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INSIDE

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Agaricus Blazei Murrill and Cancer Prevention and Treatment

By Dónal P. O'Mathúna, PhD

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MUSHROOMS HAVE A LONG HISTORY AS MEDICINAL AGENTS. Reishi mushrooms have been recommended for thousands of years as a general health food in traditional Chinese medicine. Shiitake mushrooms have been used in Japan to stimulate the immune system. "Magic mushrooms" are known for their psychedelic effects, while "Death Cap" (*Amanita phalloides*) is a clear reminder that some mushrooms are extremely toxic. All of these attest to the potent pharmacological agents present in some mushrooms.

One particular mushroom has been attracting much attention for the prevention and treatment of cancer. About half a million people in Japan are believed to use an extract of *Agaricus blazei* Murrill mushrooms to prevent cancer or as an adjunct to chemotherapy.[1] The mushroom is sometimes abbreviated as ABM, but will be referred to here as *Agaricus*.

Herbal remedies are especially popular among cancer patients, both those undergoing chemotherapy and those on palliative care.[2] Overall, about one-third of cancer patients use complementary and alternative medicine (CAM), although definitions and patterns of use vary widely.[3] While many cancer patients use CAM along with conventional medications, awareness of the potential for herb-drug interactions is often limited. Clinicians should be aware of all the supplements being used by patients, especially newer remedies that are growing in popularity, like *Agaricus*.

Background

The *Agaricus* mushroom came to popular attention in Brazil, where its common name means "mushroom of God" or "mushroom of life."[4] Japanese researchers brought it to Japan in the 1960s where it is called Himematsutake. It was identified as a new species and given the scientific name, *Agaricus blazei* Murrill. However,

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controversy exists as to whether it is a distinct species or is the once-popular *Agaricus* subrufescens.[5] This species was widely cultivated and sold in the Eastern United States until early in the twentieth century when it was replaced by the edible button mushroom.

Regardless of debate over its scientific name, *Agaricus* has developed a reputation for treating cancer and other diseases that has made it one of the most widely used medicinal mushrooms in Asia and South America. Surveys of Japanese patients with urological cancer have found that the most commonly used form of CAM is "health food," which includes *Agaricus*.[6] A similar survey of Japanese breast cancer patients found that *Agaricus* was the most popular nutritional supplement.[7] A recent survey of cancer patients in Norway found that *Agaricus* was one of the most popular supplements used to "fight cancer generally."[2] Word of this interest is making its way to the US and Europe where web and mass media advertising are marketing *Agaricus* dietary supplements with claims that often exceed any clinically demonstrated benefit for patients.[4]

Mechanism of Action

Extracts of *Agaricus* contain a variety of polysaccharides which are believed to be the source of anticancer activity. Foremost among these compounds are glucans, in particular a range of alpha-glucans and beta-glucans.[4] These polysaccharides contain long chains of branching sugars that interact in different ways with various receptors on cell surfaces, triggering other biochemical responses.

In vitro and animal studies have shown that various components of *Agaricus* extracts have direct anticancer activity, antimutagenic effects, and immunostimulating effects.[8] Antiangiogenic substances have also been isolated from *Agaricus*.[1] The different compounds may have additive or synergistic effects in the prevention or treatment of cancer. However, few details are known regarding the specific mechanism of action for the compounds isolated. Also, the yield and structure of glucans in any one *Agaricus* extract can vary considerably depending on the stage of maturity of the mushrooms when they were harvested. Such details are rarely reported in articles on the extracts, making it difficult to determine which extracts and ingredients are most active.[4]

Clinical Studies

While several surveys have reported on the widespread popularity of *Agaricus* among cancer patients, only one clinical trial with cancer patients was located. One hundred patients receiving chemotherapy for various gynecological cancers were recruited in South Korea.[8] All patients received either carboplatin plus etoposide or carboplatin plus taxol every three weeks for three cycles. The participants were randomly assigned to receive either a Japanese commercial *Agaricus* extract or placebo, each taken orally three times daily. The study was conducted in a double-blind fashion. Blood was withdrawn and analyzed for immunological status and the patients completed a quality of life questionnaire. A significant increase in natural killer cell activity occurred among those receiving *Agaricus* compared to placebo ($P < 0.05$). No significant differences were found in the levels of lymphokine-activated killer cells, monocytes, white blood cells, lymphocytes, or monocytes. The quality of life questionnaires demonstrated significant improvements for those taking *Agaricus* in the area of appetite, nausea and vomiting, insomnia, body strength, and mental stability.

Adverse Effects

Agaricus extracts are generally considered safe. In a clinical trial of diabetic patients, three of the 29 who received *Agaricus* for 12 weeks experienced hypoglycemic-like symptoms and two developed skin itching.[9] In a pilot study involving four hepatitis patients, one year of treatment with *Agaricus* produced neither major nor minor adverse effects.[10] However, three case reports have been published in which patients with previously treated ovarian or breast cancer developed severe liver dysfunction.[3] All three were taking *Agaricus* extracts and no other conventional or complementary drugs. These reports do not establish a direct causal connection, although one patient's liver function

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improved when she stopped taking *Agaricus* and deteriorated when she started taking the extract again.

Formulation

A variety of *Agaricus* extracts are commercially available with variable amounts of active ingredients. No information is available on the effectiveness of different formulations or doses. The clinical trial described above used a Japanese product available in packs which are dissolved in water.[8] Subjects took one pack three times daily. Surveys have found that most people take one pack daily.[11]

Conclusion

Agaricus extracts have an interesting profile of biologically active compounds. Many of these have been shown to have some potential in helping patients with cancer. The finding that the mushrooms contain compounds which could act against cancer by a variety of different mechanisms is particularly interesting. However, only one clinical study using *Agaricus* in cancer patients could be found, making it impossible to provide evidence-based conclusions to inform practice.

Recommendation

The widespread popular use of *Agaricus* extract, in Japan in particular, should not be taken to demonstrate its effectiveness. Given the almost complete lack of clinical research, cancer patients should be cautioned against its use. The three cases of liver dysfunction in previously treated cancer patients are particularly concerning. While *Agaricus blazei* holds out much potential as a source of chemotherapeutic agents, much more basic and clinical research is needed before the extracts can be recommended to cancer patients. ❖

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Mindfulness Meditation and 'Normal Stress'

By Howell Sasser, PhD

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SURVEY RESEARCH CONFIRMS THE INTUITIVE sense that stress is a common problem even among comparatively healthy people. In the interviews that formed the basis for the American Psychological Association's 2007 report, "Stress in America," 79% of respondents agreed that stress was a "fact of life," and nearly half reported having at least some highly stressful days every month.[1] Similar proportions reported that stress had an impact on their emotional or physical well-being.

An article published in the April 2008 issue of *Alternative Medicine Alert* looked at some of the recent research on the use of mindfulness meditation as a tool for coping with the stress and other consequences of serious illness.[2] Most of this literature reports work with cancer patients and survivors, although other conditions have sometimes been included. While primary care clinicians certainly see patients with life-threatening and life-altering acute and chronic illnesses, they also see many others who are generally well but feel the effects of stress in their day-to-day lives. If this technique, used successfully by many patients with major stressors, were also shown to be effective in those with "sub-acute" stress, this would provide a resource to aid in the important task of day-to-day coping.

Mindfulness meditation (or Mindfulness-Based Stress Reduction [MBSR]) is most accurately described as a group of practices that serve to focus the attention on the present, making the practitioner aware of his or her physical and mental state. In this way, unproductive rumination on unchangeable past events and worry about still uncertain future challenges can more easily be put into proper perspective. Although many meditative practices were originally developed to clear the mind for contemplation of the transcendent, a religious element need not be present in any specific form, indeed need not be present at all.

A Basic Pattern

Nearly all studies of mindfulness meditation refer directly or indirectly to the work of Jon Kabat-Zinn,

now an emeritus professor at the University of Massachusetts School of Medicine. Beginning in the early 1980s, in a series of journal articles and books, he described the elements that have come to be standard in many clinical mindfulness meditation programs.[3] Because the studies reviewed in this article patterned their interventions on this model, it is worth reviewing briefly the essential components of mindfulness meditation:

"Sweeping" or Body Scan. The meditator directs his or her attention to each area of the body in turn, focusing non-judgmentally on sensations and feelings. Attention is brought back periodically to breathing and relaxation.

Seated Meditation. The meditator focuses on the moment, awareness of breathing, and other perceptions. When the consciousness drifts to other thoughts, it is brought back gently to the present moment. Strong feelings or emotions are observed in a detached manner and then consciousness is again brought to the present moment. All thoughts and feelings are treated as equal, and are neither pursued nor rejected.

Hatha Yoga. Yoga postures are used to help develop mindfulness during movement, but also to reduce and reverse disuse atrophy and enhance joint range of motion. Although, as Kabat-Zinn notes, yoga is not a traditional part of mindfulness practice, the inclusion of a physical component in a program aimed at a state that often manifests in physical ways seems intuitively appealing.

Other factors considered to be important include the group format for weekly sessions, an explicitly stated expectation that the program will bring relief of symptoms, a philosophy of "non-striving" (ie, the deliberate avoidance of long-term goals to maximize present benefit), a variety of techniques offered to suit varying individual needs and styles, and individual responsibility for gains through sustained work. Since the practice is one of experiencing the moment, patients need not worry about failing to do meditation "correctly."

Kabat-Zinn developed a 10-week course of weekly 2-hour sessions. Later programs have reduced the length of the course to six to 8 weeks, and the duration of the individual sessions to 60 to 90 minutes.

Evidence Base

Far less research has been published with healthy participants as compared with those who are clinically ill. Most studies have been small, most likely because of the time and attention required for proper implementation of the intervention. No study has attempted to incorporate blinding or masking. Clearly, it would be impractical to keep participants naïve as to their treatment assignment, but a level of sophistication that is still lacking in the available literature would be some attempt to introduce blinded evaluation of outcomes.

Chang and colleagues recruited a group of 43 participants in a mid-career continuing education course.[4] The intervention was intensive — 150-minute sessions weekly for eight weeks, as well as a full-day retreat. In place of a control group, participants served as their own controls in a pre-post analytical design. The effect of the intervention was measured using the Pain Rating Scale (PRS) (a 10-point "Likert-like" instrument), the Positive States of Mind questionnaire (PSOM) (a 6-item instrument about healthy attitudinal habits), the Perceived Stress Scale (PSS) (a 10-item "Likert-like" questionnaire), and the Mindfulness Self Efficacy questionnaire (MSE), which assessed participants' confidence in implementing the intervention. When scores from before and after the intervention were compared, participants showed significant improvement in all the psychological dimensions (PSOM, PSS, MSE), but not in the physical (PRS). This lack of a physical effect is in contrast to the findings of studies focusing on those with chronic illnesses. The authors speculated that there might be a "floor effect," below which pain was not prominent enough to be affected.

Several other studies using more rigorous randomized designs also have been published. Oman and colleagues used advertisements and class presentations to recruit 47 college undergraduates.[5] This group was assigned randomly to a form of MBSR (N=16), another meditation-based approach called Easwaran's Eight-Point Program (EPP) (N=16), or a wait-list control group (N=15). Both the MBSR and EPP groups met weekly, 90 minutes per session, for eight weeks. Outcomes were measured in each group at baseline, at the end of the intervention, and eight weeks later. Psychological dimensions were assessed using the PSS, the Rumination and Reflection Questionnaire (RRQ) (a measure of several negative psychological and emotional states), the Heartland Forgiveness Scale (HFS) (a measure of the respondent's ability to forgive those who have hurt or disappointed him/her), and the Adult Dispositional Hope Scale (ADHS). Participants were also asked about the strength and variety of their spirituality. No questions about physical functioning or symptoms were asked. In the analysis of the study results, the authors found no significant difference in any measure between the MBSR and EPP groups, so these were combined as a global meditation group and compared with the wait-

list controls. Those in the mediation group showed positive changes in perceived stress, although interestingly, this difference was only marginally significant by the end of the intervention and continued to grow in the following eight weeks. The meditation group also showed greater improvement in forgiveness, but no significant difference in hope could be demonstrated. These outcomes did not appear to vary with participants' spirituality.

Jain et al reported another student-based study.[6] Medical, nursing, and undergraduate premedical/prehealth students were recruited. A total of 81 were randomly assigned to MBSR (N=27), another awareness-based technique called Somatic Relaxation (SR) (N=24), or to a wait-list control condition (N=30). The intervention was comparatively brief — four weeks — but the class sessions were 90 minutes in length as in other studies. Outcomes were measured with the Brief Symptom Inventory (BSI) (a 53-item measure of psychological symptoms), the PSOM, the Daily Emotion Report (DER) (a measure of distractive and ruminative thoughts associated with depression), and the Index of Core Spiritual Experiences (INSPIRIT-R). The results of the study showed significantly better scores from pre- to post-test on rumination and distraction, but the SR group showed better progress on relaxation. Both groups showed significant improvement on most measures as compared with the control group.

Two other published articles relevant to this subject have design aspects that limit their applicability to the present subject, but are worth mentioning. Moritz and colleagues recruited a group of 165 outpatients who reported moderate mood disturbance (using a Profile of Mood States (POMS) score of >40).[7] These were assigned randomly to an at-home recorded spirituality program, MBSR, or a wait-list control group. Both active interventions lasted eight weeks. The major outcomes of interest were changes in the POMS score and participants' overall assessment of their quality of life, using the SF-36 questionnaire. All groups showed improvement in both measures, but the spirituality group's changes were about twice as great as those of the MBSR group, which in turn were about twice as great as those for the control group. Grossman and colleagues conducted a meta analysis of MBSR studies.[8] The majority of the studies included involved participants with significant clinical illness, but the authors did a small sub-analysis of studies with generally healthy participants. Regrettably for the present purpose, studies of community-dwelling people were grouped for this analysis with studies of prison inmates. That aside, they found significant positive effects of MBSR on both physical and emotional well-being.

Conclusions

There appears to be moderate support for an effect of MBSR on emotional functioning and well-being in generally healthy people. Very few studies have measured the effect of MBSR on physical manifestations of stress in this population, and those that have paint an equivocal picture. This is in contrast to the literature on MBSR in those with chronic and/or life-threatening illness. As was suggested by the Chang article, this may reflect a kind of hierarchy of symptoms, but presents a challenge for the primary care clinician. If, as is often the case, a patient presents with somatic complaints as the main—or only —symptoms of stress, a recommendation of MBSR or another meditative practice may not lead to adequate relief.

Recommendations

An important guide to the clinician in recommending MBSR or related practices to a patient is a clear understanding of the patient "constructs" (the issues that led to the consultation). MBSR may be most useful for those who already have some insight into the sources and manifestations of their stress, but it may also help those who feel confused or powerless in the face of stress to (re)discover parts of themselves over which they can exercise some calming influence. MBSR's combination of optimism regarding success with an awareness that what defines success will be very individual makes it appealing as an option even for those who may be timid or skeptical. At the same time, the presence of symptoms which MBSR appears not to influence may lead to frustration and perhaps make the acceptance of subsequent therapies more difficult. For this reason, clear communication of goals and commitment between clinician and patient will be most important. ❖

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Vitamin D in The Treatment of Breast Cancer

By Maria Cayelli

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An estimated 182,460 new cases of invasive breast cancer, and approximately 40,930 breast cancer deaths (40,480 women, 450 men), are expected to occur among women in the United States during 2008.[1] While breast cancer in men is rare, breast cancer is the most frequently diagnosed cancer in women, ranking second among cancer death in women.[1] In light of this, many factors have been studied in relation to altering breast cancer risk.[2] Breast cancer is a multifactorial disease. While the cause of breast cancer is not completely understood, the major risk factors are being a woman, family history, increasing age, age of menarche, age of menopause, age of first live birth, use of oral contraceptive pill, and hormone replacement.[3] Prevention may be based on a healthy lifestyle including diet and exercise.[1]

Normal body cells grow, divide, and die in an orderly fashion, replacing worn out or injured cells.[1] Cancer cells have damaged DNA that makes it evolve abnormally.[1] Vitamins, which are nutrients that must be ingested through diet, may play a role in the possible prevention of breast cancer.[4] Decreased intake of certain vitamins have been implicated in an increased risk of chronic diseases.[4] Calcium and vitamin D have anticinogenic properties that have been studied related to breast cancer.[5]

Calcium

Calcium is a vital mineral with several important functions in bone and muscle health.[6] In adults, 99% of calcium is found in bones and teeth, while the rest is in the blood and extra cellular fluid.[6] Blood levels of calcium is helped regulated by vitamin D 1,25 dihydroxyvitamin D via a feed back loop.[2] Calcium anticarcinogenic properties include regulating cell proliferation and differentiation.[2]

Calcium Source

Supplements and dairy products are the main calcium source for humans.[2] Other foods high in calcium include sardines, salmon, kale, Chinese cabbage, broccoli, and calcium fortified foods.[6]

Clinical Effect of Calcium

Abbas et al found a moderate risk reduction for premenopausal breast cancer associated with higher dietary calcium intake but was not statistically significant.[7] In a prospective cohort study of 7,847 women, Almquist et al found an insignificant inverse relationship between serum calcium levels and premenopausal breast cancer risk.[8] High calcium levels were positively related to increased breast cancer risk in overweight peri/postmenopause women.[8] McCullough et al found a moderate risk reduction breast cancer with high calcium intake and low fat dairy products in postmenopausal women.[5] In addition, McCullough et al found intake of calcium was inversely related to estrogen receptor (ER) positive tumors but not ER negative tumors.[5]

Vitamin D

Vitamin D is a fat soluble vitamin metabolically inter related to calcium.[2,4] Vitamin D status depends on sun exposure, leading to its skin synthesis as well as dietary intake.[8] With adequate mounts of sun exposure, vitamin D3 (cholecalciferol) is produced in the skin from 7-dehydrocholesterol.[4] Vitamin D3 is then metabolized into 25-hydroxyvitamin D in the liver.[4] In the kidney, 25-hydroxyvitamin D is converted into 1,25-dihydroxyvitamin D.[4] This vitamin D active metabolite inhibits cellular proliferation of breast cancer cells mainly through binding to a nuclear vitamin D receptor (VDR) and induce differentiation of malignant breast cells.[2,4,7] 25-hydroxyvitamin D may also circulate to breast tissue and be locally converted to 1,25 dihydroxyvitamin D, which then exerts its anticarcinogenic actions.[2]

Vitamin D Source

Although diet plays a role, the main source of vitamin D in humans is sun exposure.[9] A daily ten-minute unprotected sun exposure of hands and face may be sufficient to maintain adequate levels of vitamin D.[10] In the United States, the dietary source of vitamin D are vitamin D fortified dairy products, orange juice, fish, eggs, and supplements.[2] Vitamin D3, which is more efficient in raising the levels of the active metabolites, comes from animal sources, and vitamin D2 is synthetically made from plants.[2,4]

Table 1
Selected food sources of vitamin D

Food	IUs per serving*	Percent DV**
Cod liver oil, 1 tablespoon	1,360	340
Salmon, cooked, 3.5 ounces	360	90
Mackerel, cooked, 3.5 ounces	345	90
Tuna fish, canned in oil, 3 ounces	200	50
Sardines, canned in oil, drained, 1.75 ounces	250	70
Milk, nonfat, reduced fat, and whole, vitamin D-fortified, 1 cup	98	25
Margarine, fortified, 1 tablespoon	60	15
Ready-to-eat cereal, fortified with 10% of the DV for vitamin D, 0.75-1 cup (more heavily fortified cereals might provide more of the DV)	40	10
Egg, 1 whole (vitamin D is found in yolk)	20	6
Liver, beef, cooked, 3.5 ounces	15	4
Cheese, Swiss, 1 ounce	12	4

Clinical Effect of Vitamin D

According to the National Health and Nutrition Examination Survey Epidemiologic Follow-up Study, there was no statistically significant association between dietary and supplemental vitamin D intake and breast cancer.[11] Overall, Bertone et al also found insignificant inverse association between plasma levels of 25(OH)D and breast cancer risk.[12] However, Bertone et al concluded that postmenopausal women, and older women (> 60-years-old) with higher levels of vitamin D, may be at lower risk for breast cancer.[12]

On the basis that vitamin D3 status is predominately correlated to sun exposure, Robsahm et al studied the effect of solar-induced vitamin D levels on the prognosis of breast, colon, and prostate cancer. Robsahm et al found that the highest endogenous cutaneous synthesis of vitamin D was associated with the lowest risk for cancer death. In addition, the highest survival rate was with those who were diagnosed during the fall.[10]

Garland et al assessed the association between the serum levels of 25(OH)D and breast cancer risk through a pooled analysis of two studies involving 1,760 individuals.[13] They found at levels of 52 ng/mL (corresponding to an intake of 4000 IU a day), there was a 50% lower risk of breast cancer.[13] Lowe et al had similar results, reporting a significant association of low vitamin D levels with breast cancer risk in the United Kingdom Caucasian population.[14] Colston et al found that lower serum levels (less than 50 nM) of vitamin D was associated with five times the risk for breast cancer than those with over 150 nM.[3]

In trying to find the link between vitamin D and breast cancer, studies have looked at the VDR and its link to certain types of cancer.[14] Lowe et al and Colston et al found that polymorphisms in the VDR may increase risk of breast cancer.[3,14] In addition, both studies found a greater risk of breast cancer with the combination of lower vitamin D levels and VDR polymorphism.[3,14]

High intake of dietary vitamin D was associated with a significantly decreased risk of developing breast cancer in premenopausal women.[7,15,16] Up to age 69 in women, Knight et al found an inverse association between vitamin D intake and breast cancer.[15]

In postmenopausal women, Robien et al found a lower incidence of breast cancer with vitamin D intake of greater than 800 IU a day than with less than 400 IU a day.[17] Shin et al found, among premenopausal women with more than 500 IU a day of vitamin D intake, a lower risk for breast cancer.[16] They also found significantly lower incidence of in situ breast cancer with higher total vitamin D intake.[17]

Adverse Effect

Vitamin D is generally well tolerated, but toxicity can occur causing nausea, vomiting, poor appetite, weakness and weight loss.[6] Excess intake of vitamin D can lead to hypercalcemia. Hypercalcemia may lead to impaired kidney function and decreased absorption of other vitamins and minerals.[6]

Conclusion

The results of epidemiologic studies of vitamin D and calcium intake and breast cancer risk are inconsistent. Vitamin D and calcium are metabolically interrelated, and may have anticarcinogenic properties. Limited research shows an inverse relationship between vitamin D and the risk of breast cancer in premenopausal women. In postmenopausal women, vitamin D and calcium may play a role in decreasing the risk of breast cancer.

Recommendation

Adult women older than 50-years-old are recommended to ingest a total of 1200 mg calcium (dietary and supplemental). The current adult upper limit of vitamin D3 is 2000 IU/day.[6] ❖

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With Comments from Russell H. Greenfield, MD

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A Thorny Issue—*Crataegus* and Heart Failure

Source: Zick SM, et al: The effect of *Crataegus oxycantha* special extract WS 1442 on clinical progression in patients with mild to moderate symptoms of heart failure. *Eur J Heart Fail.* 2008;10:587-593.

Goal: To determine whether a special extract of *Crataegus oxycantha* (COE) slows the clinical progression of mild-to-moderate heart failure (HF).

Study Design: Retrospective secondary data analysis from HERB CHF, a randomized, double-blind, placebo-controlled trial.

Subjects: People with NYHA HF Classes II-III of > 3 months duration whose left ventricular ejection fraction (LVEF) was < 40% and whose medication regimen had been essentially stable for a minimum of 3 months (data evaluable on n=111).

Methods: Screening took place at the end of HF clinic visits through the University of Michigan Health System cardiology department. Interested patients were asked to perform a 6-minute walk test, and those who walked between 150-450 m were invited for a baseline visit in 2 weeks, at which time clinically stable patients were asked to repeat the 6-minute walk test. Those who walked between 150-450 m again were randomized, and radionuclide ventriculography performed to assess LVEF. Subjects were then randomized to receive either placebo or 900 mg *Crataegus oxycantha* Special Extract WS 1442 (COE) in split daily doses for 6 months. Baseline, 3 and 6 month data were analyzed retrospectively from 120 people who had completed the HERB CHF trial. Primary outcome measure was progression of HF (HF death, hospitalization or sustained increase in diuretics; patients with more than one endpoint were counted only once).

Results: Progression of HF occurred in 46.6% of the COE group (odds ratio/OR=1.14) and 43.3% of the placebo group, reflecting no difference between the two groups with respect to the primary outcome in question. COE use was associated with nominally more HF deaths and HF hospitalizations, but less frequent need for increased diuretic compared with placebo. Non-proportional Cox regression analysis, however, showed that those receiving COE were 3.9 times more likely to experience an early HF progression event, with the hazard ratio (HR) decreasing with time. In adjusted analysis, the risk of early HF progression increased to 6.4 in the COE group, again with a declining risk with time. Subgroup analysis of patients with LVEF <35% showed that those who were taking COE were at significantly greater risk (HR=3.2) throughout the entire 6-month study period than those in the placebo group, and not just initially.

Conclusion: COE does not reduce HF progression in patients with mild to moderate HF, and may increase the risk of early HF progression.

Study strengths: Independent verification of product consistency.

Study weaknesses: Compliance measured by pill count; > 25% of participants ended up having an LVEF of > 40% after randomization had already occurred; small sample size; unable to continuously monitor changes in HF medications over the 6 months (only at baseline, 3 and 6 months).

Of note: *Crataegus oxycantha* has been used to treat cardiovascular disorders since the first century AD and appears to have both antioxidant and anti-inflammatory activity, with some pointing to antidysrhythmic effects, too; subjects were eligible for participation in HERB CHF if they were receiving standard HF therapy (inclusive of a diuretic, an ACE-inhibitor or angiotensin receptor blocker [ARB], and a beta blocker; those diagnosed with NYHA class III HF were also required to receive spironolactone); inflammation and oxidative stress appear to be involved in transcriptional regulatory pathways that lead to HF progression; a single batch of COE was used in this trial, standardized to 84.3 mg of oligomeric proanthocyanidins (OPCs).

We knew that: A significant amount of research suggests that *Crataegus oxycantha* may be a safe and effective treatment for the management of symptoms and diminished exercise capacity seen in people with mild-to-moderate HF; despite great advances in the management of HF, the clinical course remains that of seeming inescapable worsening; HERB CHF found that COE had a neutral effect on clinical outcomes of people with NYHA II-IV HF; the neurohumoral system is triggered early in HF disease progression.

Comments: Hawthorn has long been a valued herbal remedy, with an avid consumer base in Europe presently consuming it regularly as a "cardiac tonic." Concerns about potential interaction with digitalis glycosides were seemingly answered, and studies of hawthorn that focused on symptom management for those with HF often provided promising results, albeit with nagging questions regarding proper dosage and whether findings would be the same considering that standard HF care differs significantly from when many prior hawthorn trials were performed. Now comes a paper raising the specter of not just ineffectiveness, but actual harm from use of COE early in the disease course. Why would this be? The authors ponder this, too, wonder-

ing whether a herb-drug interaction may be at work, but a ready explanation presently escapes us.

Hawthorn has been used successfully with many HF patients, and this paper's results alone are not sufficient evidence for forgoing its use in future similar circumstances; however, the conclusions do make it incumbent upon practitioners who recommend hawthorn to intensify patient follow-up during the initial weeks of therapy in case early clinical deterioration of HF with *Crataegus oxycantha* as reported here is a newly discovered significant adverse effect.

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Tea for Two? Green Tea and Sleep Apnea

Source: Burckhardt IC, et al. Green tea catechin polyphenols attenuate behavioral and oxidative responses to intermittent hypoxia. *Am J Respir Crit Care Med.* 2008;177:1135-1141.

Goal: To assess the effects of orally administered green tea polyphenols (GTP) on cognitive, inflammatory and oxidative responses to long-term intermittent hypoxia (IH) during sleep.

Subjects: Young adult Sprague-Dawley rats (n=106).

Methods: Rats were divided into 2 groups, one that was exposed to IH, the other to room air (RA). The animals were housed in identical chambers operated under 12-hour light/dark cycles, while oxygen concentration was continually monitored. Oxygen concentration was regulated so as to provide alternating 90-second intervals of 10% oxygen (IH) and room air (RA) throughout the 12-hour light cycle, with 10 hypoxic events per hour of exposure. During the dark cycle oxygen concentration was maintained at 21%. A commercially available green tea product containing 60% catechins was administered in fresh drinking water for 3 days prior and throughout the > 14 day period of IH exposures. Spatial place learning was assessed using a Morris water maze. At the end of the study period, brain tissue was harvested, and assays for malondialdehyde (MDA, an indicator of lipid peroxidation) and prostaglandin E2 (PGE2) were performed, as were Western blotting, PCR and immunolocalization.

Results: Animals exposed to IH who received plain water had significantly higher brain MDA levels than rats in the RA-water, RA-GTP or IH-GTP groups. The IH-GTP animals had a 33% reduction in MDA compared with IH-water animals, while results for RA-GTP and RA-water were both relatively low (with RA-GTP MDA levels being lowest). PGE2 levels increased only in the IH-water group. IH-water treated animals also performed markedly worse in tests of spatial bias. Other results all showed a tendency towards worsening neural damage from oxidation only in the IH-water group.

Conclusion: Oral GTP minimizes IH-induced spatial learning deficits, and apparently reduces neural susceptibility to IH during sleep, by mitigating IH-induced oxidative stress and inflammation in rodents.

CME Questions

CME Instructions: Physicians participate in this continuing medical education program by reading the articles, using the provided references for further research, and studying the CME questions. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to test their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material.

After completing this activity, participants must complete the evaluation form provided at the end of each semester (June and December) and return it in the reply envelope provided to receive a credit letter. When an evaluation form is received, a credit letter will be mailed to the participant.

After completing the program, physicians will be able to:

a. present evidence-based clinical analyses of commonly used alternative therapies;
b. make informed, evidence-based recommendations to clinicians about whether to consider using such therapies in practice; and
c. describe and critique the objectives, methods, results and conclusions of useful, current, peer-reviewed clinical studies in alternative medicine as published in the scientific literature.

22. The active anti-cancer compounds in extracts of *Agaricus blazei* Murrill are believed to be:

a. polysaccharides
b. proteins
c. fats
d. vitamins

23. *Agaricus* extracts are proposed to benefit cancer patients by having:

a. One, well-defined compound that is toxic to one cancer type.
b. Several compounds that act in different ways, possibly synergistically.
c. A placebo effect.
d. None of the above.

Answers: 22 (a); 23 (b)

Study strengths: Uniform GTP administration; in-depth laboratory evaluation.

Study weaknesses: Model does not incorporate other important aspects of SDB, including sleep fragmentation and recurring hypercapnia; animal model may not correlate with human findings.

Of note: Green tea contains polyphenols (catechins) that exhibit antioxidant activity and may help reduce specific disease risk; IH with sleep disordered breathing (SDB) increases NADPH oxidase activity in rodents; chronic exposure to IH in rodents replicates many of the features of obstructive sleep apnea (OSA) in humans; people with OSA have increased circulating markers of oxidative stress and inflammation; the hippocampus and prefrontal cortex, both critical to learning and memory, are particularly sensitive to IH during sleep, with damage likely occurring due to oxidative stress and inflammation; in an animal model of global ischemia, EGCG (a highly active green tea polyphenol) was neuroprotective against neuronal damage.

We knew that: OSA is the most severe form of SDB and is characterized by repeated episodes of upper airway obstruction during sleep that induce IH and sleep fragmentation; the IH associated with SDB, including sleep apnea, is associated with neurocognitive deficits such as impaired spatial learning, and is likely caused by increased oxidative stress; untreated OSA can lead to significant cardiovascular, neurocognitive (learning and psychological), and metabolic morbidities.

Comments: The prevalence of SDB is increasing, and in light of seemingly ever-worsening data on rates of obesity, the numbers of people experiencing SDB will likely continue to increase for the foreseeable future. A significant number of people have SDB but have yet to be evaluated for it, diagnosed and offered treatment. Once the diagnosis has been secured, for some the solution becomes part of the problem. Many patients experience benefits from CPAP yet do not continue its use, citing discomfort and noise, among other things. Other use dams and bite blocks, while still others opt for surgical intervention. Indeed, while some people with SDB are not overweight, many are, and appropriate weight management planning is of significant help. The present study adds a potential new layer of help for people with SDB, though a human trial is needed.

SDB is more than merely a nuisance; untreated, it can have severe physiologic and cognitive/psychologic consequences. A healthy diet that includes foods high in polyphenols may help prevent sequelae of untreated or under-treated SDB. Even for those receiving appropriate treatment, polyphenols may turn out to be a useful adjunct. Polyphenols can be found not only in green tea, but also in chocolate, wine, and some fruits and vegetables, but don't be surprised if polyphenol supplements become even more popular.

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Fish for The Blues? Depression and EPA

Source: Fe'art C, et al: Plasma eicosapentaenoic acid is inversely associated with severity of depressive symptomatology in the elderly: data from the Bordeaux sample of the Three-City Study. *Am J Clin Nutr.* 2008;87:1156-1162.

Goal: To examine the relationship between plasma fatty acid concentrations and severity of depression in elderly French community dwellers.

Study Design: Cross-sectional population-based study (data taken from the Three-City Study, a prospective cohort study of vascular risk factors for dementia).

Subjects: People (average age 74.6 years) from Bordeaux who participated in the Three-City Study cohort (n=1,390 with 547 men).

Methods: A community sample of people over age 65 years was selected from electoral rolls of 3 French cities in 1999-2000, including Bordeaux. Baseline information obtained included sociodemographics, lifestyle including a food frequency questionnaire, symptoms, medical history, blood pressure, use of alcohol and tobacco. Anthropometric data and fasting blood samples were collected, and neuropsychological testing was performed. Cognitive functioning was assessed using the Mini-Mental State Examination (MMSE). Depressive symptomatology (DS) was assessed using the Center for Epidemiologic Studies Depression Scale (CES-D), which was completed during a home interview as performed by specially trained psychologists. Multiple measures of free fatty acids were performed and ratios determined. Cross-sectional analysis of the relationship between plasma fatty acid profile and DS was performed using multilinear regression.

Results: A total of 117 participants were identified to have DS. As compared to controls, subjects with DS were older, more often women who were widowed or single, had lower monthly incomes, were taking antidepressant medication more frequently, had a lower incidence of dyslipidemia, and had lower scores on MMSE. Of all the fatty acids measured, only plasma EPA levels were found to differ between those with DS and the control group, with levels lower in subjects with DS than in controls, and inversely related to severity of DS in subjects using antidepressants when data were adjusted for potential confounders. No statistically significant association between EPA levels and severity of DS was found for people not taking antidepressants, nor was there an identified interaction with specific antidepressant treatment.

Conclusion: Higher plasma levels of EPA are associated with less severe DS in elderly subjects, especially those already taking antidepressant medication.

Study Strengths: Sample size; simultaneous assessment of DS and blood tests; control for numerous confounders.

Study Weaknesses: Data based on CES-D and not clinical diagnosis of depression; no assessment of duration of antidepressant use or length of time of DS; no biological data on inflammatory and oxidative status of subjects.

Of note: Depression amongst the elderly is often under-treated or under-diagnosed; the origins of late-life depression span social, physical, biochemical and psychological domains; the increased prevalence of depression parallels fundamental dietary changes in recent decades; n-3 polyunsaturated fatty acids (PUFAs) have been reported to have a protective effect against depression, and subjects with depression have been reported to have lower levels of n-3 PUFAs; elongase and desaturase enzyme activity important to the formation of n-3 PUFAs decreases with advancing age, translating into an increased importance of dietary sources of essential fatty acids; the CES-D has been reported to be a valid and reliable measure of DS in the elderly; in this trial, the control group included people who were using antidepressant treatment and were no longer depressed; 13 subjects were unable to complete the CES-D due to severe DS; subjects with DS also took more medication than controls (75% were on 5 or more medications, mainly comprised of antidepressants), deemed their health status poorer, and performed worse on the MMSE; red blood cell fatty acid content better reflects long-term PUFA intake than does plasma fatty acid concentration.

We knew that: Older adults are at high risk for depression, and demographic trends would suggest that the age-specific prevalence of this malady will only increase; chronic illness, cognitive impairment, and disability are often accompanied by depression; n-3 PUFAs have anti-inflammatory and vascular effects, and play an important role in neuronal membrane integrity; red blood cell membranes in depressed people show evidence of oxidative damage; n-3 PUFAs have been shown to play an integral role in regulation of the serotonergic system.

Comments: It has long been suggested that a diet high in essential fatty acids can help prevent, or at least modulate, certain maladies. From a mental health perspective, the data on n-3 PUFAs for bipolar disorder have been promising, and results from trials focusing on depression have also largely been suggestive of benefit. Results of the current study support this notion, especially for seniors already being treated with antidepressants, though methodologic barriers limit firmness of the conclusions.

Depression in the elderly is a growing problem, and findings that point to a potential dietary component are both helpful and problematic. If people ate healthier fare across their lifetimes, such as foods high in essential fatty acids, perhaps mood disorders amongst senior citizens would be less severe; however, one of the numerous challenges the elderly face is eating a healthy diet. Many suffer from poor dentition, no longer cook for themselves, or eat mainly alone, which research suggests is associated with less than optimal nutrition. If further study confirms the potential benefits of n-3 PUFAs for the mental health of seniors, it will be additional fodder for practitioners to use to apply political pressure and ensure adequate exposure to such foods, and perhaps supplements, across socioeconomic barriers.

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