



## CURRENT PERSPECTIVES ON PHYTOESTROGENS: A BOON OR A CAUTION IN TODAY'S ERA

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### ABSTRACT

Phytoestrogens are plant derived compounds found in a wide variety of foods, most notably soy. An array of health benefits including a lowered risk of osteoporosis, heart disease, breast cancer, and menopausal symptoms, are frequently attributed to phytoestrogens but many are also considered endocrine disruptors, indicating that they have the potential to cause adverse health effects as well. This review describes some of the studies done and experiments performed to evaluate the effectiveness of phytoestrogens as friends or foes. Still most of the studies done are confusing whether women should consume these phytoestrogens for the health benefit so not. Whether phytoestrogens consumption can be linked to decreasing risk of breast cancer or not and if yes what should be the proportion to attain maximum benefit are still to be evaluated.

**KEYWORDS:** *phytoestrogens, osteoporosis, endocrine disruptors, menopausal symptoms*



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## INTRODUCTION

Phytoestrogens are a group of chemicals found in plants that can act like the hormone estrogen. More than 300 foods have been shown to contain phytoestrogens. Most food phytoestrogens can be classified into four chemical classes, the isoflavonoids, stilbenes, the lignans and the coumestans. Phytoestrogens are naturally-occurring plant compounds that are structurally and/or functionally

similar to mammalian estrogens. Phytoestrogens are plant derived compounds known to have an array of health benefits, but in contrast to that many are also considered endocrine disruptors, indicating that they have the potential to cause adverse health effects as well. A contradiction arises that whether phytoestrogens are beneficial or harmful to human health<sup>1</sup> The table shows the types and source of the different classes of phytoestrogens<sup>1</sup>

Type of phytoestrogens	Source
Isoflavonoids	Berries, wine, grains and nuts Beans from the legume family; soybeans and soy products
Lignan	Berries, seeds (particularly flaxseeds), cereals, vegetables and grains, nuts and fruits. cereal brans and beans;
Coumestan	Beans such as split peas, pinto beans, and lima beans; alfalfa and clover sprouts soybeans
Stilbenes (resveratrol)	Grapes, peanuts and pines

Phytoestrogens working as estrogen mimics, may either have the same effects as estrogen or block estrogen's effects and this is dose dependent. Estrogens have shown to activate a family of proteins called estrogen receptors. More information about how these receptors work is to be evaluated specially in relation to breast cancer. Phytoestrogens also affects the production and breakdown of estrogen by the body including the levels of estrogens carried in the bloodstream. Several other effects of estrogens are that they can also affect intercellular communication pathways, alter processes involved in DNA processing during cell multiplication. Several other studies have reported that there is no effect of soy on breast cancer risk. In addition, animal studies have shown that soy phytoestrogens can decrease breast cancer formation in rats. However, several other animal and human studies suggest that soy phytoestrogens can behave like estrogen and potentially increase breast cancer risk. Soy phytoestrogens can change breast cancer risk by changing the production and/or breakdown of reproductive hormones such as estrogen. The results of studies examining hormone changes among women eating soy have not been consistent, but recent studies suggest that there may be a small decrease in the levels of estrogens in the body. Some studies have also shown that eating soy phytoestrogens is associated with a decrease in the formation of forms of estrogens that may directly lead to cancer causing mutations<sup>2</sup>. Due to high estrogen exposure there may be a breast cancer risk through its ability to increase growth of milk ducts in the breast. Most breast cancer arises from these ducts. Several studies examining the effect of soy

phytoestrogens on breast growth in women have suggested that phytoestrogens have a weak estrogen-like effect. A group of 28 women were surveyed and examined for a year. These women received soy supplement for six months. While they were taking this supplement the women were found to have more growth of the milk ducts in their breasts. These studies are not conclusive, but such growth could increase breast cancer risk. The possible effects of soy phytoestrogens on growth within the breast and hormone levels in the body requires to be evaluated. A lignan phytoestrogen found in flaxseed, secoisolariciresinoldiglycoside (SDG) has been shown to interfere with mammary (breast) tumor formation in rats. SDG also has similar effects on the development of mammary gland as the soy phytoestrogen genistein<sup>3</sup>. In 1999, the US Food and Drug Administration (FDA) approved the use of the health claim that daily consumption of soy is effective in reducing the risk of coronary artery disease,<sup>4</sup> a move which had a rapid and profound impact on the prevalence of soy products. Soy isoflavones and other phytoestrogens are also widely available as dietary supplements<sup>5, 6</sup> typically at far higher concentrations than found in soy-based foods. Overall, these sales and marketing data indicate that phytoestrogen intake is rapidly increasing, emphasizing the need to critically evaluate their potential health effects, both beneficial and detrimental, across age groups and populations. Several studies showed that in Asian people there is a low incidence of breast cancer as compared to western people. This may be attributed to their average daily intake of soy and isoflavones products which is about 50g/day and 30mg/day respectively.

**Table 1**  
**Multiple modes of action of some of the phytoestrogens**

Type	Modes of action
Genistein	Inhibit pathways important for cell growth and proliferation inhibits the activity of protein tyrosine kinases (PTKs) in numerous tissues including breast cancer cells 3. inhibit other DNA replication enzymes associated with tumorigenesis including DNA topoisomerases I and II and matrix metalloprotein (MMP9) estrogen receptor (ER) binding. <sup>7-10</sup>
Resveratrol	Antioxidants and anti-inflammatory agents. <sup>11-13</sup>
Isoflavones	Alter the structure or function(s) of the endocrine system and cause adverse effects. It includes disruption of lactation, the timing of puberty, the ability to produce viable, fertile offspring, sex specific behaviour, premature reproductive senescence and compromised fertility. Even infertility and liver disease in animals. <sup>14</sup>
Coumestrol	Abnormally high rates of infertility, abortion, and reproductive abnormalities in animals. Bind both Estrogen receptor $\alpha$ (ER $\alpha$ ) and Estrogen receptor $\beta$ (ER $\beta$ ), and activate ER-dependent gene transcription. <sup>15-16</sup>

Patisaul and Jefferson in their review article have also shown that the question of whether or not phytoestrogens are beneficial or harmful to human health remains unresolved. The answer is likely complex and may depend on age, health status, and even the presence or absence of specific gut microflora. Clarity on this issue is needed because global consumption is rapidly increasing. Phytoestrogens are present in numerous dietary supplements and widely marketed as a natural alternative to estrogen replacement therapy. As weak estrogen agonists/antagonists with molecular and cellular properties similar to synthetic endocrine disruptors such as BisphenolA (BPA), the phytoestrogens provide a useful model to comprehensively investigate the biological impact of endocrine disruptors in general. This review weighs the evidence for and against the purported health benefits and adverse effects of phytoestrogens.<sup>17</sup> Studies reported by Bingham et al showed that phytoestrogens offer protection against a wide range of human conditions, including breast, bowel, prostate and other cancers, cardiovascular disease, brain function, alcohol abuse, osteoporosis and menopausal symptoms. They also reported that isoflavones from soybean have oestrogenic effects in human subjects in the cardiovascular system and bone like the anti-estrogen Tamoxifen. They concluded that investigation of the possible benefits is hampered because of inadequate methods of measurement in foods.<sup>18</sup> Research conducted by Knight and Eden from the MEDLINE data base for the years 1980-1995 for Human cell line studies, human epidemiologic studies (case-control or cohort), randomized trials, and review articles included which showed that phytoestrogens are biologically active in humans or animals. These compounds inhibit the growth of different cancer cell lines in cell culture and animal models. Human epidemiologic evidence supports the hypothesis that phytoestrogens inhibit cancer formation and growth in humans. Foods containing phytoestrogens reduce cholesterol levels in humans, and cell line, animal, and human data also show benefit in treating osteoporosis.<sup>19</sup> The effect of phytoestrogens (soybean intake) on breast cancer risk was reviewed during the <sup>13</sup> studies conducted of which the overall results none showed statistical significant breast cancer reductions.<sup>20</sup> Strauss et al in their study also reported that phytoestrogens from soy and unrefined grain products may be associated with a low risk of breast and prostate cancers and other estrogen related conditions. They also reviewed the possible adverse effects of these phytoestrogens as endocrine disruptors.<sup>21</sup> When ingested in relatively large amounts, Soybeans and flaxseed phytoestrogens have been shown to have significant estrogen agonists/antagonists effects in animals and humans. There is epidemiological, laboratory and clinical evidence which indicates that phytoestrogens, like certain selective estrogen receptor modulators, have an antiproliferative effect on the breast, and positive effects on the lipoprotein profile and bone density. They might also improve some of the climacteric symptoms.<sup>22</sup> Humfrey in his review assessed the evidence that the phytoestrogens may have adverse and/or beneficial impacts on the risk of several hormone-dependent diseases in humans. They also reported that ingestion of high levels of phytoestrogens

can produce adverse effects on reproductive endpoints including fertility. Studies in laboratory animals have also shown that exposure to high doses of phytoestrogens during development can adversely affect brain differentiation and reproductive development in rodents, but may also have possible beneficial effects. In humans, there is a lack of information concerning the possible effects of high doses of phytoestrogens in infants and this should be addressed as a matter of priority so that any risks (or benefits) can be established. At present the evidence is not sufficient to recommend particular dietary practices or changes. Encouraging findings from laboratory and clinical studies indicate the need for further research to clarify the biological activities of phytoestrogens in humans.<sup>23</sup> Chiechi in his study also reported that estrogenic effects of phytoestrogens can be useful in preventing postmenopausal osteoporosis and cardiovascular disease.<sup>24</sup> Chiechi et al studied that the anti-estrogenic effects of phytoestrogens are well known due to the possibility to prevent some tumors such as breast and prostate cancer. In menopause they have an estrogenic-like action on lipidic and bone metabolism. Phytoestrogens rich foods can positively affect the postmenopausal osteoporotic and cardiovascular pathology.<sup>25</sup> Badowski and Karłowska surveyed and suggested that phytoestrogens structurally and functionally similar to 17-beta-oestradiol could lower risk of diseases accompanied woman in menopause and postmenopausal stage. From their review study they concluded that the phytoestrogens are considered to decrease risk of breast, endometrial and ovarian cancer, osteoporosis, cardiovascular disease.<sup>26</sup> Furthermore, Stark and Madar suggested that phytoestrogens are used as a natural alternative to hormone replacement therapy and to reduce menopausal symptoms. Phytoestrogens have been shown to induce both estrogenic and anti-estrogenic effects but their biological relevance and potency have not been well characterized. In children, consumption of soy-based formulas and soy milk can lead to high levels of exposure to phytoestrogens with only limited data available concerning potential benefits or adverse effects. Phytoestrogens are considered good candidates for use in natural therapies and as chemopreventive agents in adults. Safe and efficacious levels have yet to be established.<sup>27</sup> In another review, researchers also discussed the role of phytoestrogens in the reduction of cholesterol levels, and the use of one phytoestrogen derivative, ipriflavone, in the prevention of osteoporosis. Evidence for the potential health benefits of phytoestrogens is increasing. However, the clinically proven health benefits of prescribed ERT (estrogen replacement therapy) far outweigh those of phytoestrogens. Therefore, there is insufficient evidence to recommend the use of phytoestrogens in place of traditional ERT, or to make recommendations to women about specific phytoestrogen products.<sup>28</sup> Several studies related to Hormone replacement therapy (HRT) shows that though it reduces the risk of cardiovascular disease and osteoporosis in postmenopausal women but on the other hand it also has certain side effects. Many a times questions were raised whether phytoestrogens could be used as an alternative to hormonal therapies for the management of menopausal symptoms.<sup>29</sup> Clinical and experimental studies examining the impact of soy or soy

phytoestrogen consumption on human health have produced mixed and often conflicting results. Of even greater concern is that emerging evidence suggests that exposure to these compounds may, in fact, pose a risk to some groups, particularly infants and the unborn<sup>30</sup>. Research done in this field also suggests that phytoestrogen consumption gives relief from vasomotor perimenopausal symptoms, including hot flashes and night sweats,<sup>31-32</sup> prevents osteoporosis,<sup>33-36</sup> promotes cardiovascular health and prevents heart disease.<sup>37</sup>

## CONCLUSION

It is unclear about the role that foods containing phytoestrogens play, in decreasing breast cancer risk. In view of the current data phytoestrogens are accepted

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as mostly beneficial rather than deleterious. Supplementation with high doses of pure phytoestrogens in infants and pregnant women should be taken care of. Fewer studies have been performed with dosage and purity of commercial estrogens and their possible adverse effects are unknown. Studies have to be performed with food products and not with single phytoestrogenic compound to look for the overall benefits. Significant studies on the consequences of phytoestrogens on breast cancer survival and their roles in the prevention of chronic degenerative diseases is also of much concern nowadays.

## CONFLICT OF INTEREST

Conflict of interest declared none.

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