

Nutrition and Cancer: Dr. Douglas Wilson - Honoured

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Abstract: Historical, current and future aspects of the potential value of 'phyto-oestrogens' and lifestyle in lowering the risk of endocrine cancer, and high-lighting the crucial importance of global policy makers in providing the means for a healthier diet, is the purport of this paper. Early studies in Chiang Mai, Thailand, and S.W. Australia demonstrated the potential value of oestrogen-like dietary constituents, viz. flavonoids and lignans, in treating menstrual dysfunction and acting as potential antiestrogens and anticarcinogens, acting directly through oestrogen receptor mechanisms or even indirectly. This report also listed some international migrant studies. Chemopreventative strategies need to be undertaken, based on well-designed evidence-based information, which lead to the development of functional foods. A balance has to be struck which takes all major disease causes into account and, an affordable lifestyle strategy has to be developed for *homo economicus*, at different stages of human development, from the conceptus to old age, in which epigenetics must play a very significant role in disease prevention.

Keywords: Nutrient, cancer, functional food, diet, flavonoids.

INTRODUCTION

This paper focuses on historical, current and future perspectives of chemoprevention of endocrine cancer, viz. breast and prostate: such chemoprevention implicated through nutrition, pharmaceuticals and functional foods. It is particularly relevant that this paper in this issue of The Open Nutraceuticals Journal honours Dr Douglas Wilson. As my former student (KG) of nearly 50 years ago, Douglas Wilson began his medical research career at the Tenovus Institute for Cancer Research, Cardiff investigating the prognostic value of urinary steroids, *i.a.* conjugates of androsterone, aetiocholanolone and dehydroepiandrosterone in women with breast cancer [1] and as analytical techniques became available, ably quality controlled by techniques Douglas substantially developed, research focussed on plasma and tissue and hormone receptors. In the University of Melbourne, under the aegis of Dr Gordon Sarfaty [2] at the Peter MacCallum Clinic Endocrine Laboratories, Douglas made substantial progress in the optimization of receptor-ligand interaction. Later studies focussed on phyto-oestrogens and their potential role in chemoprevention which Douglas helped to set up in the early 1990s [3]. In the years just before the Institute closed its doors, he was an invited participant at the Ettore Majorana Centre for Scientific Culture, Erice, Sicily,

the University of West China Medical Sciences, Chengdu, China, and was invited to the Royal Society of Edinburgh to talk on endocrine cancer and phyto-oestrogens. He has made several contributions on steroid hormones, phyto-oestrogens, nutrition and cancer but he was unable to finish such researches due to difficulties in funding, until many years later Professor Hungin, Dean of Medicine, at Durham University gave him the opportunity to continue his interests in this area where he continues to have international influence.

The phyto-oestrogen history involved many direct links between pioneers in endocrinology searching for naturally occurring mammalian steroid hormones [e.g. such as equol by Professor Guy Frederic Marrian (KG) [4] during the exciting era between 1923-1939 [5-11] which was substantially the time which Marrian called the "heroic age of reproductive endocrinology" [12] which enthralled Douglas both as a student and scientist given here as selective background and for their pioneering spirit. One of the major tests of the oestrogenic potency of phyto-oestrogens was the Allen Doisy test of immature or ovariectomized mice [13, 14] and for androgens it was the cockscomb test in capons or cockerels with oestrogen implants before maturity [15], a process of growth (bioassay) known to the Romans to preserve grain supplies from 'fattening hen' to better weight gain from capons [16]. These tests and pioneering endocrinologists now fade into history but Douglas had the good fortune to meet many who had direct links to that exciting era apart from myself and my contemporaries such as the group in erstwhile

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CSIRO Prospect, Australia (Shutt and Cox [17]; binding of steroids and phyto-oestrogens using cytosol fractions from uteri preparations), Gerald Pope (National Institute for Dairying, Shinfield, Reading; benzocoumarins [18] and related compounds [19]) and many pioneering endocrinologists in the late 1960s – early 1970s. The stage was set for a major step forward which, except for the seminal work of Jensen and co-workers [20, 21], Nobel Prize nominee, who discovered oestrogen receptors in the breast, generally had to wait nearly a decade, viz. for bridging the gap between edible plants and human cancer, and later research [22, 23]. This paper now focuses on the potential role of phyto-oestrogens and breast and prostate cancer risk.

PHYTO-OESTROGENS

These may be defined as “any plant substance or metabolite that induces biological responses in vertebrates and can mimic or modulate the actions of endogenous oestrogens usually by binding to oestrogen receptors”.

Research should demonstrate that phyto-oestrogens are 1. Present or derived from edible food, including through actions of the gut microflora; 2. Taken into the blood stream; 3. Taken up by tissue; and 4. Exert biological interaction with the genetic material; and 5. Demonstrate the beneficial action claimed in human health gain.

These include a wide range of compounds; early work is found in the Bradbury and White paper [24], such as isoflavonoids and lignans [25], coumestans, resorcylic acid lactones [26] which are present in our foodstuffs and those of the animal kingdom. Simply, these phyto-oestrogenic compounds can be classified into flavonoid and non-flavonoid, the former comprising isoflavones, coumestans, and prenyl flavonoids, and the latter lignans [27-35], the seminal work of Setchell being noteworthy [36-40; early communication with Dr Wilson]. They are found in human plasma: diadzein, genistein, O-desmethylandgensin, equol (isoflavan), and are constituents of soy products, chick peas, lentils, and beans [41-44]. Of relevance is the patent lodged by Novogen Research Pty Ltd [45]. In this patent, it is suggested that “Compositions enriched with natural phyto-oestrogens or analogues thereof selected from Genistein, Daidzein, Formononetin and Biochanin A” (may be used) “as food additives, tablets or capsules for promoting health in cases of cancer, pre-menstrual syndrome, menopause or hypercholesterolaemia,” (as functional foods), text in parentheses belong to authors.

It is not known what wealth of scientific value the plant kingdom will yield in the future but knowledge about the origin and diversity of ‘flavonoid’ molecular species such as resveratrol [46] must surely be in its infancy [47]. For example, anticancer effects of indoles and isothiocyanates are ‘protective’ [48, 49: Wattenberg, received a lifetime achievement award in 2011 for his work on chemoprevention from the American Association for Cancer Research] even by virtue of blocking sites of genotoxic attack. Isoflavonoids, where they exist as aglucones conjugates e.g. daidzein, genistein, formononetin, glycitein; or their glycoside conjugates daidzin, genistin, ononin, sissotrin, glycitin; or as acetyl or malonyl glucones e.g. daidzein, genistein, glycitein, etc. In humans, the aglucone is released by intestinal flora

fermentation and hydrolysis and absorbed into the blood directly or undergo further metabolism and are absorbed into the blood and excreted in the urine, and faeces, of course, as demonstrated by Adlercreutz *et al.* [50]. However, the consistency and physico-chemical properties of the digesta are important [51] not only for phyto-oestrogens but also the availability of natural oestrogens [52]; the glycoside moiety is hydrolysed free by a combination of gastric acid hydrolysis and fermentation by intestinal bacteria. Some of the isoflavones in the aglucone form are absorbed directly and circulate in the blood, while the remainder is metabolized by intestinal fermentation to a variety of compounds which are also absorbed. The absorbed isoflavones and their metabolites appear to undergo little or no further metabolism in the body, being readily transported in the bloodstream, and ultimately being excreted in the urine. Prenylated flavonoids, with a different structural orientation and therefore comparatively less water soluble than isoflavonoids, possessing oestrogenic activity also occur e.g. xanthohumol, isoxanthohumol, 8-prenylnaringenin, 6-prenylnaringenin.

Lignans constitute diphenolic compounds [53, 54] which are common in cereals, fruits and vegetables, and linseed (linseed) as matairesinol and secoisolariciresinol which are metabolized by intestinal microflora to give enterolactone and enterodiol respectively. The most common lignan described is matairesinol. Dietary lignans also appear to be metabolized fairly efficiently within the gut by bacterial fermentation, yielding metabolites such as enterodiol and enterolactone which are absorbed into the bloodstream and excreted in the urine. The two principle classes of these weak oestrogens are isoflavonoids and mammalian lignans, *vide supra*, but vegetarians excrete large quantities of the lignan enterolactone, in their urine.

The former is derived from soya-based foods and the latter from oilseeds, cereals and whole grains. Asian populations such as the Japanese have high plasma concentrations of the isoflavones, daidzein and genistein, whereas vegetarians excrete large quantities of the lignan enterolactone, in their urine.

Coumestans, relative to lignans and isoflavonoids have a generally a lesser oestrogenicity. Compared to isoflavones and lignans, oestrogenic coumestans appear to have a relatively restricted distribution in plants and generally occur at much lower levels. Sprouts of soya, and whole soybeans and other common foodstuff, and legumes also contain significant but low levels of approx. 1 part in 100,000 dry weight and even then the seed hull is discarded for human consumption.

Publicised by Kerr [55], mistakenly identified originally as a vine *Butea superba* Roxb, the tuberous roots of a leguminous plant, *Pueraria mirifica* [56, 57] (Chiang Mai; locally called kwoa keur) is eaten by Thais which had ‘rejuvenating properties’ and which was found to contain miroestrol [58]. Extracts were used in traditional medicine in Bangkok for anti-ageing and old women began menstruating again. This compound, when administered to women with amenorrhoea in the Chelsea Hospital for Women, London [59], demonstrated oestrogenic activity suggesting a supplement for the condition, as indicated also by Muangman & Cherd-

shewasart [60], a functional food, now, is possibly on the horizon and synthesis had been achieved by Corey [61], a Nobel Laureate. An even more potent oestrogenic component in this plant is deoxymiroestrol [62, 63] which is easily oxidised to miroestrol during isolation.

There is, of course, guarded optimism concerning the potential mutagenicity of phyto-oestrogens and naturally occurring oestrogens and there is possibly a dual role of oestrogen stimulating cell proliferation and as an agent of mutagenicity [64-71] but there is some disagreement [72,73] and epigenetic mechanisms have been proposed. For example, work on the hamster kidney in a series of papers by Li *et al* [74-78] suggests alternative mechanisms to covalent and/or indirect interactions with genetic material in which cathepsin D and peroxidase induction, aneuploidy and errant proto-oncogene and suppressor gene expression *i.a.* amplification of *c-myc*, *c-fos* and *c-jun*.

Some years before that equol, a compound isolated in pregnant mare's urine (and that of stallions) which exhibited circannual variation being lowest in winter; but it was none-the-less presumed not to be of dietary origin [79]. In S.W. Australia, major problems occurred with sheep infertility at a time when world production was urgently needed. The oestrogenic properties of the Dwalganup strain of subterranean clover (*Trifoliumsubterraneum* L.) are of great importance to sheep breeding in the drier areas of Western Australia and the pioneering work [80-90] that was undertaken became very important in the then future *viz.* nutrition and *i.a.* cancer. The analytical work of Gerald Pope at Shinfield [83] was an important milestone in development. The structure of oestradiol-17 β has a 10.3 Angstrom unit separation of the hydroxyl groups (Fig. 1). Similarly for the synthetic oestro-

gen, DES is also illustrated, where such separation of the hydroxyl groups relate to oestrogenicity, as also indicated by the stilbenoid, resveratrol. In the case of miroestrol the distance between c3 to c18 hydroxyl groups is also 10.3 Angstrom units. The endowment of oestrogenicity and its strength is also related to the orientation of double bonds of which the weak oestrogen (antioestrogen), Tamoxifen, is an example. Such structural elements may be key in effecting restraint in the pathogenesis of various cancers either as weak oestrogens or antioestrogens or patient management through innovative new forms of anti-oestrogenic therapies. Of course not all mechanisms of action are that simple. The principal groups of compounds are mammalian lignans, coumestans, isoflavones, resorcylic lactones, phytosterols, flavones theaflavins and there be may other polyphenolic dimers and polymers, some of which are depicted in Fig. (2) along with an example of food source. Fig. (3), implicates soy products and flaxseed as having potential in chemoprevention for hot flushes, osteoporosis, cardiovascular diseases but cancer is the main thrust behind this paper. evidence for which has been gained largely from molecular and cellular biological studies based on animal studies: human studies have posed difficulties but evidence has accrued from epidemiological studies of Doll and Peto [91], and of course from the great Japanese epidemiologist Takeshi Hirayama [92] who investigated cancers of stomach, colon, breast, prostate, in Japanese in which the consumption of green yellow vegetables reduced risk. A better understanding of the mechanisms whereby soy intake may influence the risk of breast cancer is also needed. In particular we wish to know if: epidemiological evidence will support the notion that phyto-oestrogens in foodstuff beneficially change endocrine cancer risk such as in breast and prostate; they change en-

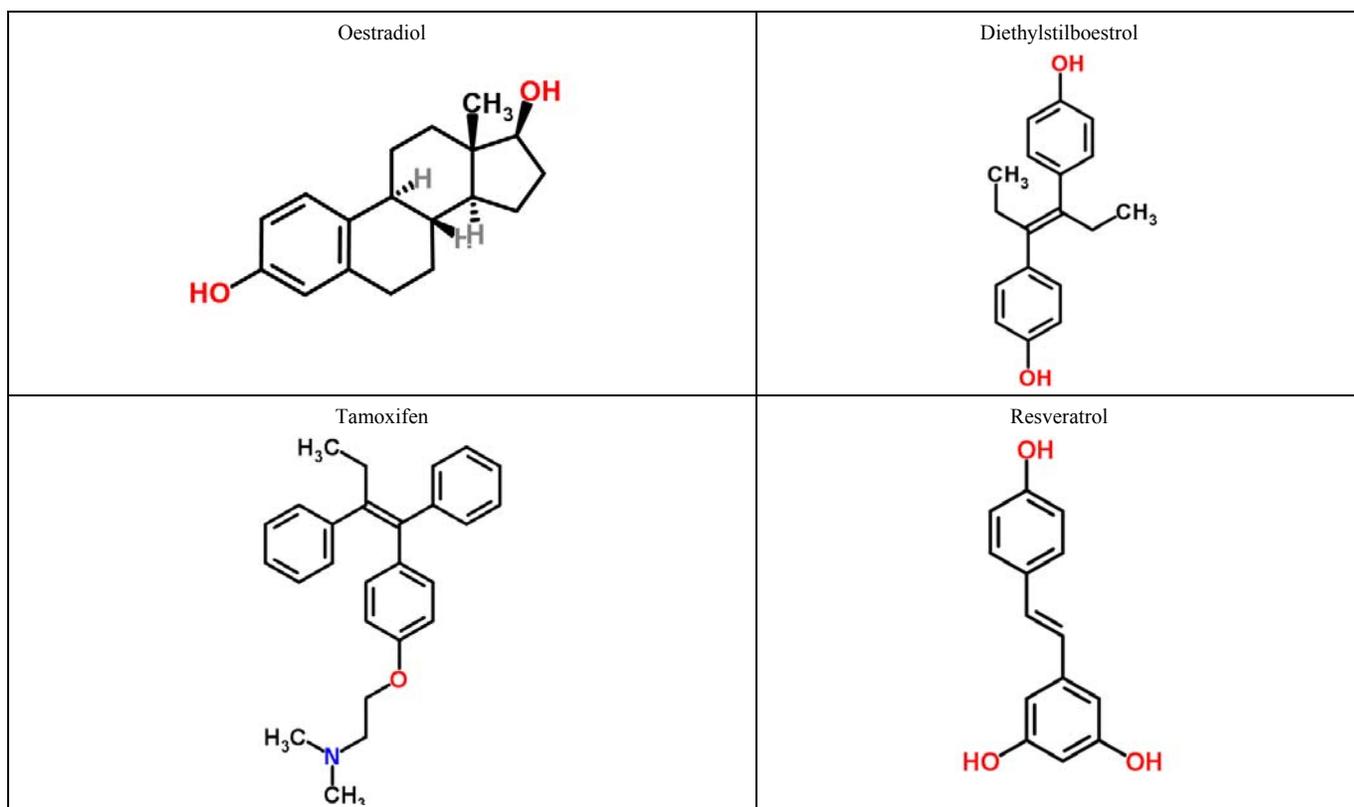


Fig. (1). Structures for oestradiol, diethylstilboestrol, Tamoxifen and resveratrol.

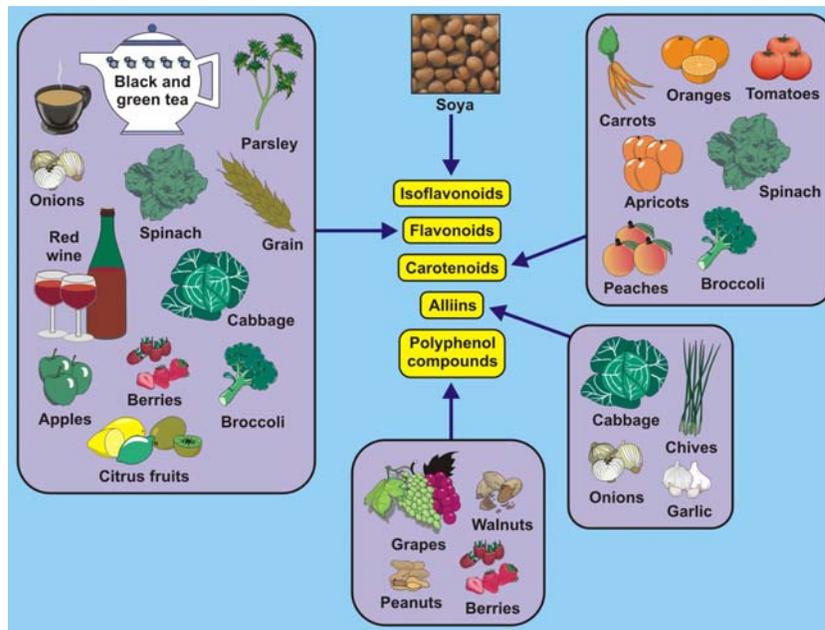


Fig. (2). Selected sources of food-containing phyto-oestrogens.

Summary: Hypothetical synthesis of health benefit food stuff supplements and extracts.

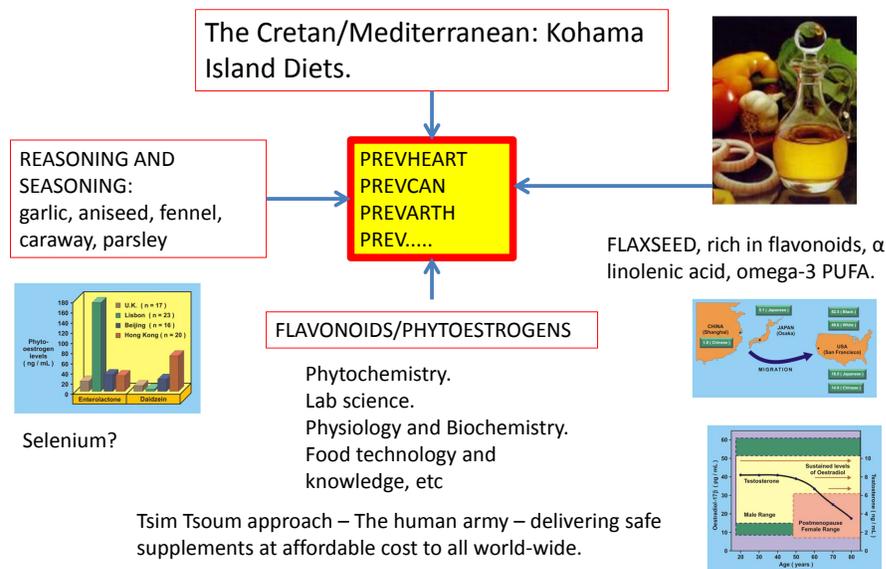


Fig. (3). Evidence for pathogenic action of phyto-oestrogens indicating components and technology necessary for functional foods (i.e. a molecular mechanism or targeted function) or a healthy diet e.g. prevention of heart disease, cancer, arthritis, etc.

ogenous levels of hormones which may affect risk; they effect growth in endocrine tissue; they are oestrogenic or antioestrogenic; if they act through the oestrogen receptor mechanism; most importantly are they chemopreventative ?

MECHANISM OF ACTION

Breast

The studies of phyto-oestrogen partly recalled by Dr Wilson on a visit to Prospect in c1971 was the work of Shutt and Cox [17] on sheep uterine binding oestrogen receptor (ER) [2] with various oestrogens and phyto-oestrogens, stems largely from *in vitro* work. Focus was placed on cell

proliferative activity inhibition particularly MCF-7 (Michigan Cancer Foundation (Detroit) breast cancer cell line [93] which *i.a.* possesses oestrogen and progesterone receptors. This cell line has a proliferative response to oestrogens [94, 95], induction of oestrogenic-specific exoprotein [96] and an increase in p52 expression [97]. Not all phyto-oestrogen is mediated through the ER dependent ‘pathway’ but concentrations of phyto-oestrogens may be unrealistically high to demonstrate cell inhibition, such as with genistein, biochanin A, and daidzein in both ER positive and negative breast cancer cell lines [98].

Prostate

Oestrogen receptors in the prostate (ER $_{\alpha}$ [99] and ER $_{\beta}$ [100,101]), which are regulated by steroid hormones, are members of a super family of ligand activated transcription factors expressed in the tissue. ER $_{\alpha}$ is the most prominent in the prostate maintaining differentiation and reducing cellular proliferation [102]. It is the receptor that is activated by phyto-estrogens [103], and would explain, in some measure, global differences in the incidence of prostate cancer [104] arising, for example, where the intake of soy-based, phytoestrogen-rich food is higher such as in China and endocrine cancer incidence is lower. The role of ER $_{\beta}$ is not so well understood and care must be taken in interpreting evidence from animal studies to those of human.

Some phyto-oestrogens are known to inhibit certain important enzyme system such as 5-alpha-reductase and tyrosine-specific protein kinases, and further discussion is beyond the scope of this report [105].

DISCUSSION

The early human and animal phyto-oestrogen studies combined with discovery of breast and prostate receptor mechanisms, and the epidemiological migrant evidence [106-110], definitely point to the use of phyto-oestrogens in chemoprevention somewhat beyond speculation. There are a number of discussion points, quite apart from difficulties on gaining a consensus e.g. in colorectal neoplasms [111]. Firstly, geographical differences may not be due to phyto-oestrogens; secondly soya products may substitute for fat and meat products in the Western diet, furthermore these diets may have a differing and higher omega-3/omega-6 ratio and other constituents (reasoning for seasoning) thus favouring the Mediterranean diet [112] which, *i.a.*, forms the backbone of Tsim Tsoum activities [113-119]; thirdly high human intakes of phyto-oestrogen could have adverse effects depending on sex, age, tissue, meal-timing; antibiotic use; maternal and paternal consumption may have little or no effect in adults but in pregnancy and following birth they may induce or modify otherwise maleness and femaleness behavioural change in the offspring, affect bone development [120] and so forth. The watchword is caution and evidence-based information leading hopefully to chemoprevention with soundly evaluated health supplements and functional food development based on properly accredited trials, whencesoever possible, is required. Taking soya products as examples, dietary intervention studies with soy will provide information on the acute effects of soy on endogenous hormone concentrations: this point is implied in work by the Griffiths and Wilson group [26(p329), 121, 122]. Cross-sectional and longitudinal studies are necessary to investigate the longer-term relations between hormone concentrations and soy intake in women. It is imperative that politicians are proactive and endeavour to provide the lay public with healthy foods, free from contamination, that will give them, *ceteris paribus*, a long and happy life [106, 123].

CONCLUSION

This paper has presented a broad brush approach to historical and current work on developing phyto-oestrogen chemoprevention platforms for future human needs. It also honours Dr Douglas Wilson for his role in this field.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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