Medicinal Plants and Alzheimer’s Disease: Integrating Ethnobotanical and Contemporary Scientific Evidence

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ABSTRACT

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 biloba 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 biloba are minimal. Old European reference books (eg, medical herbals) 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 activities 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 amnesic and dementia-inducing properties.

INTRODUCTION

In reviewing the current use in Canada of complementary or alternative medicine in dementia, Hogan and Eby (1996) suggested that “knowledge of the use of these therapies is still important and should not be neglected.” In contemporary Western science, the bridge between complementary medicines, often considered to be beyond the realm of scientific en-

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quiry, and modern pharmacology based on so-called rational drug design, is rarely crossed. Yet many drugs (or their derivatives) of therapeutic value in orthodox medicine acquired a respectable reputation in modern pharmacological terms, hundreds or thousands of years after their efficacy was established empirically (Table 1). A classic example is the discovery made in 1775 by the British physician William Withering, after his observation of a case of "dropsy" (fluid retention due to heart failure) cured by a local herbalist’s decoction, which included Digitalis purpurea (Mann, 1992). This discovery eventually led to the use of digoxin and related compounds as drugs of choice in congestive heart failure. If it were not for his astute observations, medical treatment of heart disease might have followed a different course and the common foxglove (Digitalis purpurea) or its derivatives might still belong to the domain of complementary medicine.

**MEDICINAL PLANTS FOR DEMENTIA THERAPY**

While newly introduced cholinesterase inhibitors such as tacrine (Cognex) or donepezil (Aricept) provide a minority of patients with some symptomatic relief, most patients with Alzheimer’s disease have not yet benefited substantially from the major financial investments in Western scientific research and drug development programs. Ethnobotanical evidence derived from cultural, empirical, or complementary medical uses of plants may be worth examining for new directions in therapeutic research strategies. Although only a small proportion (<10%) of the Canadian dementia patient population examined by Hogan and Eby (1996) was given complementary medicines for cognitive problems, caregivers of a population in North Carolina reported a much higher (55%) proportion (Coleman et al., 1995). European use of plant products in this context may also be more widespread than is appreciated by orthodox medical practitioners. Rosemary (Rosmarinus officinalis) for example is used by practicing medical herbalists and aromatherapists in the United Kingdom for memory problems (Price and Price, 1995; Bartram, 1995). Ginkgo biloba, popular because of its perceived antiaging properties including enhancing cerebral activity (Kleijnen and Knipschild, 1992, Vesper and Häagen, 1994), has recently been reported to be of therapeutic value in mild to moderately affected patients with Alzheimer’s disease (Burkard and Lehri, 1991; Kanowski et al., 1996; Le Bars et al., 1997). In the 1997 placebo-controlled, double-blind, randomized trial, the standardized Ginkgo biloba extract EG6761 was associated with significant improvements in cognitive function (ADAS-Cog) and caregivers rating (GERI) compared with placebo. Equally importantly there were no significant differences in the number, incidence, or severity of adverse side effects. There are numerous other documented, although more anecdotal examples of cognitive-enhancing plants in non-Westernized societies. These include components of traditional Chinese herbal prescriptions like FuQuiDiHuang and Indian Ayurvedic medicines.

Since orthodox medicine in many Westernized societies (including the United Kingdom and the United States) largely abandoned the

<table>
<thead>
<tr>
<th>Plant species</th>
<th>Principal active constituent</th>
<th>Medical use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foxglove, Digitalis purpurea</td>
<td>Digitoxin, digoxin</td>
<td>Cardiac tonic</td>
</tr>
<tr>
<td>Salix alba &amp; others</td>
<td>Salicylic acid esters</td>
<td>Analgesic and anti-inflammatory</td>
</tr>
<tr>
<td>Papaver somniferum</td>
<td>Morphine, codeine</td>
<td>Analgesic, narcotic</td>
</tr>
<tr>
<td>Erythroxylum coca</td>
<td>Cocaine</td>
<td>Local anesthetic</td>
</tr>
<tr>
<td>Rauwolfia serpentina</td>
<td>Reserpine</td>
<td>Tranquilizer, hypotensive</td>
</tr>
<tr>
<td>Ephedra esusina</td>
<td>Ephedrine (related to adrenaline)</td>
<td>Antiasthmatic</td>
</tr>
<tr>
<td>Artemisia annua</td>
<td>Quinine</td>
<td>Antimalarial</td>
</tr>
<tr>
<td>Cinchona pubescens</td>
<td>Artesminin</td>
<td>Antimalarial</td>
</tr>
</tbody>
</table>
medicinal use of plants earlier this century in favor of new synthetic pharmaceuticals (some based on original plant chemicals), documented evidence on clinical efficacy predates this period. According to John Scarborough, in his introduction to John Riddle’s historical analysis of the contribution of the Greek physician Pedanios Dioscorides to pharmacy and medicine: “One must command the ancient texts in their original tongues and one must use modern pharmacognosy in judicious association with the ancient data.”

Our search through some of the English herbals published over the last few centuries provided some interesting information on plants that might be worth investigating in relation to dementia therapy. In the 16th to 18th centuries, several plants acquired a persistent reputation for memory enhancing properties. It was, for example, noted about balm (*Melissa officinalis*) that:

> “An essence of balm, given in canary wine, every morning will renew youth, strengthen the brain” (London Dispensary, 1696).
> “Balm is sovereign for the brain, strengthening the memory and powerfully chasing away the melancholy” (Evelyn, 1699).
> “Paracelsus believed it would completely revivify a man and it was formerly esteemed of great use in all complaints supposed to proceed from a disordered state of the nervous system” (Grieve, 1931).

Also, Thomas Coghan recommended in 1584 that balm tea be drunk daily by his students to help clear the head, increase understanding, and sharpen the memory. These statements obtain a degree of support from a contemporary report: in a placebo-controlled assessment of the effects of aromatherapy using balm essential oil (combined with lavender), a small number of patients with dementia were reported to improve on measures of independence and “general functioning” in comparison with those exposed to a culinary vegetable oil (Mitchell, 1993).

*Sage* (*Salvia officinalis*) another member of the Labiatae plant family also had a reputation for memory enhancement:

> “It is singularly good for the head and brain and quickeneth the nerves and memory” (J. Gerard, 1597).
> “It also heals the memory, warming and quickening the senses” (Culpeper, 1652).
> “Sage will retard that rapid progress of decay that treads upon our heels so fast in latter years of life, will preserve faculty and memory more valuable to the rational mind than life itself” (Hill, 1756).

Sage is also used in Ayurvedic medicine, one of the longest established and still practised forms of herbal medicine: “to clear emotional obstructions from the mind and for promoting calmness and clarity” (McIntyre, 1996).

In traditional Chinese medicine, Nao Li Kang (which translates as “restore brain power granules”) contains four ingredients, one of which is *Salvia*, and is reported to be effective in 40% of Alzheimer patients (Fu and Fruehauf, 1995). The independent use of the same plant genus for a common clinical effect in such widely differing cultures such as India, China, and renaissance Europe is impressive.

Consistent with current aromatherapeutic application of rosemary to improve memory, this herb was considered by the ancient Greeks to stimulate the mind, in particular memory (Le Strange, 1977) and students then used to wear sprigs or garlands of the plant as an “aide memoire.” According to Roger Hacket, a Doctor of Divinity in 1607 (Grieve, 1980): “It helpeth the brain, strengtheneth the memorie and is very medicinable for the head”

In the Grete Herball (1526) it was recorded that: “Against weykenesse of the brayne and coldness thereof, sethe rosmaria in wyne and late the pacient receye the smoke at his nose”

Gerard noted (1597): “Rosemary comforteth the braine, the memorie, the inward sense”

It is intriguing to consider how the opinions expressed in these herbal encyclopedias were formed, whether mainly on the basis of subjective experience, independently, or originating from a common historical source. In *Hamlet*, written in 1601 by William Shakespeare who was a neighbor of John Gerard, Ophelia said “There’s rosemary; that’s for remembrance. Pray, love, remember.” Archival evidence of this kind would appear worth ex-
ploring in the context of current models of dementia such as Alzheimer's disease.

RELEVANT PHYTOCHEMICAL AND PHARMACOLOGICAL RESEARCH

The use of drugs in orthodox Western medicine is generally based on the understanding that chemical intervention in specific biological mechanisms account for clinical benefits. The therapeutic value of a medicinal plant is thus considered in terms of the interaction of one (or more) of its chemical constituents with the relevant disease-related system. For natural plant products to be incorporated into mainstream medicine, both clinical efficacy and relevant biological activity need to be demonstrated. In Alzheimer's disease potential therapeutic targets, in terms of biological mechanisms, include: enhancing cholinergic transmission, restricting oxidative stress and inflammatory reactions; preventing β-amyloid formation or toxicity; elevating circulating estrogen and levels of other neurotrophic agents such as nerve growth factor. To date, only cholinergic agents, specifically inhibitors of the enzyme acetylcholinesterase, have been licensed for treatment.

Some evidence exists for relevant bioactivities in some of the plants mentioned above. There is for example, a substantial specific literature on relevant properties of the ginkgolides—the chemical constituents of Ginkgo biloba considered to be responsible for the medicinal effects of the plant. Specific ginkgolides interact with the cholinergic system (Taylor, 1986), and have neuroprotective or regenerative activities (Bruno et al., 1993; Smith et al., 1996). Any or all of these are potentially relevant to efficacy in dementia therapy. In addition, the flavonoids present in Ginkgo biloba have antioxidant properties.

Several traditional Chinese medicinal herb extracts or chemicals have also been investigated for their effects on current dementia models. For example, peony (Paeonia suffruticosa) is a component of traditional Chinese herbal prescriptions for dementia such as Jin Gui Shen Qi Wen, which include Liu Wei Di Huang Wan. A major constituent of this plant, paeoniflorin, improves radial maze performance in rats impaired by the anticholinergic drug scopolamine (Ohta et al., 1993). Liu Wei Di Huang Wan (Hachimi-jio-gan in Japanese), also containing peony, is also antiamnesic in this model and increases cortical cholinergic activity (Hirokawa et al., 1996). Shimotus-to, also active in this animal model (Watanabe et al., 1991), contains both peony and Japanese angelica (Angelica sinensis) root. The latter species also reverses scopolamine-induced performance deficits (Ohta et al., 1993) and it would be interesting if it is chemically closely related to the European species, Angelica archangelica, which contains nicotinic activity (Wren, 1985; Perry et al., 1996).

Cholinesterase inhibitors have been chemically identified in several traditional Chinese medicinal plants, including Angelica sinensis and Evodia rutaecarpa (Park et al., 1996). Another plant cholinesterase inhibitor, huperzine, derived from the moss Huperzia traditionally used to treat inflammation and fever, is also being used in Alzheimer’s disease therapy in China (Cheng et al., 1996, 1998; Skolnick, 1997). It is a relatively selective inhibitor of cortical and hippocampal cholinesterase and of acetyl compared to butyrylcholinesterase. In placebo-controlled randomized trials, huperzine was significantly better than placebo in improving memory, cognition and behavioral function (Xu et al., 1995).

The Ayurvedic herbal formulation Mentat (which consists of 26 plant species) reverses scopolamine-induced memory impairment in animal models (Battacharia et al., 1995). Trasina (5 plant species) also reverses memory impairments associated with surgical lesions of the cholinergic basal forebrain (Bhattacharia and Kumar, 1997). Systemic administration of Withania somnifera (Indian ginseng reputed in India to attenuate cerebral deficits including amnesia) led to differential inhibition of acetylcholinesterase and enhanced M1-muscarinic receptor binding in rat brain (Schliebs et al., 1997). Korean Ginseng (Panax ginseng) is, among its numerous beneficial effects, considered to improve memory (Reid, 1986) and has also been reported to enhance cholinergic activity in similar animal models (Nitta et al., 1995, Salim et al., 1997) and to have neuropro-
tective effects in vitro (Wren et al., 1996; Lim et al., 1997).

In relation to the European plant species identified above there is some limited evidence on relevant bioactivities. Balm contains various monoterpenes such as citral and citronella, which have been reported to concentrate in the hippocampus (Mills, 1993)—a key area concerned with learning affected at an early stage by Alzheimer-type pathology.

**In vitro** effects of the crude plant extracts on human brain acetylcholinesterase and nicotinic receptor binding have been examined. Among a range of different plant extracts tested, only sage and balm exerted any notable dose-dependent inhibitory effects on the enzyme, with IC₅₀ values of <0.1 µL essential oil per milliliter (Perry et al., 1996). Several different sources and species of Salvia had similar effects, suggesting one or more of its chemical constituents are active. *Salvia officinalis* is potentially toxic in high doses on account of its thujone content (Wren, 1985). However, thujone is not present in significant amounts in *Salvia lavandulaefolia* (Spanish sage), which had equally potent inhibitory effects on the enzyme (Perry et al., 1996). The active constituents are likely to be other monoterpenoids, which inhibit acetylcholinesterase, albeit at relatively high concentrations (Miyazawa et al., 1997). Clinical trials of this species may be worth initiating in view of its cholinergic and other documented (oestrogenic and anti-inflammatory) properties and the archival clinical evidence discussed above. Synergistic therapeutic effects are common in the practice of medical herbalism. In addition to inhibitory effects on brain acetylcholinesterase, balm leaf extracts also interacted with the nicotinic receptor, inhibiting (³H)-nicotine binding with an IC₅₀ value of 2.5 mg/mL (Perry et al., 1996).

It is not unexpected to discover cholinergic activities in plants such as these. Endogenous cholinergic chemicals deter animal predators of the plant by interacting with peripheral and/or central cholinergic systems. A variety of cholinergic phytochemicals have already been established (Table 2) and new chemicals with cholinergic activity continue to be discovered; for example, berberine in Corydalis tuber (Hwang et al., 1996). These chemicals are all alkaloids (nitrogen containing secondary metabolites) that are, without exception, toxic at low concentrations. Their therapeutic value is thus restricted in terms of dosage and chronic application. Preventative, protective and sympto-

### Table 2. Plant-Derived Cholinergic Drugs

<table>
<thead>
<tr>
<th>Type</th>
<th>Chemical*</th>
<th>Plant species</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholinesterase</td>
<td></td>
<td></td>
</tr>
<tr>
<td>inhibitors</td>
<td>Physostigmine</td>
<td><em>Physostigma venenososa</em> (calabar bean)</td>
</tr>
<tr>
<td></td>
<td>Galanthamine</td>
<td><em>Galanthus nivalis</em> (snowdrops)</td>
</tr>
<tr>
<td></td>
<td>Huperzine</td>
<td><em>Narcissus pseudonarcissus</em> (daffodil)</td>
</tr>
<tr>
<td></td>
<td>Arecoline</td>
<td><em>Huperzia serrata</em> (fern)</td>
</tr>
<tr>
<td>Muscarinic agonists</td>
<td>Arecoline</td>
<td><em>Areca catechu</em> (betel nut)</td>
</tr>
<tr>
<td></td>
<td>Pilocarpine</td>
<td><em>Pilocarpus jaborandi</em></td>
</tr>
<tr>
<td></td>
<td>Muscarine</td>
<td><em>Amanita muscaria</em> (fly agaric)</td>
</tr>
<tr>
<td>Muscarinic antagonists</td>
<td>Atropine</td>
<td><em>Atropa belladona</em> (deadly nightshade)</td>
</tr>
<tr>
<td></td>
<td>Hyoscamine</td>
<td><em>Hyoscamus niger</em> (henbane)</td>
</tr>
<tr>
<td></td>
<td>Scopolamine</td>
<td><em>Mandragora officinarum</em> (mandrake)</td>
</tr>
<tr>
<td></td>
<td>(or hyoscyamine)</td>
<td><em>Datura</em> (numerous species) (eg thornapple)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Scopolia carniolica</em></td>
</tr>
<tr>
<td>Nicotinic agonists</td>
<td>Nicotine</td>
<td><em>Nicotiania tabacum</em> (tobacco)</td>
</tr>
<tr>
<td></td>
<td>Lobeline</td>
<td><em>Lobelia inflata</em> (Indian tobacco)</td>
</tr>
<tr>
<td></td>
<td>Cytisine</td>
<td><em>Laburnum anagyroides</em> (laburnum)</td>
</tr>
<tr>
<td>Nicotinic antagonists</td>
<td>Tubocurarine</td>
<td><em>Chondrodendron tomentosum</em></td>
</tr>
<tr>
<td></td>
<td>Sparteine</td>
<td><em>Cytisus scoparius</em> (broom)</td>
</tr>
<tr>
<td></td>
<td>Dihydro-β-erythroidine</td>
<td><em>Erythrina</em> (several species)</td>
</tr>
<tr>
<td></td>
<td>Methyllycaconitine</td>
<td><em>Delphinium brownii</em> (delphinium)</td>
</tr>
</tbody>
</table>

*These chemicals, all alkaloids, are with the exception of tubocurarine, centrally active. They are small molecules compared to reptilian or mollusc polypeptides with cholinergic activities such as α and κ bungarotoxins, α-cobrotoxin, α-conotoxin (nicotinic antagonists), or epibatidine and histrionicotoxin (nicotonic agonists)*
matic strategies in a progressive, degenerative disease such as Alzheimer's are likely to be longer term. The plants from which these established cholinergic phytochemicals are derived (Table 2) generally belong to the category of known poisonous species. In contrast, species such as Salvia or Melissa are not considered poisonous (unless at very high dosage). Cholinergic activities in these species are either present in very low concentrations or are non-alkaloids. The function of plant alkaloids is not clearly understood. As secondary metabolites they are not essential to plant metabolism and protection against predators is likely to be responsible for their evolution. Other types of secondary plant metabolites, such as volatile terpenes (the principal constituents of essential oils) present in many Labiatae species (which include sage and balm), more likely function to attract animals, eg, insect pollinators. There may be superior potential therapeutic value in plant products that evolved to attract rather than repel animals, including humans.

COMPARISON WITH "RATIONAL" THERAPIES

Some of the examples provided indicate the potential of a combined ethnobotanical and pharmacognostic approach to developing therapies in the treatment of Alzheimer's disease (Table 3). Current orthodox Western strategies in dementia therapy, however rationally based, are not all consistent with cultural traditions. Physostigmine for example, the prototypic cholinesterase inhibitor whose short half-life \textit{in vivo} led to the search for longer acting inhibitors, is not renowned for its traditional uses in memory enhancement. \textit{Physostigma venenosa}, the calabar bean, found in West Africa, was used locally as an emetic in trials of witchcraft by ordeal (Mann, 1992). The synthetic inhibitor tacrine was originally used to recover consciousness in cases of drug overdose (eg, of antidepressants with antimuscarinic actions). Galanthamine, a longer acting naturally occurring enzyme inhibitor derived from the bulbs of \textit{Galanthus nivalis} (snowdrop) or \textit{Narcissus} (daffodil), provides significant clinical benefit in patients with Alzheimer's disease, although adverse effects include nausea and vomiting (Fulton and Benfield, 1996). Grieve (1931) records the use of daffodils as an emetic, antidote to poisons, and for external use. None of the encyclopedias mention the use of this species for memory enhancement. Interestingly both physostigmine and galanthamine, in addition to being cholinesterase inhibitors, are also noncompetitive nicotinic channel activators (Pereira et al., 1993), which may be of added value in Alzheimer's therapy.

NICOTINIC POTENTIAL

Direct stimulation of the nicotinic receptor is likely to be a valid therapeutic approach. The principle alkaloid derived from tobacco (\textit{Nicotiana tabacum}) is nicotine. Since its original introduction into Europe as a treatment for headache (Matthee, 1995), numerous medicinal uses of tobacco have been claimed—for dropsy, epilepsy, malaria, hernia, insomnia, constipation, and even hiccoughs. In 1659, Dr. Giles Everard recorded that "to strengthen the memory, the smoke is excellent taken by the nostrils." Current epidemiological and clinical (eg, cognitive enhancing) evidence of the potential value of nicotine in Alzheimer's therapy (reviewed by Court and Perry, 1994) may thus have some precedent in traditional medical usage. Nicotine is now known to enhance memory and attention in animal models and human volunteers and the risk of developing Alzheimer's disease is, on average, halved in tobacco smokers (Lee, 1994). It is also protective in a variety of models associated with ischemic, amyloid peptide, and glutamate toxicity. Nevertheless, nicotine is a highly toxic alkaloid with adverse cardiovascular and gastrointestinal effects. If nonalkaloid nicotinic chemicals exist in plant species such as those being investigated, their therapeutic value may be greater.

CONTRIBUTION OF PHYTOCHEMICALS TO UNDERSTANDING DISEASE MECHANISMS

While traditional uses of plant medicines have not yet provided a major stimulus to new
drug development in dementia, it is interesting to consider the reverse scenario. Ethnic uses of certain plants are consistent with contemporary understanding of various forms of dementia (Perry, 1997). Plants belonging to the Solanaceae have been used since the first records of history to induce altered states of consciousness—hallucinations, memory loss, oblivion, and even dementia (reviewed by Perry and Perry, 1995). Such plants as deadly nightshade (Atropa belladonna), henbane (Hyoscyamus niger), mandrake (Mandragora officinarum), and Angel’s trumpet or jimson weed (Datura stramonium) contain the muscarinic receptor antagonists scopolamine and atropine. Although laboratory-based experiments on scopolamine-induced learning deficits in the 1970s, along with observations in the human brain, contributed to the original cholinergic hypothesis of Alzheimer’s disease, perceptual disturbances including hallucinations are a prominent feature of this drug and “experiential” evidence to support the hypothesis was available before this time. Consistent with low cholinergic activity in the cerebral cortex, patients with dementia and Lewy bodies experience visual hallucinations (Perry and Perry, 1995). In relation to contemporary understanding of dementia, archival evidence from traditional ethnobotany appears to be consistent with modern pharmacology. Integrating experiential and experimental evidence in understanding disease may be as productive as integrating complementary and orthodox medicines in developing treatment.

**INTEGRATIVE RESEARCH STRATEGIES**

The suggestion by Hogan and Ebly (1996) that “physicians and other health care practitioners should be curious about all therapies being utilised for any reason by their patients” might be extended to encourage more Western neuroscientists researching Alzheimer’s disease to be curious about traditional uses of plants. Not only is this likely to extend the portfolio of cholinergic (Table 2) and other transmitter-related drugs, but also of agents with antioxidative or anti-inflammatory activities, relevant in the treatment of neurodegenerative diseases such as dementia. In itself such an initiative would hardly compete with the capacity of the synthetic chemist to generate new compounds. But the possibility that there may be as yet undiscovered links relevant to dementia therapy, such as that between the early use of the opium poppy to control pain and insomnia (recorded as far back as 1500 B.C. in Egypt) and the discovery of endogenous opiates and their receptors in the 1970s, is worth considering. Archival and current medical herbal evidence of memory- or cognitive-enhancing agents is available in most cultures.

**Table 3. Plant Species/Phytochemicals Relevant to Cholinergic Therapy in Alzheimer’s Disease**

<table>
<thead>
<tr>
<th>Species*</th>
<th>Active chemical(s)</th>
<th>Ethnic evidence**</th>
<th>Bioactivity in model systems</th>
<th>Efficacy in controlled clinical trials***</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angelica sinensis</td>
<td>?</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Evodia rutaecarpae</td>
<td>dehydroevodiamine</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Ginkgo biloba</td>
<td>ginkgolides</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Huperzia serrata</td>
<td>huperzine</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Melissa</td>
<td>?</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Narcissus</td>
<td>galanthamine</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Nicotiana tabacum</td>
<td>nicotine</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Panax ginseng</td>
<td>?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Paeonia suffruticosa</td>
<td>paeniflorin</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Physostigma venenosus</td>
<td>physostigmine</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Rosmarinus</td>
<td>?</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Salvia</td>
<td>monoterpenoids?</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

*Excluding multispecies formulations such as the Ayurvedic Mentat and Trasina.
**Recorded as being of value in improving memory or countering mental debility in old age.
***Excludes evidence published in non-English language journals.
Schultes (1993) has, for example, identified 25 plant species used by Northwest Amazonian Indians for treating mental debility in old age. Current models of dementia and cerebral function provide new exploratory tools for pursuing such ethnobotanical clues.

Issues worth considering in establishing new research programs in this area, which also apply to medicinal plant research in general, include:

(1) Obtaining authentic evidence on medical herbal practices from primary sources which include, in Europe, translating original Greek and Latin texts.
(2) Establishing with a high degree of certainty the precise botanical species, plant part, harvesting and extracting procedures, and dose level traditionally used—not only regarding efficacy but also safety.
(3) Pursuing anecdotal evidence of the value of particular species by establishing controlled trials in clinically assessed patients with specific dementing disorders such as Alzheimer’s disease. The question of resourcing such trials needs to be resolved in the context of the limited funds available in companies that currently market complementary therapies and the lack of patent rights, underpinning the economy of pharmaceutical companies, on crude plant extracts.
(4) Controlling for variations in the chemical constituents of a given species, according to, for example, the plant part investigated and the time of year (or day) of harvesting by providing a quantitative chemical and bioactive profile in all reported studies. Such variations are liable to lead to inconsistencies in reported bioactivity and clinical efficacy that, in the absence of such control, lead to lack of credibility in phytopharmacology.
(5) Appreciating the issue of synergy; although isolating and identifying individual chemical constituents with relevant bioactivity provides a rational scientific basis for the medicinal use of a plant, synergistic bioactivity due to different constituents is common. In addition, a single plant may contain distinct chemical classes with different activity, each relevant to the treatment of a particular disease.
(6) Valuing, from an ethical viewpoint, the historical discovery and practical details of medicinal plant applications that presumably involved previous societies in prolonged experimental processes of trial and error.

NOTE

Future research in this area depends on interactions between archival, botanical, chemical, clinical, and pharmacological expertise. A new Medicinal Plant Research Centre has recently been established in Newcastle University. This interdisciplinary project includes a medical archivist in the Classics Department, a botanist in the University Botanic garden establishing a collection of the relevant, verified medicinal plants; a chemist, biochemist, and several neurochemists analyzing chemical constituents and bioactivities. The centre is keen to establish links with others interested in this area.

References include both peer reviewed scientific articles and reports based on less clearly controlled, anecdotal evidence. The latter are included for interest and to highlight a dichotomy that is intrinsic to this type of medicinal plant research.

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