

Benefits of Tocotrienols in the Aging Brain

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Our Brain



**Needs tender
loving care**

**Consumes more energy than
any other organ in the body**

**Approximately 20% of our total
energy consumption**

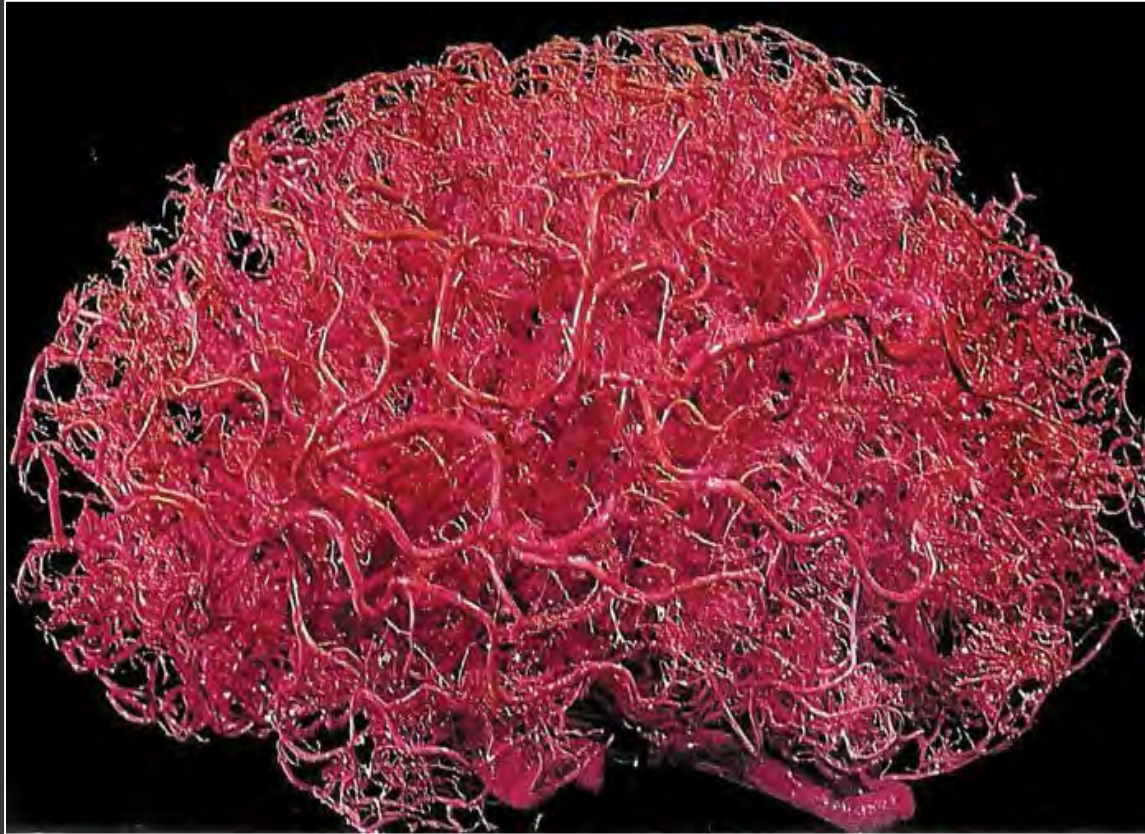
**It is just a complex
assembly of nerve
cells**

**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.**



**Educate
Inspire
Change**





Nourished by a massive network of
blood vessels

*Adapted from <http://science.nationalgeographic.com/science/photos/brain/> &
<http://biobotsprinters.tumblr.com/>*

Our brain is more susceptible to oxidative stress than other organs

- High polyunsaturated lipid content
- High oxygen consumption
- Has lower anti-oxidant capacity/defense system

Thus chronic exposure may lead to age-related injury which can affect our brain functions

Such as memory deficits, bodily functions, movements, sensations and even personality changes

How can Vitamin E Tocotrienols help?



- Essential for normal functions and health of our nervous system
- Deficiency leads to neurological deficits (*areflexia and ataxia*)
- Studies shown tocotrienols are more powerful anti-oxidants compared to tocopherols
- **Tocotrienols also shown to possess neuroprotective effects**

Early studies on neuroprotective effects

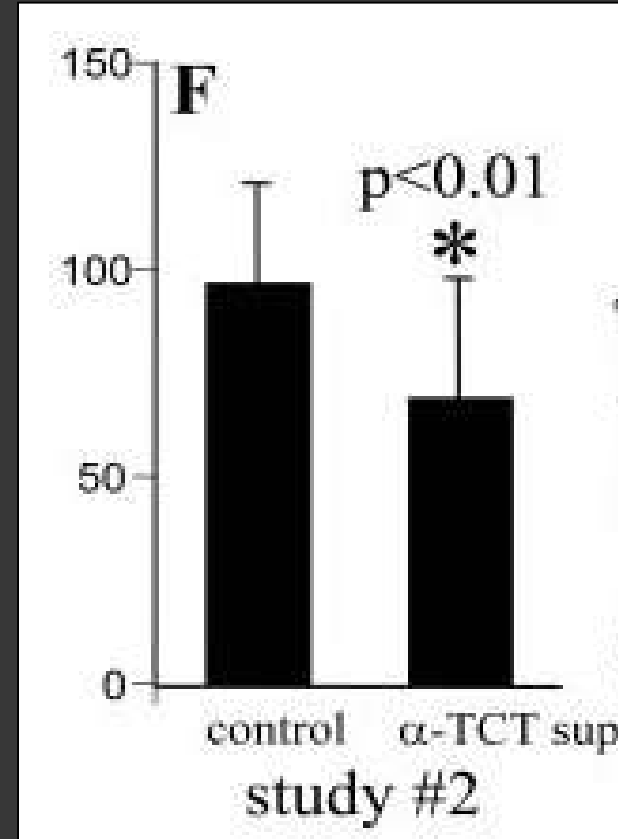
- α -tocotrienol but **not α -tocopherol** at **nM** conc shown to protect neurons from degenerating when challenged with glutamate (*Sen et al, 2000*)
- Through attenuating excitotoxic effects of glutamate by **modulating chemical signals** within the neuronal cells:
- Via suppression of **C-src kinase** (*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

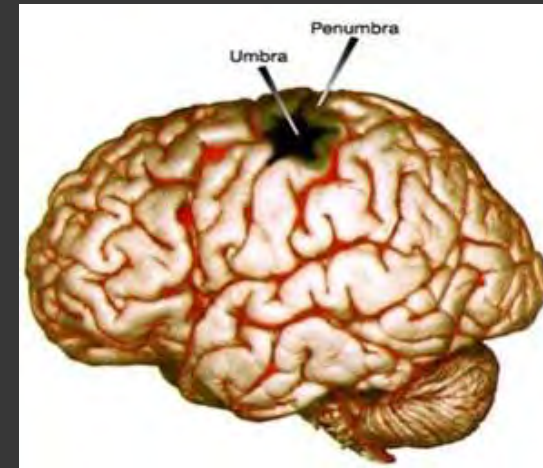
Brain lesions of treated animals significantly smaller than matched controls after induction of stroke



Professor Koji Abe from Okayama, Japan

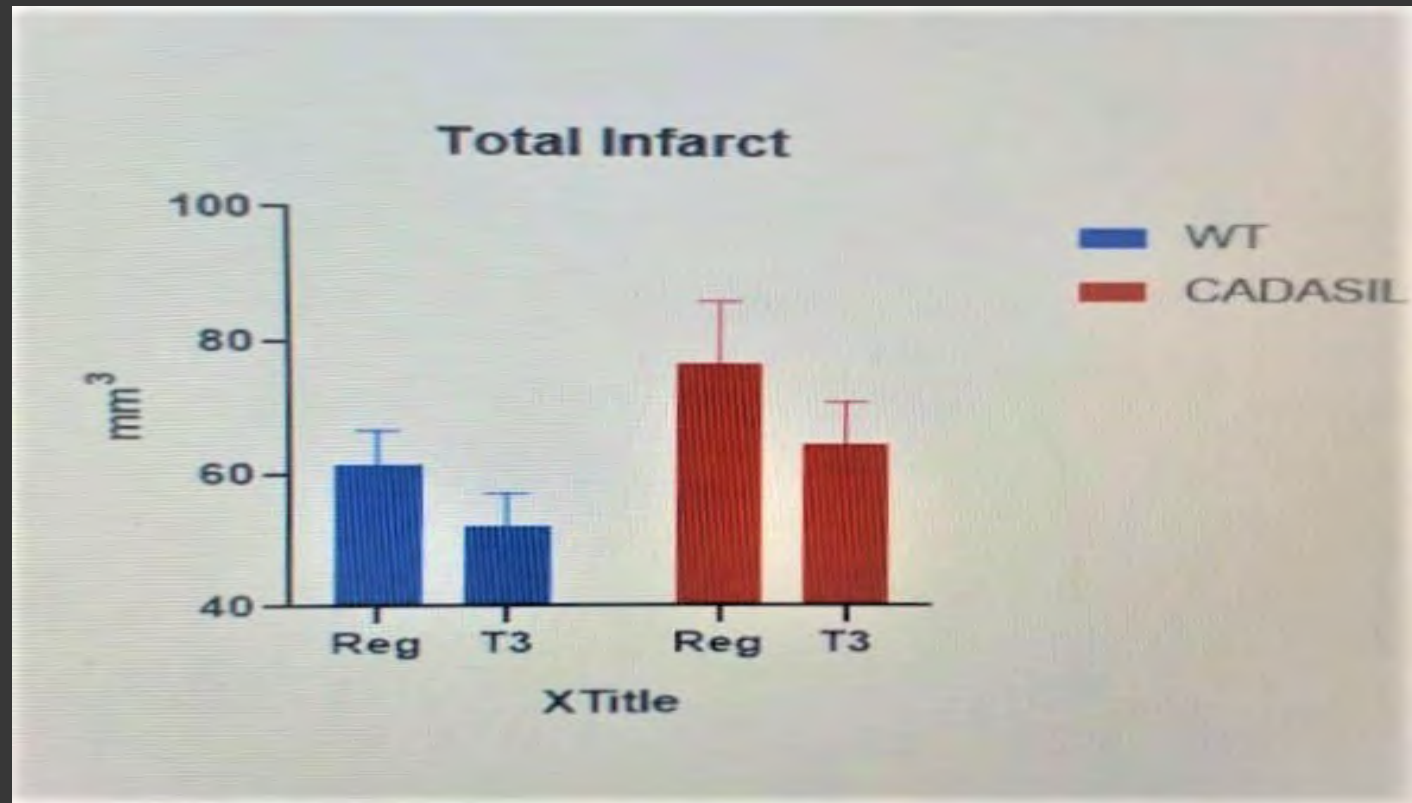
Recently published 2 papers in *Journal of Stroke and Cerebrovascular Diseases* in 2018

- Similar neuroprotective effects observed with the tocotrienols
- Reduced infarct volume in rats after induction of brain ischemia
- Decreased inflammatory markers
- Reduced neuronal apoptosis
- Reduced neurovascular unit dissociation
- **Concluded tocotrienols to be neuroprotective**



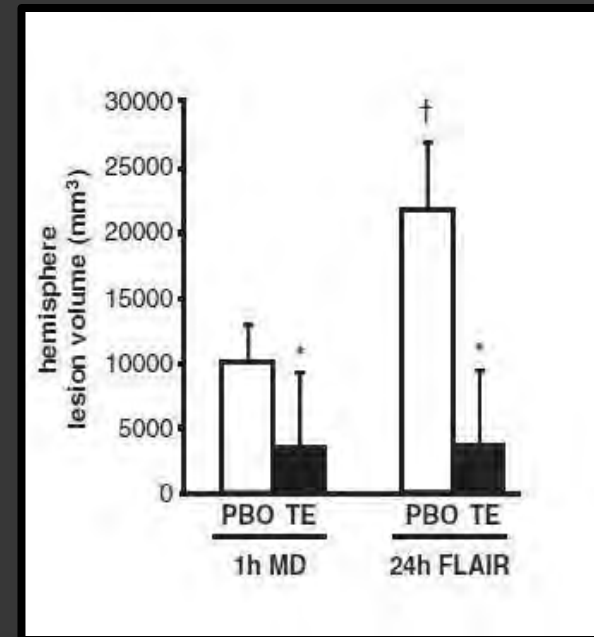
Latest study from Harvard University, 2019

Similar results observed in wild type and transgenic mice model for CADASIL during induced brain ischemia, **volume of lesions shown to be smaller with T3 supplementation**



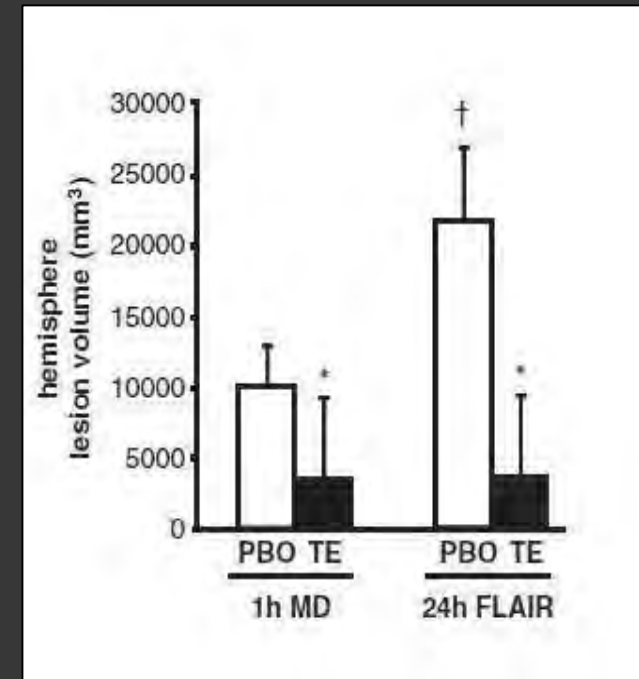
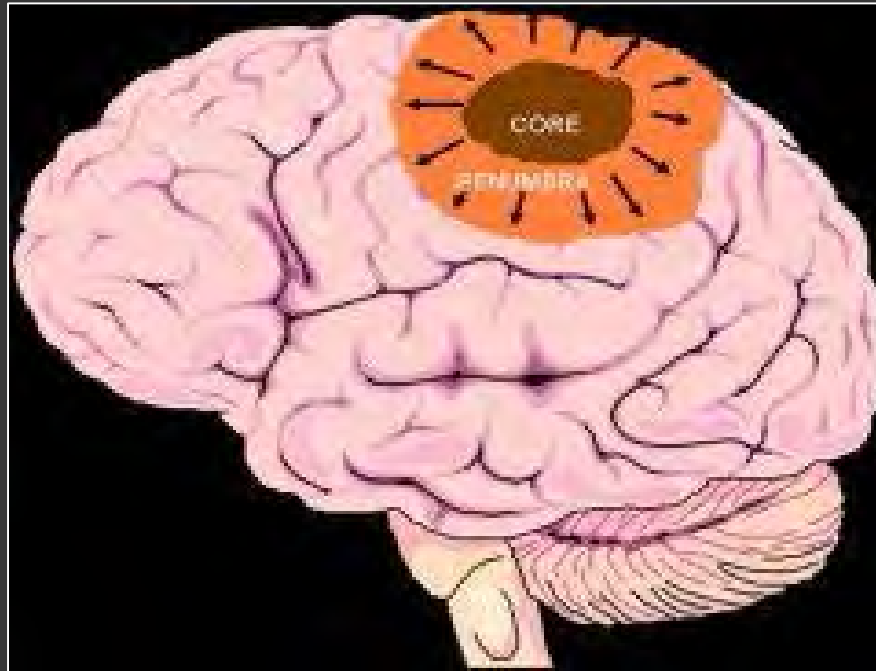
Canine study by Rink et al (2011)

- Stroke induced in dogs with and without mixed T3 supplementation
- Again, lesion volume significantly smaller with mixed tocotrienol supplementation



Another significant finding

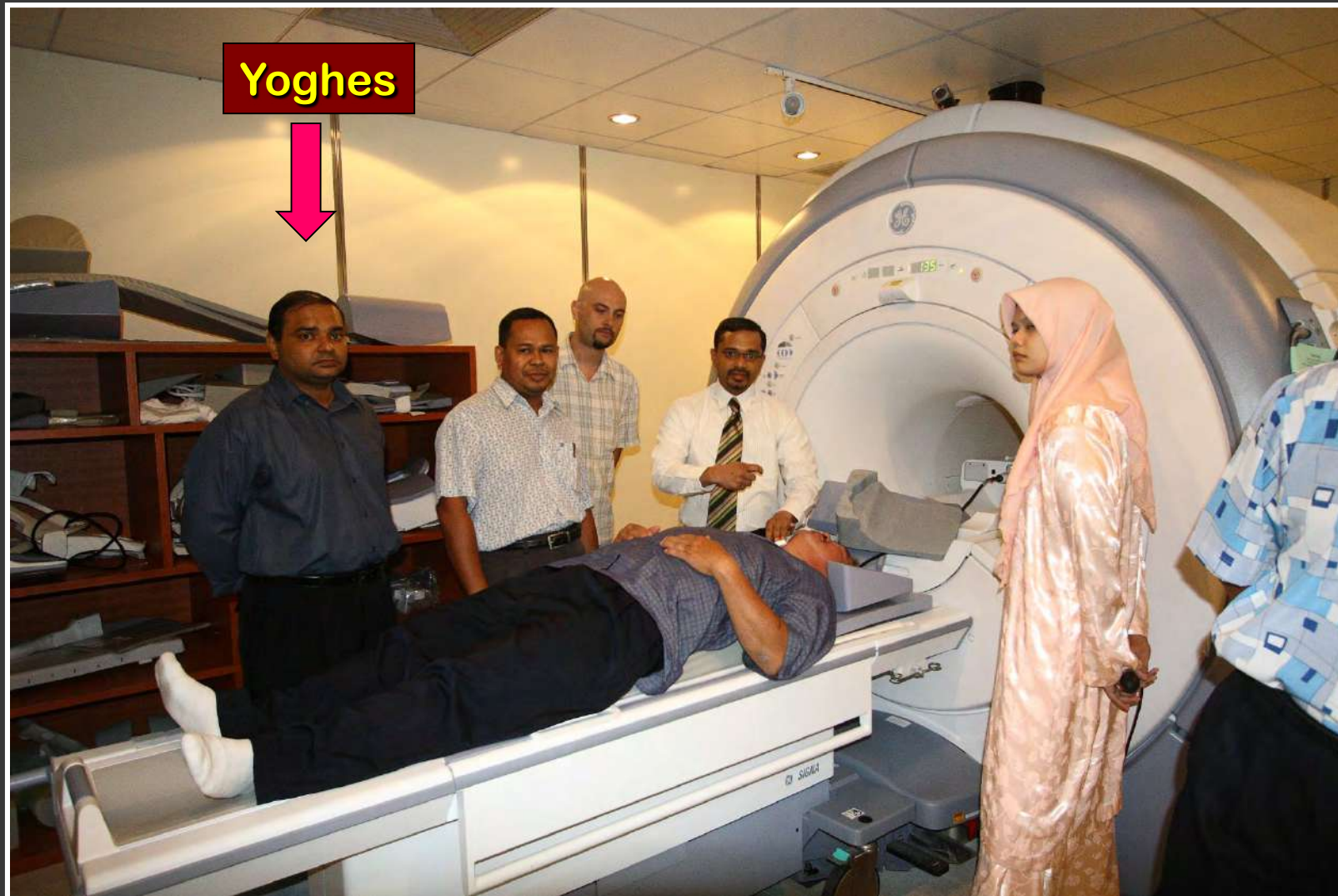
- Mixed T3 reported to increase cerebrovascular blood flow to the affected area !
- This can help reduce further injury of brain tissues and hence alter the clinical course and outcome of the stroke



Ultimate Proof is from Human Studies

- ◉ *We have conducted a double-blind placebo controlled study in human volunteers with white matter lesions (WMLs)*
- ◉ 121 subjects with MRI-confirmed WMLs were randomised to receive 200mg of mixed tocotrienols twice daily or placebo
- ◉ MRI at baseline, repeated at 1 year and 2 years

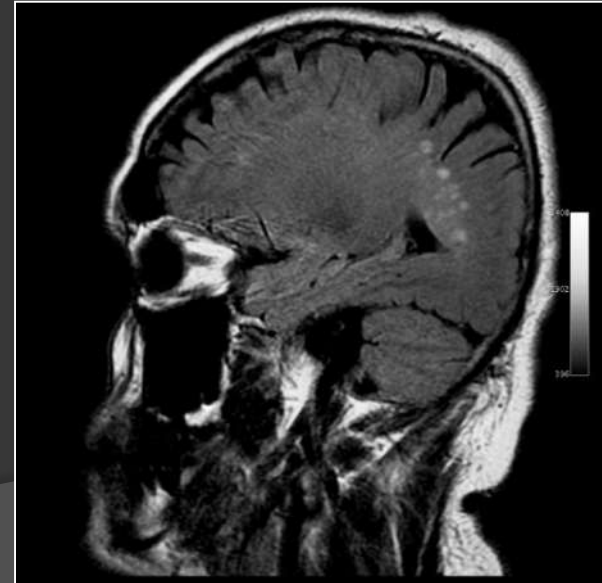
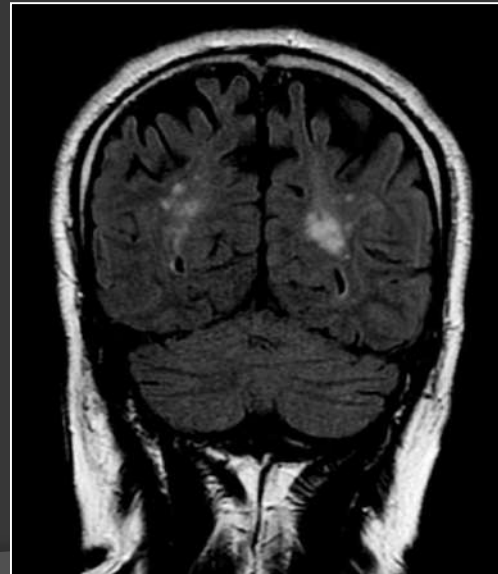
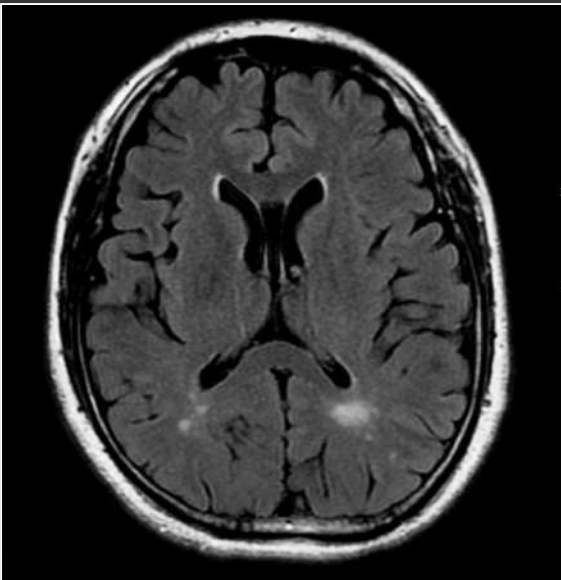
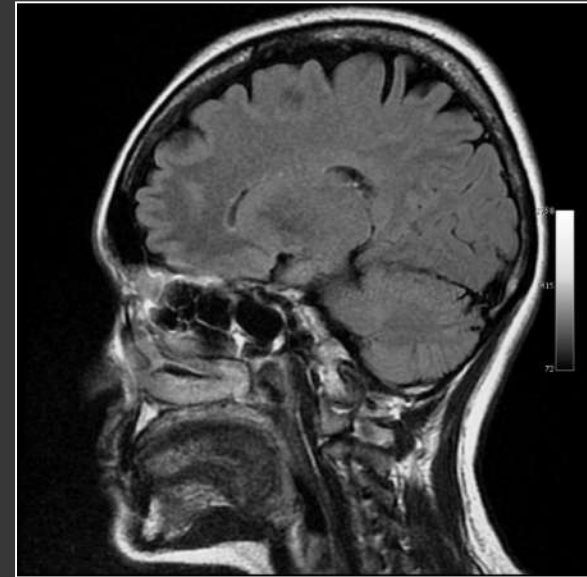
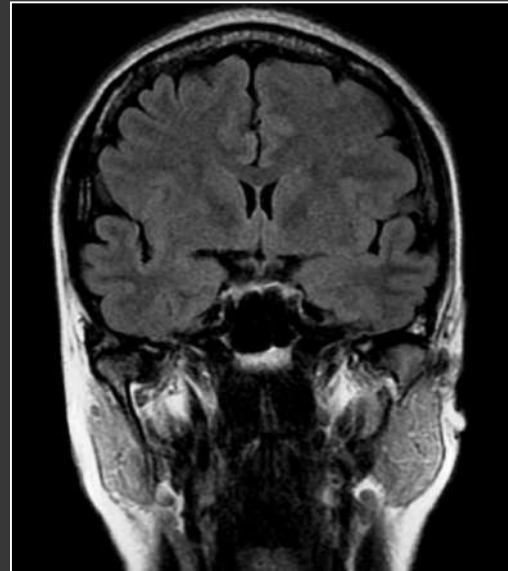
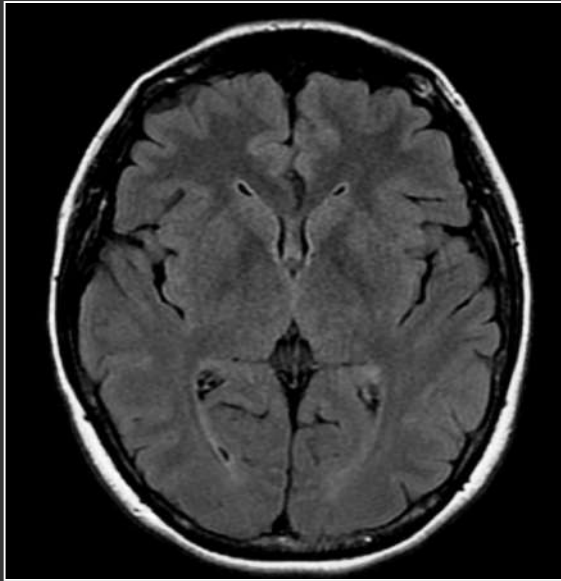
Imaging performed using our university MRI



What are White Matter Lesions (WMLs)?

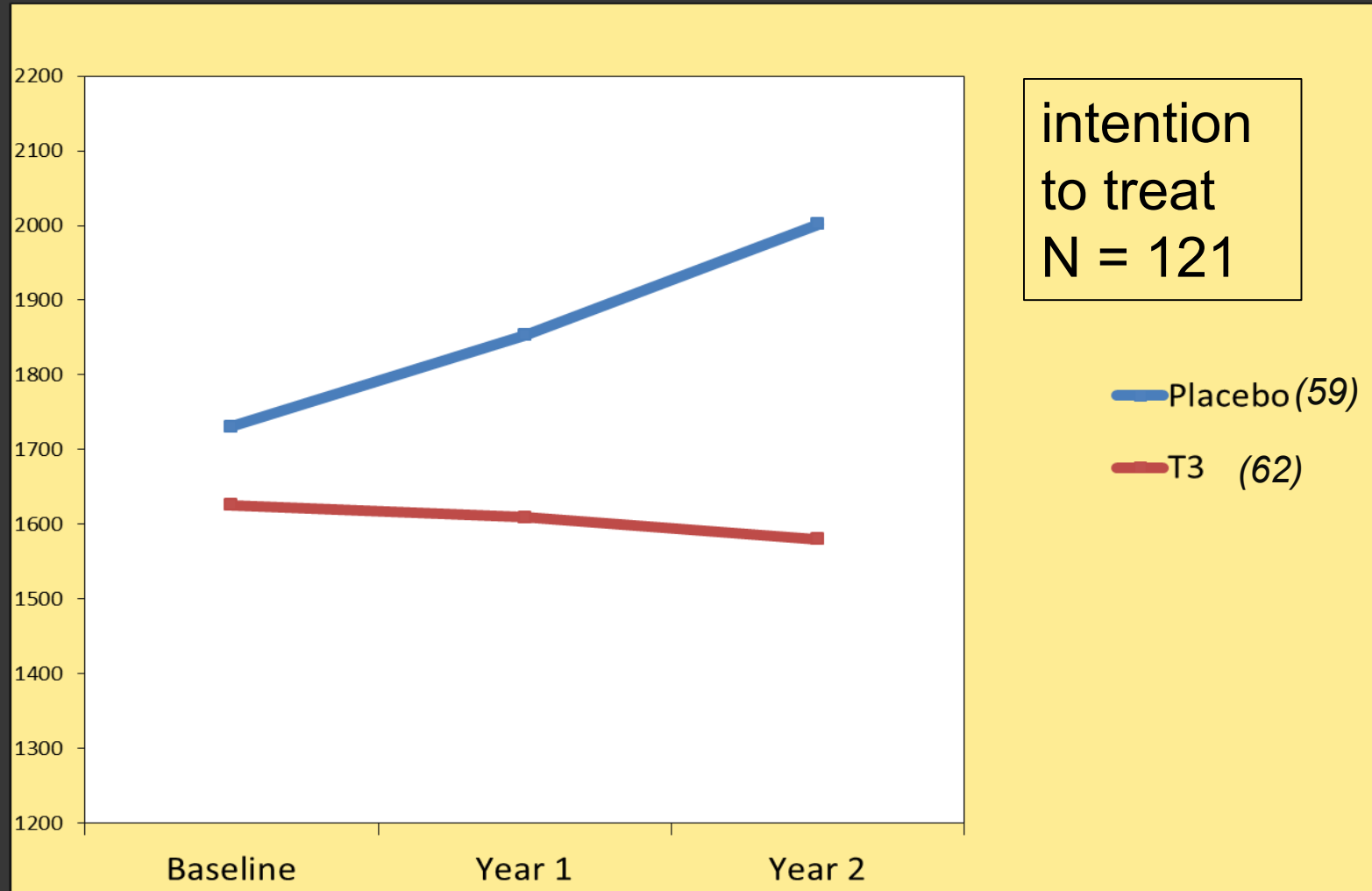
- ① *many older people have hyper-intensities (bright spots) in their brain MRI images, even with no apparent symptoms*
- ① *lesions formed from bundles of nerve fibers degenerating due to small blood vessel disease of the brain*
- ① *development increased with age and presence of CV risk factors (Schmidt et al 2002, Jeerakathil et al 2004, Murray et al 2005)*
- ① Deterioration of lesions/infarcts is **self progressive** (Veldink et al 1998, Whitman et al 2001, Schmidt et al 2002)

samples of MRI images (top=normal, bottom with WMLs)

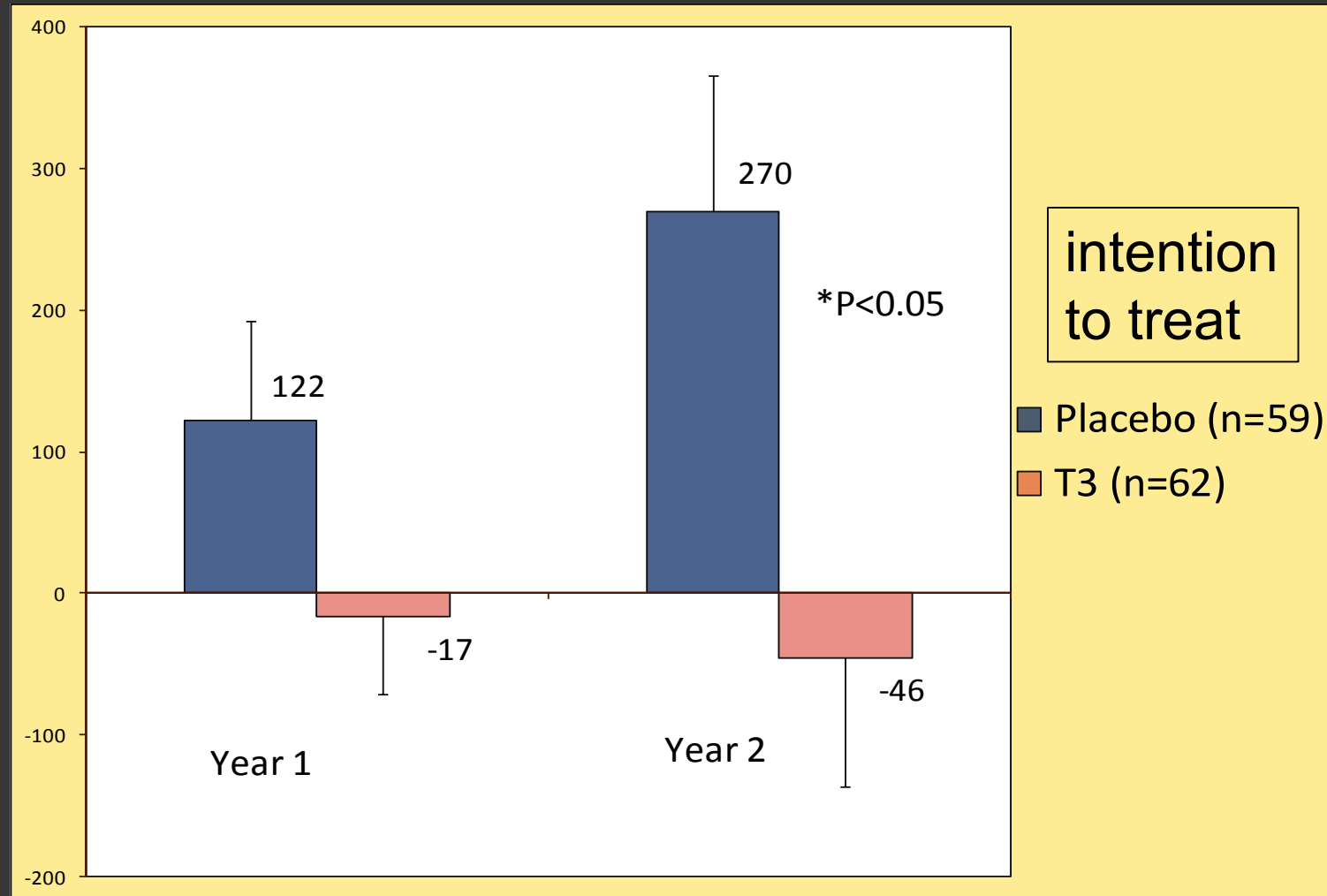


Results

Mean volume of lesions(mm³) at baseline, Yr 1, Yr 2



Change in mean volume of lesions



Average change in volume of lesions from baseline (mm³)

Stroke

JOURNAL OF THE AMERICAN HEART ASSOCIATION



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

Stroke. 2014;45:1422-1428; originally published online April 3, 2014;
doi: 10.1161/STROKEAHA.113.004449

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Today, there are ample evidence to show that WMLs are associated with various neurodegenerative disorders

- cognitive decline and dementia (*Pantoni et al, 2007, Curr Opin Neurol., 20: 390-97*)
- cognitive impairment 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*)

Mangialasche et al from Karolinska Institute

Published 3 papers: association of tocopherol plus tocotrienol plasma levels with mental health of elderly folks

- Mangialasche et al, 2010, *J Alzheimer's Disease*; 20:1029-1037
- Mangialasche et al, 2012, *Neurobiology of Aging*; 33:2282- 2290
- Mangialasche et al, 2013, *Experimental Gerontology*, 48(12): 1428-14350

Elevated plasma levels of tocopherols and tocotrienols are associated with reduced risks of cognitive impairment and Alzheimer's Disease, but the odds are increased when the levels are low

Tocotrienol improves learning and memory deficit of aged rats

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Journal of Clinical Biochemistry and Nutrition

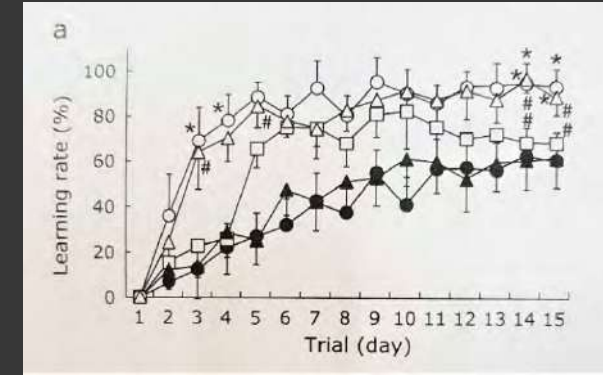
- 3 types of diet were compared:
- normal diet
 - diet fortified with α -tocopherol
 - diet fortified with tocotrienols

Snapshot of the results

Learning ability

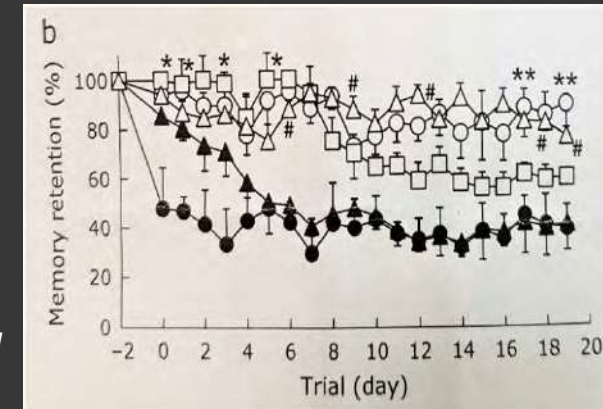
In Aged Rats

- Both α -Toc and T3 enhanced learning ability
- But effect more significant with T3



In Young rats (subjected to oxidative stress)

- Decline in learning ability
- But markedly enhanced with T3



Memory retention

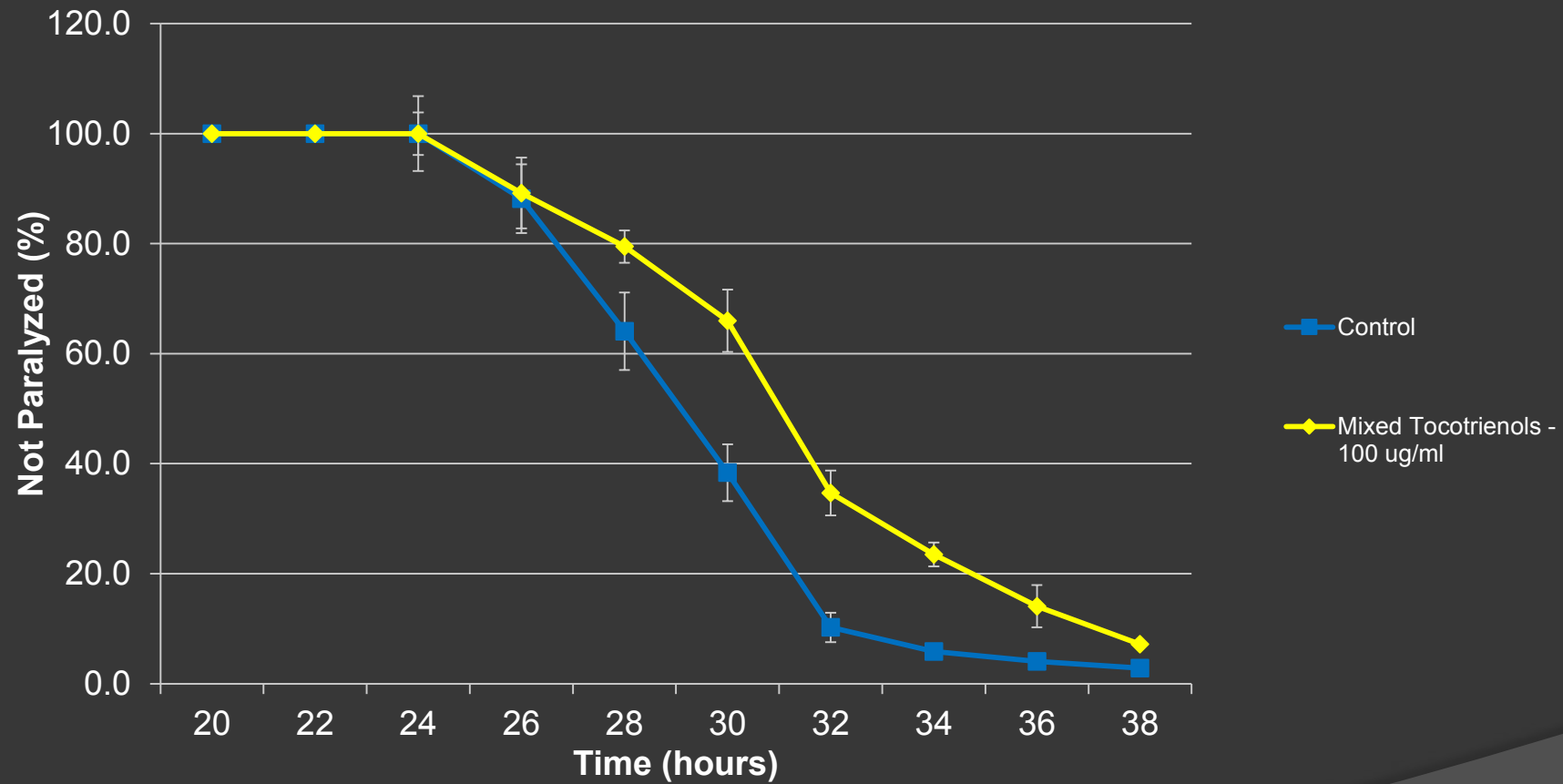
- Decline in both aged and young rats (*subjected to oxidative stress*)
- Improved in aged rats by both α -Toc and T3
- But effect more sustained with T3
- T3 also improved memory retention in young rats (*subjected to oxidative stress*)

Studies with *C. elegans* model

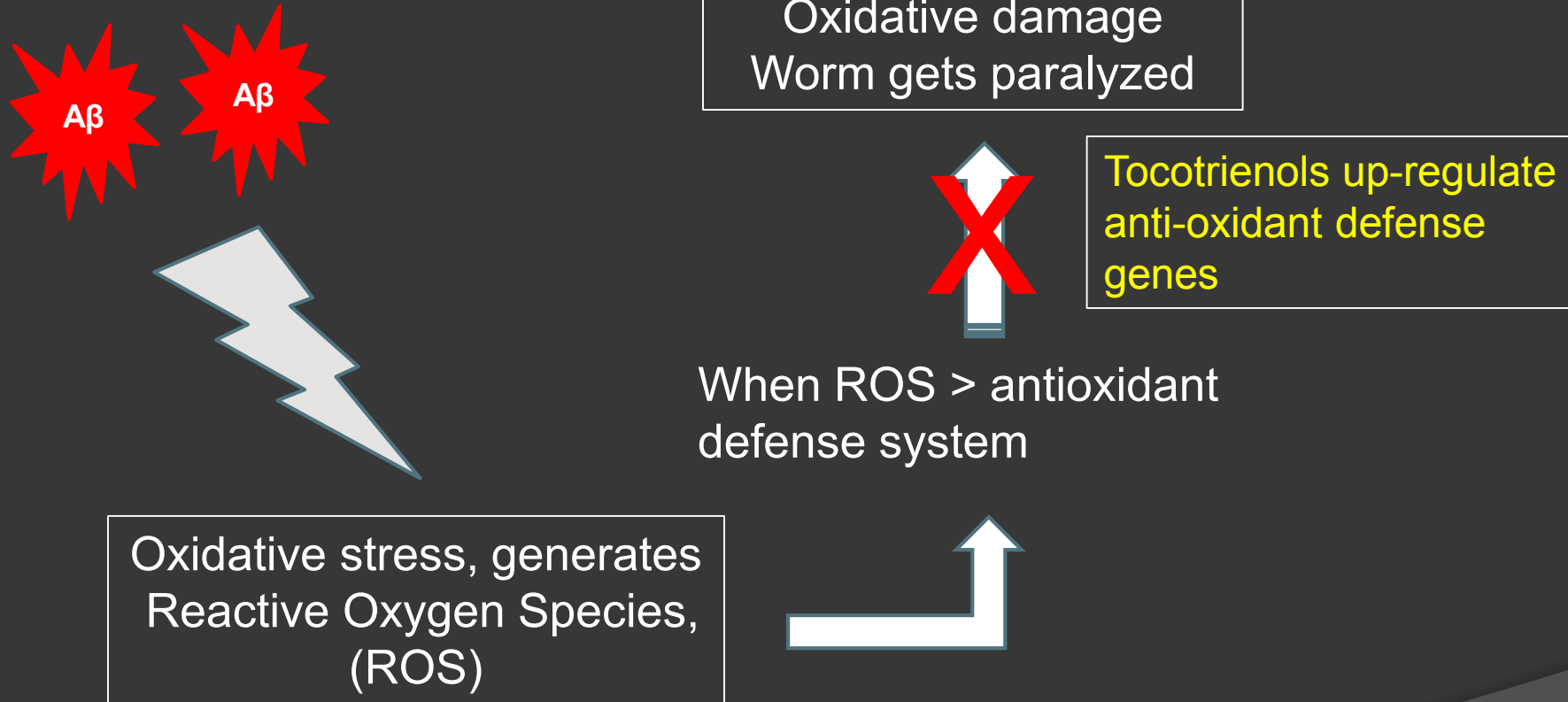
- Microscopic worm, 1mm in length
- Lifespan 15 – 30 days
- Transgenic variants can express *β -amyloid peptide* associated with *Alzheimer's Disease*
- worm becomes paralysed, head last to get paralyzed



Effects of mixed tocotrienols in protecting the *C. elegans* (GMC101) against β -amyloid toxicity ($A\beta_{1-42}$)



Mechanism leading to paralysis of the worm



Some of the antioxidant genes upregulated by tocotrienols

Gene (Gene name)	Function
<i>gst-10</i> (Glutathione S-transferase P 10)	Detoxification of reactive oxygen species produced
<i>ctl-2</i> (Peroxisomal catalysis)	Protects cells from reactive oxygen species
<i>ctl-1</i> (Cytocolic catalysis)	Protects cells from reactive oxygen species
<i>daf-16</i> (Forkhead transcription factor)	Protect animals from oxidative damage during periods without food
<i>din-1</i> (Daf-12-interacting protein 1)	Regulates antioxidant genes such as <i>gst-10</i>
<i>sod-5</i> (Minor Cu/Zn SOD)	Encodes one of five superoxide (SOD) isozymes in <i>C. elegans</i> along with SOD-1
<i>sod-3</i> (Minor Mn SOD)	Destroys superoxide anion radicals which are normally produced within the cells and which are toxic to biological systems
<i>daf-2</i> (Insulin-like growth factor receptor)	Regulates oxidative stress resistance and Mn-superoxide dismutase gene expression in <i>C. elegans</i>
<i>trx-1</i> (Thioredoxin-1)	Participates in various redox reactions through the reversible oxidation of its active center dithiol to a disulfide and catalyzes dithiol-disulfide exchange reactions
<i>ftn-1</i> (Iron storage protein ferritin)	Reduces protein carbonylation and enhances oxidative stress resistance

In Summary:

Tocotrienols can have an important role in the preventive management of neurodegenerative disorders that lead to cognitive decline and dementia

Tocotrienols are not drugs but natural vitamin E isoforms, and are safe to be taken as a long term neuroprotective supplement





Some final words.....

Lets 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.....*

**You too can, if you take
Tocotrienols !!!!**



Confucius

*Thank You
for your
attention*

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