Potential Role of Palm Vitamin E Tocotrienols in Neurodegenerative Diseases and Dementia

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“You, your joys and sorrows, memories and ambitions, sense of personal identity and free will, are in fact no more than the behaviour of a vast assembly of nerve cells and their associated molecules”

Francis Crick (1916 – 2004)
The assembly of nerve cells = brain

Requires high amount of energy for its normal functions

Nourished by an intricate and extensive vascular network

Fragile vascular network

- Aging, as well as Cerebral Small Vessel Disease (SVD) can lead to damage and structural changes of the fine vascular network.
- Subsequent hypo-perfusion will lead to injury and degeneration of affected brain tissues.
- A common manifestation of SVD is white matter lesions (WMLs).
- Pathological findings include loss of myelin and axons, and fiber degeneration (Debette and Markus (2010), BMJ;341:c3666).
- Risk factors include hypertension, diabetes, hyperlipidemia.
White matter lesions (WMLs)

- associated with many neurodegenerative diseases
- dementia in Parkinson’s Disease (Perea et al, 2013, J AD and Parkinsonism)
- progression of Alzheimer’s Disease (Prasad et al, 2011, Dement Geriatr Cogn Disord; 31:431-434)
- Progression of WMLs found to correlate with a decline in cognitive performance (Schmidt et al, 2007, Stroke, 38: 2619-25)
- WMLs have become a predictor of cognitive decline and dementia including stroke and death (Jokinen et al, 2005, J Neurol Neurosurg Psychiatry, 76:1229-33; Debette & Markus, 2010, BMJ, 341::c3666)
Dementia is a growing worldwide problem: because we live longer

Life expectancy in different regions
<table>
<thead>
<tr>
<th>Year</th>
<th>Male</th>
<th>Female</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>1960</td>
<td>52.8</td>
<td>55.9</td>
<td>54.3</td>
</tr>
<tr>
<td>1970</td>
<td>60.0</td>
<td>63.2</td>
<td>61.6</td>
</tr>
<tr>
<td>1980</td>
<td>65.0</td>
<td>68.8</td>
<td>66.9</td>
</tr>
<tr>
<td>1990</td>
<td>68.2</td>
<td>72.5</td>
<td>70.3</td>
</tr>
<tr>
<td>2000</td>
<td>70.3</td>
<td>75.1</td>
<td>72.6</td>
</tr>
<tr>
<td>2011</td>
<td>71.7</td>
<td>76.4</td>
<td>73.9</td>
</tr>
</tbody>
</table>

Source: http://www.worldlifeexpectancy.com/country-health-profile/malaysia
“In 2012, Japan has 4.62 million people aged >65yrs suffering from dementia and number would be 8.62 million if people with mild cognitive disorders were included”

“10,000 people with dementia were reported missing after wandering from home each year”
Just Ignore Gramps
He thinks he's in a nudist camp
Pharmacologic treatment of dementia

- Common agents include cholinesterase inhibitors and NMDA glutamate receptor agonist
- They are mainly indicated for dementia due to AD, but have many side effects
- Eg, Tacrine can cause liver toxicity and was withdrawn in the US
- Treatment with these agents initiated only after onset of dementia and not for prophylactic use
Better approach

- To prevent or mitigate cerebral damage/injury of the central nervous tissues

- Palm vitamin E tocotrienols can have a beneficial role in the preventive treatment of such neurodegenerative disorders which lead to cognitive dysfunction or dementia
Vitamin E consists of 8 isoforms

4 tocopherols

4 tocotrienols
Vitamin E in general

- Essential for normal functions and health of our nervous system

- Recent studies showed tocotrienols but not tocopherols also possess neuroprotective effects
Neuroprotective effects of tocotrienols

- *α*-tocotrienol but not *α*-tocopherol at nM conc shown to protect neurons from degenerating when challenged with glutamate (Sen et al, 2000)

- Through attenuating excitotoxic effects of glutamate by *modulating chemical signals* within the neuronal cells:

- By suppressing C-src kinase (Sen et al 2000) and 12-LOX as well as inhibition of phospholipase A2 activation during glutamate induced excitotoxicity (Khanna et al 2003, 2010)
Later rodent study by Khanna et al. (2005)

Stroke induced in rats with and without T3 supplementation

Brain lesions of treated animals significantly smaller than matched controls after induction of stroke
More recent canine study by Rink et al (2011)

- Stroke induced in dogs with and without mixed T3 supplementation

- Again, lesion volume significantly smaller with mixed tocotrienol supplementation
Ultimate proof will be evidence from human studies.

Hence, we conducted a human trial using volunteers with white matter lesions

( http://clinicaltrials.gov/ct2/show/NCT00753532)
Study design

- 121 subjects with MRI confirmed WMLs participated
- Randomised 200mg of mixed tocotrienols (Tocovid Suprabio) twice daily or placebo
- MRI at baseline, repeated at 1 year and 2 years
- Followed up every 3 months for blood chemistry

**Study: double-blind placebo controlled**
Imaging performed using our university MRI
samples of MRI images (top=normal, bottom with WMLs)
Results

- 121 recruited (T3 = 62, placebo = 59)
- 109 completed 1 year
- 88 completed 2 years
- Data analyzed according to
  - per protocol (n=88)
  - intention to treat principles (n = 121)
Mean volume of lesions (mm$^3$) at baseline, Yr 1, Yr 2

- **Placebo (n=42)**
- **T3 (n=46)**

The graph shows the mean volume of lesions (mm$^3$) over three time points: Baseline, Year 1, and Year 2 for two different groups: Placebo and T3. The data is presented per protocol, with a total sample size of 88 patients.
Average change in volume of lesions from baseline (mm³)

Per protocol
N = 88

YEAR 1

YEAR 2

Placebo (n=42)
T3 (n=46)

p < 0.05
Mean volume of lesions (mm$^3$) at baseline, Yr 1, Yr 2.

- **Baseline**: Placebo (59) - T3 (62)
- **Year 1**: Placebo (1800) - T3 (1600)
- **Year 2**: Placebo (2000) - T3 (1500)

_The figure shows the mean volume of lesions over time forPLACEBO (59) and T3 (62) groups. The intention to treat sample size N = 121._
Average change in volume of lesions from baseline (mm$^3$)

- **Year 1**
  - Placebo (n=59): 122
  - T3 (n=62): -17

- **Year 2**
  - Placebo (n=59): 270
  - T3 (n=62): -46

*P<0.05

intention to treat
Clinical Investigation of the Protective Effects of Palm Vitamin E Tocotrienols on Brain White Matter

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Summary

The results demonstrated that the tocotrienols are neuroprotective and could attenuate the progression of white matter lesions.

Neuroprotective effects can help reduce tissue injury during an acute ischemic event and hence influence the functional outcomes and clinical course of an acute stroke.

Ability to attenuate progression of WMLs has a beneficial role in the preventive management of neurodegenerative disorders associated with cognitive impairment or dementia.

Tocotrienols are not drugs but natural vitamin E isoforms, safe to be taken as a long term neuroprotective supplement.
Mangialasche et al from Karolinska Institute

- High plasma levels of total vitamin E (tocopherols and tocotrienols) are associated with reduced risks of AD in advanced age (Mangialasche et al, 2010, J Alzheimer’s Disease; 20:1029-1037)

- Low plasma levels of tocopherols and tocotrienols are associated with increased odds of MCI and AD (Mangialasche et al, 2012, Neurobiology of Aging; 33:2282-2290)

- Elevated levels of tocopherols and tocotrienols are associated with reduced risk of CI in a cohort of older Finnish adults (Mangialasche et al, 2013, Experimental Gerontology, 48(12): 1428-14350)
Other team members of WMLs study

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Dr Kalyana Sundram, Ph.D
Dr Ng Bee Hong, Ph.D
Dr Chinna Karuthan, Ph.D

Acknowledgment assistance from my other postgrad students
Some final words......

Let's pray, we will all grow old gracefully with our mental faculties intact, so that we can enjoy our golden years...

and not become a burden to our children, family and society.

Palm vitamin E tocotrienols may be the answer to our prayers...
I am having such fabulous time here......

all my friends in heaven will think I didn’t make it !!
Thank You for your attention

“In god I trust, all others must have evidence”

Confucius