

National Institute of Medical Herbalists

in Durham

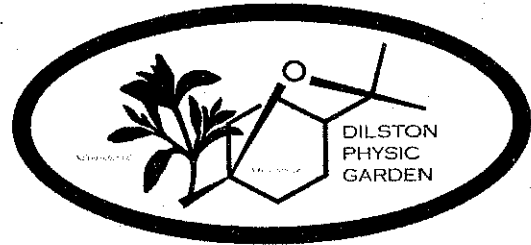
April 2006

Neuroscientist researching disorders of the mind turns to plants for new ideas for therapy

This leads to establishing a Physic Garden and to clinical/scientific projects on herbs for memory and mood enhancement and Alzheimer's

**ABOUT DILSTON PHYSIC GARDEN,
THE WISDOM OF TAKING SAGE
AND BALM TO BE CALM**

and related new research



MIND BODY SPIRIT

DILSTON PHYSIC GARDEN

Unique to northeast England
over 500 medicinal plants

Originally most practicing physicians grew their own plants for the medicines they prepared, based on knowledge handed down for generations

First European physic garden in Pisa in the 16th C



"surely it makes a garden more romantic and wonderful to know that every flower from the first snowdrop to the christmas rose is there not only for man's pleasure but also has its compassionate use for his pain"

(Hilda Leyel, Editor 'A Modern Herbal, Mrs Grieve')

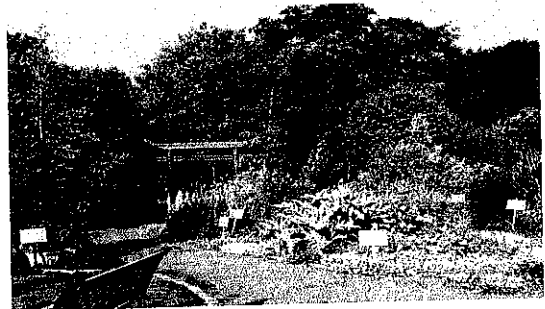
At Dilston Physic Garden (DPG), visitors can learn about herbal medicine as the plants are displayed with detailed labels about their uses, can get to see, touch and smell each of the plants through the seasons, and join courses in medical herbalism and other aspects relating to the wonderful healing properties of individual plant species.

The garden is run as a not for profit organisation which donates to charity.

**DPG is closely linked to the
Medicinal Plant Research Group (MPRC)
in Newcastle and Northumbria Universities**



While physic gardens are still few and far between...



Qualified Medical Herbalists are on the increase

Medical herbalism today

- Fastest growing complementary/alternative medicine
- £100 million business in UK
- Herbalists appearing in high streets
- In Germany herbalism is mainstream medicine
- Remarkable features to interest non medical herbalists

HERBAL MEDICINE

fascinating features:

- plants make chemicals which are healing
- man discovered which plants at what dose to use for which disorder -
pedigree / legacy / survival of safest
- new drug discoveries
- advantages over single chemical drugs -
'cocktail effect' / polypharmacology, and synergy

Crossing the divide?

How to apply current clinical and scientific criteria for the development of new 'drug' therapies based on leads from herbal medical practice?

Criteria such as :

Treatment of symptom / disease mechanism [as opposed to individual]

Activity due to specific plant chemical[s] as opposed to the whole plant

Use of in vitro/ in vivo models

Controlled clinical trials

"New treatments for memory loss, dementia and related symptoms based on neurophytopharmacology"
BOTANICAL DRUGS FOR ALZHEIMER'S DISEASE



and approaches to treating non motor symptoms of Parkinson's disease with such agents

Phytotherapeutic strategies in dementia

- 4 decades neurobiological research but few prescription drugs with queries cost effectiveness / safety.
- Use herbals or nutraceuticals increasingly attractive and traditional use bypasses safety/ toxicity testing.
- Guidance depends on clinical trials, standardised preps, scientific mechanisms.
- Phytotherapeutics for dementia moving towards this target include:
 - Ginkgo biloba*
 - huperzine A
 - other traditional Chinese medicinal herbs
 - sage (*Salvia officinalis* / *lavandulaefolia*)
 - lemon balm (*Melissa officinalis*)
 - curcumin
 - nicotine

HERBAL MEDICINE

fascinating features

plants make chemicals which treat diseases in man:

antibiotics, anti-inflammatories, chemical armoury against predators which act on the nervous or digestive systems etc.

man discovered which plants

at what dose to use for which disorder:

trial and error methods that must have been fraught with hazard as some herbs can be toxic at the wrong dose - 'survival of the fittest drug' selection procedure (balance between efficacy and safety) provides invaluable database

use herbal medicine has led to new drug discoveries with many examples in neuropharmacology

CNS drugs from plants

- | | |
|------------------------|---------------------------------------|
| • Arecoline | <i>Areca catechu</i> (betel nut palm) |
| • Atropine | <i>Atropa belladonna</i> |
| • Caffeine | <i>Coffea arabica</i> |
| • Curcumin | <i>Curcuma longa</i> |
| • Deserpidine | <i>Rauvolfia canescens</i> |
| • L-dopa | <i>Macuna</i> |
| • Ephedrine | <i>Ephedra sinica</i> |
| • Galantamine | <i>Galanthus</i> |
| • Hyoscyamine | <i>Hyoscyamus niger</i> |
| • Kava | <i>Kava kava</i> |
| • Lobeline | <i>Lobelia inflata</i> |
| • Morphine | <i>Papaver somniferum</i> |
| • Physostigmine | <i>Physostigma venenosum</i> |
| • Pilocarpine | <i>Pilocarpus jaborandi</i> |
| • Reserpine | <i>Rauvolfia serpentina</i> |
| • Scopolamine | <i>Datura/Scopolia</i> |
| • Tetrahydrocannabinol | <i>Cannabis sativa</i> |
| • Valaprotirates | <i>Valerian officinalis</i> |
| • Vasicine | <i>Vinca minor</i> |
| • Yohimbe | <i>Pausanystalia yohimbe</i> |

morphine discovered on basis traditional medicine

Numerous cultures with long history medicinal use of opium poppy extracts eg Ancient Egyptians used latex for sleep and pain relief

Morphine extracted from the plant chemically characterised in 1803

Discovery in 1970's opiate receptors and endogenous opiates (enkephalins/endorphins)



ANCIENT GREEKS USED TO INDUCE DEMENTIA AND ALSO HAD A PLANT ANTIDOTE

priestesses to the oracle of Delphi inhaled smoke of henbane to induce a kind of dementia which led to divination

deadly nightshade used by certain women to 'enslave' their male 'victims', who learned to protect themselves using a white flowered black rooted plant

*Circe, the Dread Goddess and Mistress of Potions and Spells

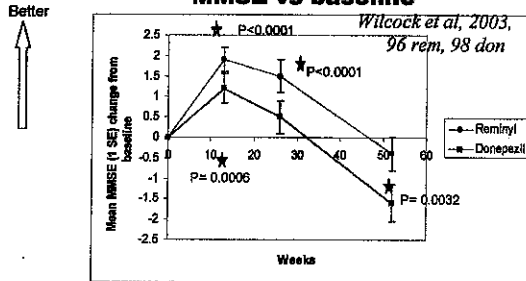


IS THE PLANT DERIVED CHOLINESTERASE INHIBITOR GALANTAMINE BETTER



?

GALANTAMINE(reminyl) VERSUS DOZEPEZIL COGNITIVE FUNCTION DURING 1 Y MMSE vs baseline



PHYTOTHERAPEUTICALS FOR DEMENTIA

HUPERZINE

Club moss, *Huperzia serrata*, used in traditional chinese medicine(TCM) treating and preventing dementia contains Huperzine A, potent anti-cholinesterase alkaloid



CLINICAL TRIAL DATA

Patients 202 AD (100 huperzine, 102 placebo) *Zhonghua Yi, 2002, Xue Za Zhi, 82, 941-4*

Treatment Huperzine Alpha, 400µg/day for 12 weeks

Outcome Cognition: ADAS Cog improved 4.8 (p=0.000)
MMSE improved 2.4 points (p=0.001)

Activities Daily Living: improved (p=0.000)

MINIMUM CHOLINERGIC SIDE EFFECTS

Adverse effects: 3% edema and insomnia on treatment

TCM PHYTOTHERAPEUTICALS FOR DEMENTIA

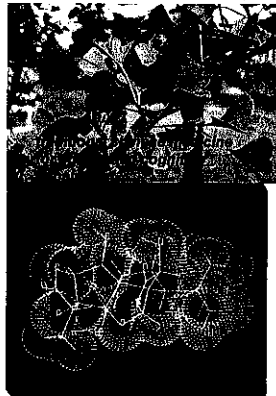
GINKGO BILOBA

Significant benefits in controlled clinical trials

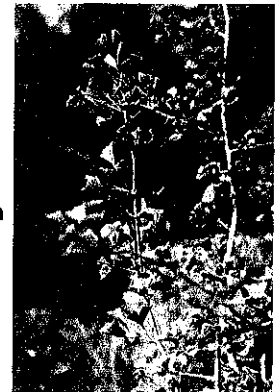
Cochrane Database Syst Rev 2002, 4, CD003120



IS YOUR GINKGO
ACTIVATING YOUR
ENTIRE BRAIN?



Ginkgo biloba
struggles
against prevailing
westerlies
at
Dilston Physic Garden
in Tyne valley



GINKGO BILOBA FOR DEMENTIA

Cochrane Database Syst. Rev 2002 (4): CD003120, Birks et al

REVIEW: all randomized, double blind controlled studies of *Ginkgo* at any strength over any period, compared to placebo, in dementia of any severity.

CONCLUSION

- Improved cognition (<200mg/day, p<0.0001; >200mg/day, p=0.02)
- Activities of daily living benefit (<200mg, p=0.05)
- Mood/emotional function benefit (<200mg/day, p<0.0001)
- No differences between ginkgo and placebo in adverse events

CONTROLLED TRIALS since: Kanowski & Hoerr (2003, *Pharmacopsychiat*, 36, 297-303) significant reduction with EGB761 in ADAS cog; Hoerr (2003, *Pharmacopsychiat*, 36, 556-61) EGB761 improves cognitive, behavioural and psychological symptoms

USERS OF GINKGO BILOBA FOR AT LEAST 2 YEARS OF DRUG INTAKE HAD SIGNIFICANTLY DECREASED ABETA42 PLASMA LEVELS (BLASKO ET AL 2006)

GINKGO BETTER TOLERATED THAN PRESCRIPTION DRUGS

Kurz A et al, *Dement Geriatr Cogn Disord*. 2004;18:217-26.

Ginkgo biloba compared with cholinesterase inhibitors in the treatment of dementia: a review based on meta-analyses by the cochrane collaboration.

- Significant benefits after 6 months on cognition vs. placebo with donepezil, 5 and 10 mg, rivastigmine, 6-12 mg, and galantamine, 16 and 24 mg. Significant benefit vs. placebo with ginkgo only when all doses pooled.
- Similar proportions patients discontinued treatment with ginkgo and placebo but significantly more patients receiving cholinesterase inhibitors discontinued vs. placebo.

SAFETY / TOLERABILITY PEDIGREE OF TRADITIONAL REMEDIES

Mechanistic data on ginkgo in vitro/ in vivo models

- Protects endothelium
- Inhibits low density lipoprotein oxidation
- Reduces mitochondrial DNA damage
- Reduces stroke damage
- **Reduces amyloid deposition/ promotes clearance and protects against A β toxicity**
- Genomic effects –**increases transthyretin* expression** (inhibits a β aggregation and toxicity)
- **Improves memory and enhances LTP in aged rodents**

Ginkgo for the prevention of dementia

2 major clinical trials in elderly non
demented /AAMI
in progress

US (NIH)

3072 non demented

Start 2000, end 2009

France (GEM /GUIDAGE)

2800 non demented with memory loss

5y duration

Other

Traditional Chinese medicines (herbal combinations) for dementia

Iwasaki K et al. J Clin Psychiatry. 2005;66:248-5252

Mild-to-severe dementia randomly assigned **Yi Gan San** (N = 27)
or control (N = 25), treated 4 weeks.

**Significant improvements NPI (from 37.9 to 19.5) and ADL
(from 56.4 to 62.9) scores in YGS group, but not control.**

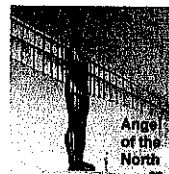
Iwasaki et al. J Am Geriatr Soc. 2004;52:1518-21

33 patients mild to severe dementia randomly assigned

ba wei di huang wan (n=16) or placebo (n=17)

**Mini-Mental State Examination (MMSE) significantly improved
from 13.5 to 16.3 (P<.01) in the BDW group. ADL score
significantly changed, from 61.8 to 78.9 (P<.01)
placebo group no significant change.**

DISCOVERING NOVEL EUROPEAN HERBAL MEDICINES FOR DEMENTIA



NEWCASTLE MEDICINAL PLANT RESEARCH CENTRE

centre without a centre

Universities of Newcastle and Northumbria

Biology, Neuroscience, Psychology, Psychiatry,

Agriculture, Chemistry/Material Products,

Ageing and Health/Clinical Brain Ageing

Links to Newcastle Botanic and Division Physics Gardens,

local Medical Herbalist and Aromatherapy practices

Identify relevant
species from
traditional / ethnic /
herbalist practises

Cultivation local
Botanic Gardens

Screen extracts for
bioactivities relevant to
disease

Chemical
characterisation

Effects on cognition
and mood in normal
volunteers

Controlled clinical
trials in patients

SEARCHING HISTORICAL ARCHIVES FOR PLANT SPECIES

16-18th century Herbals

eg

John Gerard
Nicholas Culpepper
John Hill
John Evelyn

Philippus Paracelsus

20th century

eg

Mrs Grieve
Thomas Bertram



RELEVANT TO COGNITIVE FUNCTION eg MEMORY

John Gerard Medical Herbalist

contemporary of

William Shakespeare



"Rosemary conforteth the brain
the memorie, the inward senses"



"There's rosemary for remembrance
-pray love remember"

[Ophelia in 'Hamlet']

SAGE, *Salvia officinalis*



"It is singularly good for the head and brain and quickeneth the senses and memory"
(John Gerard, 1597)

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

"Sage will retard that rapid progress of decay that trends upon our heels so fast in latter years of life, will preserve faculties and memory more valuable to the rational mind than life itself"
(John Hill, 1756)

LEMON BALM
University of Newcastle
MOORBANK BOTANIC GARDEN



Salm (*Melissa officinalis*)
Bauxm. hot and dry, cordia and exhilarating, sovereign for the brain strengthening the memory"
John Evelyn, Accademia, 1699

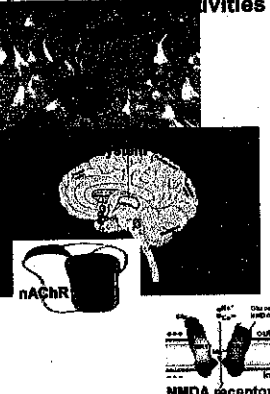
Testing selected herb extracts for bioactivities relevant to memory



Gudrun Court, Natalie Bidet, Nicolette Perry, SUMMER STUDENT PROJECT 1995

Screening plant extracts for bioactivities In vitro

neurotransmitter
beta secretase
antioxidant
anti-inflammatory
oestrogenic



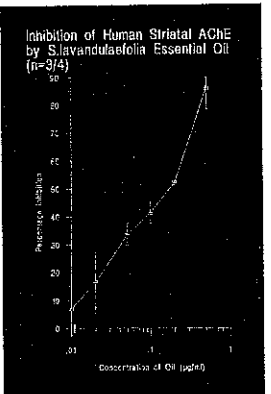
nAChR
NMDA receptor

SAGE EXTRACTS INHIBIT HUMAN BRAIN ACETYLCHOLINESTERASE

IN VITRO
Perry N et al, 1998; 2001; 2003

IN VIVO
Perry N et al, 2002

No inhibition by other plants selected for archival evidence of memory enhancement eg lemon balm, rosemary, wormwood



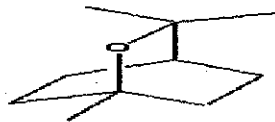
Inhibition of Human Striatal AChE by *Salvia officinalis* Essential Oil (n=3/4)



Over 20 species of sage in Dilston Physic Sage Garden

Salvia officinalis purpurea

Active terpenoids in *Salvia*



1,8-cineole: C₁₀H₁₈O

IC₅₀ (mg/ml) AChE inhibition

Spanish sage oil	0.05±0.01
1,8-cineole	0.06±0.01
α-pinene	0.09±0.005
β-pinene	0.20±0.004



α-pinene: C₁₀H₁₆

Presence does not fully account for AChEi activity
.... suggests:
-synergy?
-other unidentified active chemicals?

Sevelev et al, 2003

Plants with cholinesterase inhibitory activities discovered in last 3 years

<i>Withania somnifera</i>	
<i>Tabernaemontana australis</i>	
<i>Otostegia limbata</i>	
<i>Sarcococca saligna</i>	
<i>Sarcococca hookeriana</i>	
<i>Cynanchum atratum</i>	
<i>Lycopersicon esculentum</i>	Tomato
<i>Corydalis speciosa</i>	
<i>Nerine bowdenii</i>	
<i>Gentiana campestris</i>	
<i>Camellia sinensis</i>	Green tea
<i>Areca catechu</i>	Betel nut
<i>Cocculus pendulus</i>	
<i>Salvia miltiorrhiza</i>	Red / Chinese sage
<i>Vaccinium oldhamii</i>	
<i>Celtis chinensis</i>	
<i>Lycopodium sieboldii</i> and <i>clavatum</i>	
<i>Ptychopetalum olacoides</i>	
<i>Buxus hyrcana</i>	Caspian Box
<i>Oenothera biennis</i>	

Predator deterrents in leaves, roots, fruits, nuts, bark

SAGE and amyloid in vitro



S. officinalis and active ingredient rosmarinic acid protect PC12 cells from Aβ toxicity
Rosmarinic acid also reduces tau hyperphosphorylation and inhibits p-p38 MAP kinase

Juvone T, De Filippis D, Esposito G, D'Amico A, Izzo AA
J Pharmacol Exp Ther. 2006 Feb 22



Sage improves memory in rodent model

Eidi et al, Nutrition, 2006 Mar;22(3):321-6 Effects of *Salvia officinalis* L. (sage) leaves on memory retention and its interaction with the cholinergic system in rats.

data - administration ethanolic extract *S. officinalis* (50 mg/kg), pilocarpine (0.5 and 1 mg/rat), and nicotine (0.1 and 1 mg/rat) increased, while mecamylamine (1, 5 mg/rat) decreased memory retention in rats.

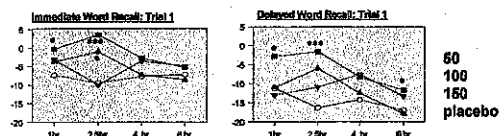
conclusion -sage interactions with muscarinic and nicotinic cholinergic systems involved in the memory retention process

TESTING SAGE EFFECTS ON COGNITION IN MAN *Salvia Lavandulaefolia* [spanish sage] enhances memory in healthy young volunteers

Tildesley N et al, Pharmacol Biochem Behaviour 2003 75: 669-674

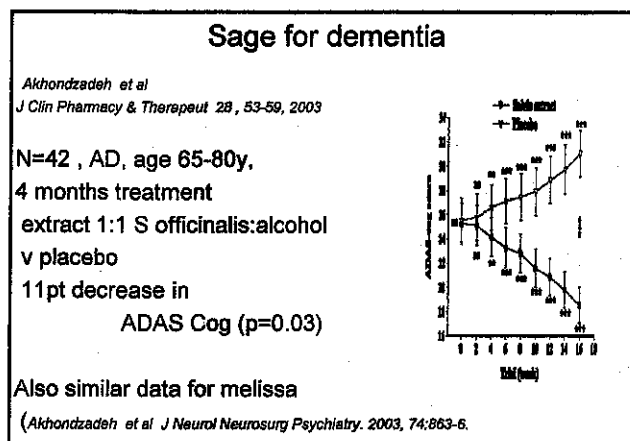
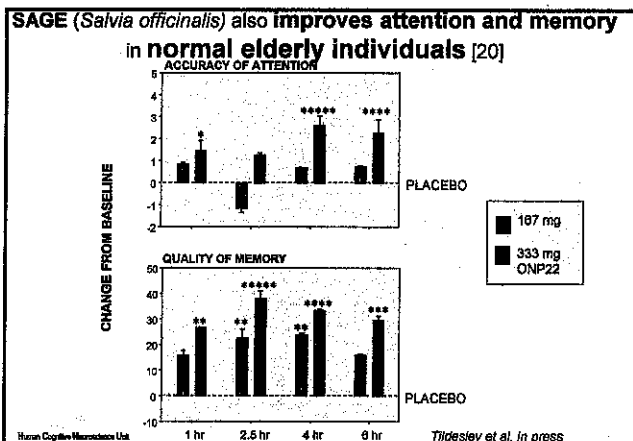
Acute effects oral (25, 50, 100 and 150μl) *S. lav* essential oil and placebo [sunflower oil] capsules

50μL significantly improved immediate and delayed word recall



First systematic evidence that sage can improve cognition in healthy young adults

Northumbria University
Human Cognitive Neuroscience Unit



Sage is also mood enhancing

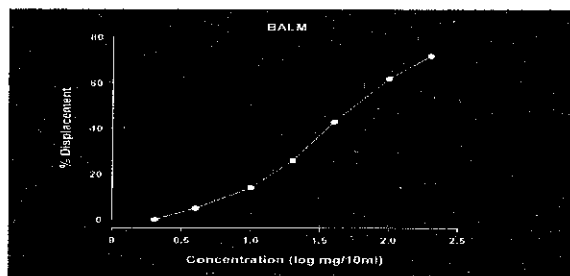
- Mood consistently enhanced, with increases in self-rated 'alertness', 'calmness' and 'contentedness' following the 50 μ l dose essential oil *S. lavandulifolia* and elevated 'calmness' following 25 μ l (Tildesley et al 2005)
- 300 and 600 mg doses dried sage leaf improved ratings of mood; lower dose reduced anxiety and the higher dose increased 'alertness', 'calmness' and 'contentedness' on the Bond-Lader mood scales (Kennedy et al 2006)



LEMON BALM HAS DIFFERENT CHOLINERGIC ACTIVITY THAN SAGE

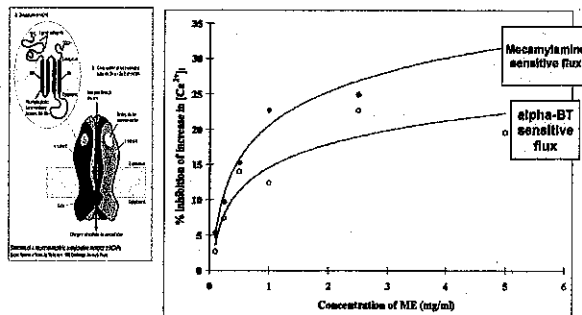
MELISSA officinalis extracts INTERACT WITH NICOTINIC RECEPTOR

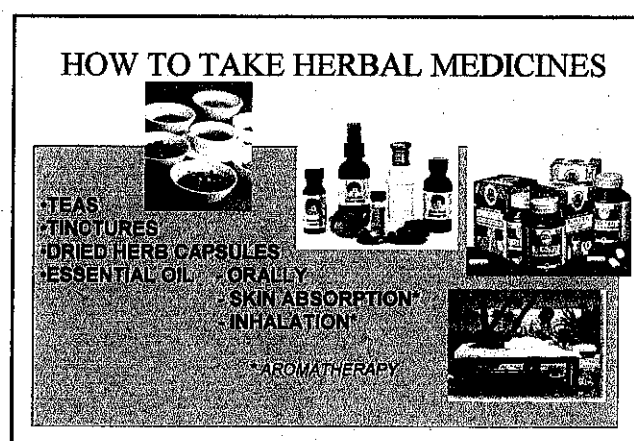
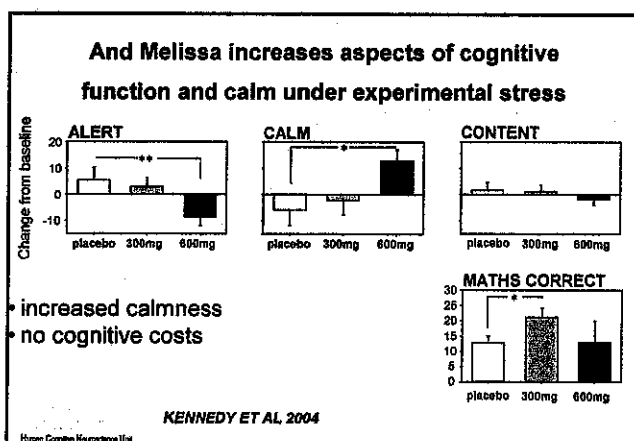
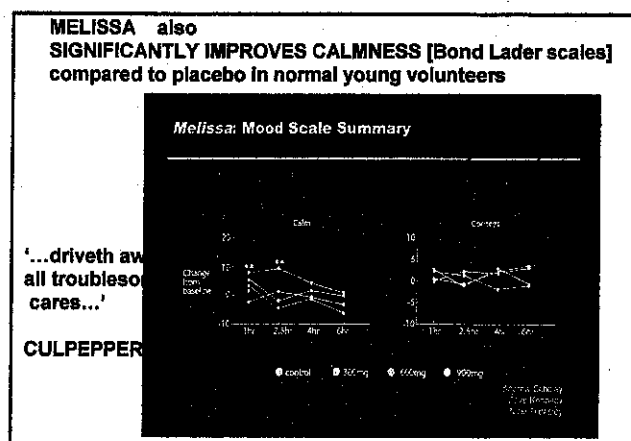
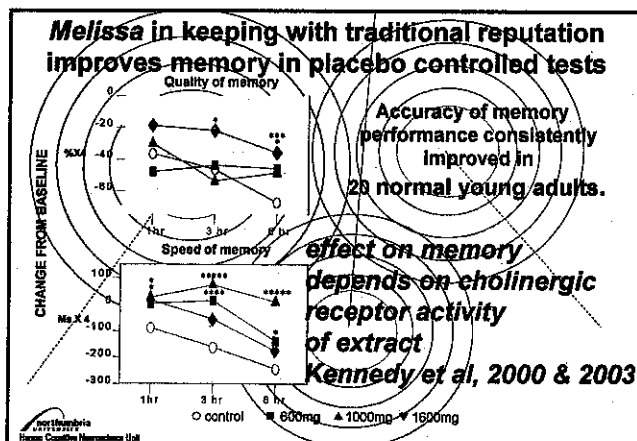
Effects herb extracts on receptor binding in human brain membranes in vitro



NICOTINIC CALCIUM CHANNEL OPENING STIMULATED BY MELISSA

dose dependent calcium flux via nicotinic receptors in neuronal cell line [SH SY5Y] sensitive to mecamylamine and lesser extent α BT suggests effects on α 3/5 > α 7 subtypes





Melissa (lemonbalm) aromatherapy for agitation in dementia
(Ballard et al 2002)

SIGNIFICANT IMPACT

- Reduced agitation
- Reduced neuropsychiatric symptoms
- Reduced social withdrawal
- Increased constructive activities

VERY WELL TOLERATED

Reduction in Agitation after 4 weeks

Melissa Aromatherapy Trial	Change in Median		Statistical Evaluation
	Melissa (N=35)	Placebo (N=36)	
Change in CMAI -total	↓ 22.0	↓ 6.5	MWU Z=4.1 p<0.0001*
CMAI -Physical aggression	↓ 6.0	↓ 3.0	MWU Z=2.5 P=0.01*
CMAI -Physical non-aggression	↓ 9.0	↓ 2.0	MWU Z=4.2 P<0.0001*
CMAI -Verbal aggression	↓ 1.0	↓ 1.0	MWU Z=0.4 P=0.71
CMAI -Verbal non-aggression	↓ 4.0	↓ 1.0	MWU Z=3.5 p=0.001*

Also reduces social withdrawal (P=0.01) and increases constructive activities (p=0.001)
Ballard et al 2002

AROMATIC ESSENTIAL OIL THERAPY CONTROLLED CLINICAL TRIALS IN PEOPLE WITH DEMENTIA – up to 4 weeks



- Mitchell et al (1993)** - 12 people, *Melissa* and lavender versus placebo.
- Holmes et al (2001)** - 21 people with agitation, lavender, cross-over
- Smallwood et al (2001)** - 21 people, lavender, randomised comparison
massage
- Ballard et al (2002)** - 72 people with agitation, *Melissa*, double blind
placebo controlled

REDUCTIONS IN AGITATION, EXCESSIVE MOTOR BEHAVIOUR
INCREASED COMMUNICATION, SOCIAL INTERACTION, CONSTRUCTIVE BEHAVIOURS

Aromatherapy for dementia- smell is not enough

- purely olfactory form of aromatherapy (lavender) ineffective in decreasing agitation in severely demented patients (Snow et al, 2004).
- cutaneous application of the essential oil necessary to achieve the effects reported (eg Smallwood et al, 2001; Holmes et al, 2001; Lee et al 2005).

New Multi-Centre Trial of herbal essential oil therapy for agitation in Dementia

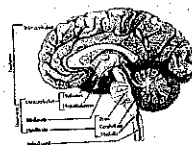


- Selection and standardisation essential oil –
Melissa / Lavender / both
based on optimal neuropharmacological
activity and GCMS

- 150pts - 50 Ess. oil in lotion on skin, 50 Donepezil, 50 placebo
(Nose clips on assessors to avoid placebo effect)

Alzheimer Society Programme Grant, 2005-2008
Alistair Burns, Clive Holmes, Clive Ballard,
Mark Elliott, Paul Francis, Paul Chazot, George Lees, Elaine Perry

AROMATHERAPEUTIC MECHANISMS: NEUROPHARMACOLOGY



Essential oil chemical constituents
(terpenoids) enter bloodstream,
via inhalation and/or transdermally,
from which - as lipophilic chemicals,
readily cross blood brain barrier
and interact with neurons



Terpenoids interact with
key receptors in
brain involved in
psychopharmacological
mechanisms

eg Anti - Agitation

GABA -A, nicotinic, 5-HT 1A /2A
receptors

Neuroactive effects in vitro/vivo of plant essential oils/terpenes relevant to agitation

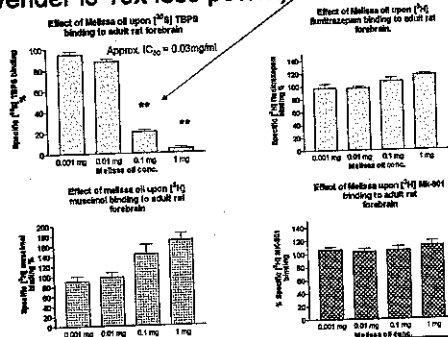
- Sedative effects of lavender in vivo correlate with serum levels of linalool
[Buchbauer et al, 1991]
- Linalool interacts with the GABA-A receptor in vitro [Silva Brum et al,
2001]
- Citronellal potentiates GABA -A receptors in vitro [Aoshima and
Hamamoto, 1999]
- Chamomile reduces stress response in vivo [Umezui et al 1999]
- 5-HT1A, 5-HT2A, H3, M1 and GABA A receptor binding effects lavender
and melissa oils in vitro (submitted, Mark Elliott, Paul Chazot)
and PD?
- Peppermint and rosemary increase locomotor activity in vivo [Umezui et
al 2001; Hohmann et al 1999]

AS Programme new data Neuropharmacology of melissa and lavender essential oils relevant to agitation in dementia

- Pharmacological screen using radioligand binding in rat cortical
membranes for interaction with G-protein coupled receptors (5-HT1A, 5-
HT2A, muscarinic M1 and histamine H3) and ligand-gated ion channel
receptors (NMDA, GABA A channel, agonist and benzodiazepine sites)
implicated in agitation in severe dementia
- effects of both oils at the H3 ([3H]-clobenpropit) and 5-HT2A ([3H]-
ketanserin) receptors.
- Melissa oil alone also inhibits binding of [3H]-8-OH-DPAT to 5-HT1A
receptors and [3H]-pirenzepine to M1 receptors and modulates TPBS
binding to GABAA channel
- Melissa oil has the broader relevant pharmacological profile and has
been selected for new multicentre clinical trial

Mark Elliott, Paul Chazot, George Lees, Paul Francis, Elaine Perry

Melissa essential oil modulates GABA_A but not NMDA receptor channel (lavender is 10x less potent)



Paul Chazot et al In prep

BEYOND SYMPTOMATIC THERAPY -PHYTOTHERAPEUTICALS FOR DISEASE PREVENTION / STABILISATION?

- SAFETY OF HERBALS ESTABLISHED THROUGH TRADITIONAL USAGE
 - toxicity data available on many used in food industry
- UNDESIRABLE SIDE EFFECTS MINIMAL compared to many synthetic drugs
 - relevant to long term / prophylactic use

Neuroprotective plants /extracts - neuroscientific evidence 2000-2005 based on animal models of brain ageing

eg Aβ / glu toxicity, ischemia

- *Ginkgo biloba* * prevention trials in progress
- *Nicotiana tobacum* / nicotine
- *Curcuma longa* / turmeric
- *Camellia sinensis* / Green tea
- *Allium sativum* / garlic
- *Cannabis sativa* /cannabinoids
- *Punica granatum* / Pomegranate
- *Vitis* / Red grape wine / flavinoids
- *Vaccinium* / Blueberries

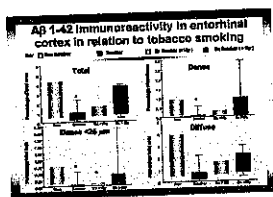
Nicotinic neuroprotection in models

NICOTINE

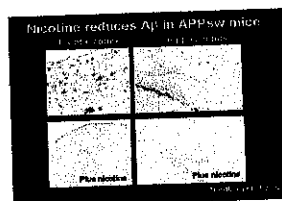
- Prevents amyloid deposition /fibrillisation
- Protects against Aβ and NMDA toxicity
- Promotes neurotrophin gene expression eg BDNF, FGF2
- Up-regulates ubiquitin-conjugating enzymes, 20S and 19S proteasomal subunits, proteasome beta subunit 1 (PSMB1) and 26S ATPase 3 (PSMC3) genes
- Prevents dopaminergic neuron loss

Alpha 4,6,7 nAChR?

NICOTINIC ANTI-AMYLOIDOGENIC EFFECTS Chronic nicotine reduces Aβ deposition in mouse and man



Dose dependent Aβ ICC reduction in human cerebral cortex related to smoking (Court et al, 2005)



10-fold reduction in Aβ ICC in nicotine treated APPsw mouse cortex and hippocampus (Nordberg et al, 2002)

GREEN TEA *Camellia sinensis* the ultimate NEUROPROTECTIVE?

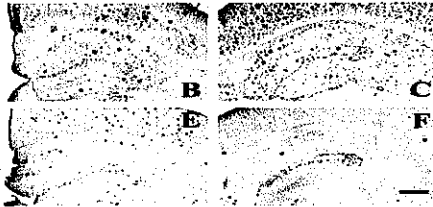
- Antioxidant (Lee et al 2000)
- Anti-AChE (Okello et al 2004) and facilitates cholinergic transmission in vivo (Katayama et al 2002)
- Activates cell survival genes and PKC signalling [Mandel et al 2005]
- Neurite outgrowth enhanced [Reznichenko et al 2005]
- Anti amyloid -reduces abeta in models [Rezai-Zadeh et al 2005, Lee SY et al 2005], reduces toxicity a beta [Levites Y et al 2003, chai YT et al 2001], inhibits beta secretase [Okello et al 2004]
- Proteasome inhibitor (Arbiser et al, 2005; Wan et al, 2005 and 2004) - low doses of proteasome inhibitors improve proteasome function with anti alpha synuclein potential

active chemicals catechins eg (-)-epigallocatechin
not caffeine or theobromine

CURCUMIN REDUCES AMYLOID

fewer amyloid deposits in curcumin treated Tg2576 transgenic mice (E and F) compared to control mice (B and C). (B and E from anterior hippocampal sections, C and F from posterior.)

(Yang et al. 2005)



GARLIC *allium sativum* (aged)

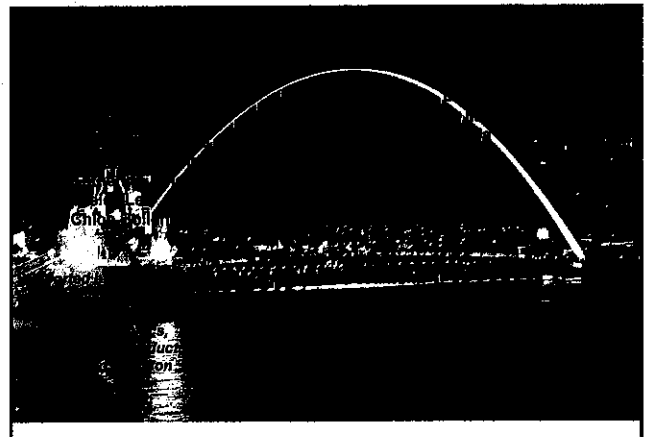
- antioxidant and ROS scavenging activities which **reduce β -amyloid induced apoptosis** by reducing caspase-3 activation and DNA fragmentation (Peng et al. 2002)
- **attenuates cytotoxicity beta-amyloid** on undifferentiated PC12 cells (Selassie et al. 1999)
- **decreases A β induced lipid peroxidation** (Griffin et al. 2000).

BOTANICAL DRUGS AS ALZHEIMER'S DISEASE TREATMENTS

For select herbal medicines

- Clinical efficacy and safety increasingly reported
- Mechanisms accounting for symptomatic improvements identified
- Potential for disease prevention
- New therapeutic leads for other dementias / psychiatric disorders

...relevance for non motor symptoms of *Parkinson's disease*.....



NEW RESEARCH PROGRAMME a botanical agent for the non motor symptoms of PARKINSON'S DISEASE

- For Parkinson's disease many plants have been studied for benefit on motor symptoms, especially the *Mucuna* bean
- However there is little or no research on potential effects of plant medicines for non motor symptoms
- Newcastle Medicinal Plant Research Group have discovered new approaches to treating disorders of cognition and mood using plant extracts.
- This research is applicable to treating some of the non motor symptoms in Parkinson's disease for which there is a need for novel, safe and effective strategies

BACKGROUND MUCUNA BEAN BETTER THAN LDOPA FOR PARKINSON'S DISEASE: clinical evidence

Katzenschlager R et al
J Neural Neurosurg Psychiatry. 2004;75:1672-7



TRADITION seed powder of leguminous plant, *Mucuna pruriens*, long used in traditional Ayurvedic Indian medicine for diseases including parkinsonism.

CLINICAL TRIAL

8 PD patients with short duration L-dopa response completed randomised, controlled, double blind crossover trial of single dose challenges with LD and *mucuna* preparation in randomised order at weekly intervals
rapid onset of action and longer on time without concomitant increase in dyskinesias on *mucuna* seed powder formulation

natural source of L-dopa possesses advantages over conventional L-dopa preparations (due to other actives?)

botanical agents relevant to non motor symptoms of Parkinson's disease

- **Ginkgo** for cognition (one report psychosis in schizophrenia)
- **Sage or lemon balm** for cognition (added effects melissa on neuropsychiatric aspects, sage on mood; more mechanistic data for sage; sage also used to reduce salivation in PD)
- agents that improve sleep such as **chamomile** – chamomile traditionally used to improve night time sleep but only one clinical trial in elderly in residential care and no relevant pharmacological studies (except mark elliot's data)
- agents that reduce apathy such as **peppermint** which also reduces daytime sleepiness – use for apathy is traditional but there are clinical trials on sleepiness (eg Norrish and Dwyer 2005) and some relevant pharmacological data (eg Mark's on 5-HT1A)
- **St John's wort** for depression (substantial clin / mech data)

Long term outlook for a positive pilot trial of a herbal treatment of non motor symptom PD

- Provide a novel safe and attractive option for treatment of a symptom that either does not respond to drugs or if it does there are unpleasant side effects
- Stimulate larger multicentre trial
- Encourage further mechanistic studies which promote acceptance of such agents and more importantly provide the potential for new drug discovery

BACKGROUND : DIVERGENT CLINICAL PRACTICES

MEDICAL HERBALISM	DRUG
Plant extract complex (thousands chemicals)	Single chemical (most synthetic)
Mechanisms of action complex/unknown	Targets disease mechanism
Efficacy based on traditional uses	Controlled clinical trials
Safety established empirically	Preclinical toxicity testing
Unlicensed / freely available	Licensed for prescription

TWO REASONS WHY THE WHOLE PLANT MAY BE POTENTIALLY SUPERIOR TO SYNTHETIC DRUG –

- Safety and efficacy established far longer due to traditional use
- Multiple chemicals provide a more effective 'polypharmacological' approach

Dilston Physic Garden Northumberland Medicinal Plants

www.dilstonphysicgarden.com

Open to public every Wed and Sat 10am to 1pm
GROUPS WELCOME

Over 500 medicinal plants



mind-body-spirit

Courses : eg Medical Herbalism, Homeopathy, Flower remedies, Shamanism

Corbridge
Northumberland

DPG FEATURES –SEE RED BROCHURE

- **Japanese torii** –the gate to a Shinto shrine (shintoism is a form of shamanism) that marks the transition from the everyday to the spirit world . constructed by local artist
- **Aromatic herbs** which on a hot day emit delightful scents that bounce off the heated gravel paths – such herbs as lavender, sage, rosemary, thyme, marjoram, lemon balm, fennel, mint, wormwood, mugwort, sweet rocket / dame's violet, scented viburnum, rose including the apothecary's rose, elder, chamomile
- **Herbal teas** – groups are treated to a refreshing herbal tea made from a selection of these aromatic herbs specially concocted for its delicate flavour with guaranteed effects to stimulate the mind and calm the mood.
- **Chamomile lawn** –a labour of love, needing to be hand weeded weekly, but immensely rewarding as a soft, aromatic carpet with built-in rest and relaxation facilities.
- **Heart and mind** section contains three herbs for the heart –foxglove, lily of the valley and hawthorn and four for the mind –sage, ginkgo, lemon balm, rosemary.
- **Woodland, hedgerow, pond, wall, orchard and culinary** sections.
- **Sage garden** with over 20 of different species that survive in Northumbria.
- **Poison garden** includes mandrake, deadly nightshade, Japanese belladonna (*Scopolia*), henbane, thornapple, angels trumpet, various species of yew, wild lettuce, monkshood, periwinkle, delphinium and daphne.

SOME OF THESE POISONOUS SPECIES ARE SHAMANIC 'PLANTS OF THE GODS'

CHOLINERGIC PLANTS OF THE GODS 3 MOST COMMONLY USED HERBS IN WITCHCRAFT

Inducing trance like states of
'spirit flight' and visions of people and animals

- **ATROPINE**
Deadly Nightshade
- **HYOSCYAMINE**
Henbane
- **SCOPOLAMINE**
Japanese Belladonna

THE HEXING HERBS



PLANTS OF THE GODS

Exploring Two Hypothesis



1. NEURO SCI -ENCE

Material / Mechanistic / Experimental / Objective knowledge

Chemicals - brain systems - neuropsychopharmacology

2 'PSI' -ENCE

Experiential / Subjective knowledge / Spirit World

'psi' ...vibrational energy -telepathy, clairvoyance, precognition, shamanic, spirit contact

CHAMOMILE LAWN AT DILSTON PHYSIC GARDEN



INVITATION

Members of the National Institute of Medical Herbalism

Do please visit us at Dilston Physic Garden



Colin Cuthbert has taken the photos of the plants at DPG