ance of encapsulated green tea supplements.  

The choice of the green tea extract for this trial was based upon what is assumed to be beneficial in both green and black teas. As is widely known, catechins (e.g., (-)-epigallocatechin gallate [EGCG]) are the predominant flavonoids in green tea and are associated with increased antioxidant activity in the body.  

After fermentation from green tea to black tea, about 15% of catechins remain unchanged and the rest are converted to theaflavins (polyphenol pigments) and thearubins.  

Despite favorable epidemiological evidence for both green and black teas, this is the first trial to actually demonstrate that a tea extract lowers LDL-C. According to the authors, the rationale to enhance the level of theaflavin is based on a previous trial of daily consumption of 3.6 g of encapsulated green tea polyphenols in which no effect on lipids was found.  

It should be noted that this earlier trial was with smokers. Also notable is the fact that human tea-drinking trials have tested exposure to 0–35 mg of theaflavins and 50–850 mg of catechins per day, again with no significant effect on lipids. As noted by the authors, more research is needed on this new proprietary theaflavin-enriched green tea extract to better understand its potential for reducing risk of cardiovascular disease. At the time of writing, the extract was rapidly making its way into products in the U.S. market. However, more clinical trials are needed to support the positive effects of theaflavins.

Practice Implications: The Third Report of the National Cholesterol Education Program Adult Treatment panel states that diet therapy is the initial recommendation for lowering LDL-C. These guidelines have included increasing fiber and plant stanols and sterols to assist in lowering LDL-C. According to data from previous observational studies as well as trials conducted on conventional statin drugs, it is estimated that each 1% reduction in LDL-C results in approximately a 1.0% to 1.5% reduction in the relative risk of major cardiovascular events. Extrapolating the results above suggests a decreased risk of 16% to 24% with regular consumption of the theaflavin-enriched green tea extract in persons with mild to moderate hypercholesterolemia.

References:

Is Black Cohosh a Selective Estrogen Receptor Modulator?


**Summary:** In a double-blind, placebo-controlled trial, 97 peri- and postmenopausal women (40–60 years), who were experiencing at least three hot flashes per day, were randomized to receive either one tablet of 20 mg of black cohosh (*Actaea racemosa* L., Ranunculaceae; syn. *Cimicifuga racemosa* [L.] Nutt.) extract corresponding to 20 mg of the rhizome, 0.3 mg of conjugated estrogens (CE), or placebo 2 times per day for 3 months. (The final analysis contained 62 postmenopausal women; 33 perimenopausal patients were excluded from the statistical analysis as well as 2 dropouts.) The black cohosh (BC) extract used in the trial (BNO 1055, sold as Klimadyn® and Menoform®, manufactured by Bionorica AG, Neumarkt, Germany) is a dried aqueous/ethanolic extract (58%, v/v) of the rhizome (standardization specifics are not provided in the paper). The change from baseline in the Menopause Rating Scale (MRS) was the primary efficacy endpoint. Subjects completed the MRS at baseline and at weeks 4, 8 and 12. The MRS covers 10 climacteric (menopausal) symptoms — hot flashes and sweating, heart palpitations, sleep disturbances, mood swings, tension and nervousness, mental fatigue and memory loss, loss of sexual drive, urinary incontinence, vaginal dryness, and joint pain. Patients were instructed to report the intensity of each symptom on a 10-point scale (0 = no symptoms, to 10 = severe symptoms). Patients were also instructed to complete a diary of symptoms each day, which included information on the number of hot flashes, the occurrence (intensity, duration) of vaginal bleeding episodes, and sleep disturbances. Blood samples were collected at baseline and at weeks 4, 8, and 12, and used to measure luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol, and progesterone. Additionally, the levels of CrossLaps (a marker of bone degradation) and bone-specific alkaline phosphatase (a marker for bone formation) were measured by immunoassays and enzymatic assay, respectively. At baseline and at week 12, all subjects had complete gynecological examinations, including transvaginal ultra-

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sound for determination of endometrial thickness and a vaginal smear to determine the maturity index of the vaginal epithelium.

Compared with placebo, both CE and BC were both equally effective in reducing menopausal symptoms as measured by all 10 MRS items \((P = 0.05)\) for both. For specific vasomotoric MRS symptoms of hot flashes and sweating, heart palpitations and sleep disturbances, CE showed a statistically significant difference compared to placebo \((P = 0.05)\), while BC showed a marked difference compared to placebo, but this was not statistically significant. For "psychic" symptoms including mood swings, tension and nervousness, and mental fatigue and memory loss, there was a distinct improvement in BC-treated patients compared to placebo while improvements in CE-treated patients were less obvious. However, neither was statistically significant. For MRS symptoms due to atrophic changes such as sexual problems (i.e., loss of libido), urinary incontinence, vaginal dryness and joint pain, there was a significant improvement in the BC group compared to placebo \((P = 0.02)\), while the improvement in CE was somewhat less notable than the BC group \((P = 0.05)\). From the evaluation of patient diaries, a decrease in the frequency of waking during the night at week 12 and waking up early at weeks 8 and 12 was observed in BC patients compared with patients in the placebo group (statistical analysis is not shown).

Bone specific collagen-1-alpha-1 (measured using CrossLaps) was significantly decreased compared to placebo at week 12 in the CE group \((P = 0.0181)\). While there was a slight decrease in the BC group, it did not reach statistical significance compared to placebo. Bone-specific alkaline phosphatase remained unchanged in the placebo group and CE groups but was increased significantly in the BC group at week 12 \((P = 0.0358)\). This suggests an increased activity of osteoblasts, which are responsible for bone formation. Endometrial thickness was significantly increased by CE (the lack of overlap of the Confidence Interval with the upper value of placebo-treated controls indicates that the effect of the CE were statistically significant even though the \(P\) value was not given) and remained unchanged in the BC and placebo groups. There was a significant increase in the number of vaginal superficial cells in the CE group compared to the BC group \((P = 0.01)\) and the placebo group \((P = 0.0001)\). The BC group showed a moderate increase which approached significance compared to placebo \((P = 0.0542)\). There was a slight decrease in the number of superficial cells in the placebo group. The incidence of adverse events was similar in all three groups (these are not specifically listed in the paper). Triglyceride levels were slightly elevated in both the CE and BC groups at the end of the trial. The paper does not report any findings regarding LH, FSH, estradiol, or progesterone.

Comments/Opinions: Based on a clinical trial’s finding no effect of BC extract on concentrations of estradiol, LH, FSH, vaginal cytology, and endometrial thickness, many researchers and reviewers have suggested that BC has no systemic estrogenic actions.\(^1\) The lack of effect for BC on LH and FSH was also noted in another clinical trial with women suffering from hot flashes with a history of breast cancer.\(^2\) Both of these trials as well as the majority of earlier clinical work on BC for hot flashes have been completed using the standardized BC extract Remifemin\(^R\) (manufactured by Schaper and Brümmer GmbH & Co., Salzgitter, Germany, licensed to GlaxoSmithKline for U.S. sales).\(^3\)

The clinical trial summarized above is one of several papers on BC presented at a conference sponsored by Biointegra AG entitled "Modern Phytotherapy in Menopause: Cnicifusia racemosa (Klimadynon, Menofem) Pharmacological and Clinical Data (June 10, 2002, Berlin). The proceedings are published in a supplemental issue of Maturitas, the official journal of the European Menopause and Andropause Society <www.womenshealthelsevier.com/doc/journals/maturitas.html>, and add a new dimension to the knowledge base about BC — namely, that the rhizome extract may be acting as a selective estrogen receptor modulator (SERM). The constituents of BC might resemble the actions of a phyto-SERM, as hypothesized earlier.\(^4\)

SERM is a relatively new concept in the spectrum of women's healthcare.\(^5\) The term has been used to describe tissue-specific effects depending on estrogen receptor (ER) distributions on target organs, and is the basis of action for the drug raloxifene (Evista\(^R\), Eli Lilly and Company, Indianapolis, Indiana). Raloxifene has been shown to have estrogenic effects on the bones and on lipid metabolism, but not on the uterus and breasts.\(^6\) The drug is currently being marketed heavily to postmenopausal women as an alternative to hormone replacement therapy (HRT) for prevention and treatment of osteoporosis. Extending the SERM label to BC suggests desired estrogenic effects in the hypothalamus, mesolimbic brain regions, bone, cardiovascular system, and vaginal epithelium without these effects in the uterus or breasts.

A rat and mouse study presented in 1996 in Maturitas was apparently one of the first indicators that BC may have SERM activities.\(^7\) It was demonstrated that BC had no vaginotrophic effects, producing no uterine growth or vaginal epithelium growth. At the Berlin conference, an ovariec-tomized (ovaries removed) rat study showed that the BN1055 extract exhibited estrogenic effects in the hypothalamus, bone (particularly in osteoblasts), and vagina but not in the uterus.\(^8\) The same study found no effect on gene expression of 17\(^\beta\)-estradiol-regulated genes. A recent publication gives further evidence on the beneficial effects on the bone metabolism in the rat model.\(^9\)

An in vitro study found that BC does not stimulate prolifera-tion or estrogen-dependent breast cancer cells (MCF-7) and actually was found to enhance the proliferation-inhibiting effect of tamoxifen.\(^10\) The authors of this trial (from Schaper and Brümmer GmbH & Co.) discuss BC's contradictory estrogen-agonistic as well as estrogen-antagonistic effects and how this may relate to the "phyto-SERM theory." (One HerbalGram reviewer noted that while this discussion of the tissue-selective, SERM-like effects is appropriate, the lack of molecular-level evidence [i.e., estrogen receptor binding] for black cohosh constituents warrants caution in extending the SERM label to BC at this time.) Obviously, further studies will be needed before the SERM label can be applied to BC.

There are some shortcomings of the trial: it does not state sample size estimation, exclusion criteria, number of centers or compliance rate. Further, no adverse events are listed followed by a discussion of which adverse events might be linked to the investigational products. Almost one-third of the randomized patient population were excluded from the ITT-collective; this might have implications on the validity of the study as well as tolerabil-
ity of the products tested. The scale used for measuring the efficacy was MRS I: this scale was created and validated as a tool for doctors, not patients. However, in the study this scale has been rated by the patient. Regarding the change from baseline, the MRS I score was equal in all 3 groups, indicating no benefits for CE and BNO 1055 in comparison to placebo.

While BC shows improvement of the overall symptom complex comparable to CE, one of the potential shortcomings of BC in the clinical trial reviewed above (i.e., Wurtke et al.) is in the relief of vasomotor symptoms such as hot flashes. As women continue to seek alternatives to HRT, it is imperative that companies sponsoring BC research sponsor more trials to demonstrate efficacy and tolerability in this arena. On the other hand, BC shows marked improvements in a wider area of symptoms than CE that warrants BC its own position independent from CE as treatment option. A recent paper has been published documenting the general safety of BC.9 Monographs from the German Commission E,10 World Health Organization,11 and the recent one from the European Scientific Cooperative on Phytotherapy,12 state the primary indication for BC as a treatment for climacteric /menopausal symptoms. While concerns about postmenopausal bone and cardiovascular health are now extended to alternative therapies such as soy bean (Glycine max (L.) Merr., Fabaceae)14 and red clover (Trifolium pratense L., Fabaceae) isoflavones as well as BC, inconsistency in managing vasomotor symptoms will severely affect patients' compliance with these products. Hopefully, future clinical trials will also seek dosages of BC that are likely to improve bone and cardiovascular health in postmenopausal women.

Practice Implications: Questions continue as to whether BC is a phytoestrogen with mild estrogenic actions or is devoid of any estrogenic activity. While earlier studies from Germany and the United States failed to find an effect of BC on serum estradiol, LH, or FSH levels, and no effect on endometrial thickness as well as vaginal cytology was observed, they did not look at markers of bone resorption (the process of bone formation) nor at superficial cells in the vagina. The results of this trial suggest that BC might have a mild effect on increasing vaginal superficial cells, however, not statistically significant to placebo. Also noteworthy were the increased levels of serum alkaline phosphatase — an indicator of increased osteoblast activity. The experimental pharmacological results as well as the above-mentioned clinical actions, together with the reported decrease (albeit not statistically significant) in MRS symptoms (e.g., depression, impaired memory, vaginal dryness, urinary symptoms), lead the investigators to conclude that BC contains substances with SERM activity that exert desired effects in the hypothalamus, the mesolimbic brain regions, and bones, without estrogenic actions in the uterus and vaginal cytology. Future trials with larger populations of postmenopausal women and longer duration are needed to confirm their conclusions. A recently published 6-month trial demonstrated no systemic estrogenic effects even for a high dose of 127 mg daily of a crude BC rhizome in which hormone levels and vaginal cytology were analyzed on a daily basis.1