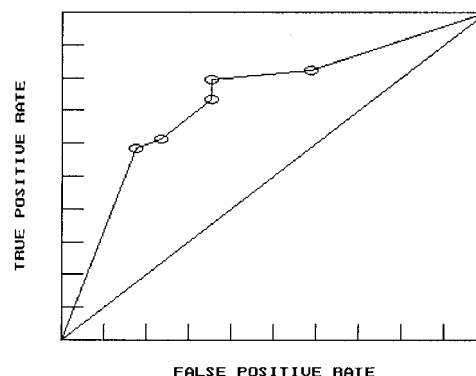


Table 1. Operational parameters, predictive values, and ROC curve for several cutoff points of the FII/FX ratio.

	Cutoff				
	2.1	2.2	2.3	2.4	2.5
Sensitivity	0.82	0.76	0.65	0.65	0.41
Specificity	0.58	0.61	0.74	0.79	0.82
LR+ ^a	1.98	1.98	2.45	3.12	2.30
LR-	0.30	0.38	0.48	0.45	0.72
PPV	0.25	0.25	0.28	0.33	0.27
NPV	0.95	0.94	0.93	0.93	0.90

^a LR+, positive likelihood ratio; LR-, negative likelihood ratio; PPV, positive predictive value; NPV, negative predictive value.



in 17 patients (13.8%; 16 heterozygous and 1 homozygous) and ruled out in 106 (86.2%). No statistical difference in age, gender, or INR was found between the two groups. FII:C was 340 units/L [95% confidence interval (CI), 290–400 units/L] among the 20210A carriers and 310 units/L (95% CI, 290–340 units/L) among the non-carriers ($P = 0.36$).

During OA therapy, the FII:C seems useless as a diagnostic tool. FX:C was not significantly lower among the carriers [140 (95% CI, 110–170) units/L vs 170 (95% CI, 150–180) units/L; $P = 0.31$], but the ratio was higher [2.54 (95% CI, 2.26–2.82)] than in non-carriers [2.01 (95% CI, 1.92–2.10); $P < 0.0001$]. The sensitivity was 0.82, and the specificity was 0.58 for a cutoff of 2.1. A good negative predictive value of 0.95 corresponded to an unacceptable positive predictive value (0.25; see Table 1). The 2.40 cutoff showed the best likelihood ratio of a positive result (3.1) but correctly classified only 77% of the patients. The nonparametric estimation for the area under the ROC curve was 0.73 (9).

In summary, although a non-anticoagulated population should be evaluated to obtain definitive conclusions, many thromboembolic patients are referred to the outpatient clinic for investigation while being treated with OA, and many recurrent cases may require lifelong treatment.

During stable OA therapy, FX activity could be a good marker of FII oscillations. In these subjects, the FII:C/FX:C ratio was significantly higher when the mutation FII^{20210A} existed (2.54 vs 2.01; $P < 0.0001$), but disappointing results were obtained when we attempted to use it for a diagnostic purpose.

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Genistein: A Potent Natural Antiandrogen

To the Editor:

Flavonoids and other polyphenolic natural compounds have attracted much attention as candidate cancer

preventive and anticarcinogenic agents, as well as antiatherogenic and antioxidant compounds (1). Although the public now consumes these compounds in substantial amounts from dietary sources, food supplements, and more recently, as "nutraceutical" tablets, their actual mode of action is not fully defined. The most compelling hypotheses correlate the biological action of flavonoids to their ability to mimic natural estrogens (2, 3) such as estradiol, or to act as antioxidants (4). Indeed, genistein, a natural soy isoflavone, is among the most potent known phytoestrogens. The ability of flavonoids to act as androgen mimics or antiandrogens has attracted much less attention. Recently, we showed that apigenin, a natural flavone found in chamomile, olive leaves, and other plant sources, has potent progestational activity (5).

We have examined the possible antiandrogenic activity of genistein using the steroid hormone receptor-positive breast cancer cell line BT-474. This cell line, when stimulated by dihydrotestosterone (DHT), produces prostate-specific antigen (PSA), which is then secreted into the tissue culture supernatant and can be measured quantitatively by immunoassay. Details of this system are given elsewhere (5). To study the antiandrogenic activity, the cells were first exposed to the putative antiandrogen (10^{-5} to 10^{-8} mol/L) for 1 h and then stimulated with DHT (10^{-9} mol/L). Controls with only antiandrogen or only DHT were included in all experiments. Nilutamide was used as a control antiandrogen. Our data (Fig. 1) clearly demonstrate the potent antiandrogenic activity of genistein, which is dose-dependent and is detectable down to 10^{-7} mol/L. Quercetin and several other flavonoids tested were devoid of such activity (data not shown).

These data clearly demonstrate for the first time that genistein exhibits potent antiandrogenic activity in addition to its well-established estrogenic activity. Indeed, the therapeutic potential of this compound in prostate can-

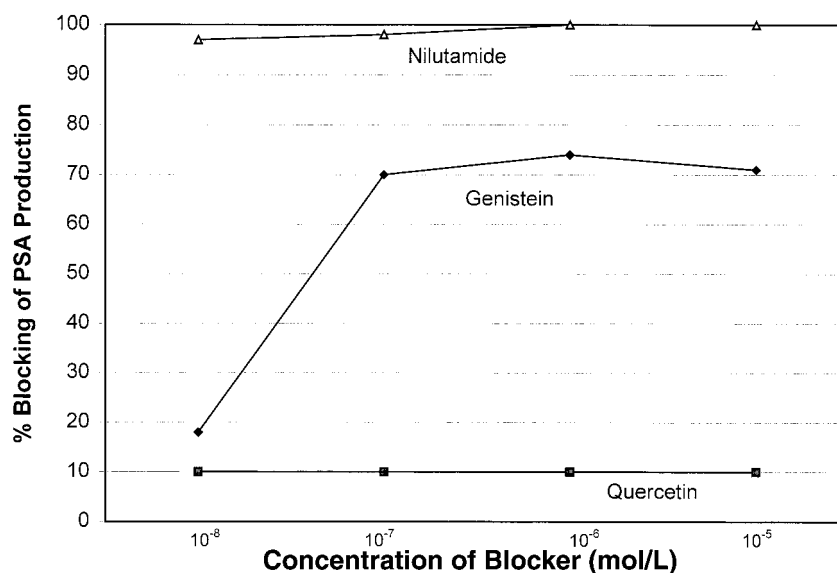


Fig. 1. Percentage of blocking of DHT, as measured by PSA production, by genistein, quercetin, and nilutamide.

BT-474 human breast cancer cells were grown to confluency in phenol-free RPMI (Life Technologies) supplemented with 100 mL/L fetal calf serum, 10 g/L insulin, and 200 mmol/L L-glutamine at 37 °C in 5% CO₂. Once confluent, they were subcultured in 24-well microtiter plates using the same medium but with substitution of charcoal-stripped fetal calf serum for the regular fetal calf serum. The cells were stimulated with candidate blocker [genistein (◆), quercetin (◻), or nilutamide (△)], blocker and steroid (DHT), or steroid alone. Blockers were tested at concentrations of 10^{-8} to 10^{-5} mol/L, and DHT was used at 10^{-9} mol/L. For the cells stimulated with blocker and steroid, the blocker was added first and incubated for 1 h; the cells were then stimulated with steroid. Alcohol was used as a negative control. The plates were then incubated for 7 days, at which time the tissue supernatants were harvested. The supernatants were then analyzed quantitatively for PSA. Blocking activity was assessed by dividing the amount of PSA produced by the candidate blocker + steroid and by steroid alone and multiplying by 100. None of the candidate blockers induced any PSA production when added alone.

cer patients may be related to its combined estrogenic and antiandrogenic properties. It will be interesting to examine large numbers of natural compounds for antiandrogenic activity, which may qualify them as candidate therapeutic and preventive agents for prostate, breast, and possibly other hormonally dependent cancers.

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