Tocomin Tocotrienols Complex

A Potent Natural Neuroprotective Vitamin

by **Dr. Sharon Ling** *(B.Pharm, Ph.D.)*

Different Strokes

According to statistics from the World Health Organization, 15 million people worldwide suffer a stroke every year. 10% or 5.5 million of the global causes of death were due to stroke (3 million women and 2.5 million men). It is the third most common cause of death in developed countries. Ischemic stroke happens when the artery supplying blood to the brain is blocked. On the other hand, hemorrhagic stroke happens when the artery ruptures, causing bleeding in the brain.

Stroke is the main cause of death and permanent disability that affects 6.5 million people in the US (Lloyd-Jones, D *et al.*, 2009). In the USA, someone dies of a stroke every three minutes and on average, every 40 seconds someone will have a stroke (Lloyd-Jones, D *et al.*, 2009), (Mackay, J., Mensah, G., 2004).

Among Asians aged 18 and above, 2% have had a stroke. In 2004, the death rate of stroke was 44.2% for Asian males and 38.9% for females (American Heart Association., 2008). In the EU, stroke is the second single most common cause of death, accounting for 1.24 million deaths in Europe each year. The incidence of death caused by stroke is higher for women (17%) than in men (11%) (European Heart Network, 2008).

Smoking and high blood pressure are important modifiable risks of stroke. Atrial fibrillation increases the risk of stroke by five times (Wolf, 1991). Heart failure and heart attack are other important risk factors (Mackay, J., Mensah, G., 2004).

The Economic Burden

Stroke is a major global public health concern that prematurely claims productive lives and burdens the healthcare systems, as many of the stroke survivors become disabled and require long term care and rehabilitation. Stroke survivors often suffer from loss of speech, co-ordination, mobility and cognition physically. A majority of them also have to deal with emotional stress and depression resulting from the loss of self-dependence.

The economic costs of stroke are staggering, as shown by some major statistics:

- The World Health Organization (WHO) estimated that global disability-adjusted life years (DALYs) lost to stroke (a measure of the burden of disease) will rise from 38 million in 1990 to 61 million in 2020 (Mackay, J., Mensah, G., 2004).
- The American Heart Association estimated in 2004 that stroke cost the nation a total of US$53.6 billion in direct healthcare cost and productivity loss. In 2001, the National Stroke Association estimated that the average cost per patient for the first 90 days after a stroke was US$15,000, although 10% of cases cost more than US$35,000 (Mackay, J., Mensah, G., 2004).
- In Singapore, the average hospital costs for stroke were reported in 2000 as US$5000 per patient (Mackay, J., Mensah, G., 2004).
- According to the European Heart Network, stroke is estimated to cost the EU economy over €38 billion a year. Around 49% is due to direct healthcare costs, 23% to productivity losses and 29% to the informal care of people with stroke (European Heart Network, 2008).

The Brain

The central nervous system consists of the brain and spinal cord. The human brain (Figure 1.) is the control center of the nervous system. The nervous system is made up of billions of nerve cells called neurons.

A neuron transmits electrical signals called nerve impulses. The axon will carry these impulses to

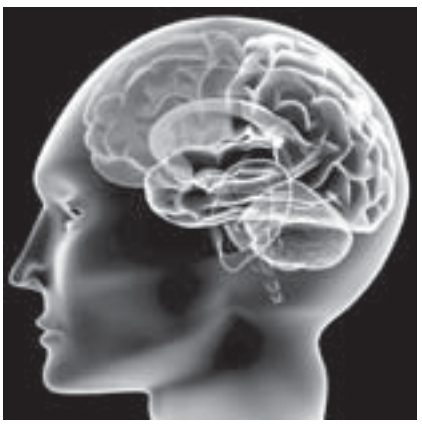

Figure 1. The human brain

dendrites which deliver them to the receiving cells or fibers.

The central nervous system does not regenerate. Therefore, neuronal loss from stroke is permanent although limited function can be regained by transferring the tasks to other neurons – a slow process which happens in stroke rehabilitation.

Glutamate is a neurotransmitter – a group of molecules that allow neurons to communicate with each other (Figure 2.). When there is excessive concentration of glutamate, neuronal death results. Ischemia, hypoxia (oxygen deprivation), brain trauma, seizures, various forms of dementia are all potential causes of glutamate toxicity.

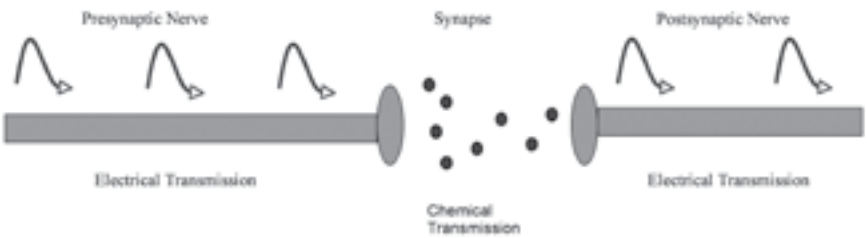

Figure 2. Diagrammatic representation of how electrical impulses are transmitted between neurons.

Treatments Available

Stroke is best prevented for neuron loss is irreversible. Currently, available medical treatment for the prevention of stroke includes cholesterol lowering drugs, antihypertensives and anticoagulant agents such as aspirin. However, these drugs often produce undesirable side effects and require strict monitoring on the dosage.

There are very few compounds that have neuroprotective properties. Although quite a number of homeopathic treatments and herbs claim to be protective against stroke, the documented efficacy of these compounds remains controversial.

Tocotrienol is unique as it is a natural vitamin E that is neuroprotective. The efficacy is proven by extensive research.

Tocomin® Tocotrienols as Neuroprotective Vitamin

The vitamin E family comprises eight chemically distinct compounds: 4 tocopherols and 4 tocotrienols (alpha, beta, gamma and delta). Tocotrienols differ from tocopherols by having an unsaturated side tail that results in significantly different biological activities (Figure 3).

Tocomin® is a natural tocotrienol complex concentrated from virgin crude palm oil through a patented mild extraction process which ensures maximum preservation of phytonutrients. It contains predominantly full spectrum tocotrienols and other phytonutrients such as tocopherols, plant squalene, phytosterols, co-enzyme Q10 and mixed carotenoids that are naturally extracted together with tocotrienols.

The Evidence

Tocotrienol confers neuroprotection through 2 main functions: its powerful antioxidant activity and mechanisms other than antioxidant function. Deficiency of vitamin E is a cause of neurological dysfunction. The brain is highly susceptible to oxidative damage due to high oxygen consumption which is continuous and independent of degree of physical activity. Furthermore, the high lipid content of the brain makes it susceptible to lipid peroxidation in an antioxidant poor environment.

Tocotrienol is 40 – 60 times more potent than α-tocopherol in protecting brain cells from peroxidation (Kamat JP, 1995).

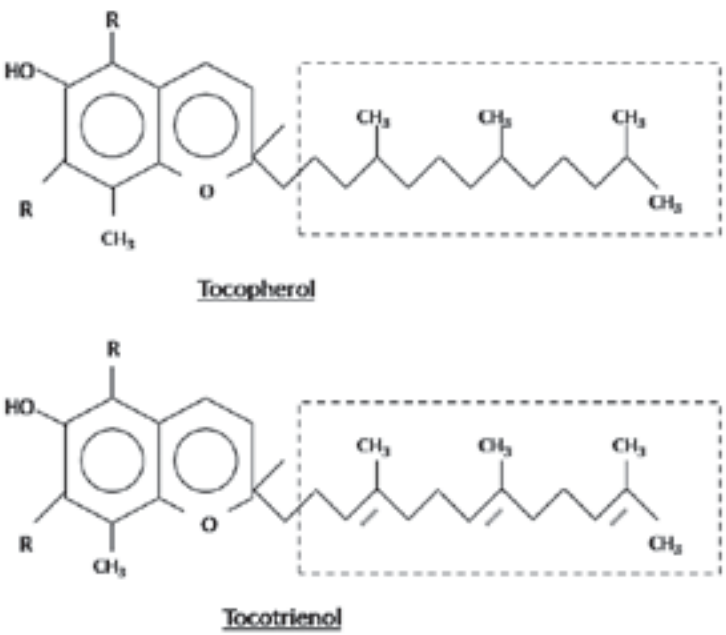

Figure 3. Chemical structures of Tocopherol and Tocotrienol. Note the 3 double bonds in the tocotrienol side tail.

The higher efficiency of α-tocotrienol in protecting brain cells from oxidative damage could be due to

- the unsaturated side chain of tocotrienol allows for more efficient penetration into tissues that have saturated fatty layers, such as the brain and liver
- tocotrienols are recycled / regenerated more effectively to be used again
- tocotrienols interact better with lipid radicals due to stronger disordering of cell membrane and higher mobility

Tocotrienol prevents neuron death by other mechanisms unrelated to its antioxidant activity. In a number of NIH-sponsored studies, Researchers at the Ohio State Medical Center showed that α-tocotrienol, but not α-tocopherol, prevented neuron's death at extremely low concentration (nanomolar, $^{10-9}$) by regulating specific mediators of cell death (Sen CK *et al.*, 2000). Tocotrienol-treated neurons maintained healthy growth and motility even in the presence of excess neurotoxic agent. The neuroprotective property seen at such low concentration of tocotrienol is independent of its antioxidant activity, as tocotrienols do not exhibit antioxidant properties at nanomolar concentrations. Tocotrienols only begin to show their antioxidant effects at micromolar concentrations (Khanna *et al.*, 2006).

The same researchers went on to demonstrate that oral supplementation of tocotrienols (Tocomin®, Carotech Inc.) reaches rats' brain in concentration that protected against stroke. There is reduced volume of cerebral infarct in tocotrienol-supplemented rats compared with un-supplemented controls (Khanna S *et al.*, 2005).

A further study showed that Tocomin®SupraBio™ (Carotech Inc.) supplementation in healthy women achieved plasma levels of tocotrienols 12 to 30 times more than the concentration of α-tocotrienol required to completely prevent stroke-related neurodegeneration (Khosla P *et al.*, 2006).

The patented SupraBio™ system is a self-emulsifying delivery system that provides more consistent and enhanced oral absorption of tocotrienols. It contains a mixture of oil and surfactants at an optimum ratio that will self-emulsify in the gastrointestinal tract. Further reactions will generate conditions essential for optimal absorption of tocotrienols. This novel delivery system results in rapid and consistent absorption of tocotrienols independent of dietary fat or food intake. Clinical study on healthy human volunteers confirmed the efficacy of SupraBio™ system, which increases the rate and extent of tocotrienol absorption by up to 300% (Figure 4) (Ho D *et al.* US Patent 6596306).

World's Largest Clinical Trial

Looking at Neuroprotective Effects of Tocotrienols

A collaborative work between researchers from the Malaysian Palm Oil Board, University of Science Malaysia and Hovid Berhad, this randomized double blind placebo controlled human study is on course to recruit some 400 participants over the next few years to study the neuroprotective effects of tocotrienols by looking at white matter changes using magnetic resonance imaging (MRI) (ClinicalTrials.gov, 2008). This allows the researchers to look into early changes of the brain without having to wait for an overt clinical endpoint such as a clinical stroke.

The secondary objectives of this human study include evaluating the effects of tocotrienols on blood parameters such as total lipid profile, Apo-B, C-reactive protein, antioxidant profile, Lp(a) and lipid peroxidation.

White matter lesions

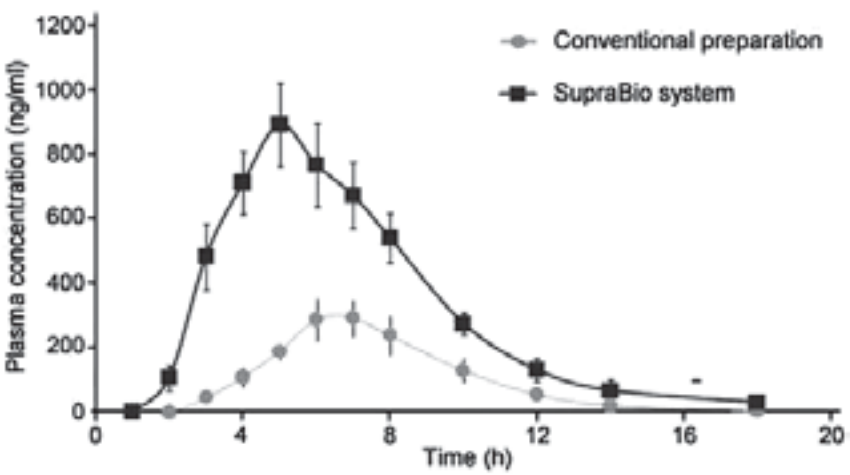

Figure 4. Mean plasma alpha-tocotrienol versus time curve of the conventional preparation and SupraBio™ system.

White matter lesions as detected on magnetic resonance imaging (MRI) (Figure 5) are closely related to vascular events of the brain. MRI and histopathological study has shown that the larger white matter lesions not usually conforming to usual areas of infarcts can actually represent areas of subclinical infarct (Marshall *et al.*, 1988). In addition, there is positive correlation between white matter lesions and established vascular risk factors (Murray *et al.*, 2005). Several recent studies showed that white matter hyperintensities may be an independent prognostic measure of future stroke risk.

The Rotterdam Scan Study showed that elderly people with silent brain infarcts and white matter lesions are at significantly higher risk of clinical stroke, which could not be explained by the major stroke risk factors alone (Vermeer *et al.*, 2003). Persons with white matter lesions have an increased risk of clinical stroke. Those with both white matter lesions and retinopathy have a much higher risk of clinical stroke (20% vs 1.4%) (Wong *et al.*, 2002). Severe white matter lesions is shown to be an independent predictor of risk for stroke from arteriolosclerosis, while progression of white matter lesions during follow up may be associated with subsequent stroke in patients with initially mild white matter lesions. (Yamauchi *et al.*, 2002).

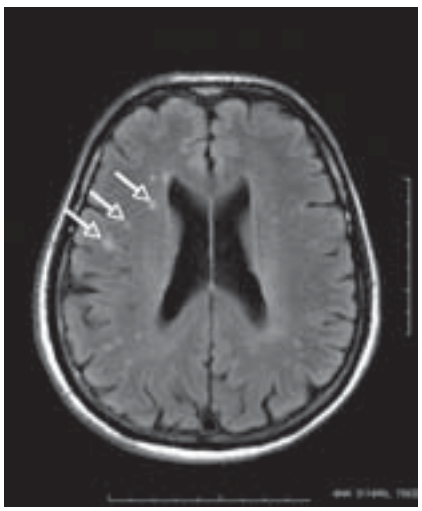

Figure 5. MRI showing white matter lesions (arrows).

Even though the nature of white matter hyperintensities on MRI is by no means totally understood, these data clearly demonstrated that white matter lesion as detected on MRI is closely related to vascular events of the brain and in certain instances represent subclinical infarcts. It is therefore conceivable to study the neuroprotective properties of tocotrienol supplementation in humans by observing serial changes of white matter disease load in the brain.

Study Protocol in Brief

400 subjects will be recruited for study on blood profiles. Among them, 120 subjects will have MRI. The MRI (both positive and negative) subjects will be randomized to receive placebo or 200mg tocotrienols (Tocovid™SupraBio™, Hovid Berhad) twice a day. Over the course of 24 months, MRI images will be taken at baseline, 12 months and 24 months. Blood profile studies will be done bimonthly over 12 months.

At the point of writing, the human study is in progress with close to 400 volunteers having been imaged. There are over 100 MRI that are positive for white matter lesion and randomized to receive placebo or tocotrienol treatment. Some of the positive cases are undergoing second imaging.

Summary/Conclusion

Globally, stroke is the 3rd most common cause of death, after heart disease and cancer. The impact of stroke on quality of life and the economy is enormous especially when the population ages as stroke is more common in the elderly. Modifying lifestyle and habits such as increasing physical activities and smoking cessation, might reduce the risk of stroke.

Tocomin® palm tocotrienols complex shows neuroprotective effects in many studies including a number of NIH-funded studies.

The first study of its kind and the world's largest clinical trial utilizing MRI of brains to evaluate the efficacy of tocotrienols in neuroprotection and antiatherogenic function is currently under way. The results of this clinical trial will shed more light on the benefits of palm tocotrienol complex (Tocomin®, Carotech Inc.) in both acute neurological disorders (e.g. stroke) and chronic neurodegenerative disorders (e.g. Alzheimer's disease; Parkinson's disease). ■

The impact of stroke on quality of life and the economy is enormous especially when the population ages as stroke is more common in the elderly.

Biography

Dr. Sharon Ling *(B.Pharm, Ph.D.)*, Vice President, Scientific Affairs, Carotech Ltd. graduated top of the class with an honours (1st class) degree in Pharmacy from The National University of Malaysia. She received the Royal Student Award & University Gold Medal for being the best overall graduate of the university in 2000. She later obtained a Ph.D. in Pharmaceutical Technology from The School of Pharmaceutical Sciences, University of Science Malaysia. Subsequently she joined Hovid Ltd. as the Product Research Manager responsible for the research and development of pharmaceutical and nutraceutical products. She has been an investigator in over 30 human clinical studies, many of which related to palm-based phytonutrients. She has been a popular speaker at numerous international conferences, universities, hospitals and community organizations on topics including biopharmaceuticals, bioenhanced and controlled release drug delivery systems, palm nutraceuticals and phytonutrients. She is currently the Vice President, Scientific Affairs, Sales & Marketing for Carotech Ltd. based in the United Kingdom.

About Carotech

Carotech, a public listed company in Malaysia ACE Market (formerly MESDAQ Board) is the first and largest GMP certified producer of natural full spectrum tocotrienol complex, natural mixed carotene complex and phytosterol complex in the world via its patented technology. Carotech is a subsidiary of Hovid Berhad (www.hovid.com), one of the largest GMP-certified pharmaceutical companies in Malaysia. *Carotech manufactures these products under the tradenames: Tocomin®, Tocomin® SupraBio™, Caromin® and Stelessterol™. These products are Non-GMO, Kosher and Halal certified.*

Websites: **www.carotech.net, www.tocotrienol.org**
Email: **info@carotech.net**

For more information, please contact:
Carotech Ltd.
Europe Sales & Marketing Office
Buckinghamshire
United Kingdom
Tel : +44(0)7541966007
Email : sling@carotech.net, info@carotech.net
Websites: www.carotech.net. www.tocotrienol.org

References

American Heart Association. (2008). Asian/Pacific Islanders and Cardiovascular Diseases : Statistics. *Statistical Fact Sheet - Populations 2008 Update*.

ClinicalTrials.gov. (2008). Neuroprotective and Cardioprotective Effects of Palm Vitamin E Tocotrienols. *ClinicalTrials.gov Identifier NCT00753532*.

European Heart Network. (2008). European Cardiovascular Disease statistics, 2008 Edition.
Ho D *et al*. (n.d.). Drug delivery system: formulation for fat-soluble drugs. *US patent 6596306*.

Kamat JP, D. T. (1995). Tocotrienols from palm oil as potent inhibitors of lipid peroxidation and protein oxidation in rat brain mitochondria. *Neuroscience Letter*, 195, 179-182.

Khanna S *et al*. (2006). Characterization of the potent neuroprotective properties of the natural vitamin E alpha-tocotrienol. *J. Neurochem*, 98(5), 1474-1486.

Khanna S *et al*. (2005). Neuroprotective Properties of the Natural Vitamin E alpha-Tocotrienol. *Stroke*, 36, e144-e152.

Khosla P *et al*. (2006). Postprandial levels of the natural vitamin E tocotrienol in human circulation. *Antioxid Redox Signal*, 8(5-6), 1059-1068.

Lloyd-Jones, D *et al*. (2009). Heart Disease and Stroke Statistics 2009 Update. A report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation*, 119, e1-e161.

Mackay, J., Mensah, G. (2004). *The Atlas of Heart Disease and Stroke*. World Health Organization: Nonserial Publication.

Marshall VG et al. (1998). Deep white matter infarction: Correlation of MR imaging and histopathologic findings. *Radiology*, 237, 517-522.

Murray AD et al. (2005). Brain white matter hyperintensities: relative importance of vascular risk factors in nondemented elderly people. *Radiology*, 237, 251-257.

Sen CK et al. (2000). Molecular Basis of Vitamin E Action. Tocotrienol potently inhibits glutamate-induced pp60 c-Src Kinase activation and death of HT4 neuronal cells. *J Biol Chem*, 275 (17), 13049-13055.

Vermeer et al. (2003). Silent Brain Infarcts and White Matter Lesions Increase Stroke Risk in the General Population: The Rotterdam Scan Study. *Stroke*, 34, 1126-1129.

Wolf *et al*. (1991). Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke*, 22, 983-988.

Wong *et al*. (2002). Cerebral White Matter Lesions, Retinopathy, and Incident Clinical Stroke. *JAMA* , 288 (1), 67-74.

Yamauchi H *et al*. (2002). Significance of white matter high intensity lesions as a predictor of stroke from arteriosclerosis. *J. Neurol Neurosurg Psychiatry*, 576-582.