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File: ■ Ashwagandha (*Withania somnifera*)
■ Chemotherapy-induced Fatigue
■ Breast Cancer

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RE: Adjunct Treatment with Ashwagandha Root Extract for Fatigue from Chemotherapy for Breast Cancer

Biswal BM, Sulaiman SA, Ismail HC, Zakaria H, Musa KI. Effect of *Withania somnifera* (ashwagandha) on the development of chemotherapy-induced fatigue and quality of life in breast cancer patients. *Integr Cancer Ther*. November 2012; [epub ahead of print]. doi: 10.1177/1534735412464551.

Breast cancer is a common form of cancer in women; 1 in 8 women in North America develop breast cancer. Breast cancer is treated with surgery, radiotherapy, and chemotherapy, with chemotherapy drugs administered in combination and given in cycles. Among the many adverse side effects of this regimen is fatigue that is not alleviated by resting. Fatigue may be treated by exercise and psychotherapy, along with yoga, psychostimulants with adverse effects (e.g., methylphenidate), and other conventional treatments. The traditional Ayurvedic medicinal plant ashwagandha (*Withania somnifera*) has been shown to have antitumor, antidepressant, and memory- and cognitive-enhancing bioactivity; however, there have been few clinical trials to study this botanical. This open-label, prospective, non-randomized, comparative clinical trial investigated the potential of ashwagandha use for the alleviation of fatigue from chemotherapy and for improving the quality of life (QoL) in patients with breast cancer.

Patients with stage I-IV breast cancer, an Eastern Cooperative Oncology Group (ECOG) performance rating of 0 to 2 (a scale assessing the overall health of patients with cancer, where 0=full activity and 5=death), and who were candidates for chemotherapy were enrolled in the study and placed alternately in either the study or control groups. Those that had prior chemotherapy or radiation treatment; were taking psychiatric drugs; or had other mental or systemic illnesses were excluded.

Prior to each chemotherapy cycle, blood counts and liver and kidney functional assessments were taken. The ECOG performance rating was taken at baseline, as well as scores for the fatigue assessment tools (the Piper Fatigue Scale [PFS], Schwartz Cancer Fatigue Scale [SCFS-6], and the QoL measurement for patients with cancer, known as the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 [EORTC QLQ-C30]). PFS scores were also taken during the

initial day of the first, third, and sixth chemotherapy cycles; and SCFS-6 and EORTC QLQ-C30 scores were measured on the initial day of all 6 cycles.

Chemotherapy treatments were either a combination of cyclophosphamide, epirubicin, and 5-fluorouracil (CEF) or Taxotere®, Adriamycin®, and cyclophosphamide (TAC). Treatments were given intravenously every 3 weeks. Patients also took ondansetron or granisetron for nausea. Patients taking the TAC combination also took granulocyte colony-stimulating factor (G-CSF) therapeutics to alleviate the lessening of white blood cells.

Ashwagandha root extract powder was supplied by Himalaya Drug Co.; New Delhi, India. Each capsule held 500 mg; patients consumed 4 capsules 3 times per day with water, during 6 cycles of chemotherapy treatments. Some patients needed to split the dosage further throughout the day due to difficulty swallowing or gastric upset, but the total daily dosage was kept constant.

In total, the study group consisted of 50 patients who had an average age of 51 years; and the control group was made up of 50 patients who had an average age of 50.5 years. Estrogen receptor-positive (ER+) cancer was present in 54% of the study group and 56% of the control group. In addition, 48% of the study group had progesterone receptor-positive (PR+) cancer, while 50% of the control group had this form of cancer. Also, 26% of patients in the study group had cancer overexpressing human epidermal growth factor receptor 2 (HER2), while this was observed in 52% of patients in the control group. Stage II and III cancers were present in 80% of the study group versus 76% of the control group. For 72% of the study group, surgery was done as the initial therapy, while 78% of the control group had surgery first. Radiation treatment was given to 90% of those in the study group and to 88% in the control group. The TAC regimen was employed with 50% of the study group and 70% of the control group. Of the total patients, 44 patients finished all chemotherapy cycles in the study group, while 41 patients finished in the control group. Reasons for some of the dropouts included voluntary withdrawal and deaths unrelated to the study. The remaining patient dropouts are not accounted for or explained.

The SCFS-6 fatigue mean score across the study was significantly higher in the control group as compared to the study group ($P<0.003$). Also, the PFS mean scores were significantly higher in the control group than in the study group ($P<0.001$). Lower scores indicate less fatigue in both of these assessments. The mean scores of the EORTC QLQ-C30 were also significantly less in the study group for the categories of fatigue, insomnia, appetite loss, constipation, financial difficulties, and pain, as compared to the control group ($P<0.001$ to $P=0.024$), indicating a lesser degree of symptoms. The scores for the categories of physical functioning, role functioning, emotional functioning, social functioning, and global health status/QoL were significantly greater in the study group as compared to the control group ($P<0.001$ to $P<0.001$). Compliance with ashwagandha treatment was 98%; and patient complaints included "oral intolerance," gastritis, and flatulence.

In summary, those patients with cancer who were taking ashwagandha had lower degrees of fatigue and a higher QoL during chemotherapy than the patients in the control group. Ashwagandha may prove to be a beneficial adjunct treatment like other standard therapeutics for fatigue, such as exercise, in those undergoing chemotherapy. Although not addressed in this study, previous preclinical research suggests that there

are limited herb-drug interactions between ashwagandha and chemotherapy regimens that enhance drug efficacy and/or reduce adverse effects, pointing to the safety of this botanical for use in patients with cancer; this needs future confirmation.

Limitations discussed include using 2 forms of chemotherapy treatment instead of just one; enrolling patients suffering from the later stages of cancer progression; and the limited sample size. In addition, this study would have benefitted from more specific data analysis. For example, baseline and endpoint comparisons would have been helpful, and information regarding patient dropouts and the adverse side effects in the control group is missing. Also, the results of the liver and kidney functional assessments at the study's end are not mentioned, making it difficult to draw conclusions about the safety of ashwagandha. Finally, failure to adequately characterize the ashwagandha root extract used, aside from noting its manufacturer, makes extrapolation of the results impractical. In conclusion, more detailed studies are necessary to confirm the use of this botanical in relation to breast cancer treatment.

—Amy C. Keller, PhD

The American Botanical Council has chosen not to reprint the original article.