ALTERNATIVE MEDICINE ALERT®

The Clinician's Evidence-Based Guide to Integrative Medicine

AHC Media LLC Home Page—www.ahcmedia.com

CME for Physicians—www.cmeweb.com

AHC Media LLC

INSIDE

Breast cancer and botanical medicine **page 64**

Anti or homeo: use in preschool children **page 71**

An Alzheimer's disease case report **page 72**

Financial Disclosure
Russell H. Greenfield, MD (executive editor), and Leslie Hamlin (managing editor) have no financial relationships with companies having ties to the material presented in this continuing education program.

Alternative Medicine Alert is available on-line. For more information, go to www.ahcmedia.com/online.html or call (800) 688-2421.

Rhodiola rosea for General Anxiety Disorder

1st of 2 Reviews

By David Kiefer, MD

Dr. Kiefer is a Clinical Instructor, Family Medicine, University of Washington, Seattle; Clinical Assistant Professor of Medicine, University of Arizona, Tucson; and Adjunct Faculty at Bastyr University, Seattle; Dr. Kiefer reports no financial relationships relevant to this field of study.

THE SUCCESSFUL TREATMENT OF GENERAL ANXIETY DISORDER (GAD) often requires a combination of a variety of modalities ranging from psychotherapy, behavior modification, pharmaceuticals, acupuncture, and/or mind-body techniques such as meditation or self-hypnosis. Practitioners and patients are also turning to dietary supplements as first-line or adjunctive therapies for GAD and, with accumulating concerns about kava kava (*Piper methysticum*, Family Piperaceae), other herbal medicines are rising to the occasion to treat this disorder. *Rhodiola rosea* is one such plant with both a rich tradition of use and clinical research suggestive of efficacy in GAD.

History and Traditional Use

There is a history of *Rhodiola rosea* being used in several traditional Asian and European medical systems for work enhancement, weight loss, longevity, depression, and fatigue, as well as stimulating the nervous system (promoting alertness, elevated mood) and preventing high-altitude sickness.[1-3] *Rhodiola rosea* is used as a tonic, or adaptogen, in Russia, and is used for lung disease in Tibetan folk medicine.[1,4] In 18th and 19th century France and Sweden, as well as German folk medicine, *Rhodiola rosea* was used as a "brain tonic" to treat headaches.[5] In more modern times, there is mention in the medical literature of Russian and Scandinavian research on the impact of *Rhodiola rosea* on neurotransmitters and the central nervous and cardiovascular systems.[2]

Although *Rhodiola rosea* was traditionally consumed as a root/rhizome decoction,[1] there are now numerous standardized and patented extracts available.

Botany and Pharmacology

There are at least 200 species in the genus *Rhodiola*, in the Family Crassulaceae.[4] *Rhodiola rosea* is a small perennial native to Europe and Asia, and is primarily found at high altitudes.[2,4] Like most herbal medicines, *Rhodiola rosea* is known by many common names, including roseroot, golden root, and Arctic root.[2]

Rhodiola rosea contains a phytochemical profile that is distinct, with some overlap from other species in the *Rhodiola* genus.[6] The underground parts (referred to alternately as rhizomes or roots) of *Rhodiola rosea* contain organic acids, flavonoids, tannins, and phenolic compounds such as phenylpropane derivatives (rosavins, including rosavin, rosine, and rosarin) and the phenylethane derivative salidroside.[3,4] One research group found 17 phenylalkanoids and monoterpene compounds in *Rhodiola rosea*, including one new compound which they named rhodioloside;[4] some researchers consider salidroside to be the same as rhodioloside.[5] Of note, salidroside is found in many *Rhodiola* species and other unrelated plants, whereas the rosavins appear to be specific to *Rhodiola rosea*.[3] Alcohol extracts of *Rhodiola rosea* stems yield other compounds: gossypetin-7-O-L-rhamnopyranoside, rhodioflavonoside, gallic acid, trans-p-hydroxycinnamic acid, and p-tyrosol.[7]

Mechanism of Action

There is some evidence that *Rhodiola rosea* leads to changes in the levels of biogenic amines in the cerebral cortex, hypothalamus, and brain stem, possibly by inhibiting the enzymes responsible for the degradation of serotonin, norepinephrine, and/or dopamine.[2,3]

Studies of *Rhodiola rosea* root extract and its isolated phytochemicals have yielded antioxidant, anti-cancer, immune stimulating, and memory enhancement effects; some researchers have attributed the central effects of this plant to the phenolic compounds (rosavine, salidroside, p-thyrosol) and the antioxidant and anti-cancer effects to the flavonoids and organic acids.[3] One study in mice demonstrated that one dose of a dry hydroalcoholic *Rhodiola rosea* root extract (3% rosavins, 1% salidroside) caused anti-depressant-like effects and anxiolytic-like effects, as well as increased ability to swim to exhaustion.

Clinical Trials

Rhodiola rosea is considered a promising treatment for both depression and anxiety, though many of the articles detailing these clinical effects are in foreign, difficult-to-access journals.[2,8]

One recent small, open-label trial followed ten people with GAD who were given 170 milligrams twice daily of a specific extract of *Rhodiola* (Rhodax, standardized to 30 milligrams total of rosavin, rosarin, salidrosides, rosin, rhodalgin, acetylrhodalgin, rosaridin, and rosaridol) for ten weeks.[1] The Hamilton Anxiety Rating Scale (HARS) and the Clinical Global Impressions of Improvement (CGI-I) were used as the primary instruments to assess effect at baseline and at weeks 3, 6, and 10. Of note, patients could take benzodiazepines up to twice weekly and stay on their regular doses of SSRIs or SNRIs. HARS scores were significantly improved ($P < 0.001$) at end point when compared to baseline; half of the subjects had at least 50% improvement in their HARS scores. In addition, four of ten subjects scored a 1 (very much improved) or 2 (much improved) on the CGI-I at the end of the study. This is an interesting initial investigation, though without a placebo arm or a larger sample size, it is difficult to draw firm conclusions.

Other psychological effects

Rhodiola rosea has been evaluated in clinical trials on other psychological effects. For example, in a double-blind, placebo-controlled trial of 161 fatigued and stressed military personnel, an improvement in fatigue was noted in the group taking 2-3 tablets in a single dose of a standardized SHR-5 extract of *Rhodiola rosea*.[5] No differences between treatment and placebo groups were noted in either psychometric testing (ie, evaluating capacity for mental work) or physiological parameters. SHR-5, approved in Denmark in 2001 for use in fatigue and convalescence, is standardized for rosavin, salidroside, and p-tyrosol content;[2] for example, a 185 milligram tablet contains 4.5 milligrams salidroside.

Alternative Medicine Alert, ISSN 1096-942X, is published monthly by AHC Media LLC, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

SENIOR VICE PRESIDENT/PUBLISHER: Brenda L. Mooney.
ASSOCIATE PUBLISHER: Lee Landenberger.
MANAGING EDITOR: Leslie Hamlin.
GST Registration Number: R128870672.

Periodicals postage paid at Atlanta, GA 30304 and at additional mailing offices.
POSTMASTER: Send address changes to ***Alternative Medicine Alert***, P.O. Box 740059, Atlanta, GA 30374.

Back Issues: $58 per issue. Missing issues will be fulfilled by Customer Service free of charge when contacted within one month of the missing issue's date.

AHC Media LLC

Subscriber Information

Customer Service: 1-800-688-2421.
Customer Service E-Mail: customerservice@ahcmedia.com
World-Wide Web: www.ahcmedia.com

Subscription Prices

United States
$299 per year (Student/Resident rate: $165).
Add $17.95 for shipping & handling.
Multiple Copies
Discounts are available for group subscriptions, multiple copies, site-licenses or electronic distribution. For pricing information, call Tria Kreutzer at 404-262-5482.
Outside the United States
$369 per year plus GST (Student/Resident rate: $180 plus GST).

Accreditation

AHC Media LLC is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

AHC Media LLC designates this educational activity for a maximum of *24 AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

This CME activity is intended for physicians and researchers interested in complementary and alternative medicine. It is in effect for 36 months from the date of the publication.

For CME credit, add $50.

Questions & Comments

Please call **Leslie Hamlin,** Managing Editor, at (404) 262-5416 between 8:30 a.m. and 4:30 p.m. ET, Monday-Friday.

This same extract was studied in healthy physicians being tested for mental performance[9] and in students stressed by exams.[10] An unstated number of students were randomized to either 50 milligrams twice daily of SHR-5 for 20 days or placebo; the treatment group showed improvements in mental fatigue, physical fitness and neurological tests ($P < 0.01$), and general well-being ($P < 0.05$). Adverse effects were not detailed, nor was an intention-to-treat analysis performed. The study in 56 healthy physicians compared overall fatigue (using the Fatigue Index, incorporating measurements of overall mental fatigue and cognitive function) after 170 milligrams of SHR-5 (approximately 4.5 milligrams salidroside) once daily for two weeks, or placebo, in a double-blind, crossover design. Though the results were reported as "significant," statistically the *P*-values were non-significant between treatment and placebo groups; it should be noted that numerous, complicated subgroup analyses were undertaken to elicit some positive effects between certain individuals and specific tests; these results need to be corroborated. No adverse effects were noted in either the placebo or *Rhodiola rosea* group.

Dosages and Forms

Some guidance about the adequate dose of *Rhodiola rosea* for GAD can be extrapolated from clinical trials using specific extracts. A range of doses is seen in such trials, from 100-170 milligrams daily. One author recommends basing dosage recommendations on the content of rosavin, aiming for 3.6-6 milligrams daily.[2]

One trial made efforts to establish the most effective dose for *Rhodiola rosea* by exploring the effect of different doses of SHR-5 (185 milligrams per capsule).[5] Their conclusion was that 2-3 capsules daily approximates the ideal dose to yield beneficial effects.

Adverse Effects, Contraindications, and Drug Interactions

Due to the fact that *Rhodiola rosea* is considered an adaptogen in some cultures, it is often dosed as such. Continuous daily use for days or months is followed by a period of abstinence (such as alternating three weeks "on" and one week "off"); the theory is that this allows for long-term use and avoids adverse effects, such as on the hypothalamus-pituitary-adrenal axis. It is difficult to determine whether that clinical recommendation helps avoid adverse effects, increases efficacy, or both.[2]

Insomnia, irritability, fatigue, and allergy (unspecified) have been reported, especially at higher dosages;[1,2] these symptoms may appear within days of beginning *Rhodiola rosea*.[2]

Additional potential side effects are surfacing from the clinical trials. Though there was no placebo arm to which to compare the side effect profile, two people experienced dizziness and four complained of dry mouth in one study.[1]

Conclusion

Rhodiola rosea has a long history of traditional use, primarily in Europe and Asia. Extracts of the roots/rhizomes yield many phytochemicals such as organic acids, flavonoids, tannins, and phenolic compounds. Most research and standardization has focused on the phenylpropane rosavin and the phenylethane salidroside. A variety of effects on neurotransmitters have been documented in basic science research, as well as behavioral effects in animal models; both of these could account for the psychological effects alluded to in traditional medicine and beginning to be studied in clinical trials. Only one open-label trial investigating the use of *Rhodiola rosea* exists for GAD. Although the effect was favorable, these results need to be corroborated.

Recommendation

Rhodiola rosea is a fascinating plant with a respectable number of phytochemical investigations and demonstrated psychotropic effects, but very little human clinical research has yet been performed with the agent. *Rhodiola rosea* appears to work primarily as an adaptogen, mood enhancer, and anti-fatigue treatment. It remains to be definitively proven whether *Rhodiola rosea* works for GAD; thus, it should not be recommended to patients for the treatment of GAD at this time. Further clinical trials will hopefully clarify use in this setting. ❖

References

1. Bystritsky A, et al. A pilot study of *Rhodiola rosea* (Rhodax) for generalized anxiety disorder (GAD). *J Altern Complement Med* 2008;14:175-180.
2. Kelly GS. *Rhodiola rosea*: a possible plant adaptogen. *Altern Med Rev* 2001;6:293-302.
3. Perfumi M, Mattioli L. Adaptogenic and central nervous system effects of single doses of 3% rosavin and 1% salidroside *Rhodiola rosea* L. extract in mice. *Phytother Res* 2007;21:37-43.
4. Ali Z, et al. Phenylalkanoids and monoterpene analogues from the roots of *Rhodiola rosea*. *Planta Med*. 2008;74:178-181.
5. Shevtsov VA, et al. A randomized trial of two different doses of a SHR-5 *Rhodiola rosea* extract versus placebo and control of capacity for mental work. *Phytomedicine* 2003;10:95-105.
6. Yousef GG, et al. Comparative phytochemical characterization of three *Rhodiola* species. *Phytochemistry* 2006;67:2380-2391.
7. Ming DS, et al. Bioactive compounds from *Rhodiola rosea* (Crassulaceae). *Phytother Res* 2005;19:740-743.

8. Sarris J. Herbal medicines in the treatment of psychiatric disorders: a systematic review. *Phytother Res* 2007;21:703-716.
9. Darbinyan V, et al. *Rhodiola rosea* in stress induced fatigue —a double blind cross-over study of a standardized extract SHR-5 with a repeated low-dose regimen on the mental performance of healthy physicians during night duty. *Phytomedicine* 2000;7:365-371.
10. Spasov AA, et al. A double-blind, placebo-controlled pilot study of the stimulating and adaptogenic effect of *Rhodiola rosea* SHR-5 extract on the fatigue of students caused by stress during an examination period with a repeated low-dose regimen. *Phytomedicine* 2000;7:85-89.

Breast Cancer and Botanical Medicine

By Steven Gomberg, LAc, CCN, RH (AHG), and Brandon Horn, PhD, JD, Lac

The authors are licensed acupuncturists and board certified oriental medicine practitioners for the Eastern Center for Complementary Medicine, Los Angeles; they both report no financial relationships relevant to this field of study.

THE FOLLOWING ARTICLE HAS TWO OBJECTIVES: TO PROvide clinically relevant information on the use of herbs in the treatment of breast cancer and to provide a context for their use. What follows is a distillation of some of the more effective botanicals, as well as some suggestions about how to use them in the setting of breast cancer.

Background

Breast cancer is one of the leading causes of cancer-related death in women.[1] The overall risk for women developing breast cancer is 1 in 8, with the highest risk occurring in women over the age of 60.[2] Breast cancer accounts for almost a third of all new cancers that are diagnosed in the United States, as well as 16% of all cancer-related mortalities in the United States.[3] Worldwide, 1 million cases of breast cancer are diagnosed annually. The five-year survival rates are almost 100% for stage I disease, but only 20% for stage IV.[4]

Risk Factors

Although there are general predisposing risk factors such as race, family history, and age, there are many individualized risk factors as well. As a broad overview, we will categorize cancer risk factors as: genetic/familial risks and environmental/ lifestyle risks.[5]

Genetic/Familial

Genetic factors seem to play a more significant role in the development of breast cancer in premenopausal women.[6] Mutations in the BRCA 1 and 2 tumor suppressor genes are among the most common genetic risk factors for developing cancer, with an overall lifetime risk of 60%-80%.[7] BRCA mutations are more prevalent among certain patient populations, such as women of Ashkenazic Jewish descent. Curiously, increased consumption of coffee may reduce breast cancer risk in these women.[8] Another genetic factor appears to be mutations in tumor suppressor genes, such as p53.[8]

Use of specific medications, or a history of certain illnesses, may also contribute to risk for breast cancer. For example, prior or current use of hormone replacement therapy,[9] obesity, certain forms of infertility, and fibrocystic breast disease are also known risk factors.

Environment/Lifestyle

Note: For an in-depth review of the various environmental/lifestyle exposures with citations, the reader is referred to: State of the Evidence 2008: The Connection between Breast Cancer and the Environment.[10]

Environmental exposures (eg, xenosteroids, organochlorines[11] and other chemicals, radiation,[12] etc.), lifestyle (eg, smoking, alcohol, etc.), and diet (eg, xenosteroidal compounds, growth hormones,[13] carcinogenic byproducts of manufacturing or cooking, food additives, etc.) may also be contributing factors. Clearly, there is substantial overlap. For example, recent studies have shown that high consumption of dietary fat does not pose a risk in and of itself.[14] However, certain high fat diets can lead to obesity, which is a risk factor for breast cancer.[15] Dietary fats can also contain high concentrations of fat soluble contaminants (eg, xenosteroids) which may contribute to cancer pathogenesis. High fat-to-complex carbohydrate ratio diets have also been associated in some studies with dense breast tissue, another known risk factor.[16]

The Strategic Use of Herbs in Breast Cancer

Many useful and novel compounds, with a wide range of effects, have been identified within the Chinese Herbal Pharmacopeia. Some are directly tumoricidal, while others inhibit aromatase, upregulate p53, induce apoptosis, inhibit cell-cell adhesion pathways, and so forth.

The choice of herbal research targets in breast cancer therapy is often derived from observance of traditional uses. Practitioners of Classical Chinese Medicine (CM) choose herbs based upon a complex synthesis of diagnostic parameters combined with an intricate theoretical model. Essentially, CM views tumors as a physiological response of the body to sequester a pathogen and attempt to keep it from spreading or harming other tissue. Metastasis, therefore, is seen as the loss of the body's ability to contain, eliminate, or repair the pathology.

Accordingly, three main factors are strategically addressed: 1) the underlying pathology (ie, aberrant cells); 2) the etiological factors involved in that pathology (ie, factors that create the microenvironment facilitating tumor development (these can include toxins, microorganisms, emotions/stressors, etc.); and 3) the body's ability to control the pathogen, prevent metastasis, and maintain homeostasis (i.e., immune system, digestive system, etc.).

Addressing the Underlying Pathology

Note to readers: please see accompanying chart for references to clinical statements.

The first factor involves directly addressing the aberrant cells in the tumor and their mechanisms of promoting abnormal cell growth (eg, estrogen receptors in an ER + tumor). In this respect, certain herbs may act synergistically with chemotherapy, radiation, and estrogen antagonists. Due to the novel actions of many herbs, it is also possible to utilize herbs where conventional therapies are not indicated, or as an option in cases where it is unclear whether conventional therapies will be more helpful or harmful.

Herbs used in this arena have various targets. Some seem to directly suppress tumor growth, induce apoptosis, or induce DNA repair mechanisms, where others seem to inhibit angiogenesis, cell adhesion pathways, metastasis, or block estrogen receptors. Several of the more useful herbs in this category include: *Curcumae longae* (eg, cell adhesion pathway inhibition), *Salvia miltiorrhiza* (eg, inhibits both estrogen receptor positive and negative tumors), *Boswellia serrata* (eg, metastasis inhibition), *Ganoderma lucidum* (eg, decreases estrogen receptor signaling and downregulates ER alpha expression), *Tanacetum parthenium* (eg, induces apoptosis), *Scutellaria baicalensis* (eg, inhibits multi-drug resistance and promotes DNA repair), and *Scutellaria barbata* (eg, selectively cytotoxic to breast cancer cells leaving normal mammary tissue unharmed).

Etiological Factors

Possibly the most important factor in tumor development is its microenvironment.[17] Indeed, recent research has shown the possibility of addressing even aggressive tumors by adjusting the microenvironment. As one Northwestern University researcher commented, "our observations highlight the potential utility of isolating the factors within the hESC [human embryonic stem cell] microenvironment responsible for influencing tumor cell fate and reversing the cancerous properties of metastatic tumor cells, such as melanoma."[18] The accumulating data on microenvironments implies that cancer therapies merely targeting the tumor itself, while leaving the original terrain intact, could possibly be less effective and leave the patient susceptible to recurrences.

Most potential etiologic factors can be roughly categorized as environmental toxins (ie, non-biological agents), infectious agents (biological), or internal issues such as digestive or emotional stressors.[19-21] While environmental toxins, dietary factors and, to some degree, chronic emotional stress are somewhat established etiological factors in conventional literature, infectious agents are a relative newcomer. Interestingly, there is a growing body of evidence implicating infectious agents, particularly viruses, in some breast cancers.[22] According to CM theory, one etiology of tumorigenesis is direct or indirect alterations in DNA by infectious agents. While the association is still unclear from a conventional standpoint, plausible mechanisms exist for both direct alterations of DNA (eg, viral) as well as collateral DNA damage caused by immunological defenses (eg, Reactive Oxygen Species, or ROS).

Further complicating matters, the etiology of many cases of breast cancer appears to be multi-factorial. For example, having a BRCA gene mutation does not, in and of itself, always result in breast cancer. Treating identifiable etiological factors is, therefore, extremely important.

Where information on exposure to particular types of carcinogenic compounds is available, herbs may be helpful in counteracting their effects. However, in many cases the exposures are unknown. Therefore, it is generally useful to take a more indirect approach that involves improving the body's detoxification capacity and downregulating hormone receptors, where appropriate. Research is demonstrating that herbs may be useful in this regard. For example, *Scutellaria barbata* (SBAR) increases the expression of the gene for glutathione S-transferase (GST) by 2.5-3.0-fold.[23] As GST increases phase II metabolism of xenobiotics, SBAR may prove helpful in a broader xenobiotic/mutagen prevention strategy. At the same time, it inhibits intratumoral aromatase expression in certain cancer cells, and so may help in other ways to prevent the promotion of tumor development.[24]

For protecting against radiation-induced damage, *Curcumae longae* may be very useful.[25] The herb paradoxically protects normal cells from radiation while sensitizing cancer cells to radiation. In addition, it may be prudent to prophylactically administer this, or other radioprotective substances, to women undergoing any kind of imaging involving ionizing radiation, such as mammography. We recommend 500 mg tid of a 5:1 concentrated aqueous extract (AE) for a course of 21 days, beginning seven days before the imaging is scheduled.

Addressing infectious agents is a complicated discussion from an herbal standpoint. In CM, there is an intricate theoretical basis for the identification and eradication of infections. If an infectious etiology is suspected, think about using herbs that combine anti-tumor and anti-microbial properties can be considered. *Andrographis* and

Scutellaria baicalensis are examples of herbs that are both strongly anti-tumor and strongly anti-microbial.

In addressing digestive and immune function, adaptogenic herbs are often employed. These herbs tend to have an overall positive effect on resistance to external stressors. Some of the more popular and effective adaptogens include Astragalus, *Poria cocos*, and Eleutherococcus. Astragalus, for example, has general anti-tumor properties and has also been shown to have beneficial effects on the gut. It was shown to both prevent and treat colitis[26] and help restore intestinal microfloral balance.[27] *Poria cocos* also has digestive and immunological benefits with the additional function of being a mild diuretic. It also has anti-tumor properties.

Emotional factors are generally involved in breast cancer, most often as the result of the diagnosis. Therefore, addressing one's psychological state is very important. Several herbs are very helpful in this regard and, in addition to having anxiolytic properties, they also have other actions that help fight various breast tumors. Examples of some of the important herbs in this category are *Passiflora incarnata* and Chrysanthemum. Both contain chrysin, an anxiolytic flavonoid that has been shown both to inhibit aromatase[28]and metastasis.[29]

Maintaining Integrity of the Body

Many therapies for cancer are fairly aggressive and can damage healthy tissue. Adaptogens are utilized to help maintain the integrity of normal cells during the assaults on the tumor tissue. Adaptogens are herbs that have a regulatory effect on the body to help it "adapt" to various stressors. Given their function, questions have been raised about an adaptogen's ability to protect a tumor as well. While a plausible concern with some adaptogens, others have significant anti-tumor activity. *Eleutherococcus senticosa* (ES), for example, can be used concurrently with chemotherapy to mitigate side effects such as nausea, dizziness, and loss of appetite in patients undergoing treatment with cyclophosphamide.[30] Eleutherococcus also helps to restore immunologic function in patients undergoing myelosuppressive chemotherapeutic regimes.[31] In addition to strengthening the patient, ES also inhibits metastatic potential and has anti-tumor[32] and anti-viral[33] activity. Other useful adaptogens in oncology include Astragalus and Ganoderma.[34]

Administration of Herbs

In CM, herbs are commonly administered in formulas of 5-20 herbs. The framework of an herbal formula should be determined by the patient's condition. For example, a strong person with an aggressive tumor may have 70% of the formula attacking the tumor, 20% dealing with the etiology, and 10% providing adaptogens. A patient that is debilitated, perhaps from multiple chemotherapy rounds, may require 70% adaptogens, 20% anti-tumor and, 10% of the formula addressing etiology. This is where clinical judgment comes in. Of course many herbs overlap categories, so these percentages serve only a rough guide.

Next are issues with herb quality. As noted multiple times in the peer-reviewed literature, and especially so for Chinese patent medicines, it is of paramount importance that herbs be tested for heavy metals and other environmental toxins. The form of extraction is also important. In many cases, oral administration of aqueous extracts are used; however, some functions of herbs can only be accessed with other extraction methods (eg, ethanol) or other routes of administration. When considering adjuvant administration of herbs in the treatment of cancer, it is prudent to use herbs that have been standardized to specific active constituents. Identifying and recommending companies that adhere to GMPs (Good Manufacturing Practices) is of great benefit to patients.

In choosing the appropriate herbs to administer, whereas clinicians use laboratory tests and tissue pathology, where others combine these tests with traditional CM diagnostic methods such as tongue and pulse diagnosis. Generally in cancer therapy, dosages of administered herbs can be quite high. Therefore, it is prudent to concurrently monitor liver and kidney function. While the tolerance of herbal formulas is generally quite good, there have been rare instances of contamination by accidental administration of an inappropriate species that have resulted in serious complications. In most cases, these risks can be avoided through prudent monitoring, and should not be a deterrent to using herbs. In fact, many of the herbs used in therapy are both nephro- and hepato-protective and may allow for much higher tolerance of aggressive therapies such as chemotherapy. Ganoderma, for example, is both nephroprotective[35,36] and hepatoprotective.[37]

Conclusion

Breast cancer is a disease exhibiting a variety of different etiological and pathological mechanisms. The current paradigm, in which the main focus of treatment is the tumor itself, may not be the most effective approach. Recent data suggest that the tumor microenvironment may be of equal, if not greater, importance.

Chinese Medicine historically emphasizes both treatment of the tumor itself and the microenvironment. As such, CM treatments may be a very useful adjunct in the treatment and prevention of breast and other cancers. Biomedical research into the actions of herbs traditionally used in the context of breast cancer has revealed a number of novel and seemingly effective compounds. This research has also confirmed a number of mechanisms for their purported efficacy (eg, inhibiting angiogenesis, upregulating

Herb Name	Categories	Specific Effects	Dosage	Cx
Astragalus membranaceus	I, E	Enhances NK cell activity, increases interferon production, anti-viral properties.[1] Paradoxically enhances effect and reduces toxicity of certain chemotherapeutic regimes,[2] improves gut mucosa.[3]	Aqueous Extract (AE): 9-30 grams per day. Ethanol Extract (EE): 1:1 20 mL per day	
• *Poria cocos*	P, I, E	Induces apoptosis of MCF-7 breast cancer cells in vitro. Increases digestive capacity, anti-proliferative, induces cell differentiation[4]	AE: 10-15 g/day	
Eleutherococcus senticosa	I, E	Mitigates side effects and increases tolerance of chemotherapy,[5] increases interferon, anti-viral, anti-tumor activity[6,7]	AE: 9-27 g/day 10:1 dried extract standardized to 150-300 mg/day of eleutherosides B and E	One report on interference with blood digoxin levels, likely due to a contaminant in the herb.[31]
• *Ganoderma lucidum*	P, I, E	Significantly inhibits proliferation of breast cancer cells (MCF-7 and MDA-MB-231) without cytotoxic effects on normal breast tissue. Immune support and modulation, anti-angiogenic,[8] decreases estrogen receptor and nuclear factor kappa beta (NF-kB) signaling in certain breast cancer cell lines, downregulates expression of ER alpha,[9] synergistic with Herceptin (trastuzumab) in suppression of Her2/neu oncogene.[10]	AE: 3-15 g/day	Experimental data suggest water extracts may potentially aggregate blood in vitro, leading to cautions about interactions with anti-coagulants
• *Curcuma longae* (curcumin)	P, E	Significantly reduces tumor volume in MDA-MB-231 breast cancer cells. Reduces mutant p53 RNA, K67, increases apoptosis, reduces proliferation,[11] inhibits angiogenesis through inhibition of VEGF, b-FGF,[12] sensitizes cancer cells to gamma radiation,[13a] impairs cell-cell adhesion pathways,[13b] and has an effect on many other biological targets in carcinogenesis	AE: 9-12 g/day standardized to 400-600 mg curcumin — up to 1800 mg/day	Curcumin may, under some circumstances decrease the efficacy of Doxyrubicin, but it is unlikely.[31] Traditionally contraindicated in pregnancy.[32]
• *Scutellaria baicalensis*	P, E	Strongly inhibits breast cancer cell growth (MCF-7). Inhibition of multi-drug resistance,[14] anti-microbial activity,[15] anti-oxidant activities related to DNA repair,[16] hepatoprotective[17]	AE: 3-10 g/day	
• *Salvia miltiorrhiza*	P, E	Inhibits both ER+ and ER- breast tumors. Neo-tanshinlactone (component of SM) showed inhibition against two ER+ breast cancer cell lines and was 10-fold more potent and 20-fold more selective compared to tamoxifen. Also potently inhibited ER-, Her2 everexpressed cell line.[18] Synergistic with SBAI for even stronger inhibitory effects on breast tumors.	AE: 5-10 g/day	May potentiate anti-coagulant or anti-platelet drugs. May falsely elevate serum digoxin levels.[32]
Boswellia serrata	P	Anti-inflammatory AKBA (Acetyl-11-keto-beta-boswellic acid) inhibits 5-lipoxygenase pathway (5-LOX),[19] inhibits angiogenesis, VEGF, EGF.[20] Case report of BoS reversing breast cancer brain metastasis.	AE: 3-10 grams; 30% AKBA 600 mg	Traditionally contraindicated in pregnancy, may cause GI distress.[32]
• *Tanacetum parthenium*	P	Anti-inflammatory. Parthenolide induces apoptosis,[21] inhibits proliferation of several different cancer cell lines including MCF-7 breast cancer cells,[22] increases the cytotoxicity of paclitaxel[23]	EE: 1:5 25% (0.2% parthenolide) 5 mL/day	Exhibits platelet inhibiting properties, which may interact with other drugs
• *Scutellaria barbata*	P, E	Inhibits intracellular aromatase production. Broad spectrum anti-cancer agent that is selectively cytotoxic to breast cancer cells (leaving normal mammary tissue unharmed), likely through ROS induced DNA damage leading to necrotic cell death.[24] Currently in phase II clinical trials at the Ohio State University Medical Center (OSUMC).	AE: 10-30 g/day	
• *Andrographis paniculata*	P, E	In vitro and in vivo anti-tumor activity in breast cancer models. Anti-microbial,[25] immune enhancement through NK cell modulation, and increases immune-dependent cytotoxicity.[26] Andrographolide directly cytotoxic to cancer cell lines.[27] Antioxidant, anti-inflammatory,[28] inhibits Bcl-2 expression and increases apoptosis,[29] anti-angiogenic[30]	AE: 6-15 g/day	Traditionally used with caution during pregnancy.[32]

p53, selectively inducing apoptosis of tumors, inhibiting tumor and peripheral expression of aromatase, increasing anti-tumor immune activity, reducing side effects of conventional therapies, etc.). While large scale human trials are just beginning, and although the majority of data regard animal or lab research, given the wealth of historical information on the safety and efficacy of various herbs (some of them having been used for thousands of years), an herbal regimen could be considered as an additional and potentially effective tool in the treatment of breast cancer.

By utilizing herbs that have both historical data and modern research demonstrating potential mechanisms for efficacy, it is possible to maximize the chances of favorable outcomes while minimizing discomfort associated with conventional therapies. Where herb formulas are combined with conventional therapies, it is prudent to monitor the patient closely during the initial stages of administration for both efficacy (improvements in tumor markers or size) and safety (kidney and liver function). As with pharmaceuticals, herbs contain powerful chemical compounds. Therefore, even where biomedical research supports the use of a single herb or component, combinations with other herbs or pharmaceuticals can produce new chemical compounds that differ from the original chemicals, potentially impacting both safety and efficacy.

However, just as the lack of definitive data on the combined effects of most pharmaceuticals does not prevent their prescription, a lack of data on the combined effects of herbs and drugs should not necessarily be a hindrance to their use. The same prudent monitoring that allows for widespread use of untested pharmaceutical combinations can enable us to successfully apply the combined use of herbs and pharmaceuticals. With proper monitoring, herbs can be a substantial asset both in the treatment and prevention of breast cancer. Of course, further research is mandated, but for those in need now, select agents could be employed with confidence. Patient, CM practitioner, and oncologist should be involved in all such decision-making. ❖

References

1. Abeloff MD, et al. Cancer of the breast. *Clin Oncol* 2004:2369-2470.
2. Cancer facts and figures. American Cancer Society. www.cancer.org
3. Key TJ, et al. Epidemiology of breast cancer. *Lancet Oncol* 2001;2:133-140.
4. How is cancer staged? American Cancer Society. www.cancer.org
5. King SE, Schottenfeld D. The "epidemic" of breast cancer in the U.S. — determining the factors. *Oncology (Williston Park)* 1996;10:453-462.
6. Vogel VG. Breast cancer in younger women: assessment and risk management. *The Female Patient* 1999;24:81-86.
7. King MC, et al. Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. *Science* 2003;302:643-646.
8. Nkondjock A, et al. Coffee consumption and breast cancer risk among BRCA1 and BRCA2 mutation carriers. *Int J Cancer* 2006;118:103-107.
9. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. *Lancet* 1997;350:1047-1059.
10. Gray J. State of the evidence 2008: the connection between breast cancer and the environment. The Breast Cancer Fund. 200810.
11. Hoyer AP, et al. Organochlorines, p53 mutations in relation to breast cancer risk and survival. A Danish cohort-nested case-controls study. *Breast Cancer Res Treat* 2002;71:59-65.
12. Baral E, et al. Breast cancer following irradiation of the breast. *Cancer* 1977;40:2905-2910.
13. Jenkins PJ, et al. Does growth hormone cause cancer? *Clin Endocrinol (Oxf)*. 2006;64:115-121.
14. Lof M, et al. Dietary fat and breast cancer risk in the Swedish Women's lifestyle and health cohort. *Br J Cancer* 2007;97:1570-1576.
15. Pischon T, et al. Obesity and cancer. *Proc Nutr Soc* 2008;67:128-145.
16. Boyd NF, et al. Effects at two years of a low-fat, high carbohydrate diet on radiologic features of the breast: results from a randomized trial. *J Natl Cancer Inst* 1997;89:488-496.
17. Park CC, et al. The influence of the microenvironment on the malignant phenotype. *Mol Med Today* 2000;6:324-329.
18. Mary JC Hendrix, MD. Professor and Scientific Director of the Children's Memorial Research Center and Proessor in The Robert H. Lurie Comprehensive Cancer Center of Northwestern University and at the Feinberg School of Medicine.
19. Kruk J. Association of lifestyle and other risk factors with breast cancer according to menopausal status: a case control study in the region of Western Pomerania (Poland). *Asian Pac J Cancer Prev* 2007;8:513-524.
20. Reiche EM, et al. Stress and depression-induced immune dysfunction: implications for the development and progression of cancer. *Int Rev Psychiatry* 2005;17:515.527.
21. Godbout JP, Glaser R. Stress-induced immune dysregulation: implications for wound healing, infectious disease and cancer. *J Neuroimmune Pharmacol* 2006;1:421-427.
22. Mok MT, et al. Mouse mammary tumor virus-like env sequences in human breast cancer. *Int J Cancer* 2008;122:2864-2870.
23. de Boer JG, et al. Protection against aflatoxin-B1-induced liver mutagenesis by *Scutellaria baicalensis*. *Mutat Res* 2005;578:15-22.

24. Lee TK, et al. Inhibitory effects of *Scutellaria barbata* D. Don. and *Euonymus alatus* Sieb. on aromatase activity of human leiomyomal cells. *Immunopharmacol Immunotoxicol* 2004;26:315-327.
25. Jagetia GC. Radioprotection and radiosensitization by curcumin. *Adv Exp Med Biol* 2007;595:301-320.
26. Ko JK, et al. Amelioration of experimental colitis by *Astragalus membranaceus* through antioxidation and inhibition of adhesion molecule synthesis. *World J Gastroenterol* 2005;11:5787-5794.
27. Yan M, et al. [Changes of intestinal flora in senile mouse models and the antagonistic activity of the root of *Astragalus membraceus* (Fisch) Bge]. *Zhongguo Zhong Yao Za Zhi* 1995;20:624-626.
28. Navarrete A, et al. Gastroprotective effect of Astragaloside IV: role of prostaglandins, sulfhydryls and nitric oxide. *J Pharm Pharmacol* 2005;57:1059-1064.
29. Chen YY, Chang HM. Antiproliferative and differentiating effects of polysaccharide fraction from fu-ling (*Poria cocos*) on human leukemic U937 and HL-60 cells. *Food Chem Toxicol* 2004;42:759-769.
30. Farnsworth N, et al. Siberian Ginseng (Eleutherococcus senticosa) current status as an adaptogen Vol 1 London: Academic Press: 1985.
31. Kupin VI, et al. [Immunomodulating action of an Eleutherococcus extract in oncologic patients. *Sov Med* 1987:114-116.
32. Campbell DR, Kurzer MS. Flavonoid inhibition of aromatase enzyme activity in human preadipocytes. *J Steroid Biochem Mol Biol* 1993;46:381-388.
33. Lin CM, et al. Chrysin inhibits lipopolysaccharide-induced angiogenesis via down-regulation of VEGF/VEGFR-2(KDR) and IL-6/IL-6R pathways. *Planta Med* 2006;72:708-714.
34. Ross G. Carbohydrate aids mabs in killing cancer cells. *J Immunol* .2004
35. Futrakul N, et al. Treatment of glomerular endothelial dysfunction in steroid-resistant nephrosis with *Ganoderma lucidum*, vitamins C, E and vasodilators. *Clin Hemorheol Microcirc* 2003;29:205-210.
36. Tseng J, Chang JG. Suppression of tumor necrosis factor-alpha, interleukin-1 beta, interleukin-6 and granulocyte-monocyte colony stimulating factor secretion from human monocytes by an extract of *Poria cocos*. *Zhonghua Min Guo Wei Sheng Wu Ji Mian Yi Xue Za Zhi* 1992;25:1-11.
37. Shi Y, et al. Hepatoprotective effects of *Ganoderma lucidum* peptides against d-galactosamine-induced liver injury in mice. *J Ethnopharmacol* 2008;117:415-419.

Chart Citations:

1 Duan P, Wang ZM. Clinical study on effect of Astragalus in efficacy enhancing and toxicity reducing of chemotherapy in patients of malignant tumor, Chengdu First People's Hospital, Chengdu 610016.
2. McCulloch M, et al: Astragalus-based Chinese herbs and platinum-based chemotherapy for advanced non-small-cell lung cancer: meta-analysis of randomized trials. *J Clin Onco*l 2006;24:419-430.
3. Hei ZQ, et al. Protective effect of *Astragalus membranaceus* on intestinal mucosa reperfusion injury after hemorrhagic shock in rats. *World J Gastroenterol*. 2005;11:4986-4991.
4. Chen YY, Chang HM. Antiproliferative and differentiating effects of polysaccharide fraction from fu-ling (*Poria cocos*) on human leukemic U937 and HL-60 cells. *Food Chem Toxicol* 2004;42:759-769.
5. Brekhman II. Report on the use of Eleutherococcus with Breast Cancer Patients. Georgia, USSR: Institute on Oncology, Ministry of Health; 1970
6. Wacker A, et al. The molecular mechanism of virus inhibition by Eleutherococcus. New Data on Eleutherococcus. Paper presented at: II International Symposium on Eleutherococcus, 1984; Moscow.
7. Glatthaar-Saalmüller B, et al. Antiviral activity of an extract derived from roots of *Eleutherococcus senticosus*. *Antiviral Res*. 2001;50:223-228.
8. Lu QY, et al. *Ganoderma lucidum* spore extract inhibits endothelial and breast cancer cells in vitro. *Oncol Rep* 2004;12:659-662.
9. Jiang J, et al. *Ganoderma lucidum* inhibits proliferation of human breast cancer cells by down-regulation of estrogen receptor and NF-kappaB signaling. *Int J Oncol* 2006;29:695-703.
10. Ross G. Carbohydrate Aids Mabs In Killing Cancer Cells, July 15, 2004. *J Immunology*. University of Louisville (KY, USA), working at the James Graham Brown Cancer Center.
11. Ramachandran C, You W Differential sensitivity of human mammary epithelial and breast carcinoma cell lines to curcumin. *Breast Cancer Res Treat* 1999;54:269-278.
12. Shao ZM, et al. Curcumin exerts multiple suppressive effects on human breast carcinoma cells. *Int J Cancer* 2002;98:234-240.
13. (a) Kunnumakkara AB, et al. Curcumin sensitizes human colorectal cancer xenografts in nude mice to {gamma}-radiation by targeting nuclear factor-{kappa}B-regulated gene products. *Clin Cancer Res* 2008;14:2128-2136. (b) Jaiswal AS, et al. Beta-catenin-mediated transactivation and cell-cell adhesion pathways are important in curcumin (diferuloylmethane)-induced growth arrest and apoptosis in colon cancer cells. *Oncogene* 2002;21:8414-27.

14. Lee Y, et al. Increased anti-P-glycoprotein activity of baicalein by alkylation on the A ring. *J Med Chem* 2004;47:5555-5566.
15. Zou YP. Chinese Materia Medica, chemistry, pharmacology and applications. Boca Raton CRC press 1998
16. Chen X, et al. Baicalin promoted the repair of DNA single strand breakage caused by H_2O_2 in cultured NIH3T3 fibroblasts. *Biol Pharm Bull* 2003;26:282-284.
17. Bae HS, et al. Hepatoprotective activity of reduohanxiao-tang (yuldahanso-tang) is related to the inhibition of beta-glucuronidase. *Am J Chin Med* 2003;31:111-117.
18. Wang X, et al. Antitumor agents. 239. Isolation, structure elucidation, total synthesis, and anti-breast cancer activity of neo-tanshinlactone from *Salvia miltiorrhiza*. *J Med Chem*. 2004;47:5816-5819.
19. Safayhi H, et al. Mechanism of 5-lipoxygenase inhibition by acetyl-11-keto-beta-boswellic acid. *Mol Pharmacol* 1995;47:1212-1216.
20. Ghosh J, Myers CE. Inhibition of arachidonate 5-lipoxygenase triggers massive apoptosis in human prostate cancer cells. *Proc Natl Acad Sci USA* 1998;95:13182-13187.
21. Cory AH, Cory JG. Lactacystin, a proteasome inhibitor, potentiates the apoptotic effect of parthenolide, an inhibitor of NF-kappaB activation, on drug-resistant mouse leukemia L1210 cells. *Anticancer Res* 2002;22:3805-3809.
22. Wen J, et al. Oxidative stress-mediated apoptosis. The anticancer effect of the sesquiterpene lactone parthenolide. *J Biol Chem* 2002;277:38954-38964.
23. Patel NM, et al. Paclitaxel sensitivity of breast cancer cells with constitutively active NF-B is enhanced by IB super-repressor and parthenolide. *Oncogene* 2000;19:4159-4169.
24. Shoemaker M, et al. Molecular mechanisms underlying selective cytotoxic activity of BZL101, an extract of *Scutellaria barbata* towards breast cancer cells. *Cancer Biol Ther* 2008;7.
25. Singha PK, et al. Antimicrobial activity of *Andrographis paniculata*. *Fitoterapia* 2003;74:692-694.
26. Sheeja K, Kuttan G. Modulation of natural killer cell activity, antibody-dependent cellular cytotoxicity, and antibody-dependent complement-mediated cytotoxicity by andrographolide in normal and *Ehrlich ascites* carcinoma-bearing mice. *Integr Cancer Ther* 2007;6:66-73.
27. Jada SR, et al. Semisynthesis and cytotoxic activities of andrographolide analogues. *J Enzyme Inhib Med Chem* 2006;21:145-155.
28. Sheeja K, et al: Antioxidant and anti-inflammatory activities of the plant *Andrographis paniculata* Nees. *Immunopharmacol Immunotoxicol* 2006;28:129-140.
29. Zhou J, et al. Critical role of pro-apoptotic Bcl-2 family members in andrographolide-induced apoptosis in human cancer cells. *Biochem Pharmacol* 2006;72:132-144.
30. Sheeja K, et al. Antiangiogenic activity of *Andrographis paniculata* extract and andrographolide. *Int Immunopharmacol* 2007;7:211-221.
31. Stargrove M, et al. Herb drug and nutrient interactions. St Louis Missouri Mosby Elsevier. 2008
32. Chen, J, Chen T: Chinese medical herbology and pharmacology. City of Industry, CA Art of Medicine Press, Inc, 2004.

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.

CME Questions

17. Into which of the following herbal medicine categories would the traditional use of *Rhodiola* fit the BEST?
a. Vulnerary
b. Bitter
c. Antihypercholesterolemic
d. Antidepressant
e. Adaptogen

18. Extracts of *Rhodiola rosea* used in clinical trials are most often standardized to a percentage of the following compounds?
a. Rosavins
b. Epicatechins
c. Salidroside
d. a and c

19. Which of the following herbs is in phase II clinical trials for its selective cytotoxicity against breast cancer?
a. *Scutellaria barbata*
b. *Scutellaria baicalensis*
c. *Andrographis paniculata*

Answers: 17. (e); 18. (d); 19. (a)

With Comments from Russell H. Greenfield, MD

Dr. Greenfield is Clinical Assistant Professor, School of Medicine, University of North Carolina, Chapel Hill, NC; and Visiting Assistant Professor, University of Arizona, College of Medicine, Tucson, AZ.

Anti or Homeo: Use in Preschool Children

Source: Wye L, et al: Complementary or alternative? The use of homeopathic products and antibiotics amongst preschool children. *BMC Fam Pract* 2008;9:8.

Goal: To determine whether use of homeopathic remedies amongst preschoolers is associated with any change in the frequency of use of antibiotics in the same age group.

Study Design: Prospective, population-based observational trial (part of the Avon Longitudinal Study of Parents and Children, or ALSPAC).

Subjects: Children aged 3-4.5 years (n = 9,723) in Bristol, UK.

Methods: The ALSPAC trial recruited pregnant women who were expected to deliver their babies between April 1991 and December 1992. Questionnaires were completed by primary caregivers during pregnancy and throughout the child's first years that included answers about maternal antenatal use of homeopathics, and at age 4.5 years, responses regarding their child's exposure to antibiotics and homeopathic remedies over the prior 18 months.

Results: A total of 62% of children received antibiotics between the ages of 3-4.5 years, while just 6% were given homeopathic remedies. Children who received homeopathic remedies were more likely to have been given antibiotics per univariate analysis; but after controlling for other factors, no association between use of homeopathic products and antibiotic exposure was identified applying multivariate analysis. Among other findings, mothers of children who received antibiotics reported themselves as being anxious and more likely to contact their child's doctor when she/he was ill as compared to mothers whose children did not receive antibiotics.

Conclusion: Use of homeopathic remedies amongst pre-school children is not associated with either decreased or increased antibiotic use, suggesting that, in this age group, homeopathics are used primarily as a complement to conventional Western medical care, not instead of it.

Study strengths: Statistical analyses; community-based trial.

Study weaknesses: Old data and usage patterns have changed over time (for example, rates of antibiotic use amongst British pre-schoolers have dropped since the early 1990's); retrospective data collection with inherent risk of recall bias; no information on the diagnoses/indications for antibiotic or homeopathic use, nor on whether products were obtained through healthcare practitioners or simply over-the-counter.

Of note: The rate of antibiotic use among pre-school children in this trial was slightly higher than what is commonly reported; factors independently associated with use of homeopathic products in this study included maternal use of homeopathic remedies, higher maternal education, lower levels of confidence in doctors, and mothers reporting that they were less likely to seek physician care when their child was ill; studies out of Scotland show that almost half of all primary care practices there offer homeopathic remedies to their patients, with the highest prevalence of use amongst children under one year of age (the most frequent reasons for prescribing homeopathics being for colic, upper respiratory tract infections, and teething); some patients have been known to consult with their conventional doctors for a diagnosis, but then use complementary or alternative therapies, including homeopathy, for treatment; the authors are careful to state that homeopathic remedies are not generally considered viable alternatives to antibiotic therapy.

We knew that: Pre-school children consume more antibiotics than any other age group in the United Kingdom, and are among the most frequent users of Britain's National Health Service (most notably for respiratory tract infections); it has been suspected that parents who use homeopathic remedies for their children expose them to antibiotics far less frequently than non-users of homeopathy, but little data exist in this regard.

Comments: Results of this study are meant in part to allay fears often held by more conventional medical practitioners regarding CAM therapies, specifically homeopathy in this instance. Doctors are rightfully concerned that CAM therapies might be utilized instead of a clearly indicated conventional intervention, thereby delaying appropriate care and potentially placing the patient, especially children, at risk. In this trial, use of homeopathics among pre-schoolers did not translate into avoidance of antibiotic therapy; however, the results are seriously flawed. Without knowing the indications for intervening with antibiotics or homeopathic remedies in the children studied, it is fruitless to assign firm conclusions regarding the philosophy of caregivers who may favor homeopathics. It is noteworthy that mothers who offered their children homeopathic remedies were less likely to bring their children to the doctor when sick. Hopefully, this is in reference to mild illness, but readers can be forgiven should they harbor continued concerns that philosophical leanings might lead parents to more self-diagnosis and treatment of their young children exclusive of the family's healthcare partner, their doctor. Perhaps this paper is really most valuable for pointing out that distrust of conventional medical care still exists. Practitioners who appropriately empower families to care for themselves while simultaneously offering a healthcare partnership based in science and compassion best serve their patients. Now we simply need a healthcare system that supports the time necessary to create that healing relationship.

What to do with this article: Keep a copy of the abstract on your computer.

The "Wow" Factor — An Alzheimer's Disease Case Report

Source: Tobinick EL, Gross H. Rapid cognitive improvement in Alzheimer's disease following perispinal etanercept administration. *J Neuroinflamm* 2008;5:2.

Goal: To detail the clinical response of an 81-year-old man with late-onset Alzheimer's disease who was given treatment with perispinal etanercept, a tumor necrosis factor-alpha (TNF-alpha) inhibitor.

Study Design: Case report.

Subject: A relatively healthy man until 2 years prior when he developed progressive cognitive deficits. He had been treated with multiple medical regimens for Alzheimer's disease, but either could not tolerate treatment or experienced no therapeutic benefit. Upon examination, the patient had difficulty naming common items and was unable to draw a clock correctly (he drew a square with a single line for the hour / minute hands, and no numbers). His score on the Montreal Cognitive Assessment test (MOCA) was 7/30, consistent with moderate-to-severe dementia.

Methods: The patient was questioned by the author of the report immediately before receiving perispinal etanercept. He knew neither the year nor his current location. He received a posterior cervical interspinous injection of 25 mg etanercept at C6-7, followed by placement into Trendelenburg position for 5 minutes, and then a return to the sitting position.

Results: At 10 minutes post-administration, the patient correctly identified his current location and appeared more calm and attentive. Two hours post-etanercept administration he was oriented to place, month, and day of the week. He was markedly better at naming common items, and drew a clock as a circle with an hour and minute hand (still no numbers). When the MOCA was re-administered, his score was now 15/30. One week after the initial administration of etanercept, the patient was oriented to year, month, season, day of the week, and state.

Conclusion: There is a rapidly reversible, TNF-alpha-related component to the cognitive dysfunction seen with Alzheimer's disease, and this reversible pathophysiologic process occurs before irreversible neuronal structural damage. It is likely that a physiologic range of cerebral TNF-alpha exists above which neurodegenerative and cognitive derangements may occur.

Of note: Recent data suggest that TNF-alpha is a gliotransmitter and exerts distinct effects on neural synapses; large molecules like etanercept cannot cross the blood-brain barrier when administered by more conventional means; markedly high levels of TNF-alpha have been found in the CSF of people with Alzheimer's disease, and progressively higher levels seem to correlate with worsening cognitive function for our loved ones, might get better.

We knew that: Neuroinflammation with overexpression of cytokines is characteristic of brain pathology in the setting of Alzheimer's disease; synaptic dysfunction also appears to be a component of the disease; TNF-alpha has been suspected of playing a role in the pathophysiology of Alzheimer's disease, as it appears to interfere with normal synaptic function, something that has been known for over a decade; TNF-alpha can promote degenerative changes when levels are chronically elevated, as it increases IL-1 expression, which increases production of the precursors to amyloid plaques, neurofibrillary tangles, and Lewy bodies; etanercept binds to TNF-alpha, blocking its interaction with cell surface TNF-alpha receptors; etanercept was initially approved for use in the treatment of another inflammatory condition, rheumatoid arthritis; participants in a previously published six-month, open-label trial of perispinal extrathecal etanercept administration in adults with probable Alzheimer's disease showed sustained cognitive improvements, but also displayed apparent rapid clinical improvement essentially immediately after the intervention, which served as the genesis of the current case report.

Comments: It is extremely unusual for the editors of *Alternative Medicine Alert* to choose a case report on which to offer abstract commentary for our readership. But this case report is unlike most others. It is an unabashed sign of hope.

The authors describe rapid clinical improvement in an elderly man with Alzheimer's disease who was given direct-to-the-brain delivery of anti-cytokine therapy in the form of etanercept. Prior study strongly suggests that clinical response to such treatment is also long-lasting.

The author of an accompanying editorial describes being present as three people diagnosed with probable Alzheimer's disease received perispinal etanercept, and how she noticed clinical improvement within minutes of treatment. She ends by saying, "I was amazed!" When was the last time any of us saw the word "amazed" used without cynicism in a peer-reviewed journal?

There are many novel ways to decrease inflammation in the body, from dietary modification, to stress management, to the use of specific herbs and supplements. Perhaps such actions begun early in life, and adhered to, can help prevent Alzheimer's disease in the first place. Still, it is remarkable that in the setting of established disease, intrathecal administration of a potent anti-inflammatory agent appears to rapidly reverse some of the cognitive deficits commonly seen with this mind-stealing disorder.

Hope springs eternal as patients, family members, and their healthcare providers struggle with the management of Alzheimer's disease. We cling to any reason to believe that we, or our loved ones, might get better. In an era of widespread chronic illness, we need more "Wow" moments; they reinforce possibility and hope. Is more research into perispinal etanercept required? Of course, but this article provides a much needed "shot" of research direction and amazement. May there be more to come.

What to do with this article: Make copies to hand out to your peers. ❖

In Future Issues:

ADHD and Dietary Supplements