochemicals, phytoestrogens, steroid hormone receptors

Summary

Soy isoflavones have been studied extensively for estrogenic and antiestrogenic properties. Other flavonoids, found in fruits, vegetables, tea and wine, have been much less tested for steroid hormone activity. We therefore assessed the estrogenic, androgenic and progestational activities of 72 flavonoids and structurally-related compounds. These compounds were tested on BT-474 human breast cancer cells at concentrations of 10^{8}–10^{-5} M, with estradiol (estrogen), norgestrel (progestin) and dihydrotestosterone (androgen) used as positive controls, and ethanol (solvent) as a negative control. pS2, an estrogen-regulated protein, and prostate-specific antigen (PSA), regulated by androgens and progestins, were quantified in tissue culture supernatants using ELISA-type immunofluorometric assays developed in-house. Of the 72 compounds tested, 18 showed estrogenic activity at 10^{-5} M. Of this subset, seven also showed progestational activity at this concentration. The soy isoflavones, biochanin A and genistein, showed the most potent estrogenic activity, with a dose-response effect up to 10^{-7} M. Of all other flavonoids, luteolin and naringenin displayed the strongest estrogenicity, while apigenin had a relatively strong progestational activity. Based on our data, we have formulated a set of structure/function relationships between the tested compounds. Flavonoids, therefore, exhibit significant steroid hormone activity, and may have an effect in the modification of cancer risk by diet, or in cancer therapeutics and prevention.

Introduction

Many studies have focused on the soy isoflavones, particularly daidzein and genistein, and their possible anticarcinogenic properties. These compounds have been demonstrated *in vitro* and *in vivo* to have estrogenic as well as antiestrogenic activity [1, 2]. These compounds have been shown *in vivo* to lengthen the follicular phase of the menstrual cycle [3], reduce urinary excretion of 17β-estradiol, and favour 2-hydroxyestrone formation [4], all of which are associated with reduced risk for breast cancer. Moreover, there is increased interest in selective estrogen receptor modulators (SERMs) which hold promise of being used to prevent osteoporosis in post-menopausal women, and at the same time reduce the risk of developing breast cancer and atherosclerosis [5–7]. Raloxifene is one SERM which is now in clinical trials [8]. Others have put forward the idea that phytoestrogens may represent natural SERMs [9]. However, we do not yet know if soy isoflavones, as natural SERMs, decrease, increase, or have neutral effects on breast and other estrogen-dependent cancers.

Isoflavones are members of a larger family of compounds, known as the flavonoids. This family also includes flavones, flavanones, and flavans, which, like isoflavones, contain a phenyl side-chain, with a variable number of hydroxyl or other groups (Figure 1). These compounds have some structural similarities to the natural estrogen estradiol, as well as other steroid hormones and steroid hormone antagonists (Figure 2).

Studies of flavonoids and their possible role in preventing chronic diseases including heart disease, and breast and prostate cancers, have increased dramatically number during in the last decade. These compounds exist in relatively large amounts in our

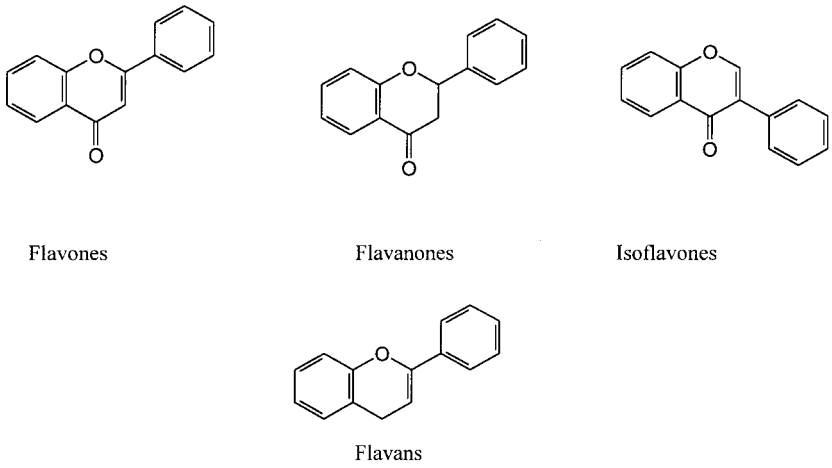


Figure 1. General structures of the flavonoid family of compounds.

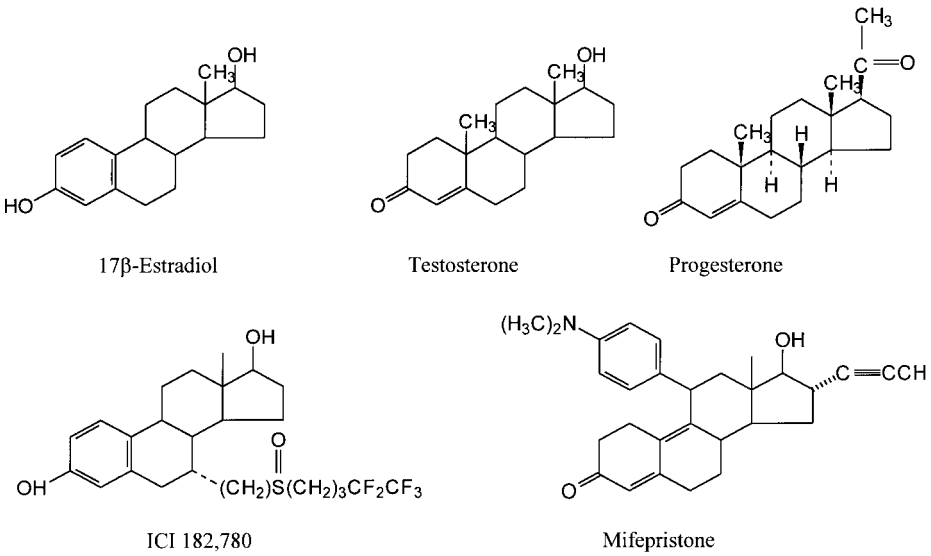


Figure 2. Structures of the steroid hormones 17β-estradiol, progesterone and testosterone, and the antagonists ICI 182,780 (antiestrogen) and mifepristone (antiprogestin).

food supply, especially in fruits and vegetables, tea, red wine, and legumes. Intakes of these compounds are now estimated to be up to 45 mg/day [10], and a database of foods with known flavonoid content has been created [11].

In vitro, flavonoids have been shown to act as antioxidants [12], arrest the cell cycle and inhibit topoisomerase II [13, 14], and exert antiproliferative activities [15–18]. Many of the observed effects are thought to play a role in preventing breast and/or prostate cancers, but this relationship remains unclear. Soy protein has been shown, in at least one study, to significantly increase normal breast cell proliferation [19]. With the exception of soy isoflavones, few studies have focused on the estrogenicity of the flavonoids per se [20–22], and to date, to our knowledge, only one study has examined the possible androgenic and progestational activities of flavonoids [23]. Furthermore, examination of flavonoid structure and correlation to biological activity (e.g. estrogenicity) has been limited [24, 25]. Whether similar structure/function relationships exist for estrogen, androgen and progesterone receptor binding of these phytochemicals is unknown.

Therefore, we assessed the estrogenic and androgenic/progestational activities of 72 flavonoids and related compounds using a human breast cancer cell line system, utilizing two steroid hormone-regulated endogenous proteins. pS2 is an estrogen-regulated protein, and prostate-specific antigen (PSA) is regulated by androgens and progestins. We have developed immunoassays to measure these secreted proteins in tissue culture supematants. The data allowed us to identify active compounds and compare activity to structure. These data may be useful for comparing relative potencies of each of the phytochemicals regarding their ability to bind and activate steroid hormone receptors.

Materials and methods

Materials

The BT-474 human breast cancer cell line was purchased from the American Type Culture Collection, Rockville, MD. The levels of estrogen receptor (ER) and progesterone receptor (PR), as quantified by commercial ELISA assays (Abbott Diagnostics, Abbot Park, Chicago, IL) were 29 and 389 fmol/mg, respectively. Although the androgen receptor (AR) content was not quantified, Northern blot studies indicated that this cell line contains AR [26]. All steroids used were from Sigma Chemical, St. Louis, MO, USA. Stock, 10^{-3} M solutions of steroids were prepared in absolute ethanol. Flavonoids and related compounds were obtained from Indofine Chemical, Summerville, NJ, and Sigma. We prepared 10^{-2} M stock solutions in absolute ethanol. Mifepristone (RU 486) and nilutamide (RU 56187) were gifts from Roussel-UCLAF, Romainville, France.

Methods

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 mM 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.

The cells were then stimulated with a flavonoid or related compound at 10^{-5} and 10^{-7} M (final concentrations) and incubated for 7 days at the same conditions as above. Estradiol, norgestrel and dihydrotestosterone (DHT) at 10^{-8} M were used as positive controls and ethanol (solvent) as a negative control. After 7 days, the supernatants were harvested and analyzed for pS2 and PSA. Compounds found to stimulate production of pS2 or PSA were then tested for dose-response, in the range from 10^{-5} to 10^{-8} M.

Assays

pS2 assay

pS2 protein was analyzed using an ELISA-type competitive fluorometric immunoassay. The details of this assay are described elsewhere [27]. The detection limit is $\sim$20 ng/ml.

PSA assay

Prostate specific antigen was quantified with an ELISA-type immunofluorometric procedure essentially as described elsewhere [28]. The detection limit of this assay is $\sim$1 ng/l.

Results

The breast carcinoma cell line BT-474 is steroid hormone receptor-positive. Hall et al. have demonstrated presence of estrogen (ER), androgen (AR) and progesterone (PR) receptor mRNAs in BT-474 cells [26]. We have further confirmed presence of ER and PR by ELISA assays and of AR by immunohistochemistry (data not shown).

Our tissue culture system is based on the principle that the selected endogenous genes pS2 and PSA are directly up-regulated by steroid hormones. The pS2 gene contains estrogen response elements in its proximal promoter and its expression is increased after estrogen induction [29], but not after androgen or progestin induction [27]. Similarly, the PSA gene contains multiple androgen response elements in its promoter/enhancer region [30] and is up-regulated by androgens and progestins but not estrogens [31]. Thus, this tissue culture system is a sensitive indicator of hormone receptor activation and induction of transcription. The principles of transcription activation by steroid hormones have been described by Beato et al. [32].

Of the 72 flavonoids and related compounds tested (Table 1, Appendix), 18 were found to have estrogenic activity. Six compounds of this subset were also found to have androgenic and/or progestational activity. Of these, one compound had strong activity (apigenin), two had significantly lower activity (fisetin, naringenin) and three had very weak activity (Table 1). Further study with progesterone and

Table 1. Flavonoids and related compounds with and without steroid hormone agonist activity

Compounds		Relative potency (%)*
Compounds with estrogenic activity		
Genistein		100
Biochanin A		95
Luteolin		58
Daidzein		55
Naringenin		40
7-Hydroxyflavone		25
6-Hydroxyflavanone		23
Resveratrol		22
6-Bromo-2-naphthol		20
Chrysin		18
Apigenin		16
6-Hydroxyflavone		15
Morin		15
Fisetin		12
Quercetin		10
7,8-Dihydroxyflavone		8
4′-Hydroxyflavanone		8
7-Hydroxyflavanone		8
Compounds with progestational activity		
Apigenin		100
Fisetin		0.8
Naringenin		0.7
Chrysin		0.2
Luteolin		0.2
Morin		0.1
Compounds without agonist activity		
Abrine	3,4-Dimethoxycinnamic acid	Mangostine
Andrographolide	7,8-Dimethoxyflavone	5-Methoxyflavanone
Ascorbic acid	Ellagic acid	6-Methoxyflavanone
5,6-Benzoflavone	Embelin	7-Methoxyflavanone
7,8-Benzoflavone	Flavanone	2′-Methoxyflavone
Bixin	Flavone	4′-Methoxyflavone
4′-Bromoacetophenone	Folic acid	5-Methoxyflavone
Caffeic acid	Gallic acid	6-Methoxyflavone
Caffeine	Gardenin	7-Methoxyflavone
Chlorogenic acid	Harmaline	6-Methylflavone
Conessine	Harmalol	L-Mimosine
Curcumine	Harmine	Naringin
2′,4′-Dihydroxyacetophenone	Harmol	Picrotin
2′,5′-Dihydroxyacetophenone	7-Hydroxyflavan	Piperine
2′,6′-Dihydroxyacetophenone	2′-Hydroxyflavanone	Pongamol
2,5-Dihydroxy-1,4-benzoquinone	3-Hydroxyflavone	Rutin
2′,6′-Dimethoxyacetophenone	5-Hydroxyflavone	Salicylic acid
2,3-Dimethoxybenzaldehyde	Karanjin	Theophylline

*Relative potency was compared based on the estrogenic activity of genistein and the progestational activity of apigenin (defined as 100%).

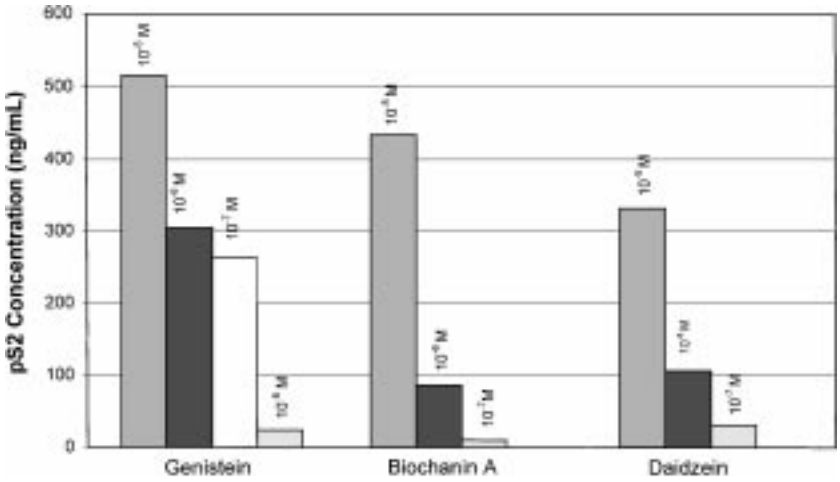


Figure 3. Estrogenic activity of three isoflavones, measured as ng of pS2 protein per milliliter in the tissue culture supernatant. The activity was dose-dependent at the concentrations shown.

androgen blockers has shown these compounds to be progestational (data not shown). No compound was found to have only progestational activity. The soy isoflavones, biochanin A, genistein and daidzein, demonstrated strong estrogenic activity; the same was true for luteolin and naringenin, two citrus flavonoids. Resveratrol, a trihydroxystilbene found in red wine, 6-bromo-2-naphthol, several hydroxyflavanones and two hydroxyflavones had moderate estrogenic activity (Table 1). A dose-response relationship for the three soy isoflavones is shown in Figure 3. Detectable estrogenic activity was seen at isoflavone concentrations around 10^{-7}–10^{-8} M. The estrogenic activity of the compounds of Table 1 below naringenin was detectable only at a concentration of 10^{-5} M.

The relatively large number of compounds tested allowed us to correlate the structure of these compounds with the potency of their activity. Below, we summarize our general observations.

1. The flavonoid core structure (diaryl ring) is important for estrogenic and progestational activity. From the 18 identified active compounds (Table 1), 16 were flavonoids. Of the 31 nonflavonoids tested, only two showed weak estrogenic activity. These two compounds were a naphthol derivative (6-bromo-2-naphthol), and a trihydroxystilbene (resveratrol). All of the compounds demonstrating progestational activity were flavonoids.
2. Hydroxyl groups appear to be crucial for activity. If hydroxyl groups are not present in the structure, no estrogenic or progestational activity is observed. For example, we observed no activity for 5,6-benzoflavone, 7,8-benzoflavone, flavone and flavanone, while we detected activity for 7-hydroxyflavone, 6-hydroxyflavone, 7,8-dihydroxyflavone, 6-hydroxyflavanone, 4′-hydroxyflavanone, and 7-hydroxyflavanone.
3. When hydroxyl groups are methylated, activity is diminished. Examples include 7,8-dimethoxyflavone, which has no estrogenic activity, versus 7,8-dihydroxyflavone (active); 7-methoxyflavone (inactive) versus 7-hydroxyflavone (active), and 6-methoxyflavone (inactive) versus 6-hydroxyflavone (active). However, this observation did not hold true for biochanin A which is as potent as genistein, despite having a methoxy group in position 3′.
4. Isoflavones, in general, were found to be more potent estrogens than other flavonoids. The isoflavones biochanin A, genistein, and daidzein showed estrogenic activity in a dose-dependent manner, from 10^{-7} to 10^{-5} M (Figure 3). The other flavonoids had no activity below 10^{-6} M. Additionally, apigenin (a flavone) and genistein (an isoflavone) differ only in the position of the benzyl ring (3 vs 2 position). This difference reduces apigenin's estrogenic activity by 84% in comparison to genistein.
5. Flavones and flavanones appear to have greater estrogenic potency than flavans (e.g. 7-hydroxyflavone > 7-hydroxyflavanone $\gg$ 7-hydroxyflavan).
6. The position of the hydroxyl groups appears to be important. Hydroxyl groups at positions 6, 7 or 4′ confer more potent estrogenic activity than

hydroxyls at positions 3, 5 or 2′. For example, 6-hydroxyflavone > 3-hydroxyflavone and 5-hydroxyflavone (inactive); 6-hydroxyflavanone > 2′-hydroxyflavanone (inactive); 7-hydroxyflavone > 3-hydroxyflavone and 5-hydroxyflavone (inactive); 7-hydroxyflavanone > 2′-hydroxyflavanone (inactive) and 4′-hydroxyflavanone > 2′-hydroxyflavanone (inactive). Remarkably, the top six compounds with estrogenic activity (Table 1) have a 7-position hydroxyl group and apigenin, the most potent progestational agent also possesses a hydroxyl group at position 7. Additionally, conjugation of the hydroxyl group at position 7 renders the conjugate inactive, e.g. naringenin (active) versus naringin (inactive). See also point 3 above.

7. The most potent estrogenic compounds have between 2 and 4 hydroxyl groups. At least one is localized in the 7 position of ring A, and another one in the 4′ position of ring B (e.g. 7,8-dihydroxyflavone is much less potent than daidzein, in which the second hydroxyl group is in the 4′ position).
8. A hydroxyl or other group at position 3 or 8 interferes with agonist activity on estrogen and progesterone receptors (e.g. luteolin > quercetin and rutin; luteolin, apigenin > fisetin; 7-hydroxyflavone > 7,8-dihydroxyflavone).
9. Specificity of flavonoids for estrogen or progesterone receptors is dependent on the position of the B ring (e.g. apigenin has progestational activity versus genistein which is an estrogen). From all compounds that have progestational/androgenic activity, none is an isoflavone; all are either flavones or flavanones (Table 1). The importance of the 4′-hydroxyl on progestational activity is further demonstrated by comparing apigenin versus chrysin, apigenin versus luteolin (which has an extra hydroxyl) and apigenin versus morin (has two extra hydroxyls).
10. A double bond between carbons 2 and 3 is important for progestin activity (e.g. apigenin versus naringenin). A single bond at this site reduces activity by 99%.

Discussion

Flavonoids, as components of our diets, have been demonstrated to have protective effects on heart disease [33], cancer [34], and other conditions and diseases [35–37]. The cardioprotective effects of isoflavones are thought to be primarily due to their estrogen-like activity. Like estrogen replacement therapy, soy isoflavones have been demonstrated to increase arterial compliance [38]. Additionally, these compounds diminish the symptoms of menopause, including hot flashes [39]. For these reasons, many women are reanalyzing the risks and benefits of hormone replacement therapy, and supplementing their diets with soy products instead. Commercial vendors have made available isoflavone tablets. Phytoestrogens are increasingly becoming a natural alternative to synthetic estrogens.

Other flavonoids (flavones, flavanones) have been examined mostly for their antioxidant capabilities. The Seven-Country Study was one of the first to link flavonoid consumption with decreased risk of heart disease [40]. Phenolics found in red wine are often used to partially explain the ‘French Paradox’ [41], above the major role attributed to ethanol [42]. Antioxidants and flavonoids have been shown to reduce LDL oxidation [43], and, their estrogenic capacity may be partially responsible for the increase in HDL, often observed in red wine drinkers [44]. These two activities may work simultaneously, providing the consumer with extra cardioprotective benefits. However, the issue of the French Paradox still remains controversial.

The role of flavonoids in cancer development, especially breast and prostate carcinomas has yet to be fully examined. Few epidemiological studies have been conducted [45]. *In vitro* studies show the antiproliferative, antioxidant and cytostatic effects flavonoids [12–16]. Currently, herbal alternatives to drugs, including PC-SPES, a Chinese herbal mixture, are being sought for prostate cancer management [46, 47]. These products have been shown to be antiproliferative and antitumorigenic [48]. However, the mechanism is not well understood, and controlled, prospective studies have not been conducted.

We have examined the estrogenic and progestational/androgenic activities of 72 flavonoids and related compounds in a human breast carcinoma cell line, by monitoring endogenously regulated genes (pS2 and PSA) in the presence of endogenous hormone receptors. Eighteen of the 72 flavonoids and related compounds showed estrogenic and/or progestational activity. The soy isoflavones demonstrated activity up to 10^{-7}–10^{-8} M. However, most of the other flavonoids did not show activity beyond 10^{-5} M. These concentrations are approximately 10-fold higher than those reported by other groups, including Miksicek [24] and Le Bail et al. [20]. Their studies used transfected estrogen-responsive reporter

plasmid systems, measured through chloramphenicol acyl transferase or luciferase enzymes. Our system, using endogenous genes and receptors, may be closer to the *in vivo* situation, in comparison to data generated with transfected indicator genes and receptors. These synthetic systems are usually too sensitive and may give distorted results. This issue was stressed recently by Xu et al. [48] for studies related to hormone receptor function.

We analyzed the structure of compounds with and without estrogenic and progestational activity and devised general guidelines, as has been done by Lien et al. for phenolic antioxidants [49]. Through the testing of a large number of compounds, we were able to establish the relative importance of flavonoid class (flavone, flavanone, isoflavone, flavan), the number and position of hydroxyl groups and double bonds on the biological activity of these compounds. It is clear that subtle changes in the structure of these compounds can bring about a large change in their biological activity and receptor specificity. Our results concur with those of Miksicek [24] and Le Bail et al. [20] regarding the importance of the diaryl ring structure, as 16 of the 18 estrogenic compounds were flavonoids. Only resveratrol (a trihydroxystilbene) and 6-bromo-2-naphthol exhibited weak estrogenic activity at a concentration of 10^{-5} M. Similarly, we agree with the importance of the 7 and 4′ hydroxyl positions. However, we found the 6 hydroxyl position to confer estrogenic activity as well (6-hydroxyflavone, 6-hydroxyflavanone). Similar to other studies, we found that a hydroxyl group at position 3 or 8, or a total of greater than 4 hydroxyl groups reduces the estrogenic activity of the flavonoid. Hydroxyl groups at positions 2′ or 5 did not significantly affect estrogenic activity, but methylation at the 7 or 4′ position (with the exception of biochanin A) decreased estrogenic activity.

We have also examined the structure/function relationship of flavonoids and related compounds for progestational activity. All of the compounds with such activity were flavonoids, demonstrating that the diaryl ring is crucial. Similarly, they all had hydroxyl groups at positions 7 and 4′. Finally, the presence of a double bond between carbons 2 and 3 appears to be highly important. Elimination of this bond (apigenin → naringenin) decreases this activity by 99%.

One of our significant observations is the specificity of the position of the B ring in relation to the flavonoid core; whether it is bound to position 2 or 3. Two compounds that have the same empirical formula and molecular weight, namely, genistein and apigenin, display the strongest biological activity, one being estrogenic (genistein) and one progestational (apigenin). The only difference between these two compounds is the position of the B ring, which qualifies the compound as being either an isoflavone (genistein) or a flavone (apigenin). This structural difference may be exploited to develop compounds that target one receptor versus the other.

The impact these estrogenic and progestational actvities may have in the prevention or development of estrogen-dependent cancers, including breast, ovarian and endometrial, is difficult to establish. In general, estrogenic agents would be expected to increase cancer risk. However, from the epidemiological evidence, this does not appear to be the case. The majority of human studies [50–53] show the opposite effect. This may be due to flavonoids with weak estrogen activity binding to ER, thereby preventing more potent, endogenous estrogens from activating possibly deleterious pathways.

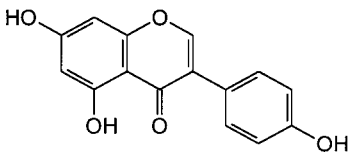
In summary, this study has demonstrated estrogenic and progestational activity of several flavonoids and other compounds by using a screening system based on a human breast carcinoma cell line. These activities should be taken into consideration to explain as to how these compounds, and the natural products in which they are found, may play a role in the prevention of breast and/or prostate cancers. The identified structure/function relationships may aid in the development of drugs or derivatized natural products with greater activity and specificity.

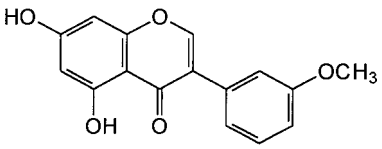
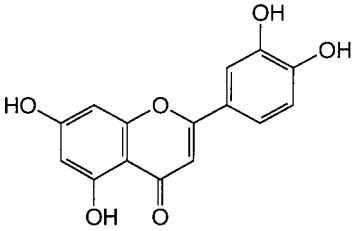
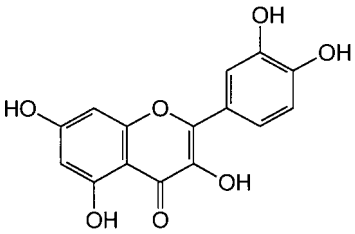
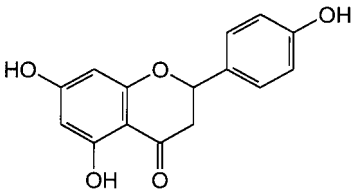
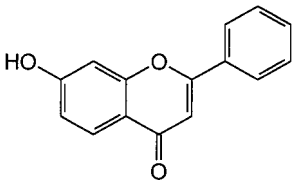
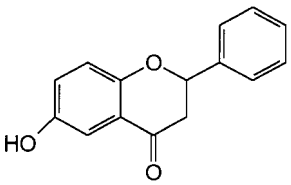
Acknowledgements

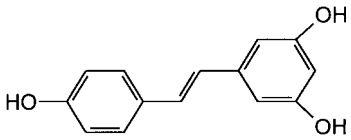
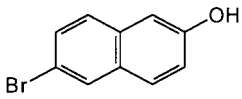
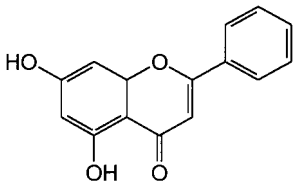
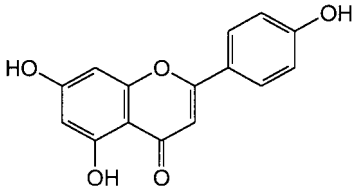
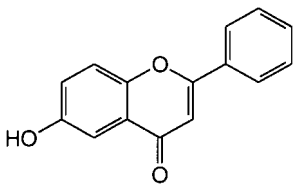
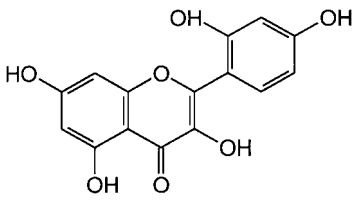
We would like to thank Dr. Vigi Bezwada from Indofine Chemical for providing phytochemicals, and the Canadian Wine Institute for financial support.

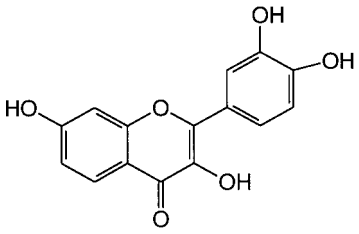
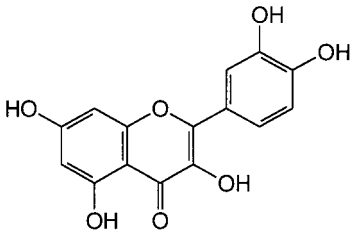
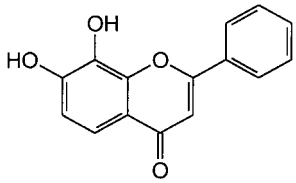
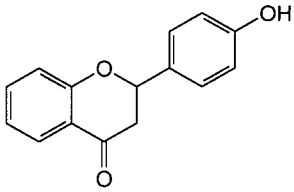
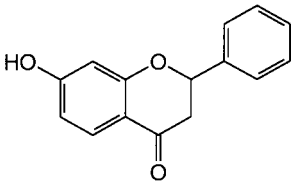
Appendix

Chemical structures of all compounds tested in decreasing order of estrogenicity

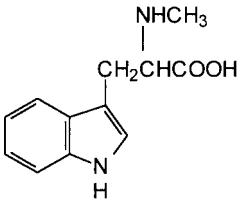
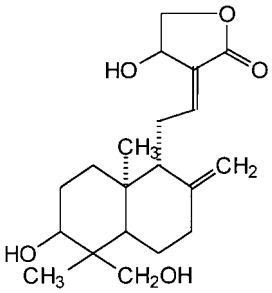
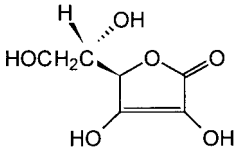
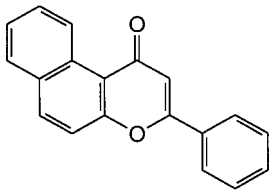
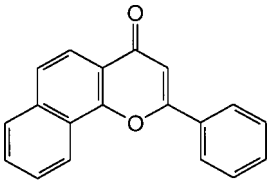
Name	Structure
Genistein	

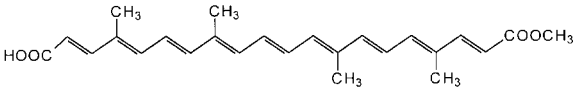
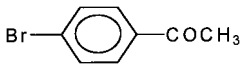
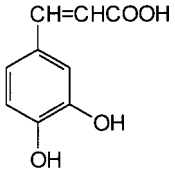
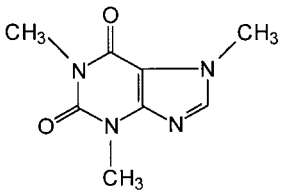
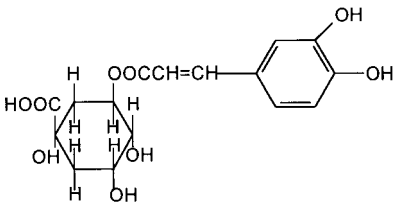
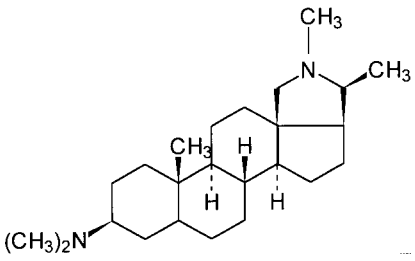
Name	Structure
Biochanin A	
Luteolin	
Daidzein	
Naringenin	
7-Hydroxyflavone	
6-Hydroxyflavanone	

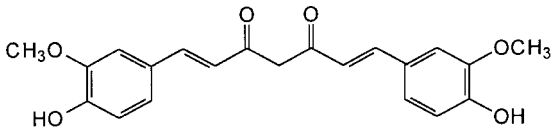
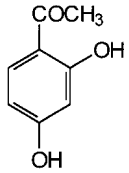
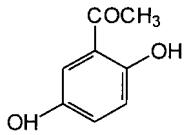
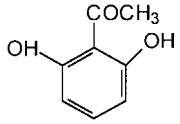
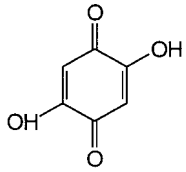
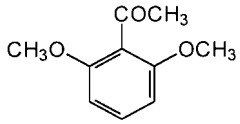
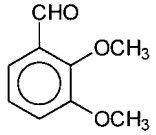
Name	Structure
Resveratrol	
6-Bromo-2-naphthol	
Chrysin	
Apigenin	
6-Hydroxyflavone	
Morin	

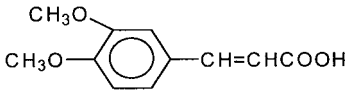
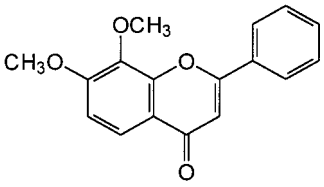
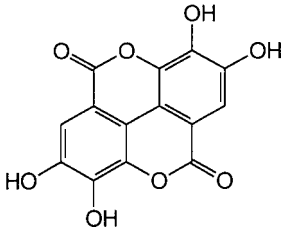
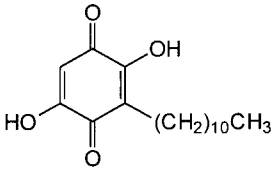
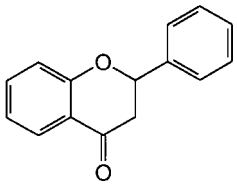
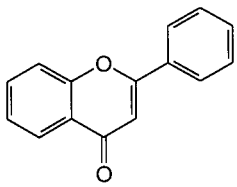
Name	Structure
Fisetin	
Quercetin	
7,8-Dihydroxyflavone	
4′-Hydroxyflavanone	
7-Hydroxyflavanone	

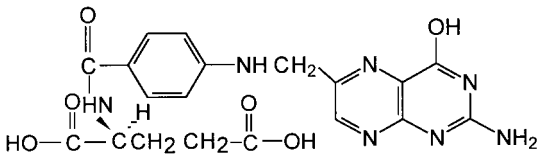
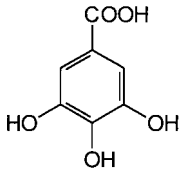
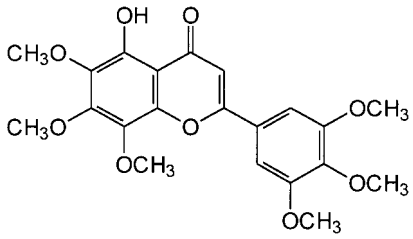
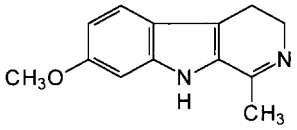
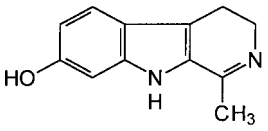
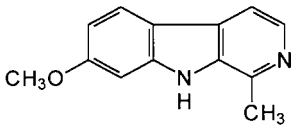
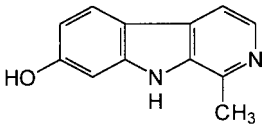
Compounds without agonist activity

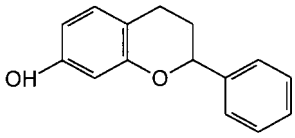
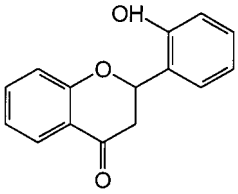
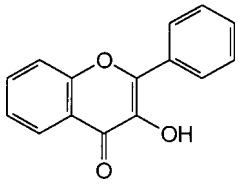
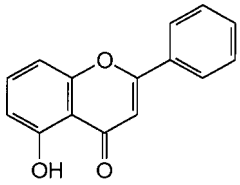
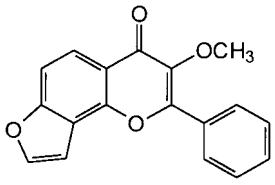
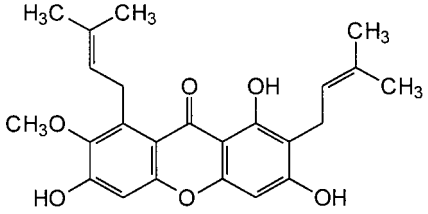
Name	Structure
Abrine	
Andrographolide	
Ascorbic acid	
5,6-Benzoflavone	
7,8-Benzoflavone	

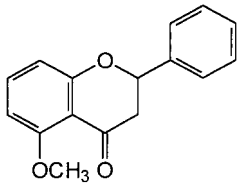
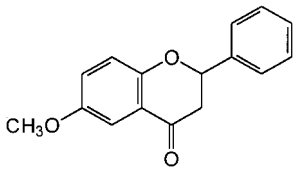
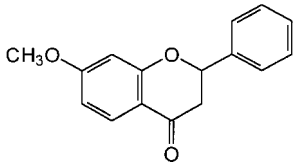
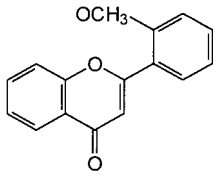
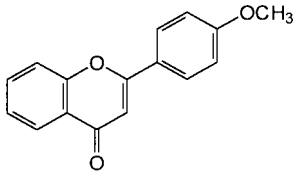
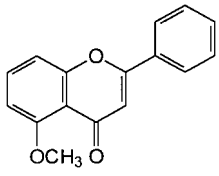
Name	Structure
Bixin	
4′-Bromoacetophenone	
Caffeic acid	
Caffeine	
Chlorogenic acid	
Conessine	

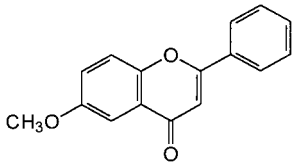
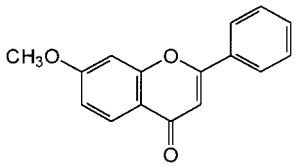
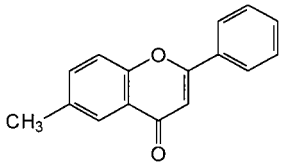
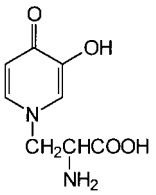
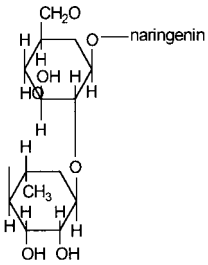
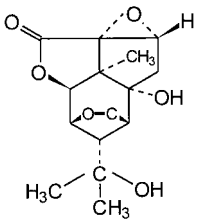
Name	Structure
Curcumine	
2′,4′-Dihydroxyacetophenone	
2′,5′-Dihydroxyacetophenone	
2′,6′-Dihydroxyacetophenone	
2′,5′-Dihydroxy-1,4-benzoquinone	
2′,6′-Dimethoxyacetophenone	
2,3-Dimethoxybenzaldehyde	

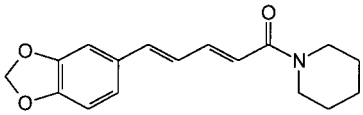
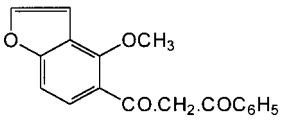
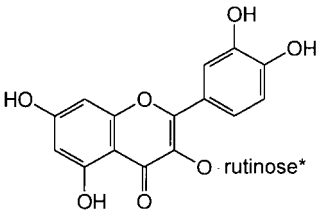
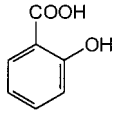
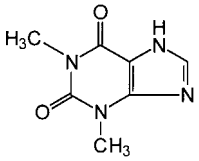
Name	Structure
3,4-Dimethoxycinnamic acid	
7,8-Dimethoxyflavone	
Ellagic acid	
Embelin	
Flavanone	
Flavone	

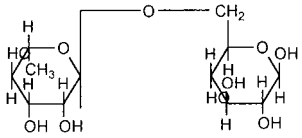
Name	Structure
Folic acid	
Gallic acid	
Gardenin	
Harmaline	
Harmalol	
Harmine	
Harmol	

Name	Structure
7-Hydroxyflavan	
2′-Hydroxyflavanone	
3-Hydroxyflavone	
5-Hydroxyflavone	
Karanjin	
Mangostine	

Name	Structure
5-Methoxyflavanone	
6-Methoxyflavanone	
7-Methoxyflavanone	
2′-Methoxyflavone	
4′-Methoxyflavone	
5-Methoxyflavone	

Name	Structure
6-Methoxyflavone	
7-Methoxyflavone	
6-Methylflavone	
L-Mimosine	
Naringin	
Picrotin	

Name	Structure
Piperine	
Pongamol	
Rutin	
Salicylic acid	
Theophylline	

*Rutinose 

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