Palm Vitamin E Tocotrienols in Neurodegenerative Diseases

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Jellyfish have survived 650 million years despite not having brains.

Yet humans, endowed with powerful brains may not survived a million
Human Brain

基本上由复杂的神经元细胞组成

需要额外的细心关爱

消耗比身体任何其他器官更多的能量

大约占我们总能量消耗的20%

The human brain is awesome. It functions 24 hours a day from the day you were born and only stops when you take an exam or fall in love.

Nourished by a massive network of blood vessels

Blood vessels can degenerate

- Aging, as well as Small Blood Vessel Disease (SVD) can lead to damage of the fine vascular network
- Which in turn lead to injury of affected brain tissues
- A common manifestation of the injury 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 disorders

- 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)
Today, dementia a worldwide problem: because we live longer
<table>
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<th>Year</th>
<th>Male</th>
<th>Female</th>
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<td>55.9</td>
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<td>63.2</td>
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<td>70.3</td>
<td>75.1</td>
<td>72.6</td>
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<tr>
<td>2011</td>
<td>71.7</td>
<td>76.4</td>
<td>73.9</td>
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“In 2012, 4.62 million people above 65yrs old were diagnosed with dementia and if people with mild cognitive disorders were included, the number would be 8.62 million.”

“About 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
What about stroke?

- Like heart disease, a leading cause of death
- >6 stroke cases occur every hour in Malaysia
- Approximately 40,000 Malaysians become disabled every year.
Post stroke care can be a heavy burden
Palm Vitamin E Tocotrienols

There are convincing evidence today, that Palm vitamin E tocotrienols can be beneficial in the preventive management of such neurodegenerative disorders including ischemic stroke.
Vitamin E consists of 8 isoforms

4 tocopherols

4 tocotrienols
Tocotrienols(T3) versus tocopherols

- Tocopherols discovered first in 1922 (Evans and Bishop)
- Tocotrienols some 25 years later
- In the past, most if not all vit E products = tocopherols
- Tocotrienols less found in nature
- Little or negligible in most edible oils
- Little is known & less research on tocotrienols until recently
- Most research (98%) in the past were mainly focused on tocopherols
Crude palm Oil

- Crude palm oil is one of the richest sources of tocotrienols
- Extracted and commercialised, today being sold worldwide

Adapted from: http://catalog.wlimg.com/1/303409/full-images/crude-palm-oil-1125326.jpg
Vitamin E in general

- Essential for normal functions and health of our nervous system
- Recent studies showed tocotrienols and tocopherols have some differences in their biological activities, especially in neuroprotective properties

[Image of a human body with a focus on the nervous system]
Neuroprotective studies with tocotrienols

- $\alpha$-tocotrienol but not $\alpha$-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:

- Via suppression of 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
Another significant finding

- Mixed T3 reported to increase blood flow to the ischemic zone via induction of arteriogenic genes!
- This can help to reduce injury of brain tissues especially the penumbra
Thus, cell based and animal studies provided convincing evidence that the tocotrienols are protective of the nervous tissues

Ultimate proof is still evidence from human studies

Hence we conducted a human study in volunteers with white matter lesions (funded by a grant from MPOB)
Study design

- Screened 1300 volunteers for inclusion/exclusion
- 390 selected for brain MRI, 177 have WMLs
- 121 gave consent to participate
- 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

Mean volume of lesions (mm$^3$) at baseline, year 1 and year 2.

intention to treat
N = 121

Placebo
T3

(59)
(62)
Average change in volume of lesions from baseline (mm³)

Year 1: Placebo (n=59) vs. T3 (n=62)
- Placebo: 122
- T3: -17 (P<0.05)

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

Intention to treat
Clinical Investigation of the Protective Effects of Palm Vitamin E Tocotrienols on Brain White Matter
Yogheswaran Gopalan, Ibrahim Lutfi Shuaib, Enrico Magosso, Mukhtar Alam Ansari, Mohd Rizal Abu Bakar, Jia Woei Wong, Nurzalina Abdul Karim Khan, Wei Chuen Liong, Kalyana Sundram, Bee Hong Ng, Chinna Karuthan and Kah Hay Yuen

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Summary

Palm Vitamin E tocotrienols can be beneficial in the preventive management of:

- neurodegenerative diseases associated with cognitive decline and dementia
- stroke by reducing tissue injury during an ischemic event
- Tocotrienols are natural Vitamin E isoforms, safe to be taken long term neuroprotective supplement
Other team members of WMLs study

Prof Ibrahim Lutfi Shuaib
Assoc Prof Dr Nurzalina AK Khan
Dr Yogheswaran Gopalan
Dr Mukhtar Alam Ansari
Dr Liong Wei Chuen (ex-UKM)
Dr Wong Jia woei
Dr Enrico Magosso
Dr Mohd Rizal Abu Bakar
Dr Kalyana Sundram
Dr Ng Bee Hong
Dr Chinna Karuthan

Acknowledgement: assistance from my other postgrad students
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)
Studies with C. elegans model

- Microscopic worm, 1mm in length
- Lifespan 15 - 30 days
- Transgenic variants can express β-amyloid peptide associated with Alzheimer’s Disease
- Worm becomes paralysed, head last to get paralysed
Lifespan at different temperatures
Take life easy
A hectic lifestyle is bad for health
Effect of tocotrienols on the lifespan of *C. elegans* (16 °C)
Transgenic worm: before & after expression of β-amyloid peptide
Effects of mixed tocotrienols in protecting the C. elegans against β-amyloid toxicity ($\text{A}\beta_{3-42}$)
Effects of mixed tocotrienols in protecting the *C. elegans* against $\beta$-amyloid$_{1-42}$ toxicity

![Graph showing effects of mixed tocotrienols](image-url)
Some final words......

Let's pray, we will all grow old gracefully with our mental and physical 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!!
A QUICK SNAPSHOT OF OUR RECENT STUDY WHICH WE HAVE JUST COMPLETED

EFFECTS OF TOCOTRIENOLS ON PERIPHERAL NEUROPATHY IN DIABETIC PATIENTS

(Funded by an NKEA Palm Oil grant from the Government)

Conducted in collaboration with CRC, Seberang Jaya Hospital, Penang
STUDY POPULATION AND DESIGN

14,289 Patient Records Screened

800 assessed and 391 Patients Presented with Peripheral Neuropathy Consented

300 Eligible Patients recruited

Placebo (n=150)  Tocotrienols (n=150)

Follow up assessments at 3, 6, 9, 12 months:
Primary outcome = Total Symptom Score (TSS)
Total Symptom Score (TSS)

Total Symptom Score: consists of 4 domains
- Lancinating pain
- Burning pain
- Pricking pain
- Numbness
Quick snapshot.....

*General Reduction of Total Symptom Score in both treatment groups
Quick snapshot of different domains.....

- **Pricking Pain Score**
  - Placebo
  - T3

- **Asleep Numbness Score**
  - Placebo
  - T3

- **Burning Pain Score**
  - Placebo
  - T3

Graphs show the comparison of placebo and T3 over time (B, 6M, 12M) for each domain.
Lancinating Pain Score (adjusted) (n=150/arm)

Lancinating Pain Score change

*P < 0.05
*P = 0.05

*Lancinating score after adjusting for baseline HbA1c and Total TSS*
Quick snapshot.....

**Mean Lancinating Pain Score**
(HBA1C > 8%)

- **Baseline**
  - Placebo: N=60
  - Tocotrienols: N=80

- **Month-6**
  - Placebo: ~1.00
  - Tocotrienols: ~0.80

- **Month-12**
  - Placebo: ~0.70
  - Tocotrienols: ~0.50

**Mean Score Change**
(HBA1C > 8%)

- **Month-6**: P=0.008
- **Month-12**: P=0.028
summary

- Close monitoring helps to improve patients’ conditions
- Tocotrienol supplementation significantly reduced lancinating pain in diabetic patients with peripheral neuropathy compared to placebo especially in those with poor glycaemic control.
On-going clinical studies

- Sen et al from Ohio State University is currently investigating the effects of tocotrienols in TIA and stroke incidence.

- We have also started another study: *Effects of tocotrienol supplementation on functional outcomes and recovery in moderate stroke patients* 

  (Funded by an NKEA Palm Oil grant from the Government)

- Co-principal investigator: Dr Irene Looi from CRC, SJH
- Screened ~500 stroke patients, >50 patients recruited
- target = 150 patients
- have 3 recruitment centers at the moment
- Soon to include UPM-Serdang Hospital and Hospital Trengganu
MRI of my brain

Now taking 200 – 400mg T3 daily
Thank You for your attention

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

Confucius