

# CORNERSTONE Critiques

Commentary by Richard A. Johnson, MD, on Current Literature

## Empiricism or Science: Which Comes First?

### Medicinal Plants and Alzheimer's Disease: From Ethnobotany to Phytotherapy

Perry EK, Pickering AT, Wang WW, Houghton PJ, Perry NSL.

*J Pharm Pharmacol.* 1999;51:527–534.

The use of complementary medicines, such as plant extracts, in dementia therapy varies according to the different cultural traditions. In orthodox Western medicine, contrasting with that in China and the Far East for example, pharmacological properties of traditional cognitive- or memory-enhancing plants have not been widely investigated in the context of current models of Alzheimer's disease. An exception is *Ginkgo biloba* in which the ginkgolides have antioxidant, neuroprotective and cholinergic activities relevant to Alzheimer's disease mechanisms. The therapeutic efficacy of Ginkgo extracts in Alzheimer's disease in placebo controlled clinical trials is reportedly similar to currently prescribed drugs such as tacrine or donepezil and, importantly, undesirable side effects of Ginkgo are minimal. Old European reference books, such as those on medicinal herbs, document a variety of other plants such as *Salvia officinalis* (sage) and *Melissa officinalis* (balm) with memory-improving properties, and cholinergic activities have recently been identified in extracts of

these plants. Precedents for modern discovery of clinically relevant pharmacological activity in plants with long-established medicinal use include, for example, the interaction of alkaloid opioids in *Papaver somniferum* (opium poppy) with endogenous opiate receptors in the brain. With recent major advances in understanding the neurobiology of Alzheimer's disease, and as yet limited efficacy of so-called rationally designed therapies, it may be timely to re-explore historical archives for new directions in drug development. This article considers not only the value of an integrative traditional and modern scientific approach to developing new treatments for dementia, but also in the understanding of disease mechanisms. Long before the current biologically-based hypothesis of cholinergic derangement in Alzheimer's disease emerged, plants now known to contain cholinergic antagonists were recorded for their amnesia- and dementia-inducing properties.

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### COMMENTARY

The authors of this review cite plant extract therapies for use in AD that go all the way back to the 16th century and describe reported efforts to use herbal substances to improve one's thinking and memory. The most gratifying aspect of this review is the demonstration that most of the plant substances people used with purported success over time have been recently shown to have some of the same chemical properties that now appear important in the pathogenesis and pharmacologic treatment of AD. These substances include anticholinesterase, muscarinic, and nicotinic activity as well as antioxidant and anti-inflammatory properties. Much science is derived from prior empiricism, but as more science becomes verifiable, we should avoid the temptation to revert to empiricism out of frustration with the lack of rapid development of highly effective AD-modifying or curative agents.

## Is Natural Better or Just a Different Dose of the Same Thing?

### Herbal Medications for Common Ailments in the Elderly

Ernst E. *Drugs Aging*. 1999;15:423–428.

The popularity of herbal medicine is at an all time peak. This article provides an overview of systematic reviews of herbal treatments for conditions common in elderly individuals. According to this evidence, there is little doubt that *Hypericum perforatum* (St. John's wort) is well tolerated and effective for mild to moderate depression. Although widely used, *Valeriana officinalis* (valerian) has not been shown beyond reasonable doubt to be effective for insomnia. There is relatively compelling evidence that *Ginkgo biloba* (ginkgo) is effective in delaying the clinical course of dementias. It has been well documented that *Aesculus hippocastanum*

(horse chestnut) seed extracts alleviate the subjective symptoms and reduce the objective signs of chronic venous insufficiency. *Serenoa repens* (saw palmetto) is effective in improving the symptoms of benign prostatic hyperplasia. Finally, yohimbine has been shown to be effective for erectile dysfunction. It is concluded that several plant-based medicines can be useful additions to our therapeutic repertoire for treating common conditions in the elderly. However, several uncertainties remain and, at present, prevent unreserved recommendations. © 2001 Elsevier Science B.V., Amsterdam. All rights reserved.

### COMMENTARY

Ernst gives the reader a nice review of many herbal medications used for treatment of common conditions that affect the elderly population. The literature that supports or refutes efficacy is reviewed along with pathophysiology that supports a rational basis for using these herbal medications for selected conditions. As we are beginning to understand, many of the “tried and true” herbal remedies have biologic properties similar to the modern pharmacologic agents. Thus, the clinician needs to be aware of the patient's use of alternative therapies, not for the purposes of condoning or chastising the patient's choice, but to understand the implications for dosing and interaction with pharmacologic agents we may be prescribing for the very same condition.

## Randomized, Double-Blinded, Placebo Controlled Trial (RDBPCT) Doesn't Fit the AD Paradigm

### Clinical Research Designs for Emerging Treatments for Alzheimer Disease: Moving Beyond Placebo-Controlled Trials

Knopman D, Kahn J, Miles S. *Arch Neurol.* 1998;55:1425–1429.

The design of clinical trials must evolve as new therapies become available. The demonstrated efficacy and clinical use of donepezil and vitamin E for Alzheimer disease (AD) has shifted the options for AD research design. There is now a compelling case for alternatives to trials that include a treatment arm with no active therapy (ie, a placebo control). With an existing therapy, such as donepezil or vitamin E, new drugs that are clearly superior to those drugs should be sought. Combination therapy is a likely strategy for the future, implying that clinical trials, if possible, should replicate actual practice. The long duration of future AD trials also will make

placebo-controlled trials more difficult to justify and more difficult to recruit for. Add-on or active-control designs represent the alternative approaches. We believe that definitive clinical trials of new AD drugs that use one or the other of these designs would be more likely to bring about therapeutic advances than would comparisons with inactive treatments. Our argument is not a general rejection of placebo-control designs. Our recommendations apply only to the circumstances in which the field of AD drug therapy now finds itself.

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### COMMENTARY

The authors do a good job of discussing why the time-honored RDBPCT approach to developing scientific knowledge does not work very well in a practical sense with diseases like AD where there are existing standard therapies and the course of the disease is long. A rational argument is made that new therapies should be compared with existing known beneficial therapies so that the clinician can decide which therapy is best rather than conclude that the therapy is better than placebo and then be left with the issue of “which is best.”