

SCIENTIFIC INFORMATION

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INNOVATIVE APPLICATIONS OF HOPS (*Humulus lupulus* L.) FOR RELIEF OF MENOPAUSE RELATED SYMPTOMS

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Menopause is best described as the period in which a woman, as a result of a decreased oestrogen and progesterone production by the ovaries, turns from fertile into infertile condition. Women are confronted with this on average when they are around 50 years old.

The so-called 'transition' – which is not a disease, but a natural phenomenon – lasts a few years. Menopause can be divided in two stages: the peri-menopause and the post-menopause. During the peri-menopause, women feel the first menopausal symptoms, one of these are hot flushes, caused by unusual fluctuations in the hormone levels and accompanied by very irregular menstruation cycles. The post-menopause starts as soon as 12 months have gone by since the last menstruation. For many women, the transitional process involves a range of symptoms and discomforts: hot flushes and waves of heat, sleeping disturbances, structural changes in bladder and vagina, strongly reduced libido, higher cardiovascular disease risks, decrease of bone density (osteoporosis or bone decalcification) with an increased risk of hip, leg and arm fractures.

Hormone replacement therapy under debate

Medicalisation of menopause is a 'hot' item. Women can expect to live for about 30 years after menopause. For a healthy, active and fulfilling post-menopausal life, women need to make some efforts, whether by adapting their lifestyles, of which nutrition is a part, or by taking extra nutritional supplements and/or treatment with medication. An adequate means for fighting the symptoms involved in menopause is the well-known **hormone replacement therapy** (HRT), in which women, in general orally, take a small dose of semi-synthetic hormones. On July 9, 2002 however, the American Women's Health Initiative (WHI), a large-scale, long-term study (8,5 years) on the advantages and disadvantages of HRT, in which 16,608 menopausal women (50-79 years old) were involved, was broken off after 5.2 years (1), as the risks of invasive breast cancer, arterial rupture, stroke and lung embolism were raised significantly. The advantages in relation to a reduced risk of hip fractures and cancers of the large intestine and of the uterus were outweighed by this (2). Moreover, on December 11, 2002, the federal US government published its two-yearly *Report on Carcinogens*, in which the steroidal oestrogens, used in HRT and in oral contraceptives, were added as a group to the official list of 'known human carcinogens' (3). In the report, the increased cancer risks, especially breast cancer, are discussed elaborately.

Very recently, the results of the *British Million Women Study*, in which 1 million menopausal women were involved, were published in the leading magazine *Lancet* (4). The conclusion of this largest study ever on the relation between HRT and breast cancer, was that HRT (combination of oestrogens and progestins) doubled the risk of breast cancer, versus a 30% rise for HRT with only oestrogens. In the last 10 years, 20,000 extra cases of breast cancer were diagnosed among British women between 50 and 64 years of age as a result of long-term application of HRT. Doctors are advised to discuss HRT with their patients on a yearly basis

and to balance the increased risk of breast cancer, which appears after only 2 years of therapy, against the decreased risk of uterus cancer. The present strategy of doctors may also be influenced by an American study, which has just been published in the medical journal valued most highly in the world, *New England Journal of Medicine* (5). A significant rise in the cardiovascular disease risk was found during the 1st year of combination HRT. In the past, it was believed that HRT would protect women from heart diseases.

These recent findings have made a deep impression, both on doctors and on patients, not only in the United States, but worldwide (in our country as well). The market for HRT products in the United States and in England has collapsed and it may be stated that HRT at this moment can only be supported in very serious cases of menopausal complaints and osteoporosis among women with a limited cancer risk. There is no more room for long term HRT, especially not when the treatment is meant as prevention.

Control of menopausal symptoms through oestrogenic plants

In these severe health problems, nature can be of great help. The fact is that many plants contain so-called **phyto-oestrogens** ('phyto' means 'plant derived'); these are non-steroidal constituents, which bear a structural resemblance to endogenous oestrogens and which imitate their activity. Phyto-oestrogens are able to fill up the hormone deficiency in menopausal women in a natural way and to relieve menopausal symptoms (6). An important additional advantage is that, since the hormonal activity of phyto-oestrogens is much weaker than that of the hormones of the body itself, the influence on hormone dependent cancers, such as breast and uterus cancers, is weakened.

Plants, which are rich in oestrogens, normally do not occur as such in western nutrition these days. As a result, they can only be ingested as derived products or nutritional supplements. It is apparent that menopausal women are massively switching from HRT to alternative preparations, based on natural phyto-oestrogens with a suitable safety profile. Numerous clinical studies support the activity of phyto-oestrogens in relation to menopausal symptoms, while there are also strong epidemiological indications of a causal connection between a typically Asian diet, in which oestrogen rich soy plays an important role, and the limited incidence of hormone-dependent cancers and menopausal complaints among Asian women.

Only a limited number of oestrogenic plants exist and they are used regularly in the treatment of menopausal symptoms. In Belgium, it seems that some 20 phyto-oestrogenic plants are commercially available, derived from soy (*Glycine max* L.,

isoflavones, such as genistein and daidzein), red clover (*Trifolium pratense* L.), coumestrol as active phyto-oestrogen), black cohosh (*Cimicifuga racemosa* L.), chaste tree or chaste berry (*Vitex agnus-castus* L.) and yam (*Dioscorea villosa* L.)

Hops (*Humulus lupulus* L.)

In 1999, the research team of Prof. Dr. Denis De Keukeleire of the Faculty of Pharmaceutical Sciences at the University of Ghent, published for the first time that hops contain the strongest natural phyto-oestrogen, that is 8-prenylnaringenin, also called hopein, which belongs to the class of polyphenols, more specifically to the subclass of the prenylflavonoids (7). This revealing and intriguing finding has meanwhile been confirmed by 5 independent research teams in Germany, England and Japan (8). What is more, a Japanese research team has discovered that hopein has a potent effect on bone decalcification (9), while a French research centre has shown that hops strongly reduce hot flushes (10). Hopein seems to be a 'miracle molecule' for menopausal women. Moreover, hops contain another substance, **xanthohumol**, which, just like hopein, belongs to the prenylflavonoid group, but, in contrast to hopein, does not show any oestrogenic activity. At the German Centre for Cancer Research in Heidelberg, the anti-cancer property of xanthohumol was studied in detail as part of an extensive study, in which more than 2,000 vegetable compounds were examined by some 20 anti-cancer tests. Only xanthohumol was active in all tests, which illustrates the exceptional value of this compound of hops. Xanthohumol shows a remarkably broad spectrum of inhibition mechanisms at the initiation, promotion and progression of cancers (11). The food supplements derived from hops available on the market at this moment are focused on the tranquilizing (sedative) effect of the plant. Generally, these are combinations with other plants, such as valerian and lemon balm. Some 1% of the world production of hops (99% is intended for breweries) is used as such or as a simple watery-

alcoholic extract. Only one registration of hops as a phytotherapeutic is known, that is in the German Pharmacopoeia. In the monograph *Lupuli strobulus*, the indications are described as sedative and sleep promoting.

Original applications of hops in the fight against menopausal symptoms

In the light of what we know at this moment, exploitation of the extremely potent oestrogenic properties of hops as food supplement and, in the longer term, as phytotherapeutic, seems appropriate. Initially, menopausal symptoms and complaints may be remedied, while the possible proliferative activity of hopein is outweighed by the anti-proliferative activity of xanthohumol. For this purpose, certain hops cultivars needed to be selected, which are particularly rich in prenylflavonoids. A highly technological extraction method was optimised, in order to obtain maximal oestrogenic power and anti-cancer activity (world primary publication; patent applied for). The process from the hops plant into the food supplement is controlled through high-quality analytical procedures, while the quality is guaranteed by calling in very selective and sensitive bioassays, which on the one hand determine oestrogenic activity exactly and on the other hand confirm the cancer-chemopreventive activity.

AUTHOR BIOGRAPHY

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Prof. Dr. Denis De Keukeleire is a Doctor in Chemistry, professor at the Faculty of Pharmaceutical Sciences of the Ghent University in Belgium and director of the Laboratory of Pharmacognosy and Photochemistry. He is a member of the Research Council of the Ghent University and also of the Advisory Committee on Plant Preparations to the Federal Ministry of Health, Safety of the Food Chain and Environment Since more than 35 years, Prof. De Keukeleire is involved in scientific research on hops (*Humulus lupulus* L.) and beer. Prof. De Keukeleire is a worldwide-recognized authority on constituents and applications of hops, not only with respect to beer properties, but also regarding beneficial effects on health.

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