

WITH CARDIOVASCULAR DISEASE BEING THE NUMBER ONE KILLER IN THE WORLD TODAY, IT IS ONLY EXPECTED THAT CONSUMERS BE PRESENTED WITH SOLUTIONS THAT ALLEVIATE RISK FOR THE DISEASE. TOCOTRIENOL-RICH FRACTION IS ONE SUCH SOLUTION. BY **DR WEI NEY YAP**, SECTION HEAD, BIOLOGICAL, DAVOS LIFE SCIENCE

## TOCOTRIENOL-RICH FRACTION: A GEM IN PALM OIL FOR CARDIOPROTECTION

**VITAMIN E** consists of two groups namely tocopherol that has a saturated phytol chain, and tocotrienol that has an unsaturated farnesyl isoprenoid chain. Each group has four homologs: alpha ( $\alpha$ ), beta ( $\beta$ ), gamma ( $\gamma$ ) and delta ( $\delta$ ), each with unique biological properties.

Tocopherols and tocotrienols are compounds naturally occurring in select vegetable oils, including palm oil, rice bran oil, wheat germ, barley, saw palmetto, annatto, and certain other types of seeds, nuts, grains, and the oils derived from them.

A complete spectrum of tocotrienol homologs ( $\alpha$ ,  $\beta$ ,  $\gamma$ ,  $\delta$ ), commonly known as tocotrienol-rich fraction (TRF), is however not found in most vegetable oils except palm oil. The palm fruit (*Elaeis guineensis*) extract contains TRF with a total concentration of up to 800 mg/kg.

Within the family of Vitamin E, tocotrienols have been found to be a more potent antioxidant (40-60 times) than  $\alpha$ -tocopherol when cells were treated with identical concentrations. The higher antioxidant potency of tocotrienols in the membrane may be supported by a more uniform distribution of tocotrienols within membrane bilayers, stronger interaction of tocotrienols with lipid radicals and higher recycling efficiency for tocotrienoxyl radicals.

Emerging scientific evidences have manifested tocotrienols, not tocopherols, as a potential ingredient that can ameliorate cardiovascular and metabolic health conditions, due to their unique biological properties especially anti-inflammatory, on top of its antioxidant function.

### CARDIOVASCULAR DISEASE

Cardiovascular disease is the number one killer today. According to the World Health Organisation (WHO), heart disease and stroke kill more than 17 million people per year globally, which indicate an estimate of 31 percent of the mortality worldwide. This statistic is projected to increase to over 24 million people per year in less than 15 years.

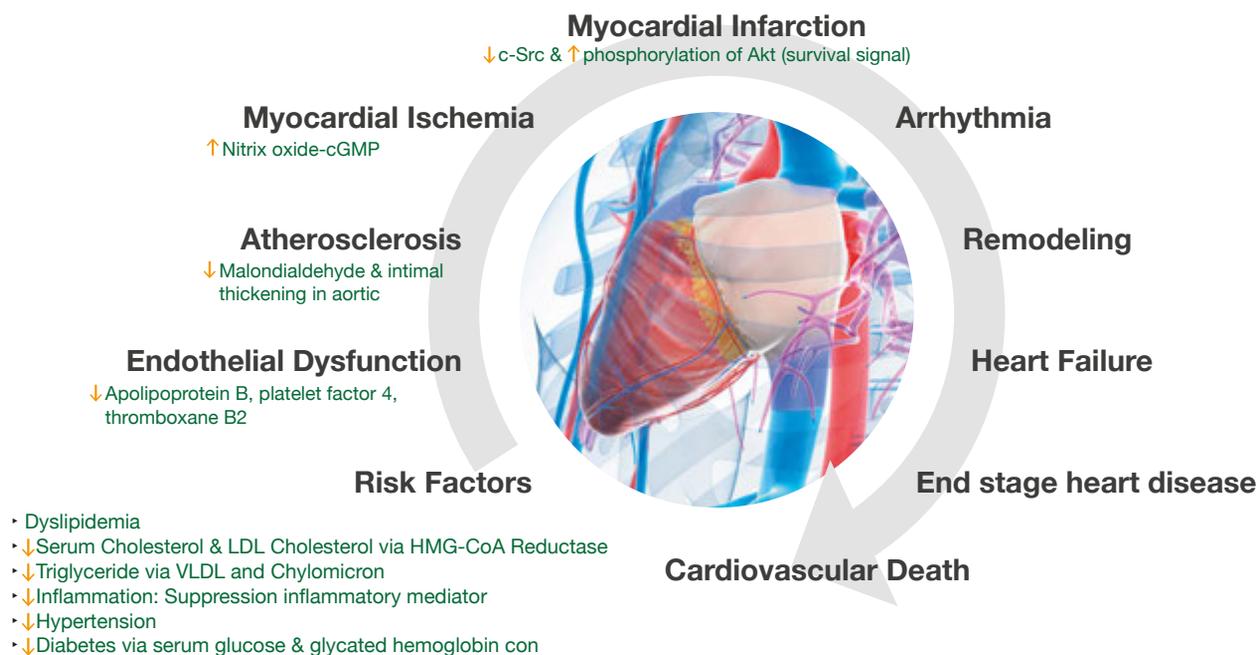


Figure 1. The protective effect of TRF in various aspects of cardiovascular health

Figure 1 demonstrates that TRF confers countless benefits in the progression of cardiovascular health, from reducing the risk of cardiovascular disorder to preventing plaque formation in blood vessels that supply oxygenated blood to the heart.

### RISK FACTORS OF CARDIOVASCULAR HEALTH

The unsaturated isoprenoid side chain of tocotrienols appears to be essential to inhibit cholesterol production due to its higher cell penetration. Tocotrienols have been reported to reduce 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, a key enzyme in regulating cholesterol production. As a result, fewer enzymes are available at a given time for cholesterol biosynthesis.

This is in contrast to how statins (a standard treatment for the dyslipidemia) work as a competitive inhibitor with unfavourable adverse effects such as abnormal liver function tests, nerve dysfunction and muscle disease.

In some clinical trials involving patients with high blood cholesterol (Figure 2A&B), tocotrienols have significantly reduced the total serum cholesterol and LDL-cholesterol by 15 percent and eight percent respectively.

Davos Life Science, in collaboration with researchers from Malaysia, Australia, China and Japan, have published evidences in peer-reviewed journals to explain the cholesterol-lowering effect with tocotrienols supplementation based on in-vitro, in-vivo models to human studies. In these studies, tocotrienols reduced the production and transport of triglycerides, and therefore triglyceride levels by 28 percent (Figure 2C).

Tocotrienols not only lower LDL-cholesterol and triglyceride levels; they are also rich in anti-inflammatory

properties. Inflammatory mediator cytokines and chemokines have been implicated in the pathogenesis of inflammation and atherosclerosis. Palm-derived TRF was found to reduce the transcription of Interleukin-8 (IL-8), Interleukin-4 (IL-4), tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ) and nuclear factor-kappa B (NF- $\kappa$ B) in human monocytic cells.

Hypertension and diabetes are the hallmarks that constitute the metabolic syndrome, increase the risks of cardiovascular disease and mortality. A study revealed that TRF prevented an increase in serum levels of advanced glycosylation end-products (AGE) in normal rats, decreased blood glucose and glycated haemoglobin levels in diabetic rats.

This is in agreement with another study that reported two-month TRF supplementation reduced plasma total cholesterol, LDL-cholesterol, and triglyceride levels, and increased high-density lipoprotein (HDL)-cholesterol compared to control untreated group. Reduction of serum glucose and glycated haemoglobin concentrations was also observed.

### ENDOTHELIAL DYSFUNCTION

Impaired endothelial function is closely associated with diabetes and hypertension, the two common risk factors in cardiovascular health. Studies demonstrated TRF may potentially improve vascular relaxation responses in the aortic rings of diabetic and hypertensive rats.

Another study reported dietary palm-derived TRF reduced the concentration of plasma cholesterol and apolipoprotein B, platelet factor 4 and thromboxane B2. This has indicated its ability to protect against platelet aggregation and endothelial dysfunction.

## Efficacy of Tocotrienols in Human Studies

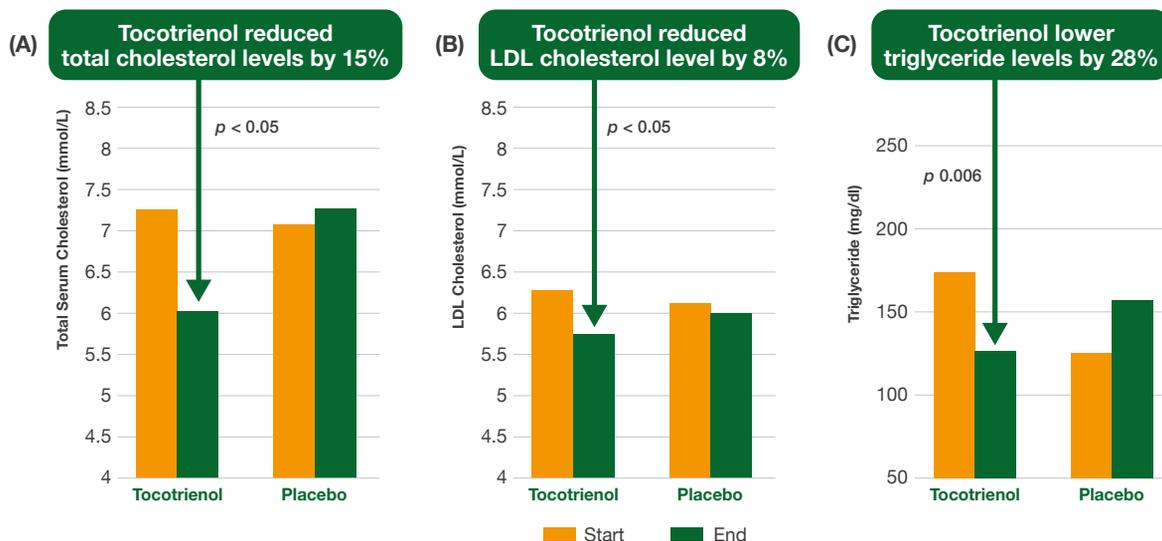


Figure 2. Cardiovascular health benefits of tocotrienols in clinical trials

### ATHEROSCLEROSIS

In atherosclerosis, build-up of fatty materials such as cholesterol or plaque will result in artery wall thickening. Arteries are blood vessels that carry oxygen-rich blood to the heart and other parts of the body. Plaque build-up ultimately narrows and impedes blood flow to the heart, leading to oxygen cut-off to the heart and possibly leading to a serious risk of heart attack.

A human study reported narrowing of neck blood vessels regressed in 32 percent of patients who received tocotrienol supplementation for two years, suggesting tocotrienols delay the plaque formation in blood vessels.

Another study revealed that supplementation with TRF for 10 weeks can reduce the intimal thickening and preserve the internal elastic lamina in cholesterol-fed rabbits. This has proposed that the antioxidant activity of TRF can improve atherosclerosis.

### MYOCARDIAL ISCHEMIA & INFARCTION

Myocardial ischemia injuries, resulting from partial or complete blockage of heart arteries, reduce the blood flow to the heart. Activation of the nitric oxide-cGMP pathway is associated with myocardial protection against ischemia. In ischemia, the function of this pathway is disturbed.

The effects of palm-derived TRF were investigated on the myocardial nitric oxide-cGMP pathway. The study demonstrated supplementation of 7 g of TRF per kg diet for six weeks significantly increased aortic output, cGMP levels and polyunsaturated fatty acid in rat heart. This has indicated palm-derived TRF protects the heart from myocardial ischemia via the nitric oxide-cGMP pathway.

Another three-month study further investigated the effects of gamma-tocotrienol on lipid peroxidation and

total antioxidant status of spontaneously hypertensive rats. Gamma-tocotrienol treatment has prevented the development of increased blood pressure, reduced lipid peroxides in plasma blood vessels, and enhanced total antioxidant status.

Another study showed a four-week TRF supplementation manifested post-ischemic ventricular function and reduced myocardial infarct size in rat model via the survival cell signalling pathway (downregulation of c-Src and upregulation of phosphorylation of AKT).

A recently published collaborative study between Davos Life Science and scientists from Singapore and Australia presented evidence that tocotrienols can ameliorate cardiac hypertrophy, reduce inflammatory cell infiltration and improve cardiac contractility in rats fed with a high fat diet.

### CONCLUSIONS

Tocotrienols have been receiving exceptional attention over the last two decades, especially with the discovery of their potentials in ameliorating cardiovascular risks, due to their superior antioxidant and anti-inflammatory activities.

Palm-derived TRF has been granted the Generally Regarded as Safe (GRAS) status by the US FDA in 2010, indicating the ingredient is safe for human consumption.

A Phase I dose escalation clinical trial revealed that tocotrienol is well tolerated up to 1600 mg/day, without any adverse effects. In addition, there are also other health benefits of tocotrienols related to reduction of oxidative stress and pathological inflammation that play a vital role the overall wellbeing of humans. **APFI**

