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Medicinal Plants and Alzheimer's Disease: from Ethnobotany to Phytotherapy**

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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 *Gingko biloba* in which the gingkolides have antoxidant, 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 Gingko 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.

In reviewing the current use in Canada of complementary or alternative medicine in dementia, Hogan & Ebly (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 enquiry, 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, following 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

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Table 1. Examples of modern, pharmacologically verified, drugs based on traditional plant medicines.

Plant species	Principal active constituent	Medical use
Foxglove, *Digitalis purpurea*, *Digitalis lanata*	Digitoxin, digoxin	Cardiac tonic
Willow, *Salix alba* (and others)	Salicylic acid esters	Analgesic and anti-inflammatory
Opium poppy, *Papaver somniferum*	Morphine, codeine	Analgesic, narcotic
Erythroxyium coca	Cocaine	Local anaesthetic
Rauwolfia serpentina	Reserpine	Tranquillizer, hypotensive
Ephedra equisetina (sinaica and others)	Ephedrine (adrenaline)	Anti-asthmatic
Cinchona pubescens (and others)	Quinine	Anti-malarial
Artemisia annua	Artimesinin	Anti-malarial

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 programmes.

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 & Ebly (1996) was given complementary medicines for cognitive problems, carers 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 practising medical herbalists and aromatherapists in the United Kingdom for memory problems (Bartram 1995; Price & Price 1995). *Ginkgo biloba*, popular on account of its perceived anti-ageing properties including enhancing cerebral activity (Kleijnen & Knipschild 1992; Vesper & Hasgen 1994), has recently been reported to be of therapeutic value in mild to moderately affected patients with Alzheimer's disease (Burkard & Lehri 1991; Kanowski et al 1996; Le Bars et al 1997). In the 1997 placebo-controlled, double-blind, randomized trial, the standardized Ginkgo extract EG6761 was associated with significant improvements in cognitive function (ADAS-Cog) and carers rating (GERRI) 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 fuqui dihuang and Indian Ayurvedic medicines.

Since orthodox medicine in many Westernized societies (including the UK and USA) largely abandoned the medicinal use of plants earlier this century in favour 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 1996)

> "Balm is sovereign for the brain, strengthening the memory and powerfully chasing away the melancholy" (John 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 was drunk daily by his students to help clear the head, increase understanding and sharpen the memory. These statements obtained 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 was 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'' (John Gerard 1597)

> ''It also heals the memory, warming and quickening the senses'' (Nicholas Culpeper 1652)

> ''Sage will retard the 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'' (John Hill 1756).

Sage is also used in Ayurvedic medicine, one of the longest established and still practiced 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 which is reported to be effective in 40% of Alzheimer patients (Fu & 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 weyknesse of the brayne and coldness thereof, sethe rosmaria in wyne and late the paycent receye the smoke at his nose''.

Gerard noted (1597):

> ''Rosemary comforteth the braine, the memorie, the inward senses''.

It is intriguing to consider how the opinions expressed in these herbal encyclopaedias 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 neighbour of John Gerard, Ophelia said ''There's rosemary; that's for remembrance. Pray, love, remember''. Archival evidence of this kind would appear worth exploring 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 accounts 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 oestrogen 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 bioactivity in some of the plants mentioned above. There is for example, a substantial scientific literature on relevant properties of the gingkolides—the chemical constituents of *Ginkgo biloba* considered to be responsible for the medicinal effects of the plant. Specific gingkolides 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 have antioxidant properties.

Several traditional Chinese medicinal herb extracts or chemicals have also been investigated for their effects on current dementia models. For example, paeony (*Paeonia suffruticosa*) is a component of traditional Chinese herbal prescriptions for dementia such as Jin Gui Shen Qi Wen which includes 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 paeony, is also anti-amnaesic in this model and increases cortical cholinergic activity (Hirokawa et al 1996). Shimotsuto, also active in this animal model (Watanabe et al 1991), contains both paeony 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, Skolnick 1997, Cheng & Tang 1998). It is a relatively selective inhibitor of cortical and hippocampal cholinesterase and of acetylcholynesterase compared with butyrylcholinesterase. In placebo-controlled randomized trials, huperzine was significantly better than placebo in improving memory, cognition and behavioural function (Xu et al 1995).

The Ayurvedic herbal formulation Mentat (which consists of 26 plant species) reverses scopolamine-induced memory impairment in animal models (Bhattacharya et al 1995). Trasina (five plant species) also reverses memory impairments associated with surgical lesions of the cholinergic basal forebrain (Bhattacharya & 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*) which is, amongst its numerous beneficial effects, considered to improve memory (Reid 1986) has also been reported to enhance cholinergic activity in similar animal models (Nitta et al 1995; Salim et al 1997) and to have neuroprotective effects in-vitro (Wen et al 1996; Lim et al 1997).

In relation to the European plant species identified above there is some limited evidence on relevant bioactivity. Balm contains various monoterpenes such as citral and citronelial 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. Amongst 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 $< 0{\cdot}1\ \mu$L essential oil per mL (Perry et al 1996). Several different sources and species of Salvia had similar effects suggesting one of its chemical constituents is 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 lavanduiaefolia* (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 [^{3}H]nicotine binding with an IC50 value of $2{\cdot}5\ \text{mg mL}^{-1}$ (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 central cholinergic systems. A variety of cholinergic phytochemicals has 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) which are, without exception, toxic at low concentrations. Their therapeutic value is thus restricted in terms of dosage and chronic application. Preventative, protective and symptomatic 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 3) 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

Table 2. Plant-derived cholinergic drugs.

Type	Chemical	Plant species	
Cholinesterase inhibitors	Physostigmine	*Physostigma venenosa*	Calabar bean
	Galanthamine	*Galanthus nivalis*	Snowdrops
		Narcissus pseudonarcissus	Daffodil
	Huperzine	*Huperzia serrata*	Fern
Muscarinic agonists	Arecoline	*Areca catechu*	Betel nut
	Pilocarpine	*Pilocarpus jaborandi*	
	Muscarine	*Amanita muscaria*	Fly agaric
Muscarinic antagonists	Atropine	*Atropa belladona*	Deadly nightshade
	Hyoscamine	*Hyoscamus niger*	Henbane
	Scopolamine (or hyoscine)	*Mandragora officinarum*	Mandrake
		Datura (numerous species)	e.g. thorn apple
		Scopalia carniolica	
Nicotinic agonists	Nicotine	*Nicotiniana tabacum*	Tobacco
	Lobeline	*Lobelia inflata*	Indian tobacco
	Cytisine	*Laburnum anagyroides*	Laburnum
Nicotinic antagonists	Tubocurarine	*Chondrodendron tomentosum*	
	Sparteine	*Cytisus scoparius*	Broom
	Dihydro-β-erythroidine	*Erythrina* (several species)	
	Methyllycaconitine	*Delphinium brownii*	Delphinium

Table 3. Plant species and phytochemicals relevant to cholinergic therapy in Alzheimer's disease.

Species[a]	Active chemical	Ethnic evidence[b]	Bioactivity in model systems	Efficacy in controlled clinical trials[c]
Angelica sinensis	?	Yes	Yes	No
Evodia rutaecarpae	Dehydroevodiamine hydrochloride	Yes	Yes	No
Ginkgo biloba	Ginkgolides	Yes	Yes	Yes
Huperzia serrata	Huperzine	No	Yes	Yes
Melissa	?	Yes	Yes	No
Narcissus	Galanthamine	No	Yes	Yes
Nicotiana tabacum	Nicotine	Yes	Yes	No
Panax ginseng	?	Yes	Yes	Yes
Paeonia suffruticosa	Paeoniflorin	Yes	Yes	No
Physostigma venenosa	Physostigmine	No	Yes	Yes
Rosmarinus	?	Yes	No	No
Salvia	Monoterpenoids?	Yes	Yes	No

[a]Excluding multi-species formulations such as Ayurvedic Mentat and Trasina. [b]Recorded as being of value in improving memory or countering mental debility in old age. [c]Excludes evidence published in non-English language journals.

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, such as insect pollinators. There may be superior potential therapeutic value in plant products which evolved to attract rather than repel animals, including man.

Comparison with orthodox therapies

Some of the examples provided indicate the potential of a combined ethnobotanical and pharmacognostical approach to developing therapies in Alzheimer's disease. Current orthodox Western strategies in dementia therapy, however rationally based, are not all consistent with cultural traditions. Physostygmine for example, the prototypic cholinesterase inhibitor whose short half-life in-vivo led to the search for longer-acting inhibitors, is not renowned for its traditional uses in memory enhancement. *Physostigma venenosa*, the calabar bean, found in West Africa, was employed locally as an emetic in trials of witchcraft by ordeal (Mann 1992). The synthetic inhibitor tacrine was originally employed to recover consciousness in cases of drug overdose (e.g. of antidepressants with antimuscarinic actions). Galanthamine, a longer acting naturally-occurring enzyme inhibitor derived from the bulbs of *Galanthus nivalis* (snowdrop) or Narcissus (daffodil), provides significant clinical benefit in patients with Alzheimer's disease although adverse effects include nausea and vomiting (Fulton & Benfield 1996). Grieve (1931) records the use of daffodils as an emetic, antidote to poisons and for external use. None of the encyclopaedias mention the use of this species for memory enhancement. Interestingly, both physostigmine and galanthamine, are, in addition to being cholinesterase inhibitors, also non-competitive 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 (*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 (e.g. cognitive-enhancing) evidence of the potential value of nicotine in Alzheimer's therapy (reviewed Court & 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 ischaemia, amyloid peptide and glutamate toxicity. Nevertheless nicotine is a highly toxic alkaloid with adverse cardiovascular and gastrointestinal effects. If non-alkaloid 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 family have been used since the first records of history to induce altered states of consciousness—hallucinations, memory loss, oblivion and even dementia (reviewed Perry & 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 contributed, together with observations in the human brain, 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 with Lewy bodies experience visual hallucinations (Perry & 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 & 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 those 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 BC 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; 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 programmes in this area, which also apply to medicinal plant research in general, include:

Obtaining authentic evidence on medical herbal practises from primary sources which include, in Europe, translating original Greek and Latin texts.

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.

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; the question of resourcing such trials needs to be resolved in the context of the limited funds available in companies which currently market complementary therapies and the lack of patent rights, underpinning the economy of pharmaceutical companies, on crude plant extracts.

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 which, in the absence of such control, lead to lack of credibility in phytopharmacology.

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, and a single plant may contain distinct chemical classes with different activity, each relevant to the treatment of a particular disease.

Valuing, from an ethical viewpoint, the historical discovery and practical details of medicinal plant applications which presumably involved previous societies in prolonged experimental processes of trial and error.

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Additional 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 analysing chemical constituents and bioactivity. The centre is keen to establish links with others interested in this area.

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