

ExcelVite



Steering the Vitamin E Tocotrienol Research

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Your Preferred Partner In Palm Nutraceutical Excellence

Table of Content

• Summary	1
• EVNol SupraBio™ Steering the Vitamin E Tocotrienol Research	2
• What Is Tocotrienol?	3
• Tocotrienol (Super Vitamin E) & Its Unique Health-Promoting Benefits	4
• Brain Health (Neuroprotection)	5
• Liver Health (Hepatoprotection)	5
• Heart Health (Cardioprotection)	6
• Skin & Hair Health (Oral & Topical)	6
• Where Can One Get Tocotrienol?	7
• Why Tocotrienol from Palm?	7
• Misconception: Tocotrienols Are Not Well-Absorbed	8
• Tocotrienol Absorption Issues	9
• EVNol SupraBio™-The Pioneer of Tocotrienol Innovation & Science	9
• Tocotrienol Innovation - The 2 nd Generation of Tocotrienol Complex	9
• Quality Assurance	10
• Bioavailability & Bioefficiency	10-11
• “You Are What You Absorb, Not What You Eat”	13
• Safety	13
• Clinical Research and Scientific Substantiation	14

● Summary

Vitamin E is a well-known powerful antioxidant that helps to protect cell membranes from free-radicals damaging effects. However, most people tend to associate vitamin E with tocopherols only. In fact, vitamin E consists of 2 families - tocopherols and tocotrienols.



Although tocotrienol is the lesser known form of the two, it has been scientifically proven to be more potent, and has demonstrated unique health beneficial properties which are not possessed by tocopherols.



a patented and bio-enhanced tocotrienol system, developed to increase the individual tocotrienol absorption up to **300%**



Due to tocotrienol's poor and inconsistent oral absorption, EVNol SupraBio™, a patented and bioenhanced tocotrienol system is developed to increase the absorption of each individual tocotrienols up to 300% in a consistent manner. Most importantly, EVNol SupraBio™ has been proven in actual human tissue distribution clinical study, to be highly bioavailable and accumulates in vital human organs such as brain, heart, liver and skin for its health-promoting effects. In addition, there are currently 15 published

human clinical studies on the unique health benefits of EVNol SupraBio™. Hence, EVNol SupraBio™ is the preferred tocotrienol of choice with clinical and scientific substantiation. We invite you to review this white paper to understand more about tocotrienol especially on its unique health benefits, the innovation of tocotrienol (EVNol SupraBio™), established quality reputation of EVNol SupraBio™ and proven bioavailability and bioefficiency of EVNol SupraBio™.

- **EVNol SupraBio™**
Steering the Vitamin E Tocotrienol Research



A building needs a strong foundation and similarly, “strong” cells are the foundation of good health. Cells are the fundamental units of life to build body tissues and organs. When body cells are in good condition, tissues and organs will operate efficiently, and minimize the onset of health diseases.

Generally, a healthy adult has approximately 30 trillion cells and each day, thousands of new cells are regenerated to replace the old or damaged cells. Therefore, it is essential to provide the right nutrients to form new cells for overall health. In fact, cells need not only proteins and healthy fats to sustain the cell structure, but also antioxidants to protect our cells against invasion of free radicals that could lead to DNA damage. Hence, it is of utmost importance to preserve the integrity of cellular membrane (structural boundary that encapsulates the cell) to safeguard cell components from physical or biochemical destruction.

Vitamin E is one of the most important lipid-soluble antioxidants that penetrates into cell membranes efficiently to protect the cells against free radical-mediated oxidative stress (crucial contributing factor to developing degenerative diseases).

Unfortunately, the US National Health and Nutrition Examination Survey III (NHANES III) reported approximately 90% of American adults do not meet the daily requirement of vitamin E due to the growing consumption of processed or convenience foods [1].

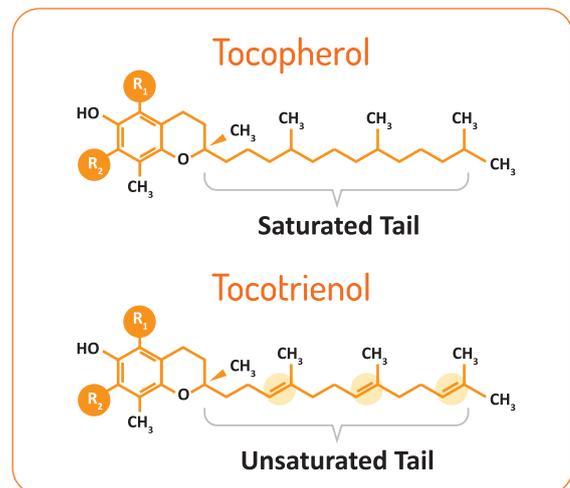
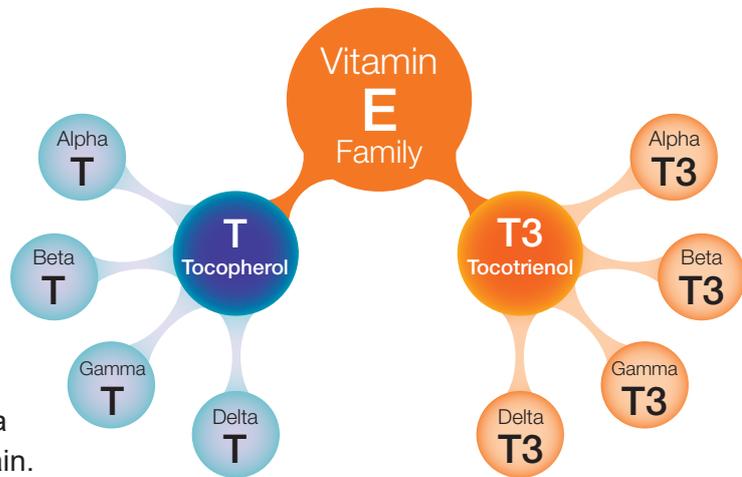
For this reason, dietary supplements or fortified foods play an important role in narrowing the gap between inadequate intake and recommended level of vitamin E.

However, most of the nutritional and scientific community still assume that vitamin E is synonymous with tocopherol only. In reality, vitamin E consists of eight chemically distinct compounds: 4 tocopherols and 4 tocotrienols (alpha-, beta-, gamma- and delta- respectively). Unfortunately, tocotrienol is like the proverbial Cinderella, often neglected and unrecognized until recent years. This hidden gem has gained significant attention among scientists and consumers alike due to its unique health benefits which are not associated with the regular tocopherol Vitamin E.

● What is Tocotrienol?

Both tocotrienol and tocopherol are members of Vitamin E family. The molecular structure for both tocotrienol and tocopherol are quite similar in that both of them consist of a chromanol ring and a phytyl side chain.

The only difference is in their phytyl side chain where the tocopherol has a saturated side chain and tocotrienol, an unsaturated side chain. It is believed that the unsaturated side chain (ie: three double bonds) of tocotrienol allows bending or flexibility of the molecule, thus enabling tocotrienol to penetrate into cell membrane efficiently and distribute in a more uniform manner^[2] to confer some of the unique biological effects such as potent antioxidant and so forth. As a result, tocotrienol is also known as the Polyunsaturated Vitamin E or Super Vitamin E of the 21st Century that exhibits unique health-promoting benefits which are not shown by tocopherol as listed in the table next page.



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● Tocotrienol (Super Vitamin E) & Its Unique Health-Promoting Benefits

Unique Health-Promoting Benefits		Tocopherol	Tocotrienol
	Brain Health (Neuroprotection)		
	<ul style="list-style-type: none"> Ameliorates neurodegeneration (nanomolar concentration) Attenuates brain white matter lesion 	-	+
	Liver Health (Hepatoprotection)		
	<ul style="list-style-type: none"> Attenuates fatty liver Mitigates liver stiffness Improves liver functions 	-	+
		-	+
	Heart Health (Cardioprotection)		
	<ul style="list-style-type: none"> Supports healthy cholesterol level Mitigates arteriosclerosis Maintains arterial compliance Antioxidant potency in preventing LDL oxidation 	-	+
		-	+
		-	+
		+	++
	Skin & Hair Health (Oral & Topical)		
	<ul style="list-style-type: none"> Preferential accumulation in stratum corneum of skin Antioxidant potency Promotes healthy hair 	-	+
		+	++
		+	++

Remarks: ++ indicates better health beneficial effects

Brain Health (Neuroprotection)



Neuroprotection is a health area of immense interest as neurodegenerative diseases such as stroke and Alzheimer's disease are on the rise especially among the elderly. It is reported that alpha-tocotrienol, but not alpha-tocopherol, at nanomolar concentration is able to prevent stroke associated glutamate-induced toxicity^[3]. Tocotrienol has also been proven to mitigate white matter lesion progression, which is an independent risk factor for a full-blown stroke^[4]. Research carried out at the Ohio State University Medical Center over the past 15 years, has identified 5 different post-stroke neuroprotective mechanisms (ie: molecular check-points)^[5-9].

Collectively, tocotrienol could help to improve the quality of life among patients experiencing neurodegenerative disorders.

Liver Health (Hepatoprotection) Fatty Liver



Fatty Liver or NAFLD (non-alcoholic fatty liver disease) occurs when fats accumulate in the liver for more than 5-10% of its weight. Fatty liver disease is often asymptomatic and if it is left unchecked, it may progress to non-alcoholic steatohepatitis (NASH) and eventually, end-stage liver disease (ESLD). Fatty liver is strongly associated with lipid peroxidation that causes oxidative stress. Hence, a high level of antioxidant helps to reduce the risks of developing fatty liver.

A peer-reviewed published human clinical trial was conducted at the University Science of Malaysia, shows that supplementation with EVNol SupraBio™ was found to be significantly effective in attenuating non-alcoholic fatty liver disease (NAFLD)^[10].

Tocotrienols are preferentially distributed and accumulated in the liver cells. Being a more potent form of antioxidant, it helps to protect oxidation of lipids and fatty acids in the liver.

Heart Health (Cardioprotection) Supports Healthy Cholesterol Level



Cholesterol is our friend when it is maintained at healthy level; conversely, cholesterol is our foe when the level is too high, particularly LDL-Cholesterol. Elevated LDL-cholesterol level might put us at risk for a heart attack or stroke. It has been shown that tocotrienol suppresses the key cholesterol synthesis enzyme “3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase” in the liver and as such, inhibits the production of cholesterol in the body ^[11,12].

HMG-CoA reductase is the same enzyme targeted by statin, the most common prescribed medication among patients having high cholesterol. However, the cholesterol lowering mechanism for both tocotrienol and statin is different. Statin diminishes the substrate of



HMG-CoA reductase, which is a precursor for producing Coenzyme Q10 to support muscle strength. Therefore, long term consumption of statin may lead to muscle weakness. By contrast, tocotrienol degrades HMG-CoA reductase enzyme but does not interfere with the substrate, therefore, tocotrienol intake in the long run will not cause muscle fatigue or weakness ^[13].

Skin & Hair Health (Oral & Topical)



Oxidative stress affects skin and hair health negatively. In order to reduce oxidative stress, strong antioxidants are needed to preserve the beauty of skin and hair. Tocotrienol possesses 40 to 60 times stronger antioxidative activity compared to tocopherols^[2], hence tocotrienol is able to decrease the oxidative stress effectively.

Additionally, tocotrienol has also been shown to distribute uniformly on the skin surface and preferentially accumulate in the stratum corneum of the skin^[14]. The polyunsaturated side chain of tocotrienol allows tocotrienol to penetrate efficiently into cell membranes compared to tocopherols^[2].

As such, tocotrienol interacts more efficiently with free radicals so that the destructive chain reactions initiated by free radicals can be reduced. Hence, tocotrienol is a major chain-breaking antioxidant that could help to attenuate free radicals-mediated oxidation processes.

Due to the unique attributes of tocotrienol, tocotrienol has been gaining tremendous attention for promoting skin health such as improves skin characteristics in harsh winter condition^[15], defends skin against UV-induced damages^[16], surgical scar healing^[17] and wound healing^[18].

● Where Can One Get Tocotrienol?

Tocotrienol is not and cannot be produced in the body and thus, one can only obtain tocotrienols through diet or supplementation. Tocotrienol is less widespread in the plant kingdom and can only be found in certain sources such as rice, barley, wheat and rye. In nature, oil palm (*Elaeis guineensis*) is the most abundant source of tocotrienols, containing up to 800mg/kg tocotrienol. For general wellness, the recommended daily intake of tocotrienols is 30-50mg/day. In order to attain this recommended level via daily regular diet alone, one has to consume about 80,000 mg (80g) of palm oil, or 1.5 to 4.0 kg of wheat germ, barley or oats, which is practically impossible. Therefore, the incorporation of tocotrienols through dietary supplements or functional foods and beverages are highly recommended.



Rice



Barley



Oil Palm



Wheat

● Why Tocotrienol from Palm?



There are four commercial sources of tocotrienol: virgin crude palm oil (palm fruits), palm fatty acid distillate (PFAD), rice and annatto seeds. Virgin crude palm oil is the most abundant natural source of tocotrienol. The total tocotrienol ratio in virgin crude palm oil is 78% whereas the tocotrienol from other sources such as PFAD and rice contain a ratio of 70% and 50% respectively. Annatto seeds, although it contains 100% tocotrienol content, it is made up of delta- and gamma-tocotrienol only without any tocopherols.

Virgin crude palm oil, apart from having high content of tocotrienol, also contains full spectrum and significant amount of individual tocotrienol - alpha, beta, gamma and delta-tocotrienol.

Whereas for other commercial tocotrienol sources, they are neither suitable to be a food source, nor a full spectrum tocotrienol complex with all the 4 isoforms of tocotrienols (ie: consists negligible or none of certain tocotrienol isoforms).

- **Misconception: Tocotrienols Are Not Well-Absorbed**

Alpha-tocopherol has always been regarded as the “culprit” that depletes the absorption of tocotrienol - which in fact, is a misconception.

A study conducted at Iowa State University evaluates the distribution of vitamin E isoforms in laying hens supplemented with different feed preparations (tocopherol-free annatto tocotrienol and alpha-tocopherol with annatto tocotrienol). The study shows that hens supplemented with both alpha-tocopherol and tocotrienol demonstrated improved uptake and enhanced gamma-tocotrienol distribution in liver, kidney and brain. On the other hand, the distribution of delta-tocotrienol was higher in almost all the tissues tested (e.g. fat pad, liver, brain, oviduct, yolk, breast and thigh meat), compared to the tocopherol-free tocotrienols preparation. Hence, it is suggested that alpha-tocopherol does not hinder but facilitate the uptake and distribution of tocotrienols in tissues and organs^[19].



Furthermore, alpha-tocopherol transport protein (α -TTP) has been traditionally believed to be the “only” transport mechanism for vitamin E as α -TTP has strong affinity towards alpha-tocopherol which bio-discriminate other vitamin E forms, including tocotrienols. Hence, this has led to the notion that tocotrienols are not well-absorbed and transported to cells or tissues efficiently. However, Professor Chandan Sen from Ohio State University Medical Center has proven that α -TTP-knockout mice was able to absorb significant amount of tocotrienols and restored fertility^[20]. This study has unequivocally proven that the absorption of tocotrienols is through an α -TTP-independent pathway.

In addition, almost all the human clinical studies have been carried out with the palm tocotrienol/tocopherol complex which consists of all the 4 isoforms of tocotrienol and alpha-tocopherol.

● Tocotrienol Absorption Issues

Similar to other fat soluble phytonutrients, the absolute oral bioavailability of alpha-, gamma- and delta-tocotrienol has been reported to be low and erratic, with the absorption of 27.7%, 9.1% and 8.5% respectively^[21]. Being a fat-soluble vitamin, the oral absorption of tocotrienol is highly dependent on the type and amount of dietary fats consumed. Additionally, the absorption or bioavailability of tocotrienols also require bile secretion and emulsification processes in the small intestine.

As documented in published pharmacokinetic studies, the absorption and bioavailability of tocotrienols are of utmost concern because it determines whether the administered tocotrienols is absorbed into the plasma and reach the cells efficiently in order to confer health-promoting properties. As such, overcoming the poor absorption and low bioavailability of tocotrienols are crucial for tocotrienols to be well-absorbed in a consistent fashion regardless of external factors such as dietary fat intake and fat digestion.

The trend in the market is towards absorption / bioavailability. In terms of dietary supplementation, what is more important is "what one absorbs" and not "what one eats". Basically - "*You Are What You Absorb, Not What You Eat*".

● EVNol SupraBio™ The Pioneer of Tocotrienol Innovation & Science

Tocotrienol Innovation

- The 2nd Generation of Tocotrienol Complex

**The SupraBio System - a Patented
Self-Emulsifying Delivery System
for Tocotrienol, protected by
US Patent : 6,596,306.**

ExcelVite together with Hovid Berhad, one of the largest generic pharmaceutical companies in Malaysia, embarked on an extensive research to develop the **SupraBio™ System** - a patented self-emulsifying delivery system for EVNol™ (Tocotrienol) that ensures enhanced and consistent absorption of each individual tocotrienol into human plasma of up to 300% compared to a regular tocotrienol oil extract.

EVNol SupraBio™ contains a self-emulsifying delivery system (SEDS) - a mixture of oil and FDA-approved food emulsifiers at optimum ratio that will self-emulsify in the gastrointestinal tract. The emulsion will then undergoes lipolysis to form particles of colloidal dimensions, mimicking the intraluminal processing, which is a critical action for optimal absorption of tocotrienols. Thus, the absorption of tocotrienols is not only being enhanced and maximized, but more importantly, allowing one to achieve therapeutic plasma level at a lower supplementation dosage, for the proven unique health benefits of tocotrienols.

Quality Assurance



The premium quality of EVNol SupraBio™ begins at the source. Tocotrienols are meticulously extracted from non-GMO and sustainably-sourced Malaysian virgin crude palm oil through a patented multi-step molecular distillation process.

ExcelVite's molecular distillation process utilizes ultra-high vacuum and low temperature processing that preserves the integrity of all other phytonutrients such as squalene, phytosterols, mixed carotene and Co-Q10 that are naturally present in palm fruits (virgin crude palm oil). Therefore, EVNol SupraBio™ ensures that all the goodness and phytonutrients from palm fruits are concentrated in one wholesome complex, as occurs in nature.

In fact, ExcelVite is the world's largest and only GMP (Good Manufacturing Practice) -certified tocotrienol producer.

We commit and prioritize quality and consistency by ensuring the ratio of tocotrienols to tocopherols in EVNol SupraBio™ are at 78% to 22%. In fact, EVNol SupraBio™ has the highest percentage of alpha-tocotrienol (most neuroprotective isoform) and gamma-tocotrienol (most cardioprotective isoform) among all commercial tocotrienol products.

Bioavailability & Bioefficiency



The efficacy of EVNol SupraBio™ has been shown in many clinical trials worldwide, including the studies funded by the prestigious National Institute of Health (NIH) on neuroprotection.

EVNol SupraBio™ as a branded tocotrienol ingredient, is the preferred tocotrienol of choice of dietary supplement companies and consumers alike. It has been selected and used by researchers all over the world due to its high quality, consistency, and established reputation as well as proven enhanced bioavailability (absorption into plasma) and bioefficiency (accumulation in vital human organs).

A two-period, two-sequence study on healthy human volunteers was conducted to determine the rate, peak absorption and extent of absorption between EVNol SupraBio™ bio-enhanced delivery system and regular tocotrienol oil system. When compared to regular tocotrienol oil system, the EVNol SupraBio system shows

- Faster rate of absorption of tocotrienols and commences at an earlier stage;
- Peak absorption of tocotrienols is significantly higher (average 250%);
- Extent of each individual tocotrienol (alpha-, gamma- and delta-tocotrienol) absorption in EVNol SupraBio™ increases by an average of 250% [22]

Fig. 1a Mean plasma delta-tocotrienol versus time curves of the EVNol SupraBio™ System and Regular Tocotrienol Oil Extract (OE)

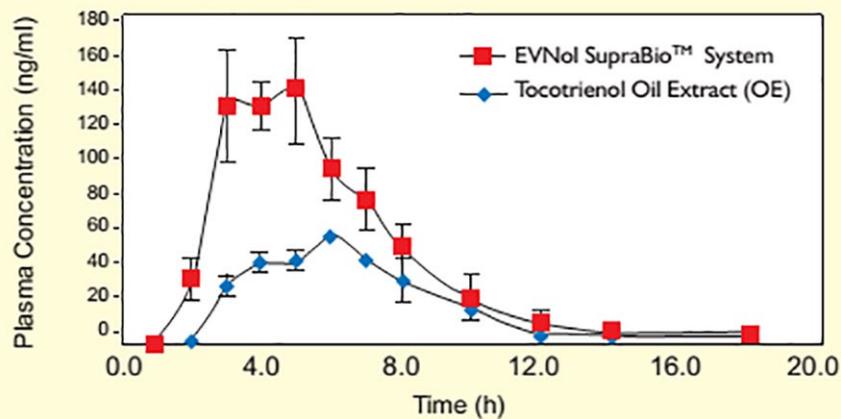


Fig. 1b Mean plasma gamma-tocotrienol versus time curves of the EVNol SupraBio™ System and Regular Tocotrienol Oil Extract (OE)

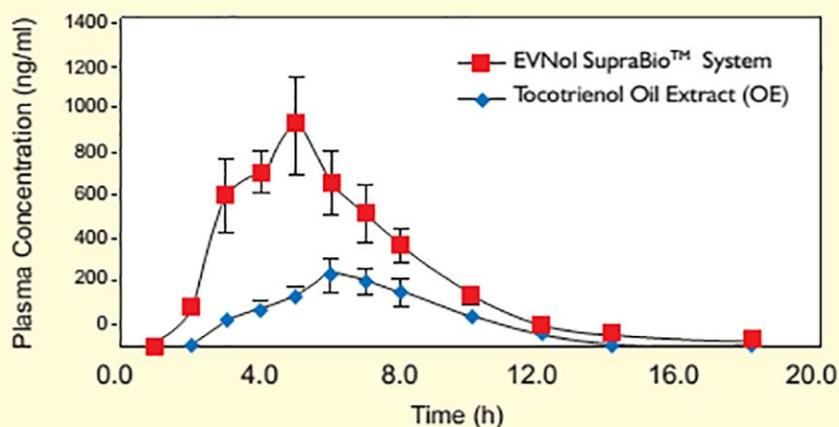
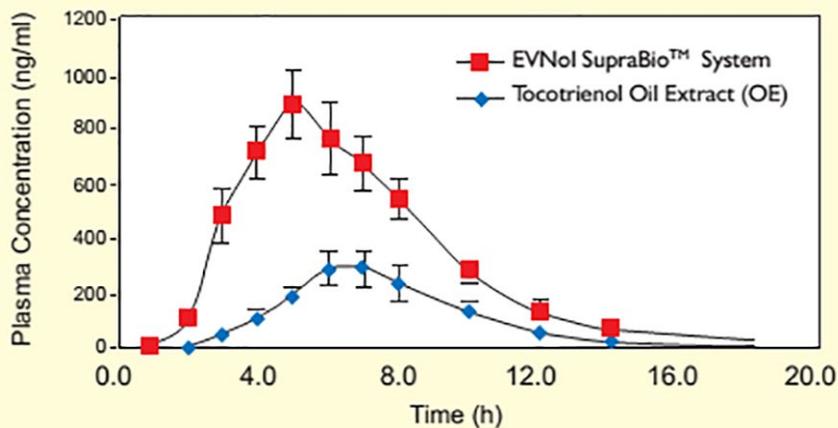


Fig. 1c Mean plasma alpha-tocotrienol versus time curves of the EVNol SupraBio™ System and Regular Tocotrienol Oil Extract (OE)



(Ho D, et al., U.S. Patent No. 6,596,306)

Oral supplementation of EVNol SupraBio™ has also been demonstrated to be rapidly delivered to lipoprotein fractions (group of soluble proteins that transport fats or lipids in blood plasma) of human plasma at concentrations sufficient to confer its reported neuroprotective functions^[3]. A recent ground-breaking human tissue distribution study conducted at the Ohio State University Wexner Medical Center (and funded by United States' National Institute of Health), shows that tocotrienols from EVNol SupraBio™ supplementation are significantly absorbed, taken up and deposited in vital human organs

such as brain, liver, heart, skin and adipose tissues. As a matter of fact, published in the *Journal of Nutrition*, this is the first ever and only actual human tissue distribution study with tocotrienols in the market^[23].

Taken together, EVNol SupraBio™ ensures bioenhanced absorption, achieves therapeutic blood plasma level at a lower dosage of supplementation and thereby delivering tocotrienols to vital organs efficiently for biological functions to sustain health.

“You Are What You Absorb, Not What You Eat”



We often hear the common quote “You Are What You Eat” but in reality, “You Are What You Absorb” is more appropriate as nutrients (ie: tocotrienols) have to be absorbed in adequate amount and delivered to where they are needed most in order to support healthy body functions. High concentration of tocotrienol in the form of capsules may not confer the intended health benefits if the tocotrienols are not well-absorbed.

The beneficial and therapeutic levels are achieved only if tocotrienols are consistently absorbed and distributed in the blood and tissues and this can be achieved with EVNol SupraBio™, the only clinically proven tocotrienol complex with guaranteed bioavailability and bio-efficiency.

Safety

Palm oil has been used in human diets as far back as 5000 years ago. In fact, Asians such as Malaysians, Indonesians, Singaporeans, Thais, Chinese and Indians have been consuming tocotrienols from palm oil for many years as these population use palm oil as their daily cooking oil. The daily average consumption of palm oil among Malaysians is about 20g per day, which is equivalent to approximately 15mg of pure full spectrum tocotrienol complex (alpha, beta, gamma and delta-tocotrienol) per day.



EVNol SupraBio™ has been used in many clinical trials with various doses of tocotrienols and is well-tolerated in humans. All the published clinical studies show no adverse events for daily dosage of up to 400mg for a duration of up to 2 years. In addition, the safety of EVNol SupraBio™ was reviewed by a panel of experts and it was granted GRAS (Generally Recognized As Safe) with no objection letter from US FDA (GRAS Notice No is GRN 000307).

Clinical Research and Scientific Substantiation

EVNol SupraBio™, being the first commercial tocotrienol brand with bioenhanced delivery system, was the foundation for many of the main significant scientific findings of the health benefits of tocotrienol. In fact, EVNol SupraBio™ has been selected and used by numerous researchers worldwide, with more than 15

published human clinical studies and at the moment, with 8 on-going human clinical trials, including NIH-funded neuroprotection studies (refer table below for the summary of all studies on EVNol SupraBio™). As such, EVNol SupraBio™ is the most clinically-researched tocotrienol in the market!

Health Area

Past Studies

On-Going Studies

Brain



- Pre and post-stroke mechanisms
- Attenuates white matter lesion, an independent risk factor for a full blown stroke

- Ischemic Stroke
- Stroke
- Dementia

Liver



- Attenuates fatty liver
- Ameliorates liver stiffness
- Improves liver functions

- End Stage Liver Disease
- Hepatitis C
- Metabolic Syndrome

Heart



- Maintains healthy lipid profile, cholesterol level
- Mitigates arteriosclerosis in carotid stenosis
- Supports arterial compliance
- Potent antioxidant in preventing LDL oxidation

Skin



- Improves skin characteristics
- Potent antioxidant (Super Vitamin E)

- Surgical scar
- Wound healing

Hair



- Promotes healthy hair

Eyes



- Peripheral neuropathy

- Glaucoma

ExcelVite continues its investment and commitment in science and research on EVNol SupraBio™ for more health evidences and scientific as well as clinical substantiation. We also continue to explore opportunities and steer EVNol SupraBio™ to the pinnacle of tocotrienol research for further enhancement of the quality of health.

Thank you very much for your time and we hope that you have benefited from this white paper on the unique characteristics and health benefits of tocotrienols as well as the EVNol SupraBio™ - patented & bioenhanced full spectrum palm tocotrienol/tocopherol complex. If you have any questions or would like to have more information about tocotrienols or EVNol SupraBio™, please contact:

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MS ISO/IEC 17025
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1 039-03/2006

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