Vitamin E:
A long overdue review

By Chee Wai FONG (PhD)
Head of Research & Development
Davos Life Science Pte Ltd (Singapore)
Herbert McLean Evans
(September 23, 1882–March 6, 1971)
was a U.S. anatomist and embryologist.

He was born in Modesto, California.

In 1908, he obtained his medical degree from Johns Hopkins University, eventually becoming its associate professor of anatomy.

Evans moved back to California in 1915 and was made professor of anatomy at the University of California, in Berkeley, California, and held that position until his death.
Recommended daily intake (RDI)
22.5 IU or 15 mg
Myth 1: There is only one form of Vitamin E
Tocopherols vs Tocotrienols

Tocotrienols

Alpha
Beta
Gamma
Delta
IU Definition of Vitamin E

The International Unit (IU) of vitamin E is the activity of 1 mg of dl-alpha-tocopheryl acetate. This is the average quantity that, administered orally, prevents resorption-gestation in 50% of female rats deprived of vitamin E.

Relative biological activities of vitamin E isomers in the rat resorption-gestation test:

<table>
<thead>
<tr>
<th>Vitamin E Isomer</th>
<th>Relative Activity</th>
<th>IU</th>
</tr>
</thead>
<tbody>
<tr>
<td>d-alpha-tocopherol (RRR)</td>
<td>100%</td>
<td>1.49 IU</td>
</tr>
<tr>
<td>d-beta-tocopherol (RRR)</td>
<td>25-50%</td>
<td>0.75 IU</td>
</tr>
<tr>
<td>d-gamma-tocopherol (RRR)</td>
<td>1-11%</td>
<td>0.25 IU</td>
</tr>
<tr>
<td>d-delta-tocopherol</td>
<td>1-3%</td>
<td>0.1 IU</td>
</tr>
<tr>
<td>d-alpha-tocotrienol</td>
<td>29-30%</td>
<td>0.45 IU</td>
</tr>
<tr>
<td>d-beta-tocotrienol</td>
<td>5%</td>
<td>0.1 IU</td>
</tr>
<tr>
<td>d-gamma-tocotrienol</td>
<td>Not known</td>
<td>NA</td>
</tr>
<tr>
<td>d-delta-tocotrienol</td>
<td>Not known</td>
<td>NA</td>
</tr>
</tbody>
</table>

Ball, 1988; Kamal-Eldin and Appelqvist, 1996
Myth 2: Synthetic vs Natural

\[ \text{BnO} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \]
\[ \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \]
\[ \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \]

\[ + \]

\[ \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \]
\[ \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \]
\[ \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \]

\[ \text{tBuLi, Et}_2\text{O, -85 °C; MgBr}_2\cdot\text{Et}_2\text{O; CuBr\cdotSMe}_2, \text{Et}_2\text{O} \]
\[ 78\% \]

\[ \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \]
\[ \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \]
\[ \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \]

\[ \text{DAVOS} \]
\[ \text{LIFE SCIENCE} \]
\[ \text{Merging Science with Nature} \]
Natural Vitamin E (RRR-α-tocopherol; d-α-tocopherol)

2R 4'R 8'R α-tocopherol

Synthetic Vitamin E (all-rac-α-tocopherol; dl-α-tocopherol)

2R 4'R 8'R α-tocopherol

2S 4'R 8'R α-tocopherol

2R 4'S 8'R α-tocopherol

2S 4'S 8'R α-tocopherol

2R 4'R 8'S α-tocopherol

2S 4'R 8'S α-tocopherol

2R 4'S 8'S α-tocopherol

2S 4'S 8'S α-tocopherol
## International Unit of Synthetic vs Natural Vitamin E

<table>
<thead>
<tr>
<th>Formulation</th>
<th>IU</th>
</tr>
</thead>
<tbody>
<tr>
<td>dl-alpha-tocopheryl acetate</td>
<td>1.00</td>
</tr>
<tr>
<td>dl-alpha-tocopherol</td>
<td>1.10</td>
</tr>
<tr>
<td>d-alpha-tocopheryl acetate</td>
<td>1.36</td>
</tr>
<tr>
<td>d-alpha-tocopherol</td>
<td>1.49</td>
</tr>
</tbody>
</table>

Bieri and McKenna, 1981

- **US$5.99**
- **US$12.99**
Have we learnt our lesson from Trans Fat?

- Made by adding hydrogen to vegetable oil through a process called hydrogenation
- Using trans fats in the manufacturing of foods helps foods stay fresh longer, have a longer shelf life and have a less greasy feel
- Long term study shows it raises your "bad" (LDL) cholesterol and lowers your "good" (HDL) cholesterol, increases Triglycerides & causes inflammation
- Increase in consumption correlated with the rise of coronary heart disease and other major illnesses including diabetes & Alzheimer’s disease
Myth 3: High Antioxidant levels can prevent cancer
Dietary AOX
↑ Vitamins E and C, α, γ, β-carotene, phytochemical, zinc, copper, selenium intake from foods

Enzymatic AOX
↑ SOD, GPX, CAT activities
↑ Blood AOX, TAS and FRAP

NON-OBSE (BMI < 30 kg/m²)

PROOXIDANT-ANTIOXIDANT BALANCE

↓ Levels of lipid and protein oxidation

ROS from exercise, diet, inflammation, leptin, hyperglycemia

OBESE (BMI ≥ 30 kg/m²)

AOX Deficit
↓ Vitamins E and C, α, γ, β-carotene, phytochemical, zinc, copper, selenium intake

Enzymatic AOX
↓ SOD, GPX, CAT depletion
↓ Blood AOX, TAS and FRAP

PROOXIDANT-ANTIOXIDANT IMBALANCE

↑ Levels of lipid and protein oxidation

OXIDATIVE STRESS

↑ ↑ ROS from exercise, diet, inflammation, leptin, hyperglycemia
<table>
<thead>
<tr>
<th>Study</th>
<th>Study cohort</th>
<th>Intervention</th>
<th>Effect of αTP versus placebo</th>
</tr>
</thead>
</table>
| ATBC (Finland: 1985-1993) | n=30k male smokers, 50-69y (5-8y) | αTP (50 mg); β-carotene (20 mg); both; placebo (2 x 2) | - Null (lung, pancreas, colon/rectum, urothelium, kidney, stomach, oral/pharynx, larynx, esophagus cancer)  
- **lower prostate cancer incidence** (RR=0.64, lack of trend & inconclusive)  
- reduced VEGF-D levels in serum  
- Men with higher serum αTP (13-14 mg/L):  
- **lower total mortality** (RR=0.82); **cancer mortality** (RR=0.79); **CVD mortality** (RR=0.81), (p for trend<0.0001)  
- also positively correlated with γTP levels and other lifestyle factors |
| Linxian (China: 1986-1991) | n=30k, 40-69y, malnourished & at risk for stomach & esophagus cancer (6y) | A (Vit A, Zn), B (Vit B), C (Vit C, Mb), D (αTP, Se, β-carotene). Combi of 2, ABCD or placebo | - Null (esophagus, lung, liver cancer incidence)  
- Group D (αTP, Se, β-carotene):  
- **lower overall** (RR= 0.91, p<0.05) and cancer (RR=0.87, p<0.05) mortality  
- **lower gastric cancer incidence** (RR=0.81, p<0.05)  
- effects were *predominantly* in adults <55y at start of study  
- **lower esophageal cancer mortality** in adults <55y (RR=0.83, p=0.025) |
| WHS (USA: 1992-2004) | n=40k women ≥45y (10y) | αTP (600 IU); β-carotene (50 mg); aspirin (100 mg); combi of 2; all 3 or placebo (2 x 2) | - Null (all cancers, breast, lung, colon cancer)  
- **lower CVD incidence** (RR=0.76, p=0.03) |
| HOPE / HOPE-TOO (World: 1993-2003) | n=9k, ≥55y, with CVD or diabetes (4.5y) | αTP (400 IU) or placebo; ACE inhibitor (ramipril) or placebo (2 x 2) | - Null (cardiovascular disease, total cancer incidence and deaths, prostate, oral/pharynx, GI, melanoma skin, breast cancer)  
- higher risk of heart failure (RR=1.13, p=0.03)  
- **lower risk of lung cancer** (RR=0.72, p=0.04), unsupported by other larger studies (ATBC, HPS) |
| HPS (UK: 1994-2001) | n=20k, 40-80y, with CVD or diabetes (5y) | αTP (600 mg), Vit C (250 mg), β-carotene (20 mg); placebo with simvastatin (40 mg) (2 x 2) | - Null (cardiovascular disease, total cancer incidence, lung, stomach, prostate) |
| SU.VI.MAX (France: 1994-2002) | n=13k, 35-60y (7.5y) | αTP (30 mg), Vit C (120 mg), β-carotene (6 mg), Se (100 µg), Zn (20 mg); placebo | - Null (health-related quality of life, total cancer incidence)  
- **lower total cancer incidence** (GI, respiratory, skin) in men (RR=0.69, p<0.05)  
- **lower prostate cancer incidence** in men with normal PSA levels of 3 ug/L (RR=0.52, p<0.05)  
- 2008: better memory scores |
Table 1: Tocopherol Clinical trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Study cohort</th>
<th>Intervention</th>
<th>Effect of αTP versus placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>WASC (USA: 1995-2005)</strong></td>
<td>n=7627 females with CVD or risk factors, &gt;40y (9y)</td>
<td>αTP (600 IU); βcarotene (50 mg); Vit C (500 mg); combi of 2; all 3 or placebo (2 x 2 x 2)</td>
<td>• Null (overall cancer incidence or mortality)</td>
</tr>
<tr>
<td><strong>PHS II (USA: 1997-2007)</strong></td>
<td>n=14k males &gt;50y (8y)</td>
<td>αTP (400 IU); βcarotene (50 mg); Vit C (500 mg); multivit or placebo (2 x 2 x 2)</td>
<td>• Null (overall cancer incidence or site-specific cancers including prostate cancer)</td>
</tr>
<tr>
<td><strong>SELECT (USA: 2001-2008)</strong></td>
<td>n=35k males with PSA &lt; 4 ng/ml, &gt;50y (7-12y)</td>
<td>αTP (400 IU); Se (200 ug); both or placebo (2 x 2)</td>
<td>• Null (overall mortality, cancer incidence, colorectal, lung cancer, diabetes and CVD)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Increased risk of prostate cancer (RR=1.17, p=0.008)</td>
</tr>
<tr>
<td><strong>CHAOS (UK: 1992-1995)</strong></td>
<td>n=2000 patients with atherosclerosis (8y)</td>
<td>αTP (400/800 IU); or placebo</td>
<td>• Reduced risk of non-fatal myocardial infarction &amp; CVD (RR=0.53, p=0.005)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Non significant increase in CVD mortality</td>
</tr>
</tbody>
</table>

- No one size fits
- No overall benefit for the general population
- Choosing your target group (age, risk factors, genetic polymorphism etc.)
Vitamin E and the Risk of Prostate Cancer
The Selenium and Vitamin E Cancer Prevention Trial (SELECT)

Eric A. Klein, MD
Ian M. Thompson Jr, MD
Catherine M. Tangen, DrPH
John J. Crowley, PhD
M. Scott Lucia, MD
Phyllis J. Goodman, MS
Lori M. Minasian, MD
Leslie G. Ford, MD
Howard L. Parnes, MD
J. Michael Gaziano, MD, MPH
Daniel D. Karp, MD
Michael M. Lieber, MD
Philip J. Walther, MD, PhD
Laurence Klotz, MD
J. Kellogg Parsons, MD, MHS
Joseph L. Chin, MD
Amy K. Darke, MS
Scott M. Lippman, MD
Gary E. Goodman, MD
Frank L. Meyskens Jr, MD
Laurence H. Baker, DO

Context The initial report of the Selenium and Vitamin E Cancer Prevention Trial (SELECT) found no reduction in risk of prostate cancer with either selenium or vitamin E supplements but a statistically nonsignificant increase in prostate cancer risk with vitamin E. Longer follow-up and more prostate cancer events provide further insight into the relationship of vitamin E and prostate cancer.

Objective To determine the long-term effect of vitamin E and selenium on risk of prostate cancer in relatively healthy men.

Design, Setting, and Participants A total of 35,533 men from 427 study sites in the United States, Canada, and Puerto Rico were randomized between August 22, 2001, and June 24, 2004. Eligibility criteria included a prostate-specific antigen (PSA) of 4.0 ng/mL or less, a digital rectal examination not suspicious for prostate cancer, and age 50 years or older for black men and 55 years or older for all others. The primary analysis included 34,887 men who were randomly assigned to 1 of 4 treatment groups: 8,752 to receive selenium; 8,737, vitamin E; 8,702, both agents, and 8,696, placebo. Analysis reflects the final data collected by the study sites on their participants through July 5, 2011.

Interventions Oral selenium (200 μg/d from L-selenomethionine) with matched vitamin E placebo, vitamin E (400 IU/d of all rac-α-tocopheryl acetate) with matched selenium placebo, both agents, or both matched placebos for a planned follow-up of a minimum of 7 and maximum of 12 years.

Main Outcome Measures Prostate cancer incidence.

Results This report includes 54,464 additional person-years of follow-up and 521 additional cases of prostate cancer since the primary report. Compared with the placebo (referent group) in which 529 men developed prostate cancer, 620 men in the vitamin E group developed prostate cancer (hazard ratio [HR], 1.17; 99% CI, 1.004-1.36, P = .008); as did 575 in the selenium group (HR, 1.09; 99% CI, 0.93-1.27; P = .18), and 555 in the selenium plus vitamin E group (HR, 1.05; 99% CI, 0.89-1.22, P = .46). Compared with placebo, the absolute increase in risk of prostate cancer per 1000 person-years was 1.6 for vitamin E, 0.8 for selenium, and 0.4 for the combination.

Conclusion Dietary supplementation with vitamin E significantly increased the risk of prostate cancer among healthy men.
What’s wrong with Vitamin E?

1. Narrow focus only on α-tocopherol

2. α-tocopherol never shown to be anti-tumorigenesis in-vitro or in-vivo; instead γ & δ isomers shown to kill cancer cells in the laboratory

3. Excessively high dose (400IU & above) over long period of time crowds out other tocopherol & tocotrienol isomers

4. Safety of synthetic form of Vitamin E at high doses for prolonged duration unknown

5. Antioxidants alone will not suppress cancer & other conditions

6. A broad spectrum of tocopherol & tocotrienol essential to overall nutrition health
## Current form of Vitamin E (alpha-Tocopherol)

<table>
<thead>
<tr>
<th>Functions</th>
<th>Vitamin E</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antioxidant</td>
<td>+++</td>
<td>Prevents lipid peroxidation</td>
</tr>
<tr>
<td>Fertility</td>
<td>+++</td>
<td>Only requires 22.5 IU</td>
</tr>
<tr>
<td>Cancer Prevention</td>
<td>-</td>
<td>High doses increase cancer risk</td>
</tr>
<tr>
<td>Metabolic Syndrome</td>
<td>+</td>
<td>Some study shows effective in fatty liver</td>
</tr>
<tr>
<td>Brain Health</td>
<td>-</td>
<td>No study</td>
</tr>
<tr>
<td>Broad Spectrum</td>
<td>-</td>
<td>Only one form</td>
</tr>
</tbody>
</table>
What is the underlying cause of disease that antioxidants failed to address?
Inflammation
the root of many diseases

- Inflammation
- Cancer
- Cardiovascular Diseases
- Auto-immune disorders
- Diabetes
- Asthma COPD
- Stroke
- Dermatitis
- Arthritis
Chronic & excessive inflammation is the root cause of many diseases
Life style Carcinogens/Risk factors
Cytokine Cascade in Atherosclerosis

N Engl J Med
Type 2 diabetes as an inflammatory disease

Marc Y. Donath* and Steven E. Shoelson†

Abstract | Components of the immune system are altered in obesity and type 2 diabetes (T2D), with the most apparent changes occurring in adipose tissue, the liver, pancreatic islets, the vasculature and circulating leukocytes. These immunological changes include altered levels of specific cytokines and chemokines, changes in the number and activation state of various leukocyte populations and increased apoptosis and tissue fibrosis. Together, these changes suggest that inflammation participates in the pathogenesis of T2D. Preliminary results from clinical trials with salicylates and interleukin-1 antagonists support this notion and have opened the door for immunomodulatory strategies for the treatment of T2D that simultaneously lower blood glucose levels and potentially reduce the severity and prevalence of the associated complications of this disease.
Development of Inflammation in Type 2 Diabetes

**From gastrointestinal tract**

- Glucose
- Free fatty acids

**Pancreatic islets**

- ↓ IL-1RA
- ↑ IL-1β

**β-cell**

**CCL2, CCL3, CXCL8**

**IL-1β**

**Pro-inflammatory cytokines and chemokines**

- IL-1β, TNF, CCL2, CCL3, CXCL8

**Obese adipose tissue**

- T cell
- Adipocyte
- Mast cell
- Macrophage
# Anti-inflammatory Treatment for Diabetes

Table 2: Clinical studies using anti-inflammatory approaches to treat type 2 diabetes or prediabetes

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Drug</th>
<th>Trial Phase</th>
<th>Number of subjects</th>
<th>Treatment duration (weeks)</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-1 receptor blockade</td>
<td>Anakinra (Kineret; Amgen/Biovitrum)</td>
<td>II</td>
<td>69</td>
<td>13</td>
<td>↓ Glycated haemoglobin, ↓ CRP, ↑ insulin production</td>
</tr>
<tr>
<td>IKKβ–NF-κB inhibition</td>
<td>Salsalate</td>
<td>II</td>
<td>20</td>
<td>4</td>
<td>↓ FBG, ↓ CRP, ↑ insulin sensitivity, ↑ adiponectin</td>
</tr>
<tr>
<td>IKKβ–NF-κB inhibition</td>
<td>Salsalate</td>
<td>II</td>
<td>16</td>
<td>2–4</td>
<td>↓ FBG, ↓ FFA, ↓ triglycerides, ↓ CRP, ↑ adiponectin</td>
</tr>
<tr>
<td>IKKβ–NF-κB inhibition</td>
<td>Salsalate</td>
<td>II</td>
<td>40</td>
<td>1</td>
<td>↓ FBG, ↑ insulin</td>
</tr>
<tr>
<td>IKKβ–NF-κB inhibition</td>
<td>Salsalate</td>
<td>IIb</td>
<td>104</td>
<td>12</td>
<td>↓ Glycated haemoglobin, ↓ FBG, ↓ triglycerides, ↑ adiponectin</td>
</tr>
<tr>
<td>IL-1β-specific antibody</td>
<td>XOMA 052 (Xoma)</td>
<td>I</td>
<td>98</td>
<td>Single injection</td>
<td>↓ Glycated haemoglobin, ↓ CRP, ↑ insulin production</td>
</tr>
<tr>
<td>IL-1 receptor blockade</td>
<td>Anakinra (Kineret; Amgen/Biovitrum)</td>
<td>II</td>
<td>12</td>
<td>4</td>
<td>Ongoing, closed for recruitment</td>
</tr>
<tr>
<td>IL-1β-specific antibody</td>
<td>ACZ885 (canakinumab; Novartis)</td>
<td>II</td>
<td>231</td>
<td>Unknown</td>
<td>Ongoing, closed for recruitment</td>
</tr>
<tr>
<td>IL-1β-specific antibody</td>
<td>ACZ885 (canakinumab; Novartis)</td>
<td>II</td>
<td>140</td>
<td>48</td>
<td>Ongoing</td>
</tr>
<tr>
<td>IL-1β-specific antibody</td>
<td>ACZ885 (canakinumab; Novartis)</td>
<td>II</td>
<td>232</td>
<td>4</td>
<td>Ongoing, closed for recruitment</td>
</tr>
</tbody>
</table>
Inflammation is a fundamental protective response that sometimes goes awry and becomes a major cofactor in the pathogenesis of many chronic human diseases, including cancer.
Anti-inflammatory Agents from Ayurvedic Medicine for Prevention of Chronic Diseases

Current Drug Targets, 2011, Vol. 12, No. 11  1609

NF-κB

Inflammation
- TNF-α
- IL-1β, IL-6, IL-8
- COX-2
- 5-LOX
- iNOS

Survival
- Bcl-2
- Bcl-xL
- ciAP1/2
- XIAP
- cFLIP

Proliferation
- Cyclin D1
- c-myc

Invasion
- MMP-9
- ICAM-1
- VCAM-1
- uPA

Angiogenesis
- VEGF
- PDGF
- HGF

Metastasis
- CXCR4

Chronic diseases
- Diabetes
- Colitis
- Inflammatory bowel disease
- Obesity
- Crohn's disease
- Asthma
- Cancer
Tocotrienol Exerts Anti-inflammatory Response by Regulating NF-κB & Inflammatory Cytokines

↓ IL6  
↓ IL8  
↓ TNF-α  
↓ IL1  
↑ IL12  
↑ IFN-γ

Evidence that Tocotrienol is an effective anti-inflammatory agent
Lindsay Brown
University of Southern Queensland, Australia

Delta-Tocotrienol in a Rat Model of Metabolic Syndrome
Tocotrienol can suppress harmful effects of metabolic syndrome

In high carbohydrate, high fat fed rats, δ-tocotrienol attenuated:

- Hypertension
- Inflammation and fibrosis in the left ventricle and liver
- Abdominal fat deposition and dyslipidaemia
- Impaired glucose tolerance

suggesting that inhibition of inflammation is the key target for this compound in metabolic syndrome.
DavosLife Study: Gamma Delta Tocotrienols Reduce Triglyceride Hepatic Synthesis & Secretion

Tocotrienol-treated subjects showed decreasing trends in average weight, body fat mass, body fat percentage and waist measurement.

Mechanism of Tocotrienol on Lipid Regulation

γ-T3 reduces HMG-CoA levels post-transcriptionally

Tocotrienols Regulate Cholesterol Production in Mammalian Cells by Post-transcriptional Suppression of 3-Hydroxy-3-methylglutaryl-Coenzyme A Reductase*

(Received for publication, November 6, 1992, and in revised form, February 1, 1993)

Rex A. Parker‡, Bradley C. Pearce§, Ronald W. Clark, David A. Gordon, and J. J. Kim Wright§

From the Department of Metabolic Diseases, Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, New Jersey 08543 and the §Division of Central Chemistry, Bristol-Myers Squibb Pharmaceutical Research Institute, Wallingford, Connecticut 06492
Upcoming clinical trial using Natural $e^3$
Effect of Tocotrienol on Serum Lipids in Hypercholesterolemic Subjects Taking Statin

Principal Investigator: Dr David Heber
Director, UCLA Center for Human Nutrition

Study Design:
• 3 arm study of patients, who are on statin medication, but unable to achieve target cholesterol levels
• Statin together with Placebo, 60 mg or 120 mg Natural $e^3 \gamma/\delta$-tocotrienols.
• Total of 99 patients to be enrolled
Mokenge Malafa
Moffitt Cancer Center
US Florida

Delta-Tocotrienol in Subjects with Resectable Pancreatic Exocrine Neoplasia
Tocotrienol increases expression of p27 an important protein in cell cycle regulation

In collaboration with Moffitt Cancer Center & Research Institute (Florida, USA), oral treatment with Natural e3 in patients with resectable pancreatic cancer showed that:

- Tocotrienol increases cancer cell death in human pancreatic tumours
- Tocotrienol increases expression of p27 an important protein in cell cycle regulation

Clinical Trial on:
Natural Tocotrienol Against Ischemic Stroke Event

Subjects: 210 patients with Hyperlipidemic between 40 and 70 years of age currently taking statins with LDL>130mg/dL; TG>150mg/dL; HDL<40mg/dL

• Placebo pills, Tocotrienol pills (400 or 800mg)
• Low-dose 81 mg aspirin (commonly used for secondary prevent stroke),
• Tocotrienol and aspirin

• Duration: 6 months

• Primary Endpoint: to determine the effects of orally supplemented Tocotrienol on platelet function and cholesterol

• Lead Investigator: Chandan K Sen & others from Ohio State University, April 2012
<table>
<thead>
<tr>
<th>Rank</th>
<th>Product</th>
<th>Manufacturer</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Lipitor</td>
<td>Pfizer</td>
<td>Cholesterol lowering</td>
</tr>
<tr>
<td>2</td>
<td>Nexium</td>
<td>AstraZeneca</td>
<td>Gastric ulcer &amp; reflux</td>
</tr>
<tr>
<td>3</td>
<td>Plavix</td>
<td>Bristol-Myers Squibb</td>
<td>Oral anti-platelet: reduce blood clot from stent &amp; stroke</td>
</tr>
<tr>
<td>4</td>
<td>Advair Diskus</td>
<td>GlaxoSmithKline</td>
<td>Asthma (steroid + bronchodilator)</td>
</tr>
<tr>
<td>5</td>
<td>Abilify</td>
<td>Otsuka</td>
<td>Antidepressant, bipolar disorder</td>
</tr>
<tr>
<td>6</td>
<td>Seroquel</td>
<td>AstraZeneca</td>
<td>Antidepressant, bipolar disorder</td>
</tr>
<tr>
<td>7</td>
<td>Singulair</td>
<td>Merck</td>
<td>Asthma</td>
</tr>
<tr>
<td>8</td>
<td>Crestor</td>
<td>AstraZeneca</td>
<td>Cholesterol lowering</td>
</tr>
<tr>
<td>9</td>
<td>Actos</td>
<td>Takeda</td>
<td>Anti-diabetic</td>
</tr>
<tr>
<td>10</td>
<td>Epogen</td>
<td>Amgen</td>
<td>Anemia – increase red blood cells</td>
</tr>
<tr>
<td>11</td>
<td>Remicade</td>
<td>Centocor Ortho Biotech</td>
<td>Anti-inflammatory: UC, RA, Crohn’s disease</td>
</tr>
<tr>
<td>12</td>
<td>Enbrel</td>
<td>Amgen</td>
<td>Anti-inflammatory: autoimmune, psoriasis</td>
</tr>
<tr>
<td>13</td>
<td>Cymbalta</td>
<td>Lilly</td>
<td>Antidepressant,</td>
</tr>
<tr>
<td>14</td>
<td>Avastin</td>
<td>Genentech</td>
<td>Anti-angiogenic &amp; anti-cancer: colorectal, lung, breast, kidney &amp; glioblastomas</td>
</tr>
<tr>
<td>15</td>
<td>OxyContin</td>
<td>Purdue</td>
<td>Analgesic, pain relief</td>
</tr>
<tr>
<td>16</td>
<td>Neulasta</td>
<td>Amgen</td>
<td>Prevents neutropenia during chemotherapy</td>
</tr>
<tr>
<td>17</td>
<td>Zyprexa</td>
<td>Lilly</td>
<td>Anti-psychotic: schizophrenia &amp; bipolar disorder (manic depression)</td>
</tr>
<tr>
<td>18</td>
<td>Humira</td>
<td>Abbott</td>
<td>Anti-inflammatory: rheumatoid arthritis, psoriatic arthritis, Crohn's disease</td>
</tr>
<tr>
<td>19</td>
<td>Lexapro</td>
<td>Forest</td>
<td>Antidepressant: major depressive disorder</td>
</tr>
<tr>
<td>20</td>
<td>Rituxan</td>
<td>Genentech</td>
<td>Anti-inflammatory &amp; anti-cancer: rheumatoid arthritis, leukemias and lymphomas</td>
</tr>
</tbody>
</table>
Benefits of Natural e³

Natural e³

Alpha Tocopherol

Antioxidants

Tocotrienols

Anti-inflammation
## Comparison of Natural e³ with Vitamin E

<table>
<thead>
<tr>
<th>Functions</th>
<th>Vitamin E</th>
<th>Natural e³</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antioxidant</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Fertility</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Cancer Prevention</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>Metabolic Syndrome</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Brain Health</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>Broad Spectrum</td>
<td>-</td>
<td>+++ (5 isomers)</td>
</tr>
</tbody>
</table>
Sources of Tocotrienol

- Red annatto: 940 mg/kg
- Palm oil: 910 mg/kg
- Barley: 465 mg/kg
- Rice bran: 380 mg/kg
- Oat: 210 mg/kg
- Hazelnut: 209 mg/kg
- Maize: 200 mg/kg
- Wheat germ oil: 189 mg/kg
- Olive oil: 180 mg/kg
- Buckthorn Berry: 130 mg/kg
- Rye: 92 mg/kg
- Flax seed oil: 25.1 mg/kg
- Poppy seed oil: 20.5 mg/kg
- Safflower oil: 11.8 mg/kg
Sabah, Malaysia plantations are fully certified.

Peninsula Malaysia plantations certification is due by 2013.

Indonesian plantations are planned to be certified by 2014.
Natural e³
Palm-derived Tocotrienol
Natural $e^3$ contains 25% of alpha-Tocopherol
Natural e³ Product Range

GRAS Affirmed

World Leader in Quality
Broad Applications

Multi-functional ingredient with scientifically proven health benefits

Cosmetics and Personal Care Products

Functional Food & Beverages

Nutraceutical
Natural e³ Food Applications

Anything that is currently using Vitamin E!
Natural e³ is a good preservative for Omega-3 fish oil
Davos – Reliable Supplier

- World’s largest tocotrienol manufacturing and R&D facility
- Reliable supplier
  - Integrated supply chain with feedstock fully traceable to parent company’s plantations (RSPO-certified)
  - State-of-the-art proprietary molecular distillation process – no front-end biodiesel process required unlike competitors
- Highest purities of up to 97% (Sigma Aldrich tocotrienol isomers supplied by DavosLife)
- Original published research by DavosLife Scientists

Frost and Sullivan 2010 Asia Pacific Excellence in Research Award in the Natural Vitamin E Market
Strong R&D Team
Derived from Nature, Driven by Science

DavosLife Tocotrienols
Providing Science-Driven Solutions for Your Evolving Needs
Tocotrienols: Lipid-Balancing Action