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Black cohosh: just another phytoestrogen?

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Most clinical trials on phytoestrogens detected no significant effects on classic menopausal symptoms. Soy-rich diets positively influence certain aspects (e.g. sleep disturbances and mood swings), but the level of relief is low. Duration of the specific diet before menopause onset predicts the extent of the benefit. Isoflavones exert competitive effects at the estrogen receptor and might interfere with anti-proliferative properties of endocrine anti-cancer therapies. Clinical trials on effects of *Actaea racemosa* (black cohosh) extracts on menopausal symptoms have yielded more positive results. Two recent studies showed excellent efficacy against classic menopausal complaints and osteoprotective properties, and extracts were deemed safe even when the dosage was increased threefold. Furthermore, several studies suggest that *A. racemosa* extracts might help control psychic problems typically found during menopausal transition.

Introduction

After the premature end of the Womens Health Initiative (WHI) study [1], additional alarming news concerning negative side effects of hormone therapy (HT) with estrogens and progestins came from the Million Women Study, in which a significant increase in incidence and fatality of breast cancer was found for 'European-type' HT (e.g. estradiol and norethisterone) [2]. Although major criticisms have been expressed with regard to the design and interpretation of these studies, many women now try to avoid HT and suffer from menopausal symptoms, such as hot flushes, night sweats and psychic problems, that reduce their quality of life. Therefore, the search for alternative treatment options is of considerable scientific and public interest.

One such option lies in naturally occurring estrogenic substances of plant origin, mostly polyphenols, which are frequently summarized by the term 'phytoestrogens' (Box 1). Although they are less potent than genuine estrogens, extraordinarily high serum levels can compensate for their comparatively low affinity for the estrogen receptor (ER) [3].

Epidemiological data suggest a connection between the scarcity of climacteric complaints and a diet rich in phytoestrogens, and postulate preventive effects of phytoestrogens on tumors of the breast, the uterus and the ovaries. ER-mediated long-term modulatory effects on receptor and coregulator status or non-hormonal effects, such as inhibition of tyrosine kinases and DNA toposomerases, anti-angiogenic antioxidant effects [3] and several other mechanisms, have been put forward as putative explanations (Table 1, Figure 1).

Extracts of the rootstock (rhizoma) of black cohosh [*Actaea* (previously *Cimicifuga*) *racemosa*] or partly purified components bind to the ER, a fact that suggested black cohosh as a systemic 'estrogen-like' compound (Box 2). However, the broad range of components is extremely complex, mainly comprising triterpene glycosides and phenolic substances (i.e. cinnamic acid esters), but including none of the 'classic phytoestrogens' (Box 1). All studies failed to find estrogen agonistic effects [4–6]. It is interesting that an aqueous ethanolic extract did not bind to recombinant ERα or ERβ protein, but bound to cytosolic uterine extracts, where the extract competed with radioactively labeled estradiol for the yet unidentified estrogen-binding proteins [7]. Rootstock extracts of black cohosh, which are presently on the market, represent standardized up-to-date products mainly used to treat menopausal symptoms [8]. Owing to various monographs recently published by, for example, the World Health Organization (WHO) [9,10], they have become a well accepted treatment alternative to HT.

Here, we summarize the data currently available on differences and similarities between phytoestrogens and black cohosh. Differences are to be expected between premenopausal, perimenopausal or postmenopausal women [11] because net effects on single cells, organs or an organism depend on levels of endogenous estrogens or other competitive receptor ligands (Box 3). Endogenous estrogens might competitively be displaced at the ER, thus

Box 1. Sources of phytoestrogens

Isoflavones
- Soybeans
- Red clover

Coumestans
- Alfalfa
- Soybeans
- Clover sprouts

Lignans
- Flaxseed
- Grains

Flavonoids
- Hops
- Red wine

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Table 1. Phytoestrogens (isoflavones) and black cohosh: putative mechanisms of action[a]

Effects	Putative modes of action	Phytoestrogens[b]	Black cohosh[b]	Refs
Decreased menopausal symptoms	Serotonin agonist		+	[44]
	Dopamine agonist		+	[7]
	Organ-dependent ER agonist–antagonist (SERM)		+	[45]
	Estrogen agonist	(+)		[46]
Ovarian cycle	Inhibition of 5α-reductase	+		[3]
	Inhibition of 17β-hydroxysteroid dehydrogenase	+		[3]
	Aromatase inhibition	+	(+)	[11]
Coronary heart disease	Reduction of LDL cholesterol and triglyceride	+		[3]
	Increase of HDL cholesterol	+		[3]
	LDL oxidation	+		[3]
Bone protection	ER agonistic on osteoblasts	+	+	[47]
	Inhibition of topoisomerase II	+		[47]
	Inhibition of osteoclasts (via osteoblast-derived inhibitory cytokines)	+	+	[48]
	Inhibition of tyrosine kinase	+		[47]
	Organ dependent ER agonist–antagonist (SERM)	+	+	[47]
Inhibition of tumor growth	Inhibition of topoisomerase II	+		[49]
	Inhibition of EGF receptor autophosphorylation	+		[49]
	Inhibition of tyrosine kinase	+		[49]
	Downregulation of EGF receptor	+		[49]
	Inhibition of angiogenesis	+		[11]
	Inhibition of cell cycle progression	+		[11]
	Antioxidant activity (superoxide anion production, hydrogen peroxide production)	+		[50]
	Transforming growth factor β enhancement	+		[50]
	Modulation of transcription factors c-fos and c-jun	+		[50]

[a]Abbreviations: EGF, epidermal growth factor; GABA, γ amino butyric acid; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SERM, selective estrogen receptor modulator.
[b]Effects: +, proven effect; (+), disputed effect.

phytoestrogens would act as an 'anti-estrogen'. Therefore, only under the 'estrogen-free' conditions found postmenopausally would the agonistic or 'estrogen-like' effects of phytoestrogens become predominant. Because black cohosh and phytoestrogens are mainly used peri- and postmenopausally, this review focuses on their potential clinical applications in this phase of life, and in the treatment of symptoms such as hot flushes, night sweats and psychic problems. However, when further differentiating within this target population, it has to be borne in mind that in survivors of hormone-dependent cancers, in particular breast cancer, HT is even more strictly avoided than in the general population. These women, who are often undergoing adjuvant tamoxifen treatment, tend to

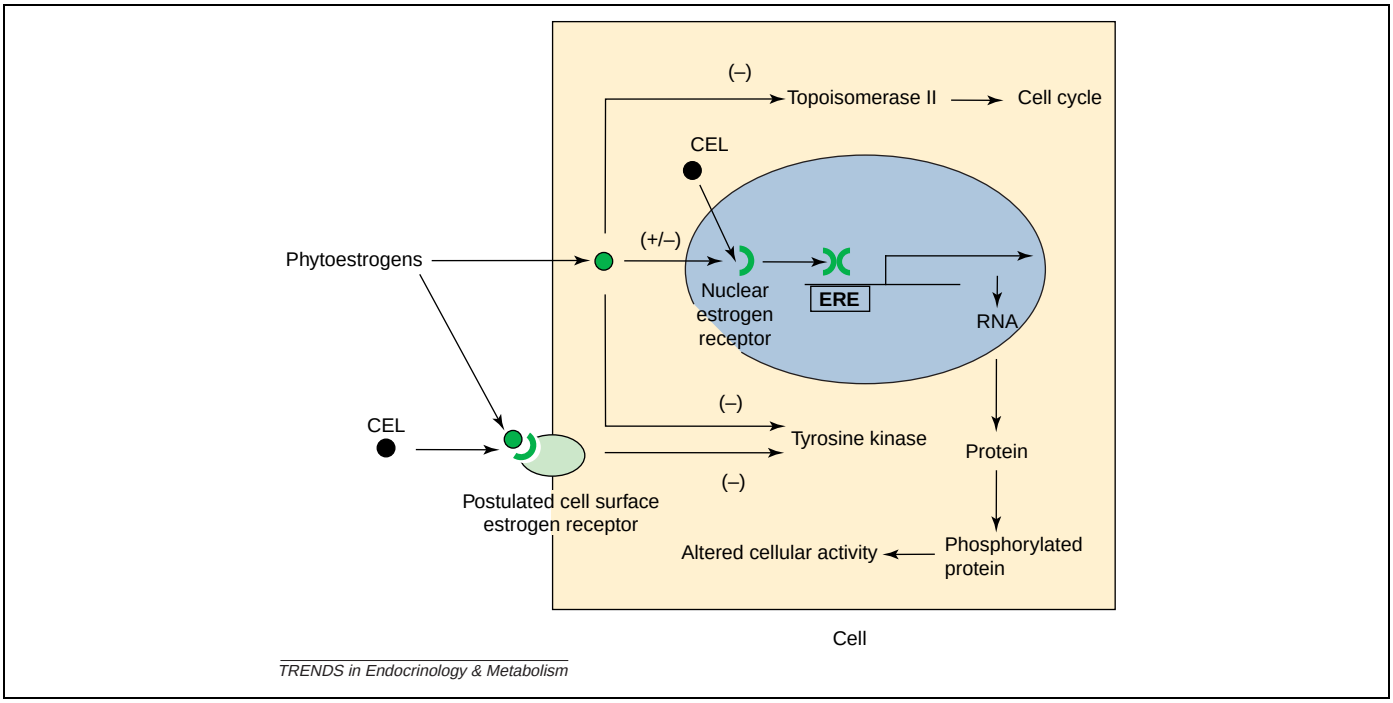

Figure 1. The putative effects of phytoestrogens on cell function can be separated into ER-mediated and non-receptor-mediated effects. As in the case of natural or synthetic estrogens, receptor-mediated effects of phytoestrogens are exerted via mRNA transcription and protein biosynthesis or through postulated cell surface ERs. The direction and extent of effects depend on competing endogenous estrogens. Non-receptor-mediated (i.e. enzyme-inhibitory) effects might interrupt the cell cycle or regulate secondary enzymes and/or proteins. CEL, competing estrogenic ligand; ER, estrogen receptor; ERE, estrogen-responsive element; GABA, γ amino butyric acid.

Box 2. Preclinical findings: phytoestrogens versus black cohosh

Phytoestrogens

Gene transcription and protein synthesis studies show that an estrogen agonistic effect can be induced in all relevant cell systems tested so far. The extent of this effect depends on phytoestrogen concentration and the absence of endogenous estrogens. Thus, phytoestrogens might be of potential benefit for some estrogen deficiency-induced ailments. Nevertheless, proliferative stimuli of phytoestrogens on crucial target tissues and interference with other drugs or endogenous hormones (e.g. antagonism to adjuvant anti-hormonal tumor treatments) have to be considered.

Black cohosh

Preclinical findings suggest that the efficacy of extracts of black cohosh to ameliorate menopausal symptoms might be a result of substances with dopaminergic or serotoninergic activity (Figure 2). Significant binding of black cohosh ingredients to ER might be one explanation for its bone protective activity (Figure 2). Because it has ER-binding and putative estrogen agonistic activity on bone tissue, but no stimulatory effects on mammary or endometrial tissue, it has been proposed that it should be classified as a selective estrogen receptor modulator. The absence of proliferative effects on crucial estrogen-responsive tissues, together with the induction of apoptosis in human mammary tumor cells [41,42], might make black cohosh a safe alternative to HT, even in patients with a history of hormone-responsive neoplasias.

have more pronounced climacteric symptoms, which are less readily antagonized.

Clinical and epidemiological findings of treatment with phytoestrogens

Menopausal symptoms

The efficacy of any treatment on psychosomatic symptoms such as climacteric complaints, particularly hot flushes, is subject to a large placebo effect. Therefore, only double-blind, placebo-controlled studies provide conclusive data. Twelve randomized clinical trials on classic phytoestrogens performed between 1995 and 2002 have recently been reviewed by Kronenberg and Fugh-Berman [12], who come to the conclusion that phytoestrogens exert only modest effects on the severity of hot flushes, and that furthermore most of this benefit disappears after six weeks. Here, only the four most recent double-blind, placebo-controlled studies need to be covered. Nikander *et al.* [13] concluded 'pure isoflavonoids did not alleviate subjective menopausal symptoms in breast cancer patients'. Tice *et al.* [14], studying the effects of red clover-derived isoflavones, concluded 'neither supplement had a clinically important effect on hot flushes or other symptoms of menopause'. Penotti *et al.* [15] wrote 'the daily administration of 72 mg of soy-derived isoflavones is no more effective than placebo in reducing hot flushes in postmenopausal women' and finally Burke *et al.* [16] bring up another point in stating that 'soy protein containing 42 or 58 mg of isoflavone is no more effective than isoflavone-extracted soy protein for improving the number and severity of vasomotor symptoms'. Hence, Burke *et al.* found some reduction of symptoms, although this was not caused by the isoflavones but other components of soy protein. Such observations were also made for another estrogen withdrawal disease, namely arteriosclerosis [17].

Box 3. Effects of phytoestrogens during the prepubertal phase

Only a few clinical trials have specifically investigated putative connections between a diet rich in phytoestrogens and the risk of breast cancer. Retrospective studies quantified soy consumption mainly in Asian countries, where there is a very high intake of such nutrients during all stages of life. Thus, the contemporary hypothesis is that protective effects against breast cancer and other neoplasias are only to be expected in women who regularly consumed large amounts of soy products from early childhood [56]. Epidemiological evidence shows that there is a significantly reduced incidence of breast cancer in Japanese girls who grew up in Japan and then moved into the Western hemisphere compared with their Caucasian counterparts. This could be explained by results from animal experiments of prepubertal exposure of female rats to genistein: the observed protective effect on later development of carcinogen-induced mammary cancers [56] is thought to be caused by down-regulation of an epidermal growth factor driven mechanism [57] and by an upregulation of *BRCA1* [58].

In humans, however, all relevant information is based on the intake of phytoestrogen-rich nutrients that also contain considerable amounts of other secondary plant compounds. It is possible that substance classes other than phytoestrogens are responsible for the reduced cancer incidence, or that phytoestrogens and other secondary metabolites act synergistically.

Besides dietary patterns, other lifestyle habits or hereditary factors (low caloric diet, multiparity, prolonged breastfeeding) [59] could be of considerable importance for the different incidences of certain diseases between Asian and Caucasian populations.

The gradually declining endogenous production of sex hormones is accompanied by a multitude of symptoms differing in severity and incidence. Furthermore, ethnic peculiarities often influence the way a woman experiences menopause. The two extremes could be described as either 'menopause-associated disease' or 'menopausal transition', defining an illness requiring treatment or a physiological process, respectively. This might also, at least partially, explain the lower incidence and the differences between menopausal symptoms in Asian and Caucasian women [3].

Psychic parameters are of great concern during the menopause and thus are a frequent target of pharmacological interventions. The cognitive performance of postmenopausal women was significantly improved after the application of soy isoflavones (daily dose of 110 mg) for six months in a randomized double-blind, placebo-controlled clinical trial [18]. However, another clinical trial in 11 postmenopausal women found that 12 weeks of isoflavone treatment did not influence the patients' verbal memory [19]. An observational study associated the intake of large amounts of tofu with an increased risk of dementia, reduced brain weight and reduced cognitive function [20]. This finding was substantiated by another trial where patients with a low tofu intake were better protected from cognitive impairment than patients with high tofu consumption. Possibly, this again reflects the profound differences between short-term effects of high-dose soy isoflavones and observations after prolonged, and possibly excessive, intake of soy food. Of special interest in this context is the recent finding of the US WHI that an estrogen–progestagen hormone replacement combination did not prevent the postmenopausal decrease of cognitive function, but rather increased the risk of dementia [21].

Bone

The efficacy of phytoestrogenic isoflavones in the treatment or prevention of postmenopausal osteoporosis has been intensely studied *in vitro*, in animal studies and in clinical trials (Box 2). Most studies suggest bone-sparing effects of a phytoestrogen-rich diet only after long-term application, and of speculative magnitude and mechanism of action.

Clinical trials showed that, after six months of treatment with a daily dose of 90 mg of isoflavones, women had an increase in bone density ($+0.02\ g\ cm^{-2}$) and bone mineral content ($+1.2\ g\ cm^{-1}$) [22]. After three months of treatment with daily doses between 60 and 114 mg isoflavones, a decrease in specific parameters of bone resorption, albeit of marginal clinical relevance (only small alterations in osteocalcin, bone-specific alkaline phosphatase, deoxypridinoline and C-terminal telopeptide of 11%, compared with 15% in untreated patients), was detected [23,24].

After treatment for 12 months, standardized red clover isoflavones (40 mg daily dose) induced a significant retardation of bone loss, as measured by lumbar spine bone mineral content and bone mineral density, when compared with placebo in a double-blind randomized placebo-controlled clinical trial comprising 174 women (49–65 years of age) [C. Atkinson *et al.* (2000) The effects of isoflavone phytoestrogens on bone; preliminary results from a large randomized controlled trial. Proceedings from the 82nd Annual Meeting of the Endocrine Society, Toronto, Canada, 21–24th June 2000].

Similarly, red clover (daily dose of 28.5 or 57 mg isoflavones) was tested for six months in 50 postmenopausal women, and resulted in a significantly increased bone density at the proximal radius and ulna, with absence of effect at the distal ends of both bones [25]. A soy preparation rich in isoflavones clinically tested for nine months in postmenopausal women exerted no detectable effect on hip or vertebral bone [26]. No influence by either soy protein or an isoflavone extract of red clover origin (daily dose of 100–160 mg) was found on bone turnover rate in a 12-week clinical trial [27].

Breast and endometrium safety

Four prospective clinical trials have been performed on the connection between soy phytoestrogens and risk of breast cancer [3]. None of these showed a significant protective effect. An animal study suggests that a reduced incidence of breast cancer might only be expected in women who regularly consume large amounts of soy from infancy [28].

None of the above studies included individuals with a high risk for breast cancer. Therefore, final conclusions about the safety of soy supplementation cannot be drawn at this time. Contradictory results from a clinical trial in which postmenopausal women were administered a food additive rich in soy protein (daily dose of 73 mg isoflavones) showed a significant increase in serum interleukin 6 levels, whereas male participants from the same age group showed no effect. Similarly, serum levels of proinflammatory cytokines and C-reactive protein remained unchanged [29].

Because isoflavones induce the synthesis of sex hormone-binding globulin in postmenopausal (but not in premenopausal) women, a parallel decrease in free (i.e. active) serum estradiol is seen [30].

The effect of soy phytoestrogens on vaginal cytology was tested in a double-blind randomized crossover study in 44 postmenopausal women. Epithelial alterations indicative of estrogenic activity were detected in this trial [31].

Most studies in postmenopausal women found no stimulatory effects of soy or isoflavones on endometrial thickness [15,32]. However, in a recent placebo-controlled clinical study covering an administration period of five years, Unfer *et al.* found endometrial hyperplasia, which is known eventually to result in cancer, in several patients [33]. A group of 154 postmenopausal women, all with an intact uterus, were treated with 150 mg of isoflavones per day for five years; another 165 women were concomitantly treated with placebo. After completion of the five-year treatment period, 70% of soy-treated women, compared with 81% of placebo-treated women, had atrophic or non-assessable endometrium. The occurrence of endometrial hyperplasia was significantly higher in soy-treated women (n=6, 3.8%) than in placebo-treated women (n=0) [33].

Ischemic coronary heart disease, a multifactorial syndrome of high lethality, especially in the menopausal period, is often anticipated by an increase in serum cholesterol. Statin therapy effectively reduces cholesterol levels, an effect that has also been attributed to an enhanced phytoestrogen intake. Unfortunately, this effect has not been proven in a controlled clinical trial, and neither is it necessarily associated with a decrease in mortality [34].

The positive effects of isoflavones on coronary heart disease are thought to be mediated by anti-atherosclerotic and anti-thrombotic processes. The extent of therapeutic benefit depends not only on different pathogenetic factors (e.g. lipid profile or cholesterol level), but also on the nature of the phytoestrogen (i.e. nutrients rich in the natural mixture of isoflavones are superior to isolated compounds). Isolated genistein antagonizes the activation and aggregation of porcine thrombocytes and the expression of thrombin, via either its antioxidant or its Ca^{2+} channel-blocking activities [35].

In contrast to the data on isolated isoflavones, a meta-analysis of 38 controlled studies on soy protein proved the benefits it exerts on lipid metabolism (i.e. a significant decrease in cholesterol, low-density lipoprotein and triglycerides) [3]. Possibly because of their markedly different composition (in red clover, isoflavones formononetin and biochanin A represent a considerably bigger fraction than in soy), red clover phytoestrogens did not reproducibly alter the lipid profiles of hypercholesterolemic or normocholesterolemic individuals. However, no clinically relevant reduction in coronary heart disease-induced mortality has been seen in large-scale clinical trials of isoflavone consumption [34,36].

Summary of clinical and epidemiological findings

Several clinical trials have suggested that a diet rich in phytoestrogens reduces the risk of menopause-associated

symptoms such as hot flushes, night sweats and mood swings. However, most of these successful studies were performed with whole food products and not with isolated phytoestrogens. Single isoflavones – often from different sources – frequently failed to reproduce the findings obtained after soy consumption. Other components present in these food products, in addition to 'Asian' lifestyle factors, might contribute to the observed effects. In general, results from epidemiological studies should only be used with caution when deriving recommendations for therapeutic intervention.

Black cohosh

Menopausal symptoms

Since the second half of the 19th century, black cohosh has been used for the treatment of menopausal symptoms. The efficacy of rootstock extracts of black cohosh in counteracting climacteric complaints, such as hot flushes, night sweats and psychic disorders, has been shown in two randomized clinical trials [37,38], using either the Kupperman Menopause Index (KI; an internationally recognized and validated scale for the quantitative determination of menopausal symptoms) or the frequency and severity of selected symptoms (e.g. hot flushes or sweating) as primary endpoints. Statistically significant superiority over placebo has been shown with these methods. A recent randomized clinical trial of black cohosh in breast cancer patients failed to show a significant improvement of the overall KI. This might be because most patients were also undergoing treatment with tamoxifen [39]. Hot flushes, induced by tamoxifen, cannot be controlled like normal climacteric symptoms. They differ in severity, duration, kinetics and most probably in their susceptibility to be antagonized, so that a higher dose of black cohosh might have achieved the desired symptom reduction. Nevertheless, the important and extremely bothersome subtopic 'sweating' as contained in the KI was significantly improved after black cohosh treatment in breast cancer patients on tamoxifen [39].

The most recent good clinical practice (GCP)-compliant, multicenter, double-blind, randomized, placebo-controlled clinical trial demonstrated significant superiority of a daily dose of 40 mg of a standardized isopropanolic extract of black cohosh over placebo. This study was performed in 300 postmenopausal women who were treated for 12 weeks and whose menopausal symptoms were assessed via the validated Menopause Rating Scale (MRS I) [40].

Bone

The first indications from a human clinical trial about bone protective effects of black cohosh have recently been published. Significant superiority of black cohosh over placebo was demonstrated when measuring the bone metabolic index, which comprised both bone catabolic and bone anabolic parameters. This reduced bone resorption with black cohosh therapy [37] clearly warrants further studies, investigating fracture reduction as a clinical endpoint.

Breast and endometrium safety

Two recent clinical trials demonstrated the low incidence of adverse reactions with black cohosh extracts [37,38]. No alterations in endometrial thickness, vaginal cytology or serum pituitary hormone levels were seen, although in one of the trials, the tested dose exceeded the recommended daily dose by more than threefold [38].

Concomitant administration of black cohosh and adjuvant tamoxifen therapy to 26 patients with a history of breast cancer showed no negative influences on cancer recurrence or cancer spread, although only short periods of time (up to three months) were investigated in this placebo-controlled double-blind randomized clinical trial [39]. Corresponding data come from preclinical experiments, where no proliferative effect of black cohosh on human mammary tumor cells was found. Moreover, black cohosh and its main components (triterpene glycosides and phenolic substances) are potent inducers of apoptosis in human mammary tumor cells [41,42].

Summary of findings on black cohosh

Only a few randomized, placebo-controlled clinical trials have investigated the efficacy of extracts of black cohosh to control menopausal symptoms. Furthermore, only the main indication, menopausal complaints, was tested as an endpoint, mostly using complex questionnaires such as the KI or the MRS. Most of these trials demonstrated significant symptom improvement compared with placebo. However, its mode of action remains largely unknown. In the light of recent, mainly preclinical, findings, the suggested systemic 'estrogen-like' effect can no longer be sustained. Most of the properties of black cohosh in pharmacological and clinical settings might be explained by the concomitant presence of ER-mediated, but mixed (i.e. tissue-selective) agonistic and antagonistic properties, and by its central nervous actions, which could be receptor-mediated or of a receptor-modulatory type (e.g. involving serotonin, γ amino butyric acid and dopamine receptors) (Figure 2).

Practical conclusions

Epidemiological data obtained in Asia indicate that a phytoestrogen-rich diet has a beneficial effect on the severity and composition of postmenopausal symptoms. Frequent intake of isoflavones, especially during the prepubertal years, and in their natural form as soy nutrients, diminishes circulating levels of sex hormones and might thus contribute to this beneficial effect and also to the reduced incidence of hormone-dependent tumors later in life (Box 3). Low caloric dietary patterns causing late onset of menarche, in addition to multiparity, younger age at first delivery, prolonged breastfeeding episodes, lifelong reduced hormone levels and hereditary factors are also of considerable importance in explaining the different incidences of ovarian, breast, endometrial, and prostate cancer, and might also explain, in part, the lower incidence of menopausal symptoms in Asian compared with Caucasian populations (Box 3).

Randomized clinical trials that tested the efficacy of isoflavones in the treatment of menopausal symptoms produced mostly negative results. Many other issues,

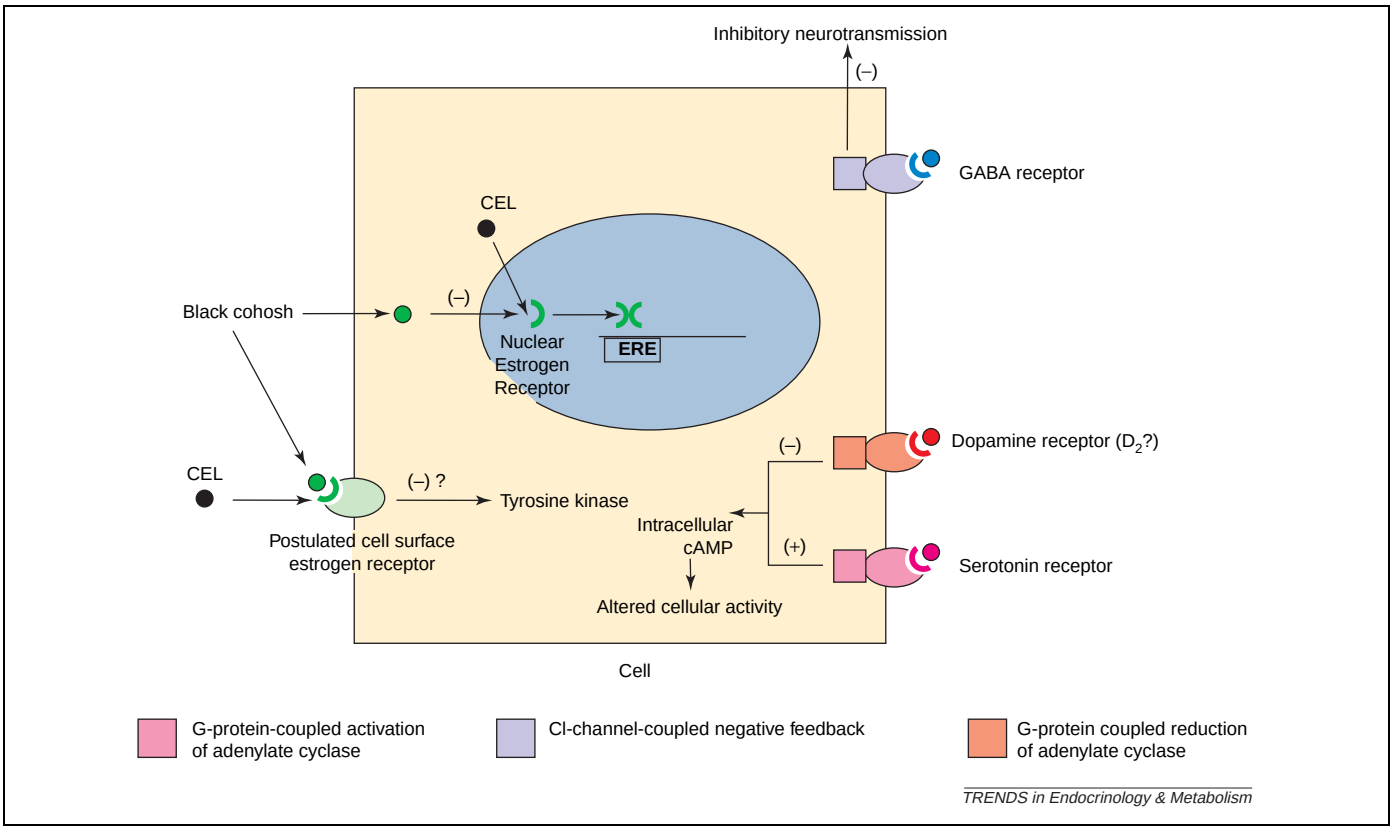

Figure 2. The effect of black cohosh on cell function has two distinct putative pathways. On the left-hand side of the figure, estrogen receptor-mediated effects depend on competing residual endogenous estrogen. In contrast to phytoestrogens, so far, only competitive inhibitory effects have been observed; no agonistic function under estrogen-free conditions has been found. In addition, on the right-hand side of the figure, neuroreceptors, such as serotonin, GABA or dopamine receptors, are further targets for black cohosh extracts. Agonistic, cAMP-increasing and/or -decreasing effects have been described, possibly exerting anti-depressive or anxiolytic effects or influencing the diurnal rhythm. These might account for the effect of black cohosh on vasomotoric and psychic disorders. CEL, competing estrogenic ligand; ERE, estrogen-responsive element; GABA, γ amino butyric acid.

especially mammary safety, remain unaddressed. This is probably a result of the short history of phytoestrogen concentrates as treatment alternatives. Therefore, today's knowledge about soy and red clover extracts and isolated isoflavones does not refute the British Medical Journal's editorial of 2001, which stated that there are no conclusive data available showing that phytoestrogens are better for the treatment of menopausal symptoms than placebo [43].

Successful treatment of climacteric complaints with standardized extracts of black cohosh has been verified in recent double-blind, randomized clinical trials, either placebo-controlled or designed as a controlled dose-finding study [37,38] (Table 2).

In patients with an estrogen-responsive tumor (e.g. breast or endometrial cancer), treatment of menopausal symptoms with soy or isoflavones might have

Table 2. Evidence for effects of phytoestrogenic isoflavones and black cohosh during the peri- and post-menopausal phases

Organ system	Effect	Evidence level	Consequence	Refs
Phytoestrogens				
Breast	Antagonizes tamoxifen	*In vitro* experiment	Caution	[49]
	Antagonizes tamoxifen	Animal study	Caution	[50]
Climacteric symptoms	None	Double-blind, randomized, crossover clinical trial	None	[31]
	No significant influence	Randomized clinical trial	None	[13]
	No significant influence	Randomized clinical trial	None	[15]
	No significant influence	Randomized clinical trial	None	[51]
	Significant improvement	Randomized clinical trial	Significantly increased 17β-estradiol levels in the soy group caused concern	[52]
	No significant influence	Randomized clinical trial	None	[53]
	No significant influence	Randomized clinical trial	None	[54]
	Significant improvement	Randomized clinical trial	Promising	[55]
Black cohosh				
Bone metabolism	Significant improvement	Randomized clinical trial	Promising	[37]
Climacteric symptoms	Significant improvement	Randomized clinical trial	Promising	[40]
	Improvement	Randomized clinical trial	Promising	[37]
	No overall significant influence	Randomized clinical trial	Problematic concomitant tamoxifen treatment	[39]

detrimental side effects, as stated in a recommendations bulletin issued by the American College of Obstetricians and Gynecologists in June 2001 (http://www.acog.org/from_home/publications/misc/pb028.htm). No analogous action has yet been directed against black cohosh therapy. Other peri- and post-menopausal symptoms, such as osteoporosis, urogenital complaints or cardiovascular disease, have been suggested to be modulated by both phytoestrogens and black cohosh extracts. However, because most of the data come from either laboratory experiments or animal trials, their use in humans for these indications has to be evaluated in placebo-controlled clinical trials. In addition, larger trials in high-risk (e.g. breast cancer) patients with a special emphasis on early markers of disease progression or with a focus on long-term consequences, such as deep vein thrombosis or stroke, are recommended.

For the sake of clarity in future discussions, terminology should mirror the profound differences between classic phytoestrogens (isoflavones, being the most intensely tested and the prime example) and extracts of black cohosh. Therefore, extracts of black cohosh or their isolated compounds should not be termed phytoestrogens. GCP-compliant, especially long-term safety-oriented, human clinical trials are urgently needed to differentiate further between two substance classes that have – apart from their target populations – not much in common.

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References

1 Writing Group for the Women's Health Initiative Investigators. (2002) Risks and benefits of estrogen plus progestin in healthy postmenopausal women. *JAMA* 288, 321–333
2 Beral, V. (2003) Million Women Study Collaborators. Breast cancer and hormone-replacement therapy in the Million Women Study. *Lancet* 362, 419–427
3 Cos, P. *et al*. (2003) Phytoestrogens: recent developments. *Planta Med.* 69, 589–599
4 Zierau, O. *et al*. (2002) Antiestrogenic activities of *Cimicifuga racemosa* extracts. *J. Steroid Biochem. Mol. Biol.* 80, 125–130
5 Bodinet, C. and Freudenstein, J. (2002) Influence of *Cimicifuga racemosa* on the proliferation of estrogen receptor-positive human breast cancer cells. *Breast Cancer Res. Treat.* 76, 1–10
6 Dixon-Shanies, D. and Shaikh, N. (1999) Growth inhibition of human breast cancer cells by herbs and phytoestrogens. *Oncol. Rep.* 6, 1383–1387
7 Jarry, H. *et al*. (2003) *In vitro* effects of the *Cimicifuga raceomosa* extract BNO 1055. *Maturitas* 44, S31–S38
8 Borrelli, F. and Ernst, E. (2002) *Cimicifuga racemosa*: a systematic review of its clinical efficacy. *Eur. J. Clin. Pharmacol.* 58, 235–241
9 Commission E of the German Federal Health Bureau. (1989) Monography *Cimicifugae racemosae* rhizoma. *Bundesanzeiger*, 43
10 World Health Organization (2002) Rhizoma *Cimicifugae racemosae*. In *WHO Monographs on Selected Medicinal Plants* (Vol. 2), World Health Organization
11 Benassayag, C. *et al*. (2002) Phytoestrogens as modulators of steroid action in target cells. *J. Chromatogr. B Analyt. Technol. Biomed. Life Sci.* 777, 233–248
12 Kronenberg, F. and Fugh-Berman, A. (2002) Complementary and alternative medicine for menopausal symptoms: a review of randomised, controlled trials. *Ann. Intern. Med.* 137, 805–813
13 Nikander, E. *et al*. (2003) A randomized placebo-controlled crossover trial with phytoestrogens in treatment of menopause in breast cancer patients. *Obstet. Gynecol.* 101, 1213–1220
14 Tice, J.A. *et al*. (2003) Phytoestrogen supplements for the treatment of hot flashes: the isoflavone clover extract (ICE) study: a randomized controlled trial. *JAMA* 290, 207–214
15 Penotti, M. *et al*. (2003) Effect of soy-derived isoflavones on hot flushes, endometrial thickness, and the pulsatility index of the uterine and cerebral arteries. *Fertil. Steril.* 79, 1112–1117
16 Burke, B.E. *et al*. (2002) Randomized, controlled trial of phytoestrogen in the prophylactic treatment of menstrual migraine. *Biomed. Pharmacother.* 56, 283–288
17 Wagner, J.D. *et al*. (2003) Soy protein with isoflavones, but not an isoflavon-rich supplement, improves arterial low-density lipoprotein metabolism and atherogenesis. *Arterioscler. Thromb. Vasc. Biol.* 23, 2241–2246
18 Kritz-Silverstein, D. *et al*. (2003) Isoflavones and cognitive function in older women: the SOy and Postmenopausal Health In Aging (SOPHIA) Study. *Menopause* 10, 196–202
19 Hochanadel, G. *et al*. (1999) Phytoestrogens in the treatment of the cognitive and somatic symptoms of menopause. *J. Neuropsychiatry Clin. Neurosci.* 11, 131
20 White, L.R. *et al*. (2000) Brain aging and midlife tofu consumption. *J. Am. Coll. Nutr.* 19, 242–255
21 Shumaker, S.A. *et al*. (2003) Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. *JAMA* 289, 2651–2662
22 Potter, S.M. *et al*. (1998) Soy protein and isoflavones: their effects on blood lipids and bone density in postmenopausal women. *Am. J. Clin. Nutr.* 68, 1375S–1379S
23 Wangen, K.E. *et al*. (2000) Effects of soy isoflavones on markers of bone turnover in premenopausal and postmenopausal women. *J. Clin. Endocrinol. Metab.* 85, 3043–3048
24 Nikander, E. *et al*. (2004) Effects of phytoestrogens on bone turnover in postmenopausal women with a history of breast cancer. *J. Clin. Endocrinol. Metab.* 89, 1207–1212
25 Clifton-Bligh, P.B. *et al*. (2001) The effect of isoflavones extracted from red clover (Rimostil) and bone metabolism. *Menopause* 8, 259–265
26 Gallagher, J.C. *et al*. (2000) Effect of soy protein on bone metabolism. *J. Nutr.* 130, 667S
27 Mackey, R. and Eden, J. (1998) Phytoestrogens and the menopause. *Climacteric* 1, 302–308
28 Hilakivi-Clarke, L. *et al*. (1999) The influence of maternal diet on breast cancer risk among female offspring. *Nutrition* 15, 392–401
29 Jenkins, D.J.A. *et al*. (2002) Effects of high- and low-isoflavone (phytoestrogen) soy foods on inflammatory biomarkers and proinflammatory cytokines in middle-aged men and women. *Metabolism* 51, 919–924
30 Burton, J.L. and Wells, M. (2002) The effect of phytoestrogens on the female genital tract. *J. Clin. Pathol.* 55, 401–407
31 Dalais, F.S. *et al*. (1998) Effects of dietary phytoestrogens in postmenopausal women. *Climacteric* 1, 124–129
32 Balk, J.L. *et al*. (2002) A pilot study of the effects of phytoestrogen supplementation on postmenopausal endometrium. *J. Soc. Gynecol. Investig.* 9, 238–242
33 Unfer, V. *et al*. (2004) Endometrial effects of long-term treatment with phytoestrogens: a randomized, double-blind, placebo-controlled study. *Fertil. Steril.* 82, 145–148
34 Simons, L.A. *et al*. (2000) Phytoestrogens do not influence lipoprotein levels or endothelial function in healthy, postmenopausal women. *Am. J. Cardiol.* 85, 1297–1301
35 Liu, W. *et al*. (1998) Effects of genistein on aggregation and cytosolic free calcium in pig platelets. *Zhongguo Yao Li Xue Bao* 19, 540–542
36 Nestel, P.J. *et al*. (1999) Isoflavones from red clover improve systemic arterial compliance but not plasma lipids in menopausal women. *J. Clin. Endocrinol. Metab.* 84, 895–898
37 Wuttke, W. *et al*. (2003) The Cimicifuga preparation BNO 1055 vs. conjugated estrogens in a double-blind placebo-controlled study: effects on menopause symptoms and bone markers. *Maturitas* 44, S67–S77
38 Liske, E. *et al*. (2002) Physiological investigation of a unique extract of black cohosh (*Cimicifugae racemosae* rhizoma): a 6-month clinical study demonstrates no systemic estrogenic effect. *J. Womens Health Gend. Based Med.* 11, 163–174

39 Jacobson, J.S. *et al*. (2001) Randomized trial of black cohosh for the treatment of hot flashes among women with a history of breast cancer. *J. Clin. Oncol.* 19, 2739–2745
40 Osmers, R. *et al*. (2005) Efficacy and safety of isopropanolic black cohosh extract for climacteric symptoms. *Obstet Gynecol.* 105, 1074–1083
41 Hostanska, K. *et al*. (2004) *Cimicifuga racemosa* extract inhibits proliferation of estrogen receptor-positive and -negative human breast carcinoma cell lines by induction of apoptosis. *Breast Cancer Res. Treat.* 84, 151–160
42 Hostanska, K. *et al*. (2004) Evaluation of cell death caused by triterpene glycosides and phenolic substances from *Cimicifuga racemosa* extract in human MCF-7 breast cancer cells. *Biol. Pharm. Bull.* 27, 1970–1975
43 Davis, S.R. (2001) Phytoestrogen therapy for menopausal symptoms? *Br. Med. J.* 323, 354–355
44 Burdette, J.E. *et al*. (2003) Black cohosh acts as a mixed competitive ligand and partial agonist of the serotonin receptor. *J. Agric. Food Chem.* 51, 5661–5670
45 Seidlova-Wuttke, D. *et al*. (2003) Evidence for selective estrogen receptor modulator activity in a black cohosh (*Cimicifuga racemosa*) extract: comparison with estradiol-17β. *Eur. J. Endocrinol.* 149, 351–362
46 Allred, C.D. *et al*. (2004) Dietary genistein results in larger MNU-induced, estrogen-dependent mammary tumors following ovariectomy of Sprague-Dawley rats. *Carcinogenesis* 25, 211–218
47 Setchell, K.D.R. and Lydeking-Olsen, E. (2003) Dietary phytoestrogens and their effect on bone: evidence from *in vitro* and *in vivo*, human observational, and dietary intervention studies. *Am. J. Clin. Nutr.* 78, 593S–609S
48 Viereck, V. *et al*. (2002) Phytoestrogen genistein stimulates the production of osteoprotegerin by human trabecular osteoblasts. *J. Cell. Biochem.* 84, 725–735
49 Jones, J.L. *et al*. (2002) Genistein inhibits tamoxifen effects on cell proliferation and cell cycle arrest in T47D breast cancer cells. *Am. Surg.* 68, 575–577
50 Ju, Y.H. *et al*. (2002) Dietary genistein negates the inhibitory effect of tamoxifen on growth of estrogen-dependent human breast cancer (MCF-7) cells implanted in athymic mice. *Cancer Res.* 62, 2474–2477
51 Van Patten, C.L. *et al*. (2002) Effect of soy phytoestrogens on hot flashes in postmenopausal women with breast cancer: a randomized, controlled clinical trial. *J. Clin. Oncol.* 20, 1449–1455
52 Han, K.K. *et al*. (2002) Benefits of soy isoflavone therapeutic regimen on menopausal symptoms. *Obstet. Gynecol.* 99, 389–394
53 Burke, G.L. *et al*. (2003) Soy protein and isoflavone effects on vasomotor symptoms in peri- and postmenopausal women: the soy estrogen alternative study. *Menopause* 10, 147–153
54 Knight, D.C. *et al*. (2001) Effects on menopausal symptoms and acceptability of isoflavone containing soy powder dietary supplementation. *Climacteric* 4, 13–18
55 Faure, E.D. *et al*. (2002) Effects of a standardized soy extract on hot flushes: a multicenter, double-blind, randomized, placebo-controlled study. *Menopause* 9, 329–334
56 Lamartiniere, C.A. *et al*. (1998) Genistein alters the ontogeny of mammary gland development and protects against chemically-induced mammary cancer in rats. *Proc. Soc. Exp. Biol. Med.* 217, 358–364
57 Cotroneo, M.S. *et al*. (2002) Genistein action in the prepubertal mammary gland in a chemoprevention model. *Carcinogenesis* 23, 1467–1474
58 Cabanes, A. *et al*. (2004) Prepubertal estradiol and genistein exposures up-regulate BRCA1 mRNA and reduce mammary tumorigenesis. *Carcinogenesis* 25, 741–748
59 Collaborative Group on Hormonal Factors in Breast Cancer. (2001) Familial breast cancer: collaborative reanalysis of individual data from 52 epidemiological studies including 58 209 women with breast cancer and 101 986 women without the disease. *Lancet* 358, 1389–1399