DEMENTIA, COGNITION, AND ALZHEIMER'S DISEASE

BOTANICAL AND NATURAL INTERVENTIONS

DEMENTIA

- Neurogenerative diseases are on the rise and have a high global economic, emotional, and societal impact.
- Alzheimer's disease, is an age-related neurodegenerative disease and the most common cause of dementia, with a global prevalence estimated at 26.55 million in 2006.
- There are no curative treatments. Despite considerable efforts, the available drugs are not highly effective, and there is great interest in searching for novel compounds.
- Preventatives show the most promise, as we search for both palliative symptomatic therapies, and the so-far non-existent restorative or truly effective treatments.

PHARMACEUTICAL THERAPIES FOR DEMENTIA

ONLY FIVE DRUGS HAVE BEEN DEVELOPED TO ALLEVIATE COGNITIVE SYMPTOMS:

- **Acetylcholinesterase inhibitors –** 2 are inspired by naturally occurring compounds, Galantamine and Rivastigmine
- **N-methyl-D-aspartate (NMDA) antagonists -** Memantine
- **Piracetam -** is a nonprescription nootropic drug designated by the FDA as an orphan drug for myoclonic seizures
- **Antipsychotics –** offer Sx relief but increase risk of strokes and other morbidity.

All of these provide some symptomatic relief in dementia, but do not prevent progression.

PHARMACEUTICAL THERAPIES FOR DEMENTIA

Protein aggregates contribute to neuronal death and neurotransmitter deficits in AD including:

- **extracellular plaques of Abeta-peptide**
- **intracellular neurofibrillary tangles**

J Nutr Health Aging. 2011 Jan;15(1):45-57. *Progress in the development of new drugs in Alzheimer's disease.* Piau A1, Nourhashémi F, Hein C, et al

PHARMACEUTICAL THERAPIES FOR DEMENTIA

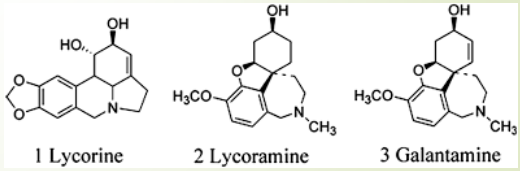
Drugs that target the production, accumulation and toxicity of these substances are being investigated and include:

- **Statins**
- **Advanced Glycation End Products (AGE) receptor inhibitors**
- **Thiazolidinediones**
- **Insulin**
- **Hormonal therapies**
- **Beta Secretase Inhibitors**

ALL SUCH DRUGS MAY HAVE NATURAL REMEDIES ACTING VIA WHOLISTIC MECHANISMS

CHOLINESTERASE INHIBITORS

- **Tacrine [Cognex®],**
- **Donepezil [Aricept®],**
- **Rivastigmine [Exelon®, Exelon Patch®],**
- **Galantamine [Reminyl®, Razadyne®])**



1 Lycorine 2 Lycoramine 3 Galantamine

RESEARCH HORIZONS FOR AD

- **Because amyloid-β (Aβ) has been implicated in AD pathogenesis, the use of β secretase inhibitors as well as immunotherapy against Aβ is being investigated.**

Expert Rev Neurother. 2014 Dec 8:1-3. *Pharmacotherapy of Alzheimer's disease: current and future trends.* Geldenhuys WJ1, Darvesh AS.

PHYTOCHEMICALS FOR DEMENTIA

- **CANNABINOIDS – Such as cannabidiol from *Cannabis sativa* for BPSD.**
- **RESVERATROL – In Red Grapes, Peanut skins may delay the progression.**
- **CURCUMINOIDS – Flavonoids in *Curcuma longa* may delay the onset of dementia.**
- **GINGKOLIDES – Antioxidant and anti-inflammatory cerebrovascular agents found in *Gingko biloba*.**
- **SESQUITERPENE LACTONES – Found in Asters *Erigeron, Inula***

BOTANICALS FOR DEMENTIA

- Saffron (*Crocus sativus*)
- Ginseng (*Panax species*)
- Sage (*Salvia species*)
- Lemon balm (*Melissa officinalis*)
- Yokukansan (*Polygala tenuifolia*)
- Tobacco (*Nicotiana tabacum*)

NUTRIENTS THAT MAY SUPPORT COGNITION

- Clinical research on nutrients are lacking, but as molecular research advances, many nutrients are being identified as important to preventing and retarding neurodegeneration.

Acta Clin Belg. 2014 Jan-Feb;69(1):17-24. *Rationale and clinical data supporting nutritional intervention in Alzheimer's disease.* Engelborghs S, Gilles C, Ivanoiu A, Vandewoude M.

IMPORTANT BRAIN NUTRIENTS

- Uridine monophosphate
- Choline
- Omega-3 fatty acids
- Medium Chain Fatty Acids
- Phospholipids.
- B-Vitamins
- Amino Acids (DMAE)

HEAD TRAUMA AND DEMENTIA

HEAD TRAUMA (TBI) AND DEMENTIA RISK

- **Younger adults may be more resilient to the effects of recent mild TBI than older adults.**
- **Patients suffering TBI at 55 years or older or mild TBI at 65 years or older show an increased risk of developing dementia.**
- **Older veterans having suffered a TBI show a 60% increased risk of developing dementia than veterans without TBI.**
- **A large cohort study conducted in Sweden found a strong association between young onset dementia and traumatic brain injury.**

- **JAMA Neurol.** 2014 Dec 1;71(12):1490-7. *Dementia Risk After Traumatic Brain Injury vs Nonbrain Trauma: The Role of Age and Severity.* Gardner RC1, Burke JF2, Nettiksimmons J3, et al.
- **Neurology**. 2014 Jul 22;83(4):312-9. *Traumatic brain injury and risk of dementia in older veterans.* Barnes DE1, Kaup A2, Kirby KA2, et al.
- **Ann Neurol.** 2014 Mar;75(3):374-81. *Traumatic brain injury and young onset dementia: a nationwide cohort study.* Nordström P, Michaëlsson K, Gustafson Y, Nordström A.

HERBS FOR HEAD TRAUMA

- *Hypericum perforatum*
  St Johnswort
- Traditional remedy for head, spine, nerve, and fingertip injuries, neuralgia and nerve inflammation, contusions and vascular weakness.
- Use tea, tincture, encapsulations, and topical preparations.

HERBS FOR HEAD TRAUMA

- *Centella asiactica*
  Gotu Kola
- Traditional for memory and cognition, as well as fractures, ulcers, tissue healing.
- Use tea, tincture, encapsulations, and topical preparations.

HERBS FOR HEAD TRAUMA

- *Withania* Ashwagandha
- *Ganoderma* Reishi
- *Gingko* Maidenhair Tree
- *Curcuma* Turmeric
- *Arnica* Leopard's Bane

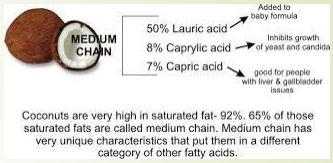
NUTRIENTS

- Fish Oil, MCTs
- Co-Q10
- Flavonoids

LIPIDS, STEROLS, AND DEMENTIA

MEDIUM CHAIN TRIGLYCERIDES (MCT) FOR DEMENTIA

- Supplementing with Medium Chain Triglycerides (MCT) is aimed at increasing neuronal metabolism as this may have a protective effect against further degeneration in AD.
- MCTs are metabolized to ketone bodies that serve as an alternative source of energy for neurons.



MCT FOR DEMENTIA

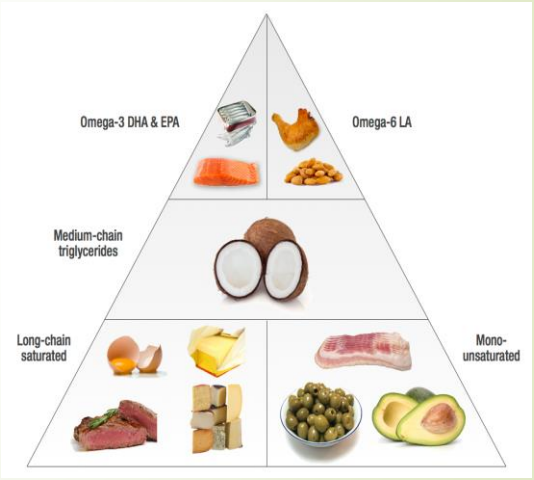
PLANTS HIGH IN MCT

- *Cocos nucifera* Coconut
- "Palm" oil
  - Butter contains MCT and LCT
  - Olives and some palms are high in LCT, and low in MCT

MEDIUM CHAIN TRIGLYCERIDES

- **Clinical trials suggest that MCTs improve cognition in patients with mild to moderate AD in apolipoprotein E4-negative patients. Adverse events observed were mild and included minor gastrointestinal problems such as diarrhea, dyspepsia, and flatulence.**

Am J Alzheimers Dis Other Demen. 2014 Jan 9. *Role of Medium Chain Triglycerides (Axona(R)) in the Treatment of Mild to Moderate Alzheimer's Disease*. Sharma A1, Bemis M, Desilets AR.



MEDIUM CHAIN TRIGLYCERIDES

- **Axona(®)**
- **Souvenaid(®)**
- **CerefolinNAC(®)**

3 nutraceutical medicinal foods based on MCTS aimed at increasing ketone bodies as alternative energy source to neurons and enhance synaptic function.

Clin Pract (Lond). 2012 Mar;9(2):199-209. *Use of medical foods and nutritional approaches in the treatment of Alzheimer's disease.* Thaipisuttikul P1, Galvin JE.

PUFAS FOR DEMENTIA

- **Fish oils provide the PUFAs (EPA) and (DHA), both associated with reducing the risk of dementia in epidemiological studies.**
- **Mouse models of AD suggest that these oils reduce amyloid accumulation, as do consumption of plant sterols.**

J Nutr Biochem. 2014 Feb;25(2):157-69. *Special lipid-based diets alleviate cognitive deficits in the APPswe/PS1dE9 transgenic mouse model of Alzheimer's disease independent of brain amyloid deposition.* Koivisto H1, Grimm MO2, Rothhaar TL3, et al.

PUFAS AND DEMENTIA

- **Supplementing these oils plus all the nutrients and cofactors needed to synthesis neuronal membranes, including uridine-monophosphate; choline; folate; vitamins B6, B12, C and E; phospholipids and selenium improves spatial learning and other models of cognitive strength.**

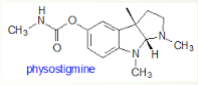
PHYTOCHEMICAL CHOLINESTERASE INHIBITORS

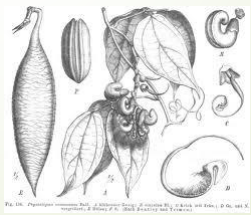
CHOLINESTERASE INHIBITOR THERAPY

- Cholinesterase inhibitors are among the most effective palliative treatments for AD.
- Two of the licensed cholinesterase inhibitors are naturally derived (galantamine and rivastigmine), creating much interest in similar plant derived compounds to treat dementia.
- Many WHOLE PLANT extracts may be superior to isolated alkaloids or other plant compounds, because they are synergistic and can work via multiple mechanisms at once.
- There is very limited research on whole plants for dementia and no human studies, but growing animal research, and research on identifying new cholinesterase inhibitors.

PHYTOCHEMICAL CHOLINESTERASE INHIBITORS

- The alkaloid physostigmine, is a cholinesterase inhibitor from the Calabar Bean, *Physostigma venenosum*.
- This molecule has been used as a template for the development of synthetic cholinesterase inhibitors such as rivastigmine.





MOSS and LIVERWORT FAMILY

PHYTOCHEMICAL CHOLINESTERASE INHIBITORS

- The Chinese liverwort, *Marsupella alpine*, has cholinesterase inhibitory activity credited to six "marsupellins" and three longipinane sesquiterpenoids.

Nat Prod. 2014 Apr 25;77(4):1031-6. *Marsupellins A-F, ent-longipinane-type sesquiterpenoids from the Chinese liverwort Marsupella alpine with acetylcholinesterase inhibitory activity.* Zhang J1, Fan P, Zhu R, et al.

MOSSES AND LIVERWORTS

- *Lycopodium*
- *Huperzia*
- *Marsupella*
- *Lycopediella cernua*

PHYTOCHEMICAL CHOLINESTERASE INHIBITORS

- *Lycopediella cernua*, a Club Moss, has been used in Vietnamese folk medicine for treating central nervous system conditions. Alkaloids in the plants have been found to inhibit cholinesterase.

Neurosci Lett. 2014 Jul 11;575:42-6. *Anti-amnesic effect of alkaloid fraction from Lycopodiella cernua (L.) Pic. Serm. on scopolamine-induced memory impairment in mice.* Chuong NN1, Trung BH2, Luan TC1,

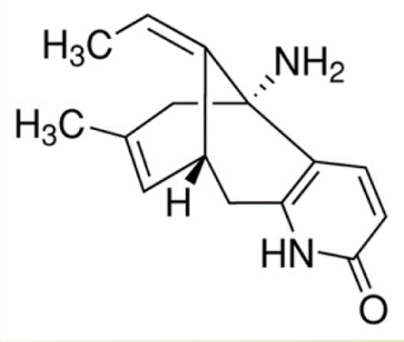
PHYTOCHEMICAL CHOLINESTERASE INHIBITORS

- The alkaloid huperzine from *Huperzia serrata* , Club Moss is a cholinesterase inhibitor.
- Huperzine and similar alkaloids are referred to as Huperzines, and many or a combination found to improve cognition.
- Huperzines are also found in other plants besides *Huperzia*.

HUPERIZIA RESEARCH

"Huperzines" are a group of alkaloids found in many species of *Huperzia* and sometimes referred to as Lycopodium Alkaloids. The Huperzines are widely studied for cholinesterase inhibition.

- ***Huperzia serrata***
- ***Huperzia squarrosa***
- ***Huperzia saururus***
- ***Huperzia quadrifariata***
- ***Huperzia reflexa***



HUPERZIA AND DEMENTIA

CHOLINESTERASE INHIBITING ALKALOIDS:

- ***Huperzia squarrosa*** **contains lycosquarosine A, acetyl-aposerratinine, huperzine A and B**
- ***Huperzia serrata*** **contain huperzines A-E.**
- ***Huperzia saururus*** **contains alkaloids sauroine, 6-hydroxylycopodine and sauroxine and huperzine A.**

Molecules. 2014 Nov 19;19(11):19172-9. *Anti-Cholinesterase Activity of Lycopodium Alkaloids from Vietnamese Huperzia squarrosa (Forst.) Trevis.* Chuong NN1, Huong NT1, Hung TM2, Luan TC3.

Fitoterapia. 2014 Dec;99:72-7. *Huperserines A-E, Lycopodium alkaloids from Huperzia serrata*. Jiang WW1, Liu F1, Gao X1, et al.

HUPERIZIA RESEARCH

- *Huperzia* goes by the name *Qian Ceng Ta* where it is a licensed AD drug in China.

NON-CHOLINERGIC EFFECTS INCLUDE:

- Protection against amyloid beta-induced oxidative injury
- Protection against mitochondrial dysfunction
- Up-regulation of nerve growth factor
- NMDA antagonism

Front Aging Neurosci. 2014 Aug 19;6:216. *Huperzine A: Is it an Effective Disease-Modifying Drug for Alzheimer's Disease?* Qian ZM1, Ke Y2.

- Huperzine-A appears to be water-soluble, and taking with food is not needed.
- Although its initial spike is quick, it appears to have a long half-life; however the pharmacokinetic profile might change when changing dosages.

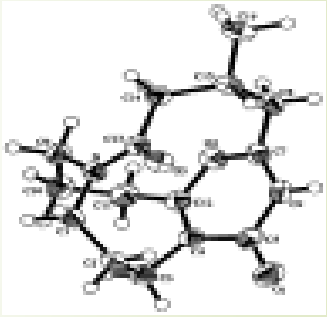
HUPERIZIA RESEARCH

- Many *Huperzia* species are high in amino acids including arginine, a known precursor to nitric oxide synthesis.
- Thus enhanced cerebral vascular flow are additional mechanisms of improved cognition in addition cholinergic enhancement.

Pharm Biol. 2013 Oct;51(10):1341-5. *Amino acid content and acetylcholinesterase inhibition of Huperzia saururus infusion and decoction.* Vallejo MG1, Dimmer JA, Ortega MG, et al

HUPERIZIA RESEARCH

- **Huperzine may also reduce brain iron accumulation that contributes to neurodegeneration.**



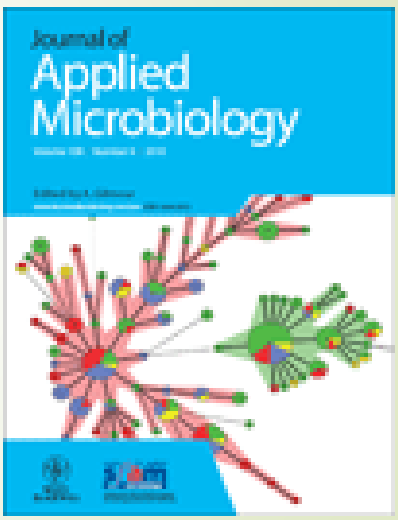
HUPERIZIA RESEARCH

- **Huperzine A ameliorates diabetes-associated cognitive decline in animal models of dementia.**
- **One mechanism appears to be via reduction in oxidative stress and inflammation.**

Int J Mol Sci. 2014 May 5;15(5):7667-83. *Huperzine A ameliorates cognitive deficits in streptozotocin-induced diabetic rats*. Mao XY1, Cao DF2, Li X3, et al

*** A fungus on *Huperzia* contributes huperzines to the plant.**

J Applied Microb *A novel endophytic Huperzine A–producing fungus, Shiraia* sp. Slf14, isolated from *Huperzia serrata* D. Zhu[1,2], J. Wang[1], Q. Zeng[1], Z. Zhang[1] and R. Yan[1]



HUPERIZIA RESEARCH

- **Animal studies also show Huperzine A to promote the proliferation of cultured neural cells, but extremely high doses decrease proliferation.**
- **Huperzines also activate protein kinase signaling pathways.**

Phytomedicine. 2012 Nov 15;19(14):1321-4. *Huperzia quadrifariata and Huperzia reflexa alkaloids inhibit acetylcholinesterase activity in vivo in mice brain.* Konrath EL1, Neves BM, Passos Cdos S, et al.

J Mol Graph Model. 2013 Jul;44:136-44. *Study of the interaction of Huperzia saururus Lycopodium alkaloids with the acetylcholinesterase enzyme.* Puiatti M1, Borioni JL, Vallejo MG, et al.

Brain Res. 2013 Apr 19;1506:35-43. *Huperzine A promotes hippocampal neurogenesis in vitro and in vivo.* Ma T1, Gong K, Yan Y, Zhang L, Tang P, Zhang X, Gong Y.

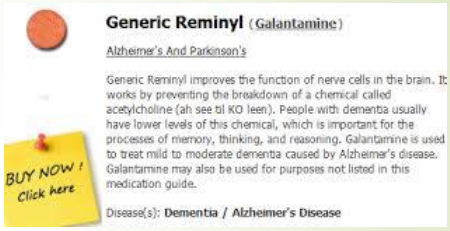
AMARYLLIS FAMILY
PHYTOCHEMICAL CHOLINESTERASE INHIBITORS

- *Galanthus* **Snow Drop**
- *Lycoridis*

AMARYLLIS FAMILY
PHYTOCHEMICAL CHOLINESTERASE INHIBITORS

- ***Galanthus cilicicus*** **is an Amaryllidaceae family plant whose bulbs contain the cholinesterase inhibiting alkaloids lycorine and galanthamine.** ***Galanthus tojanus*** **was not found to contain these alkaloids.**

Nat Prod Commun. 2014 Aug;9(8):1157-8. *Quantititative determination of lycorine and galanthamine in Galanthus trojanus and G. cilicicus by HPLC-DAD.* Kaya GI, Polat DC, Sarikaya B, Onur MA, Somer NU.



PHYTOCHEMICAL CHOLINESTERASE INHIBITORS

- **Galantamine is an alkaloid from snowdrop bulbs** ***Galanthus woronowii*** **that is a natural cholinesterase inhibitor and has been shown to improve cognitive functions in AD patients.**

PHYTOCHEMICAL CHOLINESTERASE INHIBITORS

- ***Lycoridis radiatae*** **bulbs contain the acetylcholinesterase inhibitors ungerimine and galanthamine, reported to act synergistically, the duo being more powerful than either used alone.**

J Chromatogr A. 2014 Jun 6;1345:78-85. *Identification of effective combinatorial markers for quality standardization of herbal medicines.* Shi ZQ1, Song DF1, Li RQ1, et al.

ARALIACEAE FAMILY CHOLINESTERASE INHIBITORS

- ***Panax ginseng***
- ***Acanthopanacis radicison***

PHYTOCHEMICAL CHOLINESTERASE INHIBITORS

- **The bark of *Acanthopanacis radicison*, a Ginseng relative, has been demonstrated to improve memory in mouse models of dementia.**
- **Hyperin, a flavonoid glucoside found in the plant, has been shown to be a cholinesterase inhibitor.**

J Tradit Chin Med. 2014 Feb;34(1):57-62. *Ameliorating effects of constituents from Cortex Acanthopanacis Radicis on memory impairment in mice induced by scopolamine.* Nam Y, Lee D.

OTHER BOTANICAL CHOLINESTERASE INHIBITORS

- *Cistanche* - **Phenylpropanoid glycosides**
- *Inula* - **Sesquiterpene lactones**
- *Erigeron* - **Sesquiterpene lactones**
- *Citrus* - **Essential oils**
- *Dichapetalum* - **Dichapetalin triterpenes**
- **Many plants - Flavonols**

PHYTOCHEMICAL CHOLINESTERASE INHIBITORS

- ***Cistanche tubulosa*** **is a traditional memory-enhancing herb in China. It has been found to contain phenylpropanoid glycosides including echinacoside and acteoside, found to decrease amyloid deposition and support cholinergic and dopaminergic transmission.**

BMC Complement Altern Med. 2014 Jun 26;14:202. *Reversal by aqueous extracts of Cistanche tubulosa from behavioral deficits in Alzheimer's disease-like rat model: relevance for amyloid deposition and central neurotransmitter function.* Wu CR1, Lin HC, Su MH.

PHYTOCHEMICAL CHOLINESTERASE INHIBITORS

Sesquitepene lactones cholinesterase inhibitors:

- *Inula oculus-christi*
- *Inula aucheriana*

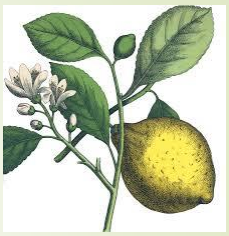
Of various sesquiterpene lactones studied, gaillardin, britannin and pulchellin, laillardin are most potent cholinesterase inhibitors

An Acad Bras Cienc. 2014 May 14;0(0):0. *Natural sesquiterpen lactones as acetylcholinesterase inhibitors.* Hajimehdipoor H1, Mosaddegh M1, Naghibi F1, et al.

PHYTOCHEMICAL CHOLINESTERASE INHIBITORS

- ***Citrus limoni,*** **lemon peels are high in volatile oils including sabinene, limonene, a-pinene, β-pinene, neral, geranial, 1,8-cineole, linalool, borneol, a-terpineol, terpinen-4-ol, linalyl acetate and β-caryophyllene, all shown to inhibit acetylcholinesterase and butyrylcholinesterase.**
- **This, along with notable antioxidant properties are believed to prevent oxidative stress-induced neurodegeneration.**

J Oleo Sci. 2014;63(4):373-81. *Essential oil from lemon peels inhibit key enzymes linked to neurodegenerative conditions and pro-oxidant induced lipid peroxidation.* Oboh G1, Olasehinde TA, Ademosun AO.



PHYTOCHEMICAL CHOLINESTERASE INHIBITORS

- ***Salvia*** **species are traditional herbs used for memory and some species contain cholinesterase inhibitors.**
- ***Salvia*** **is a large genus with many antioxidant, and vascular protectant traditional medicines:**
  - ***Salvia officinalis*** **– Sage**
  - ***Salvia miltiorrhiza*** **– Dan Shen**

PHYTOCHEMICAL CHOLINESTERASE INHIBITORS

- ***Salvia* officinalis has multiple medicinal effects including protecting the body against oxidative stress, free radical damages, angiogenesis, inflammation, bacterial and viral infection, and neuroendocrine and hormonal actions.**

PHYTOCHEMICAL CHOLINESTERASE INHIBITORS

- **Studies on *Saliva officinalis* conducted in Asia and India suggest possible utility for dementia.**

J Tradit Complement Med. 2014 Apr;4(2):82-8. *Chemistry, Pharmacology, and Medicinal Property of Sage (Salvia) to Prevent and Cure Illnesses such as Obesity, Diabetes, Depression, Dementia, Lupus, Autism, Heart Disease, and Cancer.* Hamidpour M1, Hamidpour R2, Hamidpour S2, Shahlari M2.

An old English saying:

"Why should anyone die who as Sage in their garden?"

PHYTOCHEMICAL CHOLINESTERASE INHIBITORS

- ***Dichapetalum gelonioides*** **is a tropical plant with known toxic properties.**
- **Over a dozen dichapetalins , a group of triterpenoids, have been identified and shown have cholinesterase inhibiting properties.**

J Nat Prod. 2014 Apr 25;77(4):882-93. *Biologically active dichapetalins from Dichapetalum gelonioides.* Jing SX1, Luo SH, Li CH, et al

BOTANICALS WITH OTHER MECHANISMS OF ACTION

ACTIONS THAT BENEFIT COGNITION

In addition to cholinesterase inhibition, botanical may prevent and treat AD via many other mechanisms of action:

- **Inhibit Amyloid formation, deposition, accumulation.**
- **Affect metabolism glucose, cholesterol, AGE formation**
- **Protect the Endothelium, Blood Cells, Vasculature.**
- **Protect neurons, synapse function, neurotransmitter balance.**

ESTROGEN AGONISM/ANTAGONISM WITH AMYLOID INHIBITION

- ***Erigeron breviscapus*** **contains Scutellarin shown to have estrogenic effects at alpha ERs, inhibit the aggregation of beta-amyloid, and beta-amyloid mediated neuronal cell death according to in vitro research.**

Planta Med. 2009 Nov;75(14):1489-93. *Estrogenic and neuroprotective properties of scutellarin from Erigeron breviscapus: a drug against postmenopausal symptoms and Alzheimer's disease.*Zhu JT1, Choi RC, Li J, Xie HQ, et al.

Erigeron breviscapus

Chin J Integr Med 2012 Jun;18(6):427-444 -437-

ORIGINAL ARTICLE

Caffeic Acid Ester Fraction from *Erigeron Breviscapus* Inhibits Microglial Activation and Provides Neuroprotection*

WANG Shao-xia (王少霞)[1], GUO Hong (郭 红)[2], HU Li-min (胡利民)[1], LIU Ya-nan (刘亚楠)[1], WANG Yue-fei (王跃飞)[1], KANG Li-yuan (康立源)[2], and GAO Xiu-mei (高秀梅)[1]

ABSTRACT **Objective:** To investigate the effects of caffeic acid ester fraction (Caf) from *Erigeron breviscapus*, mainly composed of dicaffeoylquinic acids (DCQAs), on microglial activation in vitro and focal cerebral ischemia in vivo. **Methods:** The production of nitric oxide (NO), tumor necrosis factor-α (TNF-α), and interleukin-1β (IL-1β) induced by lipopolysaccharide (LPS) treatment in rat primary cultured microglia were measured by Griess reaction or enzyme-linked immunosorbent assay. Cell viability of cortical neurons was measured using AlamarBlue reagent. The behavioral tests and the infarct area of brain were used to evaluate the damage to central nervous system in rat middle cerebral artery occlusion (MCAO) model of cerebral ischemia. Real time polymerase chain reaction was used to determine the expression of inducible nitric oxide synthase (iNOS), TNF-α and IL-1β mRNA in ischemic cerebral tissues. **Results:** Caf inhibited the production of NO, TNF-α and IL-1β induced by LPS treatment in primary microglia in a dose-dependent manner. Exposure of cortical neurons to conditioned medium from Caf-treated microglia increased neuronal cell viability ($P<0.01$) compared with conditioned medium from LPS-treated alone. In MCAO rat model of cerebral ischemia, Caf could significantly improve neurobehavioural performance and reduce percentage infarct volume compared with the vehicle group ($P<0.05$). Caf could also significantly inhibit the up-regulation of iNOS, TNF-α, and IL-1β gene expressions in ischemic cerebral tissues. **Conclusion:** Caf could suppress microglial activation, which may be one mechanism of its neuroprotective effect against ischemia.

KEYWORDS microglia, inflammation, dicaffeoylquinic acid, neuroprotection

In ischemic stroke, neurons localized in the ischemic core die within minutes after the ischemic episode.[1,2] However, the brain damage produced by cerebral ischemia maturates over a period of several hours or days.[3] Accumulating evidence shows that cerebral inflammation mediated by activated microglia plays a key role in the pathological process of ischemia. Microglia, the resident immune cells of the brain, are among the first cells activated by neuron necrosis in the core. Activated microglia exert a cytotoxic function by releasing proinflammatory cytokine factors (such as tumor necrosis factor alpha (TNF-α), interleukin(IL)-1β, IL-1α, IL-6, IL-12, etc.), nitric oxide (NO) and reactive oxygen species (ROS), which are recognized as significant contributing subsequent secondary damage after stroke.[4,5] Microglia are also involved in blood-brain barrier disruption and white blood cell infiltration.[6] Thus inhibiting microglia activation may be useful for reducing ischemic damage and improving the outcome after ischemic insult.[4,5]

Erigeron breviscapus (vant.) Hand-Mazz (Herba *Erigerontis*), a traditional Chinese medicinal plant, has been widely used in the treatment of cerebrovascular diseases for a long time in China. Dengzhan Xixin Injection (灯盏细辛注射液) has been officially listed in the Chinese pharmacopoeia.[7] And it is one of the most widely used drugs for treatment of cerebral ischemia in China at present.[8,9] Experimental data also proved that *Erigeron breviscapus* can rescue retinal ganglion cells in the optic nerve crush[10] and N-methyl-D-aspartic acid[11] induced retinal

*Supported by National Natural Science Foundation of China (No. 81173556), 81001854, 81102169), the Funds from the Ministry of Science and Technology of China (No. 2008ZX09310), PCSIRT-IRT0970), and Tianjin Natural Science Fund (No.11JCZDJC21100, 08JCYBJC10800)
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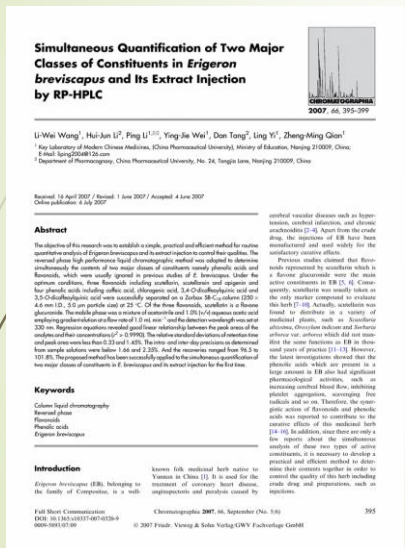
DOI: 10.1007/s11655-012-1114-y

Erigeron breviscapus



Simultaneous Quantification of Two Major Classes of Constituents in *Erigeron breviscapus* and Its Extract Injection by RP-HPLC

CHROMATOGRAPHIA
2007, 66, 395–399

Li-Wei Wang[1], Hui-Jun Li[2], Ping Li[1,2,*], Ying-Jie Wei[1], Dan Tang[2], Ling Yi[2], Zheng-Ming Qian[1]

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Received: 16 April 2007 / Revised: 1 June 2007 / Accepted: 4 June 2007
Online publication: 6 July 2007

Abstract

The objective of this research was to establish a simple, practical and efficient method for routine quantitative analysis of *Erigeron breviscapus* and its extract injection to control their qualities. The reversed-phase high performance liquid chromatographic method was adopted to determine simultaneously the contents of two major classes of constituents namely phenolic acids and flavonoids, which were usually ignored in previous studies of *E. breviscapus*. Under the optimum conditions, three flavonoids including scutellarin, scutellarein and apigenin and four phenolic acids including caffeic acid, chlorogenic acid, 3,4-O-dicaffeoylquinic acid and 3,5-O-dicaffeoylquinic acid were successfully separated on a Zorbax SB-C_{18} column (250 × 4.6 mm I.D., 5.0 μm particle size) at 25 °C. Of the three flavonoids, scutellarin is a flavone glucuronide. The mobile phase was a mixture of acetonitrile and 1.0% (v/v) aqueous acetic acid employing gradient elution at a flow rate of 1.0 mL·min^{-1} and the detection wavelength was set at 230 nm. Regression equations revealed good linear relationship between the peak areas of the analytes and their concentrations ($r^2 > 0.9990$). The relative standard deviations of retention time and peak area were less than 0.33 and 1.43%. The intra- and inter-day precisions as determined from sample solutions were below 1.66 and 2.33%. And the recoveries ranged from 96.5 to 101.8%. The proposed method has been successfully applied to the simultaneous quantification of two major classes of constituents in *E. breviscapus* and its extract injection for the first time.

Keywords

Column liquid chromatography
Reversed phase
Flavonoids
Phenolic acids
Erigeron breviscapus

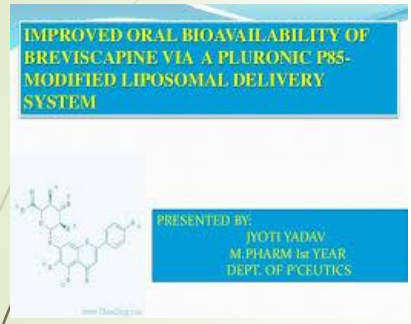
Introduction

Erigeron breviscapus (EB), belonging to the family of Compositae, is a well-known folk medicinal herb native to Yunnan in China [1]. It is used for the treatment of coronary heart disease, angina pectoris and paralysis caused by cerebral vascular diseases such as hypertension, cerebral infarction, and chronic arachnoiditis [2–4]. Apart from the crude drug, the injections of EB have been manufactured and used widely for the satisfactory curative effects.

Previous studies claimed that flavonoids represented by scutellarin which is a flavone glucuronide were the main active constituents in EB [5, 6]. Consequently, scutellarin was usually taken as the only marker compound to evaluate this herb [7–10]. Actually, scutellarin was found to distribute in a variety of medicinal plants, such as *Scutellaria altissima*, *Oroxylum indicum* and *Sorbaria arborea* var. *arborea* which did not manifest the same functions as EB in thousand years of practice [11–13]. However, the latest investigations showed that the phenolic acids which are present in a large amount in EB also had significant pharmacological activities, such as increasing cerebral blood flow, inhibiting platelet aggregation, scavenging free radicals and so on. Therefore, the synergistic action of flavonoids and phenolic acids was reported to contribute to the curative effects of this medicinal herb [14–16]. In addition, since there are only a few reports about the simultaneous analysis of these two types of active constituents, it is necessary to develop a practical and efficient method to determine their contents together in order to control the quality of this herb including crude drug and preparations, such as injections.

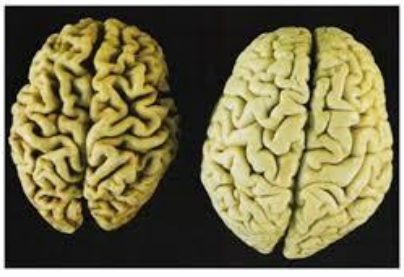
DOI 10.1365/s10337-007-0328-9
0009-5893/07/09

Erigeron breviscapus



NEUROPROTECTION (AND REGENERATION?)

- *Panax ginseng* may benefit the brain in senile dementia due to an ability to protect cortical neurons from inflammation and degeneration.
- *Withania somniferum*
- *Curcuma*



INCREASED MUSCARINIC RECEPTOR EXPRESSION

- ***Urtica dioica* leaves significantly ameliorate diabetes induced associative and spatial memory deficit in mice, via up-regulation of muscarinic acetylcholine receptor expression**.

Metab Brain Dis. 2014 Dec 17. *Urtica dioica leaves modulates muscarinic cholinergic system in the hippocampus of streptozotocin-induced diabetic mice*. Patel SS1, Parashar A, Udayabanu M.

CEREBROVASCULAR TONICS

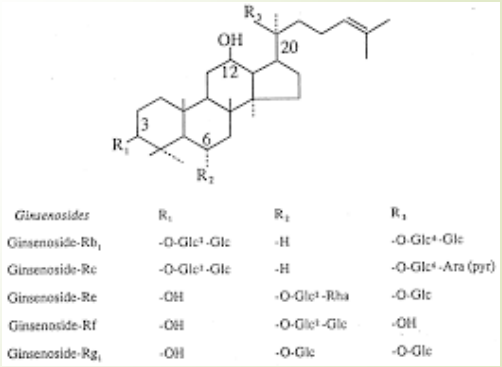
- *Ginkgo biloba*
- *Salvia species*
- *Angelica species*
- *Vinca*
- *Allium*
- *Zingiber*
- *Curcuma*
- *Panax*

PANAX GINSENG AND DEMENTIA

GINSENOSIDES :

- **Protect against overproduction of nitric oxide,**
- **Preserve optimal levels of SOD**
- **Inhibit malondialdehyde production during lipid peroxidation.**
- **Protects against the neurotoxicant glutamate.**

J Neurosci Res. 1998 Aug 15;53(4):426-32. *Ginsenosides Rb1 and Rg3 protect cultured rat cortical cells from glutamate-induced neurodegeneration.* Kim YC1, Kim SR, Markelonis GJ, Oh TH



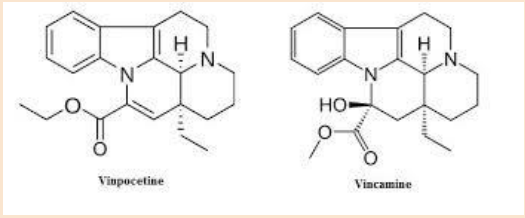
Ginsenosides	R_1	R_2	R_3
Ginsenoside-Rb_1	-O-Glc^{II}-Glc	-H	-O-Glc^{II}-Glc
Ginsenoside-Rc	-O-Glc^{II}-Glc	-H	-O-Glc^{II}-Ara (pyr)
Ginsenoside-Re	-OH	-O-Glc^{II}-Rha	-O-Glc
Ginsenoside-Rf	-OH	-O-Glc^{II}-Glc	-OH
Ginsenoside-Rg_1	-OH	-O-Glc	-O-Glc

VINCA FOR DEMENTIA

- ***Vinca*** **Madagascar Periwinkle**
- **Vinca is in the Apocynaceae Family known for its powerful alkaloids and many both toxic and medicinal members.**
- **Contains alkaloids previous studied to inhibit mitosis**
- ***Vinca*** **species are the source of Vinpocetin.**

VINCA FOR DEMENTIA

- **Vinpocetin is an alkaloid in *Vinca*.**
- **Vinpocetine may improve perfusion to retinal neurons following metabolic insult.**



EUROPEAN JOURNAL OF DRUG METABOLISM AND PHARMACOKINETICS, 1990, Vol. 15, No. 1, pp. 1-5

Pharmacokinetics of vinpocetine and its main metabolite apovincaminic acid before and after the chronic oral administration of vinpocetine to humans

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Department of Pharmacokinetics and Drug Metabolism, Chemical Works of Gedeon Richter Ltd, Budapest, Hungary

Received for publication : February 2, 1988

Keywords : Pharmacokinetics, vinpocetine apovincaminic acid, healthy volunteers

SUMMARY

The pharmacokinetics of vinpocetine (Cavinton®) and of its main metabolite apovincaminic acid (AVA), has been studied in 5 healthy male volunteers after the administration of 3 x 5 and 3 x 10 daily doses of vinpocetine for seven days. The pharmacokinetic curves of both vinpocetine and AVA have been determined prior to the chronic administration and on the last day of the treatment, whereas between the 2nd and 6th days, concentration was measured once daily. On the basis of these pharmacokinetic studies it can be concluded that both vinpocetine and AVA show linear pharmacokinetics at the doses used and that there is no accumulation or autoinduction.

INTRODUCTION

Vinpocetine is used in the therapy of different cerebrovascular disorders (1, 2). The drug improves cerebral utilization of oxygen and protects brain cells against ischaemic anoxia (3). It dilates cerebral blood vessels and increases cerebral blood flow (4, 5). Its pharmacokinetics in healthy volunteers (6), elderly subjects (7) and in patients with cerebrovascular (8), liver (9), and renal (10) insuffiency have been studied by GC-MS and GLC methods. The aim of the present study was to obtain data on the oral pharmacokinetics of the parent drug and AVA after single and repeated administration of vinpocetine.

Send reprint requests to : Dr P. Miskolczi, Department of Pharmacokinetics and Drug Metabolism, Chemical Works of Gedeon Richter Ltd, P.O. Box 27, H-1475, Budapest 10, Hungary

MATERIALS AND METHODS

Trial design

Vinpocetine (5 mg tablet) was administered at a dose of 5 or 10 mg to 5 healthy male volunteers in crossover studies (Table 1). Time of administration of vinpocetine: 8 h on the first day; 8, 14 and 20 h on the 2nd–6th day; and 8 h on the last day. Meals were allowed 4 h after the administration of vinpocetine on the first and last days, and 30 min after the intake of the tablets on the 2nd–6th days.

Blood samples were pooled at 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 and 24 h after the administration on the 1st and 7th day and once in the interval of 1.33 and 2.16 h after the first dosage on the 2nd–6th days. A two-week period was observed between administration of the 5 and 10 mg doses.

Analytical method

Vinpocetine was determined in human plasma by a GLC method (11). The apparatus was an HP 5730A

VINCA FOR DEMENTIA

- **Reperfusion injury can result following ischemic stroke and involves NF-kappa B and TNF-a mediated inflammatory responses.**
- **Vinpocetine has been shown to decrease NF-κB and TNF-a levels at 24h and 3 days after reperfusion.**
- **Neurosci Lett.** 2014 Apr 30;566:247-51. *Anti-inflammatory effects of vinpocetine on the functional expression of nuclear factor-kappa B and tumor necrosis factor-alpha in a rat model of cerebral ischemia-reperfusion injury.* Wang H1, Zhang K2, Zhao L3, et al.

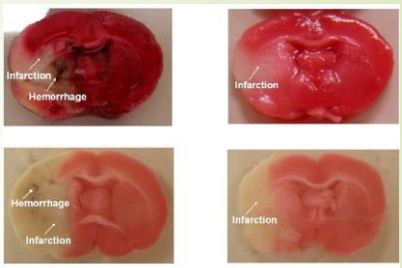
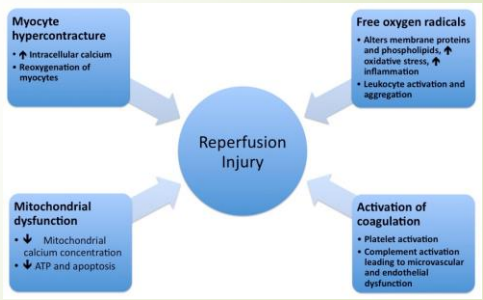


Fig. 2. APT102 significantly reduced infarct size and hemorrhage in stroke in rats



VINCA FOR THE BRAIN

Eur J Clin Pharmacol (1985) 28: 567–571

European Journal of Clinical Pharmacology
© Springer-Verlag 1985

Psychopharmacological Effects of Vinpocetine in Normal Healthy Volunteers

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Human Psychopharmacology Research Unit, Department of Psychology, University of Leeds, Leeds, UK

Summary. Twelve healthy female volunteers received pre-treatments with vinpocetine 10, 20, 40 mg and placebo (t.d.s.) for two days according to a randomised, double-blind crossover design. On the third day of treatment and 1 h following morning dosage, subjects completed a battery of psychological tests including Critical Flicker Fusion (CFF), Choice Reaction Time (CRT), Subjective Ratings of Drug Effects (LARS) and a Sternberg Memory Scanning Test. No statistically significant changes from placebo were observed on CFF, CRT or subjective ratings of drug effects. However, memory as assessed using the Sternberg technique was found to be significantly improved following treatment with vinpocetine 40 mg when compared to placebo and results suggested a localised effect of the drug on the serial comparison stage of the reaction process.

Key words: vinpocetine; cognitive function, information processing, memory, healthy volunteers

Vinpocetine (ethyl apovincaminate) is a vincamine derivative used for the treatment of disorders arising from cerebrovascular and cerebral degenerative diseases. In animal experiments, vinpocetine has been shown to significantly increase circulatory parameters including total cerebral blood flow under normal conditions and in arterial hypoxia (Bencsáth et al. 1976). This activity may be attributable to a decrease of peripheral vascular resistance indicating a vasodilatory effect of the drug (Szmolenczky and Tóthk 1976). There is additional evidence from human studies of improved circulation following treatment with vinpocetine particularly in patients with damaged vascularisation (Orosz et al. 1976; Fényes and Földes 1976).

Rosdy et al. (1976) studied cerebrobiochemical effects of vinpocetine in isolated tissues and reported a lasting increase of cerebral 5-hydroxyindole acetic acid (5-HIAA) levels after treatment and transitorily enhanced 5-HT levels 2 h following (i.p.) treatment. Catecholamine levels were similarly increased 4–6 h following administration of vinpocetine. The authors also reported an inhibition of phosphodiesterase enzyme (PDE) suggesting a possible mechanism by which cerebral ATP levels seemed to be increased after administration of the compound.

The effects of vinpocetine on cognitive symptoms of cerebrovascular disorders have not been fully investigated although Hadjiev and Yancheva (1976) reported an improvement of memory function using a simple word recall test (both immediate and delayed recall) following oral treatment (5 mg t.d.s.) with the drug for 1 month.

The aim of the present study was to investigate the influence of a range of oral doses of vinpocetine on cognitive function and information processing in normal volunteer subjects. The battery of behavioural measures used in the study were chosen to represent both subjective appraisals of drug effects and objective assessments of CNS arousal, psychomotor performance and short-term memory.

Methods

Subjects

Twelve female volunteers aged between 25 and 40 years (mean age 32 years) were admitted to the study. All were in normal physical health without a history of cardiovascular, gastric, renal or hepatic disorder. Concurrent medication (excluding the contraceptive pill), actual or possible pregnancy and a

EUROPEAN JOURNAL OF DRUG METABOLISM AND PHARMACOKINETICS, 1993, Vol. 18, No. 4, pp. 317-321

Study on the absorption of vinpocetine and apovincaminic acid

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Chemical Works of Gedeon Richter Ltd, Budapest, Hungary

Received for publication : November 5, 1990

Keywords : Absorption, apovincaminic acid, vinpocetine, excretion

SUMMARY

The absorption of vinpocetine (Cavinton) and apovincaminic acid, compounds showing a marked difference in their physico-chemical properties, was studied in rats in *in situ* loop experiments by using radiolabelled compounds. In the case of apovincaminic acid, the investigations also involved the estimation of the portion of radioactivity excreted in urine and faeces after i.v. and p.o. administration of the compound. According to our results, it can be concluded that both vinpocetine and apovincaminic acid are absorbed from the gastrointestinal tract – apovincaminic acid mainly from the stomach, while vinpocetine is absorbed from the small intestine.

INTRODUCTION

Vinpocetine (Cavinton) is a cerebral vasodilator and since 1977 it has been widely used in clinical practice for treating cerebrovascular diseases. Apovincaminic acid (AVA) is the main metabolite of vinpocetine and is formed via ester hydrolysis (1). Apovincaminic acid (mol. mass 322) is a hydrophilic acid with pK values of 2.4 and 8.3 (Fig. 1).

MATERIALS AND METHODS

Chemicals

Tritium labelled compounds were used in the experiments. Compounds were synthesized by the Central Research Institute for Chemistry of the Hungarian Academy of Sciences (Budapest, Hungary). The specific activity of AVA was 1.3 mCi/mg = 15.48 GBq/mmol and of vinpocetine 0.473 mCi/mg = 6.14 GBq/mmol with higher than 96% radiolabelled purity (Fig. 1). Non-labelled apovincaminic acid and vinpocetine were synthesized by the Chemical Works of Gedeon Richter Ltd.

Acetonitrile and n-octanol were purchased from Janssen (Beerse, Belgium) and were of spectroscopic purity. All other reagents and chemicals used for the preparation of buffers were of analytical reagent grade and purchased from Reanal (Budapest, Hungary).

Animals

Male RG-Wistar rats weighing 180–210 g were used as experimental animals.

Please send reprint requests to : Dr Piroska Pudleiner, Chemical Works of Gedeon Richter Ltd, 1475 Budapest 10, PO Box 27, Hungary.

* *Present address* : Biores R&D, PO Box 67, 1540 Budapest, Hungary.

VINCA RESEARCH

- **Vinpocetine may exert an anti-seizural effect via inhibiting Na+ ion channel permeability, and thereby hyperexcitability.**
- **This may reduce the reactivity of NMDA sensitive glutamate receptors and reduce cerebral inflammation.**

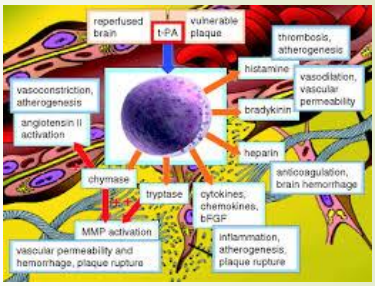
Neurochem Int. 2014 Jan;66:1-14. *Vinpocetine regulates cation channel permeability of inner retinal neurons in the ischaemic retina.* Nivison-Smith L1, Acosta ML2, Misra S3, O'Brien BJ4, Kalloniatis M5

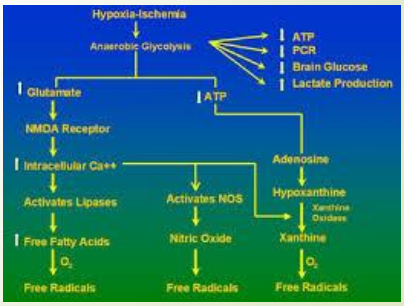
J Neurochem. 2014 Sep;130(6):770-9. *The anti-seizure drugs vinpocetine and carbamazepine, but not valproic acid, reduce inflammatory IL-1β and TNF-a expression in rat hippocampus.* Gómez CD1, Buijs RM, Sitges M.

VINCA RESEARCH

- ***Vinca* also contains Glutamic and Apovincaminic acids reported to have neuroprotective effects in animal models of acute brain ischemia.**

Eksp Klin Farmakol. 2014;77(2):12-5. *Effect of a new derivative of glutamic and apovincaminic acids on brain metabolism in post-ischemic period.* Makarova LM, Prikhod'ko MA, Pogorelyĭ VE, et al.





CLINICAL STUDIES

CLINICAL TRIALS
GINKGO FOR DEMENTIA

- **A survey conducted in Germany revealed that over 57% of physicians were recommending *Gingko* to enhance cognition in the elderly in 2012.**
- **A review of clinical trials investigating Ginkgo biloba for 1,200 dementia patients, found the herb to delay the deterioration of mental status by at least 22.3 months compared to placebo, and the therapy was cheaper compared to typical cholinesterase inhibiting drugs.**

- **Wien Klin Wochenschr**. 2013 Jan;125(1-2):8-15. *Ginkgo biloba extract EGb 761 in the treatment of dementia: a pharmacoeconomic analysis of the Austrian setting.* Rainer M1, Mucke H, Schlaefke S.

- **Age (Dordr).** 2014 Feb;36(1):435-44. *The use of Ginkgo biloba in healthy elderly*. Franke AG1, Heinrich I, Lieb K, Fellgiebel A.

CROCUS CLINICAL TRIALS

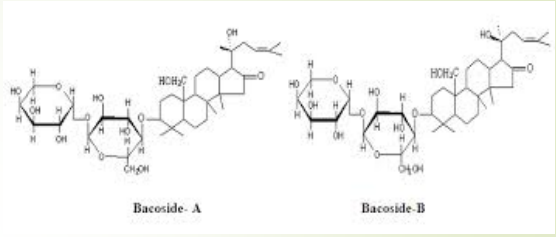
- ***Crocus sativus*, Saffron, has been investigated for Alzheimer's disease.**
- **One clinical trial conducted in Iran found saffron capsules, 15 mg twice a day to be as effective as donepezil in the treatment for mild to moderate AD**.

- **Psychopharmacology** (Berl). 2010 Jan;207(4):637-43. *A 22-week, multicenter, randomized, double-blind controlled trial of Crocus sativus in the treatment of mild-to-moderate Alzheimer's disease*Akhondzadeh S1, Shafiee Sabet M, Harirchian MH, al et

BACOPA CLINICAL TRIALS

- **A clinical trial conducted in Australia dosed healthy adults, over the age of 55 with *Bacopa monnieri* extract or placebo for 12 weeks.**
- ***Bacopa* significantly improved memory acquisition and retention in healthy older Australians.**
- ***Bacopa* caused GI side-effects of increased stool frequency, abdominal cramps, and nausea.**

J Altern Complement Med. 2010 Jul;16(7):753-9. *Does Bacopa monnieri improve memory performance in older persons? Results of a randomized, placebo-controlled, double-blind trial.* Morgan A1, Stevens J.



BACOPA CLINICAL TRIAL

- **A small trial aimed at establishing *Bacopa* safety, dosed adults with 300 mg of *Bacopa monneira* for 15 days, and 425 for another 15 days.**
- **Detailed examination of clinical, hematological, biochemical and electrocardiographic parameters done in pre and post-treatment periods did not indicate any untoward effects in any of the treated volunteers.**
- **Mild adverse events related to gastrointestinal system were observed in the trial, which subsided spontaneously.**

- **Phytomedicine.** 2007 May;14(5):301-8. *Safety evaluation of BacoMind in healthy volunteers: a phase I study.* Pravina K1, Ravindra KR, Goudar KS, et al.

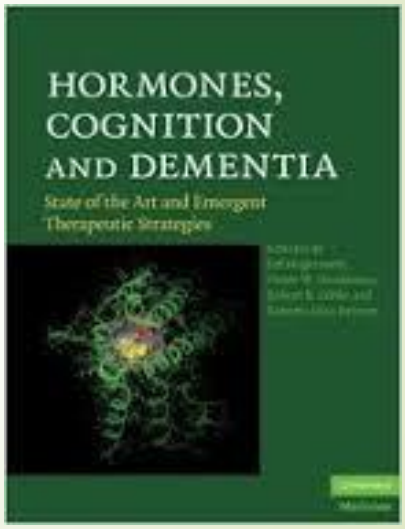
HORMONES AND DEMENTIA RISK

HORMONES AND DEMENTIA

EVIDENCE THAT REPRODUCTIVE HORMONES OFFER NEUROPROTECTION:

- **Anti-estrogen and anti-androgen hormonal therapies used in the treatment of breast and prostate carcinomas, respectively, can have a negative impact on cognitive function in older adults as a side effect.**

Semin Oncol. 2008 Dec;35(6):569-81. *Cognitive effects of hormonal therapy in older adults.*Mitsiades N1, Correa D, Gross CP, Hurria A, Slovin SF.



HORMONES AND DEMENTIA

- **Mitochondria play a central role in regulating neuronal viability and neurodegenerative diseases.**
- **Estrogens have multiple effects on mitochondria enhancing function during pathologic excitotoxicity, oxidative stress, and other pathologies.**
- **As such, estrogens may protect neurons against both acute brain injury and chronic neurodegeneration.**

Biochim Biophys Acta. 2010 Oct;1800(10):1113-20. *Mitochondrial mechanisms of estrogen neuroprotection.* Simpkins JW1, Yi KD, Yang SH, Dykens JA

HORMONES AND DEMENTIA

- **17β-estradiol (E2) has neuroprotective effects in the brain and affects memory, learning, and mood.**
- **E2 binds both (ERα) (ERβ) receptors.**
- **As estrogen levels change with age, especially in females, the number and ratio of these ERs may be down regulated and contribute to cognitive decline.**

Age (Dordr). 2013 Jun;35(3):821-37. *Aging and substitutive hormonal therapy influence in regional and subcellular distribution of ERα in female rat brain.* Navarro A1, Del Valle E, Ordóñez C,

HORMONES AND DEMENTIA

- The significantly higher incidence of AD in women than in men has been attributed to tissue changes associated with rapid estrogen decline, and related cellular and molecular mechanisms.
- Estrogen has been proposed to have neuroprotective roles against AD-related pathology.
- Studies show estrogen may reduce amyloid-β peptides and tau aggregates, yet clinical trials have failed to show any benefit and, in fact, had a negative outcome on cognition.
- The research is now investigating selective ERa or ERβ receptors aiming to develop effective therapies.

Mol Neurobiol. 2014 Feb;49(1):39-49. *Targeting estrogen receptors for the treatment of Alzheimer's disease.* Lee JH1, Jiang Y, Han DH, Shin SK, Choi WH, Lee MJ.

HORMONES AND DEMENTIA

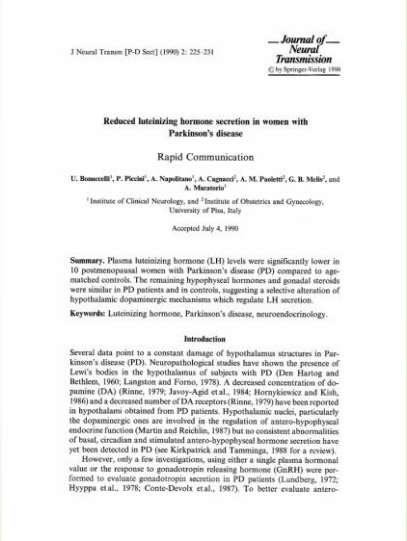
General reproductive history appears to play an obvious role in AD.

- One group of researchers examined the degree of dementia in older women and compared it to the estrogen exposure of a women's entire life by noting the number of menstrual cycles and the number of months using estrogen replacement therapy.

Psychoneuroendocrinology. 2013 Dec;38(12):2973-82. *Cumulative estrogen exposure, number of menstrual cycles, and Alzheimer's risk in a cohort of British women.* Fox M1, Berzuini C, Knapp LA.

HORMONES AND DEMENTIA

- It was revealed that the greater the number the menstrual years, the lesser the occurrence of AD.
- In fact, for every additional month with estrogen exposure, women experienced on average a 0.5% decrease in AD risk.
- The total number of months spent pregnant in ones life also correlated with a protective effect.



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Reduced luteinizing hormone secretion in women with Parkinson's disease

Rapid Communication

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Summary. Plasma luteinizing hormone (LH) levels were significantly lower in 10 postmenopausal women with Parkinson's disease (PD) compared to age-matched controls. The remaining hypophyseal hormones and gonadal steroids were similar in PD patients and in controls, suggesting a selective alteration of hypothalamic dopaminergic mechanisms which regulate LH secretion.

Keywords: Luteinizing hormone, Parkinson's disease, neuroendocrinology.

Introduction

Several data point to a constant damage of hypothalamus structures in Parkinson's disease (PD). Neuropathological studies have shown the presence of Lewi's bodies in the hypothalamus of subjects with PD (Den Hartog and Bethlem, 1960; Langston and Forno, 1978). A decreased concentration of dopamine (DA) (Rinne, 1979; Javoy-Agid et al., 1984; Hornykiewicz and Kish, 1986) and a decreased number of DA receptors (Rinne, 1979) have been reported in hypothalami obtained from PD patients. Hypothalamic nuclei, particularly the dopaminergic ones are involved in the regulation of antero-hypophyseal endocrine function (Martin and Reichlin, 1987) but no consistent abnormalities of basal, circadian and stimulated antero-hypophyseal hormone secretion have yet been detected in PD (see Kirkpatrick and Tamminga, 1988 for a review).

However, only a few investigations, using either a single plasma hormonal value or the response to gonadotropin releasing hormone (GnRH) were performed to evaluate gonadotropin secretion in PD patients (Lundberg, 1972; Hyyppa et al., 1978; Conte-Devolx et al., 1987). To better evaluate antero-

HORMONES AND DEMENTIA

- A long reproductive period is associated with better verbal fluency, compared to a short reproductive period.
- However, women who had their first child at a young age performed significantly worse on measures of cognitive function than others having children at a later age.

Psychoneuroendocrinology. 2009 Feb;34(2):287-98.*Life-time estrogen exposure and cognitive functioning in later life*. Ryan J1, Carrière I, Scali J, Ritchie K, Ancelin ML.

HORMONES AND DEMENTIA

HOWEVER….

- **Nine randomized clinical trials on ERT for AD have suggested that hormone therapy does NOT improve cognition in women with Alzheimer's disease.**
- **One clinical trial suggested that continuous, combined estrogen plus progestogen initiated at age 65 years or older INCREASES the risk of dementia.**
- **Estrogen as a preventative has not been clinically studied, nor have SERMS such as raloxifene, or phytoestrogens.**

J Steroid Biochem Mol Biol. 2014 Jul;142:99-106. *Alzheimer's disease: review of hormone therapy trials and implications for treatment and prevention after menopause.* Henderson VW1.

HORMONES AND DEMENTIA

- **Several studies have suggested that estrogen and progesterone therapy may reduce the risk of dementia in older women, in particular those with the apolipoprotein E gene polymorphism**
- **One study of 214 women, half of whom were using HRT, reported those using hormones showed worse memory, verbal memory and processing speed compared to those not using hormones.**
- **The only exception was those women with the apolipoprotein polymorphism for whom hormone use correlated with superior cognitive function.**

Neuro Endocrinol Lett. 2013;34(7):635-42.*Cognitive functions, apolipoprotein E genotype and hormonal replacement therapy of postmenopausal women.* Bojar I1, Gujski M2, Raczkiewicz D3, Rothenberg KG4.

HORMONES AND DEMENTIA

- **The negative effects on the vasculature and increased risk in CAD revealed with the initial results of WHI study in 2002 lead to fear regarding the use of hormonal therapy after menopause, and resulted in a dramatic reduction in HRT prescriptions in the United States and around the world.**

J Clin Endocrinol Metab. 2013 May;98(5):1771-80. *Where are we 10 years after the Women's Health Initiative?* Lobo RA1.

HORMONES AND DEMENTIA

- **The use of conjugated equine estrogens increases the risk of stroke and dementia in women over 65.**
- **Factors that contribute to the neuroprotective effects of estrogen in youth, BUT neurodegenerative effects in older decades is still being explored.**

Trends Endocrinol Metab. 2011 Dec;22(12):467-73. *Neuroprotective actions of estradiol revisited.* Azcoitia I1, Arevalo MA, De Nicola AF, Garcia-Segura LM.

HORMONES AND DEMENTIA

- **Some researchers have proposed a "*window of opportunity*" philosophy regarding HRTs effects on dementia, where estrogen over the reproductive life, or possibly in early menopause offers protection, but estrogen supplementation over the age of 65 is detrimental.**

Brain Res. 2011 Mar 16;1379:188-98. *Oophorectomy, menopause, estrogen treatment, and cognitive aging: clinical evidence for a window of opportunity.* Rocca WA1, Grossardt BR, Shuster LT.

THANKS!!