New fermented soy ingredient containing S-equol significantly reduced hot flash frequency

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Daily doses of a soy germ-based nutritional supplement containing S-equol significantly improved menopausal symptoms, including significantly reducing hot flash frequency after 12 weeks according to a placebo-controlled study in postmenopausal Japanese women published in the peer-reviewed *Journal of Women's Health*.

"It is believed that S-equol, produced from the isoflavone daidzein during the fermentation of soy germ, interacts with specific estrogen receptors to promote the improvement in menopausal symptoms. Data from this study and other clinical studies, including those done in U.S. women, shows that the supplement SE5-OH containing S-equol may serve as a promising alternative for reducing the frequency of hot flashes and perhaps other menopausal symptoms," said Belinda H. Jenks, Ph.D., director of Scientific Affairs & Nutrition Education at Pharmavite LLC, the makers of NatureMade® vitamins and minerals.

In the double-blind, randomized study, the daily frequency of the women's hot flashes after 12 weeks of treatment decreased by 58.7 percent (-1.9 ± 1.8 daily compared to 3.2 ± 2.4 daily at the study start) for the 66 women receiving a daily dose of 10 milligrams (mg) of S-equol contained in SE5-OH , significantly more than the 34.5 percent reduction (-1.0 ± 2.0 daily vs. 2.9 ± 2.1 daily at study start) experienced by the 60 women receiving a placebo (P=0.009). Of the 34 women who enrolled with at least three hot flashes daily, the women receiving

SE5-OH had a 62.8 percent reduction in their daily hot flash frequency (-2.9 ± 2.0), significantly greater than 23.6 percent reduction experienced by the 28 women in the placebo group (-1.2 ± 2.9) (P=0.009).

Moreover, the women in the SE5-OH with S-equol group experienced significant decreases in the severity of their hot flashes (P=0.012), as measured by the Climacteric Symptom Evaluation Form Checklist, which measured the severity of 22 menopausal symptoms as well as the hot flash frequency. The women recorded the severity of their menopausal symptoms in a diary at the study start, and at the end of the treatment (week 12) using a four-point scale (0: none, 1: mild, 2: moderate and 3: severe). A decrease in a symptom score of one or more points was classified as an improvement.

The women receiving SE5-OH with S-equol had significant improvements in the severity of their neck or shoulder muscle stiffness scores compared to those in the placebo group (P=0.004). Of note, women in Japan in general experience fewer hot flashes but experience more neck and shoulder stiffness than women in the United States.

The severity of hot flashes, sweating, sleeplessness, depression, and neck or shoulder muscle stiffness, were measured by the validated assessment tool, the Visual Analog Scale(VAS). The VAS indicated a significant decrease in neck and shoulder stiffness for women receiving SE5-OH with S-equol compared to those in the placebo group (-11.9 ± 26.7 mm vs. -1.6 ± 17.1 mm, P=0.007). Also, scores on the sub-scales of the Greene Climacteric Scale revealed a significant difference on the somatic subscale in the SE5-OH group compared to the placebo group (P=0.043) and a strong positive trend on the vasomotor subscale score the SE5-OH group, compared to the placebo group (P=0.052). The women also rated their quality of life using a standardized Short Form 36 Health Survey, its general health perception scale scoring trended

positively toward improvement in the SE5-OH containing S-equol group compared to the placebo group (P=0.090).

The trial also evaluated safety and adverse treatment-related effects. No adverse events were reported in this study and the supplement was well tolerated. The use of SE5-OH containing S-equol showed no serious treatment-related adverse effects on the women's hormones including sex hormones, gonadal, and thyroid hormones, which is in agreement with the results of other clinical trials of SE5-OH containing S-equol.

Because the large placebo effect typically observed in clinical trials of hot flashes often complicates interpretation of results, this trial included a four-week placebo run-in period. Participants reported the severity of their symptoms as well as their frequency of hot flashes at both the start and end of the run-in period, and those who had less than one hot flash per day, low menopause symptom scores or a positive placebo response were excluded from the study, as were women who were S-equol producers.

S-equol [7-hydroxy-3-(4'-hydroxyphenyl)-chroman] is a compound resulting -- when certain bacteria are present in the digestive tract -- from the natural metabolism, or conversion, of daidzein, an isoflavone found in whole soybeans. Not everyone can produce S-equol after soy consumption, as the production depends on the types of bacteria present in the large intestine and may be influenced by the amount of soy consumed. About 50 percent of Asians and 20 to 30 percent of North Americans and Europeans, who in general consume less soy than Asians, have the ability to produce high levels of S-equol.

The trial, a randomized, double-blind, placebo-controlled, parallel-group study, enrolled 160 post-menopausal Japanese women aged 45 to 60 years, all of whom were S-equol non-producers. The enrolled women did not take hormonal drugs or menopause symptom treatments. The

postmenopausal enrollment criteria included estrogen levels of less than 21 picograms per milliliter (ml), follicle stimulating hormone (FSH) values greater than 30 milli international units (mIU)/ml, a minimum of one hot flash daily, body mass index between 18.6 and 25 and S-equol non-producer status, based on results of a soy challenge test during the screening period.

The trial used supplement tablets which each contained 5 mg of S-equol, and the trial participants took one tablet twice daily. SE5-OH is the product of fermentation of soy germ by the bacterial strain Lactococcus 20-92 using a patented and proprietary process by the Otsuka Pharmaceutical Co., Ltd. The process results in the conversion of the daidzein to S-equol. SE5-OH is created under current Good Manufacturing Practices. Following fermentation, the bacteria undergo heat denaturation and are deactivated. The process is designed to produce a S-equol-rich product, or nutraceutical ingredient. The ingredient has self-affirmed GRAS (Generally Recognized As Safe) status. Development and ongoing research of SE5-OH containing S-equol is conducted by the Saga Nutraceuticals Research Institute of Otsuka Pharmaceutical Co., Ltd. Pharmavite, a subsidiary of Otsuka, is studying SE5-OH containing S-equol as a dietary supplement for the management of menopausal symptoms.

Otsuka Pharmaceutical Co. Ltd. supported the study. The study data were presented in an oral presentation at the North American Menopause Society annual meeting in October 2009.

Preliminary evidence from other, observational studies suggests that Japanese women who produce S-equol naturally may have fewer menopausal symptoms. Controlled clinical trials have documented that SE5-OH containing S-equol reduces the frequency of hot flashes as well as muscle discomfort associated with menopause, both in women in Japan and the United States.

S-equol binds to the same estrogen receptors as naturally occurring estrogen, but with a stronger affinity for the estrogen beta receptor. On binding to these receptors, S-equol mimics some, but not all, activities of estrogen. The safety of SE5-OH containing S-equol previously was confirmed by standard animal testing, including a study documenting that S-equol itself, as well as SE5-OH containing S-equol, did not increase or stimulate the growth of breast cancer cells. Studies involving postmenopausal women who consumed SE5-OH containing S-equol have not observed any safety problems, including analysis of breast and reproductive tissues and of hormone levels. More information about S-equol and SE5-OH is at http://www.naturalequol.com.

More information: *Journal of Women's Health*, ahead of print. doi:10.1089/jwh.2011.2753

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