International Journal of Medical and Health Research
ISSN: 2454-9142
Received: 06-09-2018; Accepted: 08-10-2018
www.medicalsciencejournal.com
Volume 4; Issue 11; November 2018; Page No. 25-29

Flaxseed subsides biological markers in cancer breast: A study

Dr. Anil Batta
Head, Department of Medical Biochemistry, Govt. Medical College, Amritsar, Punjab, India

Abstract
Lignans are compounds found in a variety of plant materials including flaxseed, pumpkin seed, sesame seed, soybean, broccoli, and some berries. The major lignan in flaxseed is called secoisolariciresinol diglucoside (SDG). Once ingested, SDG is converted in the colon into active mammalian lignans, enterodiol, and entero-lactone, which have shown promise in reducing growth of cancerous tumors, especially hormone-sensitive ones such as those of the breast, endometrium, and prostate. Known for their hydrogen-donating antioxidant activity as well as their ability to complex divalent transition metal cations, lignans are propitious to human health. The extraction methods vary from simple to complex depending on extraction, separation, fractionation, identification, and detection of the analytes. Flax lignan is also a source of useful biologically active components found in plant foods, such as phytochemicals, and it is considered a functional food. The safety issues in flaxseed are also briefly discussed.

Keywords: words, lignans, analytes, flax, phytochemicals, fractionation, breast

Introduction

Flax is grown as either an oil crop or as a fiber crop, with fiber (for linen) derived from the stem of fiber varieties and oil from the seed of linseed varieties. (Diederichsen and Richards 2003; Vaisey-Genser and Morris 2003). Freeman (1995) reported that the seed of flax is flat and oval with a pointed tip, and varies in color from dark brown to yellow. Depending on the cultivar and growing conditions, flaxseed contains 40% to 50% oil and meal, comprised of 23% to 34% protein, 4% ash, 5% viscous fiber (mucilage), and lignan precursors (9 to 30 mg/g of defatted meal) (Muir and others 1996; Muir and Westcott 2003). Annual world production of flax was 3.06 million metric tons in 1999 to 2000 with Canada the world's largest producer of flax (about 38% of total production) (Anonymous 2000). Flax is currently the 2nd-most important oilseed crop in Western Canada and is grown primarily in the prairie provinces of Saskatchewan (70%), Manitoba (26%), and Alberta (4%) (Anonymous 2000). Flax is making its mark in the world's food supply as a functional food. It delivers a health boost beyond what might be expected from their traditional nutrient content. Flax fits this description perfectly, being rich in alpha-linolenic acid (ALA), the essential omega-3 fatty acid, and phytochemicals such as lignans (Morris 2003). Flaxseed has been the focus of increased interest in the field of diet and disease research due to the potential health benefits associated with some of its biologically active components: oil containing approximately 59% a-linolenic acid) and the presence of plant lignan secoisolariciresinol diglucoside (SDG;). Lignans are found in most fiber-rich plants, including grains such as wheat, barley, and oats; legumes such as beans, lentils, and soybeans; and vegetables such as garlic, asparagus, broccoli, and carrots (Tham and others 1998; Murphy and Hendrich 2002). Plant lignans are phenolic compounds (Harris and Haggerty 1993). Flax is a particularly rich source of a lignan called secoisolariciresinol diglycoside (SDG). SDG is a plant lignan that is converted by bacteria in the colon of humans (and other animal also) to mammalian lignans known as enterodiol (ED) and enterolactone (EL). We live in a world where free radicals can come from many sources and contribute to the deterioration of health. Sources of free radicals include pollutants, drugs, metal ions, radiation, and high intakes of polyunsaturated fatty acids, and also strenuous exercise, mitochondrial dysfunction, and smoking. These may result in damage to membrane lipids, proteins, nucleic acids, and carbohydrates, which can result in cancer, neurological diseases, lung diseases, diabetes, vascular diseases, autoimmune diseases, premature aging, and eye diseases (Lachance and others 2001). Lignans are found in many cereals and grains, with the highest amounts occurring in flaxseed. Despite their more widespread occurrence in foods and their greater consumption in Western populations the lignans have received comparatively little attention. Phytoestrogen supplementation with flaxseed or soy flour have been reported to increase vaginal cell maturation, an indication of estrogen activity in postmenopausal women (Wilson and others 1990), and to significantly reduce menopause symptom scores, particularly hot flashes and vaginal dryness (Brzezinski and Debi 1999). Dietary studies indicate substantial reduction in breast cancer risk among women with high urinary excretion of phytoestrogens, particularly the is flavones equal and lignan entero-lactone (Ingram and others 1997). The lower incidence of prostate cancer in Asian men compared to men from North America and Europe has also been speculated to be due to higher dietary intake of isoflavones and lignans (Adlercreutz 1990; Morton and others 1997) [3]. Recent research has demonstrated the ability of SDG to scavenge hydroxyl radicals and shown that SDG have potent antioxidant activity. They are biologically active phytochemicals with apparent

anticancer and antioxidant potential. It stands to reason that a review is in order on the extraction, synthesis, metabolism, and antioxidant potentiality of flaxseed lignan, a naturally occurring compound because people everywhere have started to think more about health issues and have taken an interest in natural antioxidant from foods.

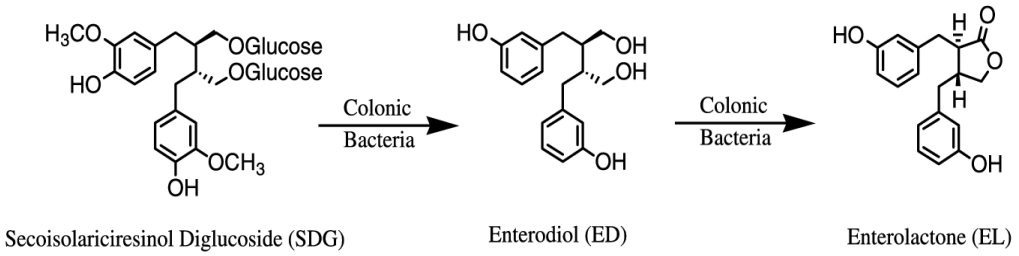

Fig 1: Metabolism of plant lignans to mammalian lignans

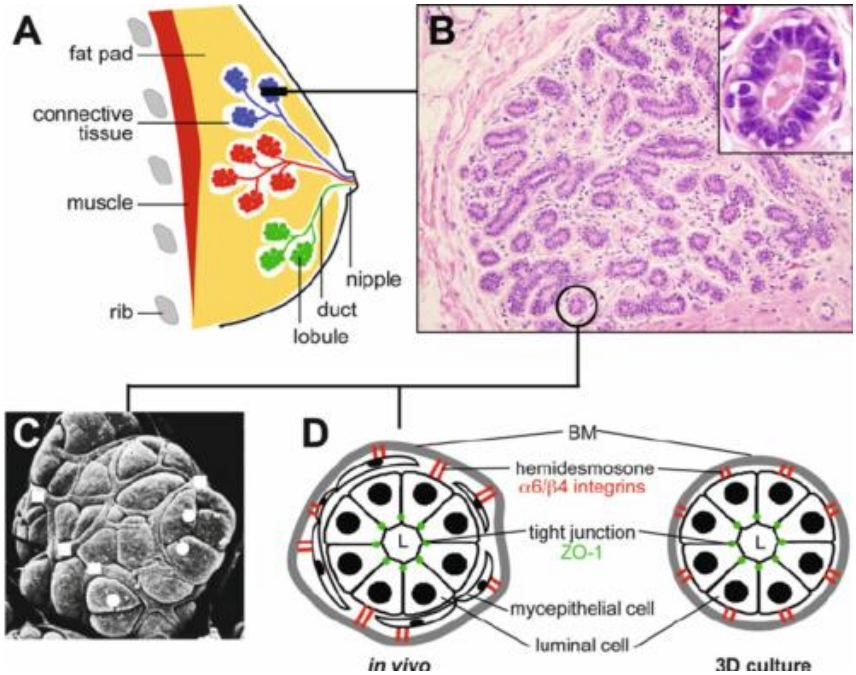

Fig 2: Histology of Breast cancer

Lignans

Biosynthesis of lignans

The biosynthesis of lignan has recently been revised based on the discovery of the dirigent proteins that guide phenolic radical coupling (Davin and others 1997; Davin and Lewis 2000). Lignans are derived mainly via differential partitioning of the monolignol, coniferyl alcohol, to yield the lignan pinoresinol, which in turn serves as the precursor of both secoisolariciresinol and matairesinol, two genes encoding the corresponding protein involved in the formation of pinoresinol and lariciresinol have been obtained from developing flaxseed

Health benefits

Breast cancer

Lignans could be a significant part of a treatment regimen for cancer based on the large number of small- scale studies. Although the lignans have been shown to be protective against breast cancer, minor structural alterations may influence overall. Thus, many of the aforementioned benefits might be the results of specific structural features needed for lignans to bind to ER.

Prostate cancer

A subsequent study by those authors further supported the role of flaxseed in combination with a low- fat diet as a means to control prostate growth (Demark- Wahnefried and others 2004). In this study, prostate- specific antigen level and cell proliferation both decreased from baseline after only 6 mos on the dietary regime.

Diabetes prevention

Low- glycemic- index foods containing soluble fiber may not only prevent certain metabolic ramifications of insulin resistance, but also reduce insulin resistance (Reaven and others 1993). Soluble fiber and other components of flaxseed fractions could potentially affect insulin secretion and its mechanisms of action in maintaining plasma glucose homeostasis. Flaxseed was shown to reduce the postprandial blood glucose response in humans (Cunnane and others 1993; Jenkins and others 1999).

Study in breast cancer during postmenopausal

We conducted a double-blind cross-over study to compare the

effects of whole flaxseed and sunflower seed, as part of the daily diet, on the lipid profile of postmenopausal women. During two 6-wk periods, thirty-eight mild, moderate, or severely (5.85–9.05 mmol/L) hypocholesterolemic postmenopausal women were randomly assigned to one of the two regimens: flaxseed or sunflower seed. The subjects were provided with 38 g of either treatment in the forms of breads and muffins. The first treatment period lasted six weeks and was followed by a two-wk washout phase. After the washout phase, subjects switched regimens and treatments continued for another 6 weeks. Blood samples were collected at baseline, 6, 8, and 14th wk of the study periods. Significant (p<0.01) reductions in total cholesterol were observed for both treatments (6.9 and 5.5% for flaxseed and sunflower seed, respectively). However only flaxseed regimen was able to significantly (p<0.001) lower LDL-cholesterol (14.7%). Serum HDL-cholesterol and triglyceride concentrations were unaffected by either of the treatments. Most interestingly, lipoprotein (a) [Lp (a)], a strong predictor of cardiovascular disease, concentrations were significantly (p<0.05) lowered by the flaxseed treatment (7.4% compared to baseline values). Regression analyses showed the strongest association between age and both total and LDL-cholesterol concentrations. Among the dietary variables, total and soluble fiber intakes were negatively correlated with serum total and LDL-cholesterol concentrations. The cholesterol lowering effects of flaxseed and sunflower seed may be due to the activity of single or multiple components, including α-linoleic or linoleic acids, total and soluble fiber, and non-protein constituents present in these seeds.

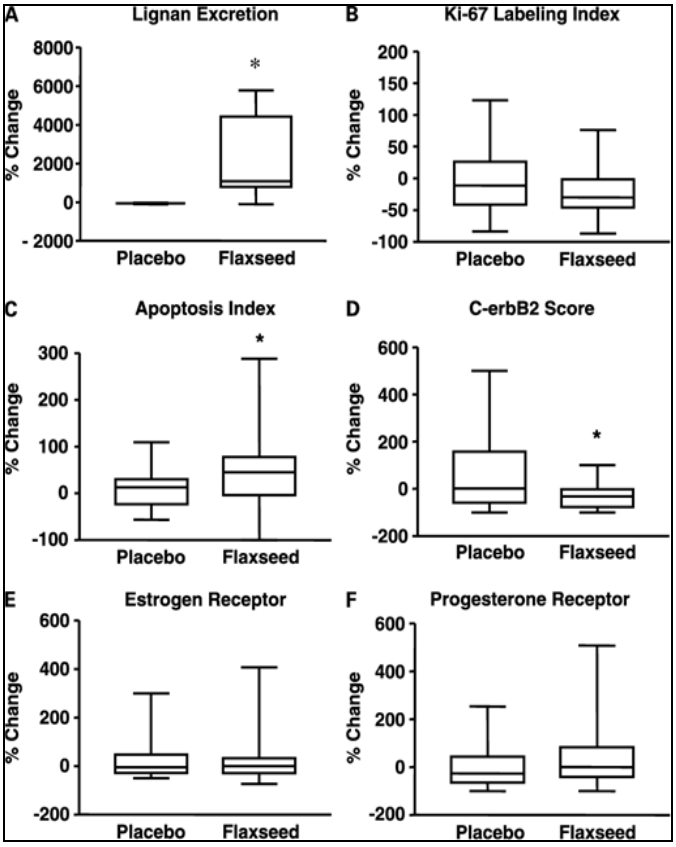

Fig 3

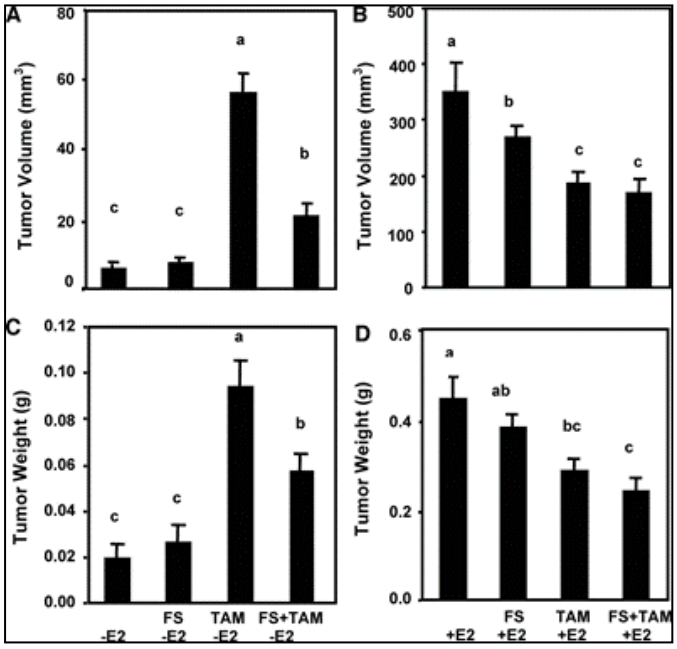

Fig 2

Results

Recently there has been a moderate resurgence in the use of flaxseed food. However, the scientific basis of the benefits of flaxseed consumption and which components of flaxseed offer these beneficial effects are not known. Flaxseed contains 32-45% of its mass as oil, of which 51-55% is alpha-linoleic acid (n-3 fatty acids, omega-3 fatty acids). Flaxseed lignin (secoisolariciresinol diglucoside; SDG) is isolated from defatted flaxseed. Flaxseed has been shown to have variable effects on plasma lipids. Serum triglycerides (TG), total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) have been reported to be elevated, lowered or unchanged with flaxseed consumption in rats. In humans, flaxseed lowers serum TC and LDL-C; however, it has no effect on serum high-density lipoprotein-cholesterol (HDL-C) and TG. Flaxseed oil also lowers TG and TC in rats, but the effect is smaller than that of flaxseed. Flaxseed oil in human subjects had no effect on serum TG, TC, LDL-C or HDL-C. Flaxseed with very low alpha-linoleic acid reduced serum TC, LDL-C and the risk ratio, elevated serum TG and very low-density lipoprotein cholesterol (VLDL-C) and had no effect on serum HDL. SDG isolated from defatted flaxseed reduced serum TC, LDL-C and the TC/HDL-C risk ratio. Serum levels of HDL-C, TG and VLDL-C remained unchanged. These results suggest that the hypocholesterolemic effect of flaxseed probably resides in the non-oily part and not in the alpha-linoleic acid. Reductions in hypocholesterolemic atherosclerosis by flaxseed, flaxseed with very low alpha-linoleic acid and SDG were 46%, 69% and 73%, respectively. The antiatherogenic effect of SDG could be due to its antioxidant activity and also its lipid-lowering effect.

Materials and Methods

Patients and study design. We conducted a randomized, placebo controlled, double-blind, prospective study involving postmenopausal patients with primary breast cancer. The

patients (from the University Health Network, Toronto) were women who presented with a newly diagnosed lump suspicious for cancer and needed a confirmatory breast core biopsy. Eligibility criteria included: menopause for at least 6 months; histologically diagnosed by core biopsy as having breast carcinoma; not having taken hormone therapy and soy foods or flaxseed within 90 days of the first biopsy; not having taken antibiotics within 3 days of the first biopsy; no known allergy to flaxseed, lactose, wheat or certain spices; had sufficient tissue specimen taken from core biopsy for assessing biomarkers. Sixty-five postmenopausal patients volunteered, but after the initial biopsy, 18 did not meet the criteria of inclusion because their initial tumor was evaluated as benign. Another 15 volunteers withdrew due to difficulty eating a bulky muffin, difficulty traveling to the hospital, depression due to a recent diagnosis of breast cancer, or a busy schedule. Thus, 32 eligible patients were entered into and completed this randomized trial of preoperative dietary intervention.

The characteristics of the patients are summarized in Table 1. There were no significant differences in any of the baseline variables.

Results

Muffin intake compliance was good (95.4% in the placebo and 92.5% in the flaxseed group) and did not differ significantly

Between the groups. This translated into a significant increase (1,300%; $P < 0.01$) in mean urinary lignans in the flaxseed group but not in the placebo group (Table 2). The only side effects reported were abdominal fullness and increased bowel movements. No significant differences in caloric and macronutrient intake were observed between the treatment groups and between the pre- and post-treatment periods (data not shown). The mean treatment times were 32 and 39 days (median 30 and 37 days) for the flaxseed and placebo groups, respectively (Table 1). Table 2 and Fig. 2 summarize the results of biological markers measured in tumor specimens pre- and posttreatment. No significant differences between the treatment groups were observed in baseline values of all tumor variables. After completion of treatment, decreases in tumor cell proliferation and c-erbB2 expression, and an increase in cell apoptosis were observed in both groups but a greater number of patients showed these changes in the flaxseed (74-84%) than in the placebo group (54-61%). Tumor cell proliferation (Ki-67 labeling index; Fig. 2A) significantly decreased by 34.2% (median), the apoptotic index (Fig. 2B) significantly increased up to 30.7% (median) and the expression of c-erbB2 (Fig. 2C) significantly decreased by 71.0% (median) in the flaxseed, but not in the placebo group. No significant differences in ER and PR levels were seen between the pre- and post-treatment periods in any group. A comparison between the two groups for the percentage of changes in pre- and post-treatment in individual subjects is illustrated in Fig. 3. The percentage of changes in urinary lignan excretion (Fig. 3A), apoptotic index (Fig. 3C), and cerB2 score (Fig. 3D) were significantly higher ($P < 0.05$) in the flaxseed group than in the placebo group. The percent change in Ki-67 labeling index (Fig. 3B) was also higher in the flaxseed than in the placebo group, but did not reach statistical significance. No significant differences in the percentage of changes in ER and PR levels were found between the two groups (Fig. 3E and F). The total intake of flaxseed was significantly correlated with changes in c-erbB2 score ($r = \_0.373$; $P = 0.036$) and apoptotic index ($r = 0.495$; $P < 0.004$), but not with changes in Ki-67 abeling index, ER, or PR. No significant relationship was observed between patient age and weight, baseline tumor characteristics such as tumor grade and ER or PR status, and the changes observed during the treatment period (data not shown).

Discussion

Our study shows that daily intake of 25 g flaxseed can significantly reduce cell proliferation, increase apoptosis, and affect cell signaling by reducing c-erbB2 expression of human breast cancer cells. The percentage of reduction in tumor c-erbB2 expression and percentage of increase in cell apoptosis did not relate to baseline tumor characteristics, i.e., patient age, weight, tumor grade, ER, and PR status, but they significantly correlated with the total amount of flaxseed eaten. Although reductions in cell proliferation and c-erbB2 expression and an increase in apoptosis were also observed in some patients in the placebo group; they were small and insignificant. They may be attributed to other phytochemicals such as antioxidants, physic acid, phytoesterols, minerals, and vitamins in the whole wheat flour used in the placebo muffin, which have been related to reduced cancer risk (44). Expression of c-erbB2 (HER2) has been associated with more aggressive phenotypes of breast cancer and an increased potential for forming metastases (45–47). In addition, it plays a role in cell differentiation, adhesion, and motility (48, 49). In recent studies, a negative correlation between HER1/2 expression and response to anti estrogenic, but not aromatase inhibitor therapy, has been shown (39). Our results therefore suggest that the intake of flaxseed has the potential to delay disease progression of pervasive or invasive breast cancer by changing the phenotype of the cancer cells to a less aggressive form. The changes caused by flaxseed have also been shown by other endocrine agents such as tamoxifen (37, 40, 50), faslodex (51), raloxifene (41), and the aromatase inhibitors vorozole (52), letrozole (37, 38, 40), and anastrozole (38). A recent study concluded that the magnitude of www. Ki-67 reduction can be taken as a surrogate end point biomarker for the efficacy of endocrine agents in breast cancer treatment, and that the efficacy of breast cancer endocrine therapy is dependent on the successful induction of the arrest of cell proliferation (40). This is the basis for numerous ongoing trials of novel endocrine agents and cell signaling inhibitors in the preoperative setting.

Conclusion

Our study is small and the results need to be confirmed in a larger number of patients for a longer treatment period before it can be definitively concluded that flaxseed has the potential to reduce the growth and invasiveness of breast cancer. Its excellent tolerability, however, may make flaxseed particularly attractive for studies in breast cancer prevention, where

Healthy women should be offered well-tolerated interventions for long-term use. The interaction of flaxseed and its lignan

And oil components with other hormonally active agents also needs to be addressed in the future. If the therapeutic
Index seen in this short-term study can be sustained over a long-term period, flaxseed, which is inexpensive and readily
Available, may be a potential dietary alternative or adjunct to currently used breast cancer drugs.

References

1. Rose DP Diet. Hormones and cancer. Annu Rev Public Health 1993; 14:1 ^ 17.
2. Clemons M, Goss PE. Mechanisms of disease: estrogen and the risk of breast cancer. N Engl J Med. 2001; 344:276 ^ 85.
3. Adlercreutz H. Western diet and Western disease: some hormonal and biochemical mechanisms and associations. Scand J Clin Lab Invest. 1990; 50:3 ^ 23.
4. Clemons M, Danson S, Howell A. Tamoxifen (Nolvadex): a review. Cancer Treat Rev. 2002; 28:165 ^ 80.
5. Smith IE, Dowsett M. Aromatase inhibitors in breast cancer. N Engl J Med. 2003; 348:2431 ^ 42.
6. Thompson LU. Analysis and bioavailability of lignans. In Thompson LU, Cunnane SC, editors. Flaxseed in human nutrition, 2nd ed. Champaign: AOCS Press; 2003, p. 92 ^ 116.
7. Nesbitt PD, Lam Y, Thompson LU. Human metabolism of mammalian lignan precursors in raw and processed flaxseed. Am J Clin Nutr. 1999; 69:549 ^ 55.
8. Sathyamoorthy N, Wang TTY, Phang TM. Stimulation of pS2 expression by diet-derived compounds. Cancer Res. 1994; 54:957 ^ 61.
9. Adlercreutz H, Bannwart K,Wahala T, *et al*. Inhibition of human aromatase by mammalian lignans and isoflavonoid phytoestrogens. J Steroid Bio chem. Mol Biol. 1993; 44:147 ^ 53.
10. Wang C, Makela T, Hase T, Adlercreutz H, Kurzer MS. Lignans and flavonoids inhibit aromatase enzyme in human preadipocytes. J Steroid Bio chem Mol Biol 1994; 50:205 ^ 12.
11. Brooks JD, Thompson LU. Mammalian lignans and genistein decrease the activities of aromatase and 17h-hydroxysteroid dehydrogenase in MCF-7 cells. J Steroid Biochem Mol Biol. In press, 2005.
12. Garreau B, Vallette G, Adlercreutz H, *et al*. Phytoestrogens: new ligands for rat and human a-fetoprotein. Bio chem Bio phys. Acta. 1991; 1094:339 ^ 45.
13. Mousavi Y, Adlercreutz H. Enterolactone and estradiol inhibit each other's proliferative effect on MCF-7 breast cancer cells in culture. J Steroid Bio chem Mol Biol. 1992; 41:615 ^ 9.
14. Welshons WV, Murphy CS, Koch R, Calaf G, Jordan VC. Stimulation of breast cancer cells *in vitro* by the environmental estrogen enterolactone and the phytoestrogen equol. Breast Cancer Res Treat. 1987; 10:169 ^ 75.
15. Wang C, Kurzer MS. Effect of phytoestrogens on DNA synthesis in MCF-7 cells in the presence of estradiol or growth factors. Nutr Cancer. 1998; 31: 90 ^ 100.
16. Adlercreutz H, Mousavi Y, Clark J, *et al.* Dietary phytoestrogens and cancer: *in vitro* and *in vivo* studies. J Steroid Bio chem Mol Biol. 1992; 41:331 ^ 7.