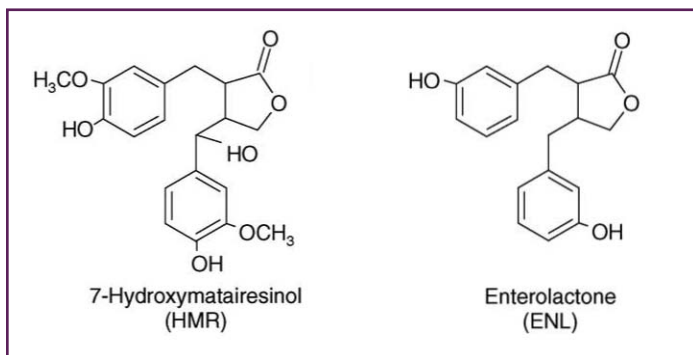


Getting the Balance Right

Lignans are a relatively obscure sub-category of phytonutrients that have recently been gaining an increasing amount of attentive interest from the scientific community. Phytonutrients themselves are broadly defined as beneficial, naturally-occurring plant compounds, with phytoestrogens being one of the most significant types. True to their name, phytoestrogens mildly mimic the effects of human estrogen. That being said, lignans are widely recognized as one of the two major categories of phytoestrogens (the other being isoflavones). Lignans can be found in trace amounts in certain plants, unrefined grain products, fruits, vegetables, and seeds - notably flax and sesame. One lignan in particular, namely the patented HMRlignan(tm), is 7-hydroxymatairesinol, which is found naturally in the Norway Spruce (*Picea abies*), a species of tree native to the Scandinavian Peninsula.

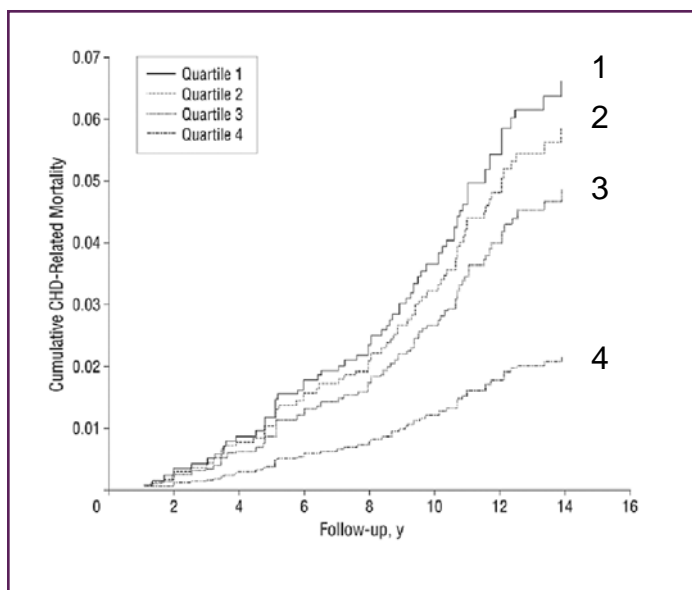


Finland, where 7-hydroxymatairesinol was developed, is a center of academic excellence for the study of phytoestrogens. It was researchers at the prestigious University of Helsinki who established the relationship between the lignan 7-hydroxymatairesinol and lower incidences of breast cancer, prostate cancer and cardiovascular disease. Upon ingestion, 7-hydroxymatairesinol is directly converted into 'human lignans', primarily enterolactone, which exerts a mild, estrogen-like activity. Put more succinctly, enterolactone is formed by intestinal bacteria from precursors in plant foods. The gentle, hormone-like action of enterolactone is beneficial in menopausal and post-menopausal women as well as middle-aged men due to its protection against gender-related hormonally induced cancers (i.e. of the breast and prostate) as well as its overall cardiovascular benefits. 7-hydroxymatairesinol does not need to be cleaved in the gastrointestinal tract before it can be metabolized into the desired molecule enterolactone, effectively making 7-hydroxymatairesinol the world's first and only direct enterolactone precursor.

Upon ingestion, 7-hydroxymatairesinol is directly converted into 'human lignans', primarily enterolactone, which exerts a mild, estrogen-like activity

Enter Enterolactone

Enterolactone is one of the most recent factors to be isolated and identified for its direct association with cardiovascular health. In fact, large-scale human studies published in 2002 and 2003 in both the United States and Finland respectively established the link between cardiovascular mortality rates and plasma enterolactone levels in both men and women. The US study, known as the Framingham Offspring Study, was cross-sectional and highly extensive in its scope, involving 939 post-menopausal women.¹ It found that the women with the lowest intake of lignans were three times more likely to experience some sort of cardiovascular condition according to a test called the Metabolic Syndrome Score, designed in accordance with WHO (World Health Organization) criteria.² As noted earlier, lignans are the precursors to enterolactone and their intake increases plasma enterolactone levels. The Finnish study examined 1,889 middle-aged men over an average period of 12 years and found "significant associations between elevated serum enterolactone concentration and reduced risk of coronary heart disease and cardiovascular disease - related mortality".³



Cumulative coronary heart disease (CHD)-related mortality in men according to quartiles of serum enterolactone concentration, adjusted for age and year of examination and of serum enterolactone measurement. Quartile 1 indicates a serum enterolactone concentration of 0.2 to 6.9 nmol/L; quartile 2, 7.0 to 13.7 nmol/L; quartile 3, 13.8 to 23.8 nmol/L; and quartile 4, 23.9 to 88.7 nmol/L.)

The diets of the women in the Framingham offspring study in fact included a variety of lignans and isoflavones, including: Secoisolariciresinol, Genistein, Daidzein, Formononetin, Matairesinol, Coumestrol, and Biochanin A.⁴ The variety of lignans and isoflavones in the diets of the men in the Finnish study were of course equally assorted. However, scientists eventually determined that matairesinol, in the form of 7-hydroxymatairesinol, is the most readily converted to enterolactone.

Antioxidant - Tip of the Iceberg

Due to the biphenolic (two-ringed) structure of enterolactone (a feature shared by most antioxidants), it demonstrates what can be defined as potent anti-oxidant capabilities - thus contributing to its role in cardiovascular health. These capabilities were identified in a study where low serum enterolactone levels were directly associated with increased in-vivo lipid peroxidation.⁵ This is an important discovery since lipid peroxidation is a cornerstone in the study of free radical generation, as lipids form the backbone of cell membranes and their oxidative degeneration precedes a free radical chain-reaction.

ANTIOXIDANT FEATURE	7-hydroxymatairesinol	Trolox
Inhibition of lipid peroxidation ($\mu\text{mol/L}$)*	0.06	0.22
Inhibition of LDL oxidation (nmol/mg LDL)*	6.7	15.5
LDL incorporation (nmol/mg LDL)*	130	744
Superoxide anion scavenging ($\mu\text{mol/L}$)*	5.6	18.8
Peroxy radical scavenging (ratio)	1 : 4	1 : 2

Amounts of 7-hydroxymatairesinol or Trolox to elicit activity

In fact, 7-hydroxymatairesinol has been shown to exhibit greater free radical-scavenging capabilities than the standard reference antioxidant compounds Trolox (a water-soluble form of vitamin E), butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT). A highly detailed study examining the antioxidant properties of 7-hydroxymatairesinol in direct comparison with Trolox, BHA and BHT revealed some specifically interesting capabilities on the part of 7-hydroxymatairesinol.⁶ Tests with laboratory mice revealed that 7-hydroxymatairesinol was a more effective antioxidant than Trolox in all assays and more effective than BHT or BHA in lipid peroxidation and superoxide scavenging assays.⁷ Enterolactone's antioxidant capability may also encompass an anti-inflammatory capacity as well.

Basic Chemoprotective Pharmacokinetics

An early study with laboratory mice indicated that 7-hydroxymatairesinol (or simply hydroxymatairesinol - and by extension enterolactone) mediates its chemopreventive effect through the Apc-beta-catenin pathway.⁸ Scientists based this hypothesis on the fact that hydroxymatairesinol normalized beta-catenin levels in adenoma tissue in the aforementioned study.⁹ Beta-catenin is a central component in the operation of cadherins, which are a class of proteins that ensure proper intracellular binding. The Apc (or the adenomatous polyposis coli gene - found in most colorectal cancer polyps) is important for the transduction of beta-catenin. This remains the most explicit hypothesis behind hydroxymatairesinol's mechanism of action.

HORMONAL HEALTH

Breast

Breast cancer is widely considered by the medical community to be a hormone-regulated disease with estrogen known to play a disproportionately large role in its development. Enterolactone inhibits estrogen by gently binding to the estrogen receptors, effectively serving as a mild anti-estrogen in its own right.¹⁰ Furthermore, enterolactone stimulates the production of a natural biochemical called sex hormone-binding globulin (SHBG), which also binds to circulating estrogen, effectively lowering the estrogen level available to the cancer cell and inhibiting its growth.¹¹ Finally, there is evidence that enterolactone compromises the very synthesis of estrogen itself by blocking aromatase, a key enzyme required for the synthesis of estradiol (an important estrogenic hormone).¹² This too, results in lower amounts of circulating estrogen available to any abnormal cells.

These chemopreventative effects in relation to anti-estrogenic activity were outlined in a study examining the influence of hydroxymatairesinol on uterine carcinogenesis among laboratory rats. This study demonstrated, in a dose-dependent manner, that incidences of uterine adenocarcinoma among the study group animals were up to 50% lower than those among the control group.¹³ The same study also revealed a delay in the start of persistent estrus (observed at eight months of age) among the 7-hydroxymatairesinol groups compared with the control group.¹⁴

These observations have led to other studies examining 7-hydroxymatairesinol supplementation with regard to breast cancer itself. One such study at the National Cancer Research Institute of Italy in Genoa examined 258 women diagnosed with the development of at least one breast cyst and epidermal growth factor (EGF) concentration values, with 12 women developing breast cancer during the course of the study.¹⁵ The researchers were trying to determine if enterolactone accumulates in breast cyst fluid and whether it correlates with the risk of breast cancer development. They found that while enterolactone does indeed accumulate in cysts, it appears to significantly decrease the risk of breast cancer development among patients whose cysts have high EGF concentrations.¹⁶ These findings added depth to a previous study conducted in Finland at the National Public Health Institute in Helsinki. This study, conducted among 194 breast cancer cases (68 premenopausal and 126 postmenopausal) and 208 community-based controls, examined the direct correlation

between serum enterolactone levels the risk of breast cancer.¹⁷ The researchers clearly determined that elevated serum enterolactone levels were "significantly inversely associated with [the] risk of breast cancer".¹⁸

Prostate

In prostate health, an increasing body of evidence points to the benefits of lignans in the maintenance of prostatic well-being, and suggests that enterolactone may directly inhibit the growth and signaling of cancer cells. The first official study to verify this took place in 2001 at Duke University Medical Centre in Durham, North Carolina, USA, where scientists examined enterolactone's effect on three human prostate cancer cell lines (PC-3, DU-145 and LNCaP) *in vitro*.¹⁹ They found that enterolactone was in the rather unique position of having 'significantly inhibited the growth of all [3] cell lines' in comparison with the other compounds tested, namely enterodiol and genistein.²⁰ Research has also indicated that enterolactone's specific anti-estrogenic activities may reduce the growth of a hormone-dependent prostate via the 'significant decreases' in circulating levels of prostate-specific antigen (PSA) and total cholesterol.²¹

A landmark *in vivo* study took place in 2003 using purified lignans to determine their inhibitory effects on prostate cancer.²² Laboratory mice were injected subcutaneously with cancerous LNCaP cells and then fed either a control diet or diets enriched with 7-hydroxymatairesinol.²³ At the end of the nine-week study, the animals fed the 7-hydroxymatairesinol-enriched diets had tumor cell apoptosis rates that were four times higher than that of the control group.²⁴ Furthermore, the average weights of the tumors in the control group animals were between just under two-and-a-half to nearly three times greater than those of the study groups.²⁵

Managing Menopause

There are other areas where 7-hydroxymatairesinol can exert benefits as well. It must be remembered that enterolactone serves as both a mild estrogen and anti-estrogen. This is of particular importance to the management of menopause, namely the several-year period when estrogen levels are in flux, leading to a cessation of menstruation. When estrogen levels decline, enterolactone exerts a weak estrogenic effect, mimicking the presence of estrogen. When estrogen levels are too high, enterolactone occupies and blocks estrogen receptors, thereby smoothing the peaks and valleys.



In fact, a recent Dutch study conducted at the Julius Center for Health Sciences and Primary Care in Utrecht examined how dietary intake of two phytoestrogens - lignans and isoflavones - in the typical Western diet may affect cognitive function in postmenopausal women. The study involved 394 healthy postmenopausal women who had not used hormonal replacement therapy since their last menstrual period.²⁶ Their intake of phytoestrogens during the year prior to enrolment in the study was estimated by a validated food frequency questionnaire.²⁷ Cognitive function was assessed by a mini-mental state examination (MMSE), which involved questions and tasks associated with orientation, registration, attention, calculation, recall and language.²⁸ After adjustment for confounders, women who consumed higher levels of lignans performed better in the MMSE, whereas isoflavone intake appeared to have no effect on cognitive function.²⁹

Bone Health

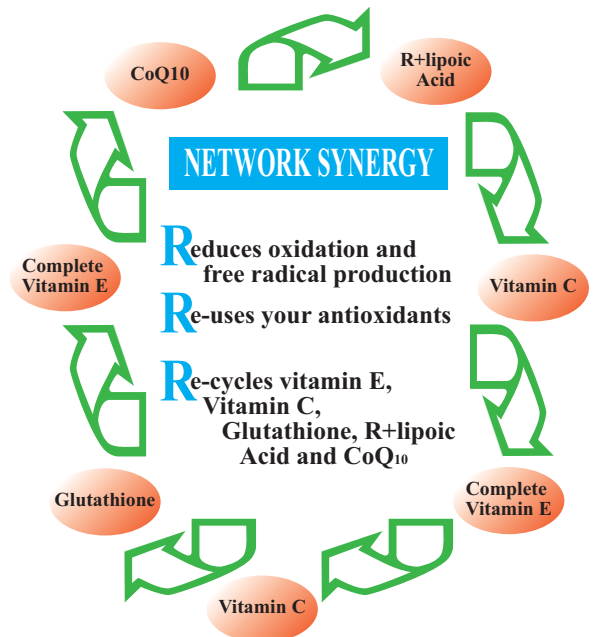
The aforementioned estrogen-stabilizing capability may also have implications for bone health, and indeed a 2002 Korean study identified a link between enterolactone levels and incidence of osteoporosis in post-menopausal women.³⁰ The scientists concluded that Bone Marrow Density (BMD) of the lumbar spine (L2-L4), the femoral neck and Ward's triangle 'correlated positively with urinary enterolactone' among the 75 post-menopausal women (ages ranging from 52-65 years) who participated in the study.³¹

In summation, 7-hydroxymatairesinol, which most readily converts to enterolactone in the human body, can accurately be described as a phytonutrient stabilizer of estrogen. This elemental definition underlies the complex biological mechanism of action by which 7-hydroxymatairesinol exerts its hormonal cascade. This cascade results in precisely the biochemical changes required for optimal health.

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