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

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®]
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.


**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.


**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.

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 asiatica**
  - 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
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.

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
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.


Axona(R)
Souvenaid(R)
CerefolinNAC(R)

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

**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.


**PUFAS AND DEMENTIA**

- Supplemeneting 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.
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.
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.

The Chinese liverwort, Marsupella alpine, has cholinesterase inhibitory activity credited to six “marsupellins” and three longipinane sesquiterpenoids.

MOSS and LIVERWORT FAMILY

Mosses and Liverworts

- Lycopodium
- Huperzia
- Marsupella
- Lycopodiella cernua

**PHYTOCHEMICAL CHOLINESTERASE INHIBITORS**

- *Lycopodiella 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.


**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*.
“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.


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


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.

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.

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

Huperzine A ameliorates diabetes-associated cognitive decline in animal models of dementia.

One mechanism appears to be via reduction in oxidative stress and inflammation.


* A fungus on Huperzia contributes huperzines to the plant.

J Apdied Microb. A novel endophytic Huperzine A–producing fungus, Shirata sp. SII14, isolated from Huperzia serrata D. Zhu1,2, J. Wang1, Q. Zeng1, Z. Zhang1 and R. Yan1
**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.


**AMARYLLIS FAMILY**

**PHYTOCHEMICAL CHOLINESTERASE INHIBITORS**

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


- **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**

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


**ARALIACEAE FAMILY CHOLINESTERASE INHIBITORS**

- *Panax ginseng*
- *Acanthopanax 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.


OTHER BOTANICAL CHOLINESTERASE INHIBITORS

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


Sesquiterpene 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;86(2):2. 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, α-pinene, β-pinene, neral, geranial, 1,8-cineole, linalool, borneol, α-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.

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**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
"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.

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

An old English saying:

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

*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.
**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.


**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 brevissinus* 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.

Erigeron breviscapus

**Original Article**

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

**Abstract**

Eradication of damaged neurons is essential in maintaining neural circuitry. Pioneering studies have demonstrated that caffeine and its derivatives offer neuroprotection. This study investigated the effects of caffeine and its derivatives on injured neurons.

**Keywords**

Caffeine, Caffeic acid, Neurons, Neuroprotection

**Introduction**

Erigeron breviscapus is a species of flowering plant in the family Asteraceae. It is commonly known as "Chinese Forget-Me-Not". This species is native to China and is often cultivated for its attractive blue flowers. It has been reported to have various medicinal properties, including neuroprotective effects.

**Methods**

The study involved the administration of caffeine and its derivatives to injured neurons and the assessment of their effects on neuronal survival and function.

**Results**

The results showed that caffeine and its derivatives significantly improved neuronal survival and function, indicating potential neuroprotective effects.

**Conclusion**

Caffeine and its derivatives may provide neuroprotection and warrant further investigation as potential therapeutic agents for neurological disorders.

Erigeron breviscapus, a traditional Chinese medicinal plant, is known for its potential neuroprotective effects.
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.


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**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.


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.

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-kB and TNF-a levels at 24h and 3 days after reperfusion.

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

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.


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.

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.


BACOPA CLINICAL TRIAL

- A small trial aimed at establishing Bacopa safety, dosed adults with 300 mg of Bacopa monniera 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.

HORMONES AND DEMENTIA RISK

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.

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.


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.

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 ERα or ERβ receptors aiming to develop effective therapies.


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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.

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 one's life also correlated with a protective effect.

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.

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.


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.

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.

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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.

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!!