

Tocotrienols: Emerging Evidence of Health Benefits from Clinical Trials

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INTRODUCTION

Vitamin E was discovered in the 1920s and has exhibited various health protective effects (Aggarwal *et al.*, 2010; Fu *et al.*, 2014). It consists of tocopherols (TP) and tocotrienols (T3) with tocotrienols being different from their counterpart due to the presence of an unsaturated side chain. Compared to other natural sources such as soybean, corn and rice bran, palm oil has a higher ratio of tocotrienols to tocopherols (Kannappan *et al.*, 2012). For many years, vitamin E has been referred to synonymously as alpha tocopherol. However, in the last three decades, scientific evidence has shown that tocotrienols are much more potent as antioxidants than alpha tocopherol. In addition, tocotrienols have shown such therapeutic effects as neuroprotective, cardioprotective and anti-cancer, and as a cholesterol lowering agent as shown in *Figure 1* (Fu *et al.*, 2014). From pre-clinical studies to clinical trials, many mechanisms have been elucidated in the quest of an explanation for tocotrienols' health-promoting qualities. This article will discuss the important findings from clinical trials that can serve as a bridge to connect scientists and clinicians.

CARDIOVASCULAR HEALTH

Long-term supplementation with vitamin E has been associated with reduced risk of cardiovascular disease. Fueled by promising results from pre-clinical research, numerous human clinical studies have been carried out to investigate the effects of tocotrienol supplementation on lipid parameters such as triglycerides (TG), total cholesterol (TC), high-density lipoprotein

(HDL) and low density lipoprotein (LDL) (Meganathan and Fu, 2016). Tocotrienols have been reported to exert cholesterol-reducing activity (Yuen *et al.*, 2011; Fu *et al.*, 2014). A study was conducted on hypercholesterolemic subjects supplemented with tocotrienol-rich fractions (TRF). Statistically significant decreases in TC and LDL were reported following TRF supplementation in these subjects (Qureshi *et al.*, 1991; 1997; 2001; 2002; Yuen *et al.*, 2011). However, no remarkable outcomes were observed in two subsequent studies involving hypercholesterolemic subjects supplemented with up to 240 mg TRF per day (Wahlqvist *et al.*, 1992; Mensink *et al.*, 1999).

Interestingly, a combination of 50 mg of TRF, lovastatin (a cholesterol-lowering drug) and the American Heart Association (AHA) step 1 diet resulted in a reduction in TC and LDL levels (Qureshi *et al.*, 2001). It was postulated that the plasma T3 levels were insufficient to exert any physiological effect and that there also existed individual variations (Qureshi *et al.*, 1991).

TRF supplementation in type 2 diabetes mellitus patients was shown to decrease LDL, TC and TG. Notably, plasma glucose as well as glycated hemoglobin (HbA1c) levels were also reduced after 60 days of supplementation (Baliarsingh *et al.*, 2005). Increased risk of cardiovascular diseases is commonly linked with end-stage renal disease. In a study conducted in Detroit, USA, a decrease in plasma TG was reported in chronic hemodialysis patients supplemented with TRF for 16 weeks (Daud *et al.*, 2013).

CANCER

Apart from being a potent antioxidant, T3 has shown anti-cancer activities by preventing the proliferation of and contributing to the programmed death of cancer cells, preventing the growth of new blood vessels in the tumour site, and enhancing immune surveillance to eliminate the mutated cancer cells (Nesaretnam *et al.*, 2012). Fueled

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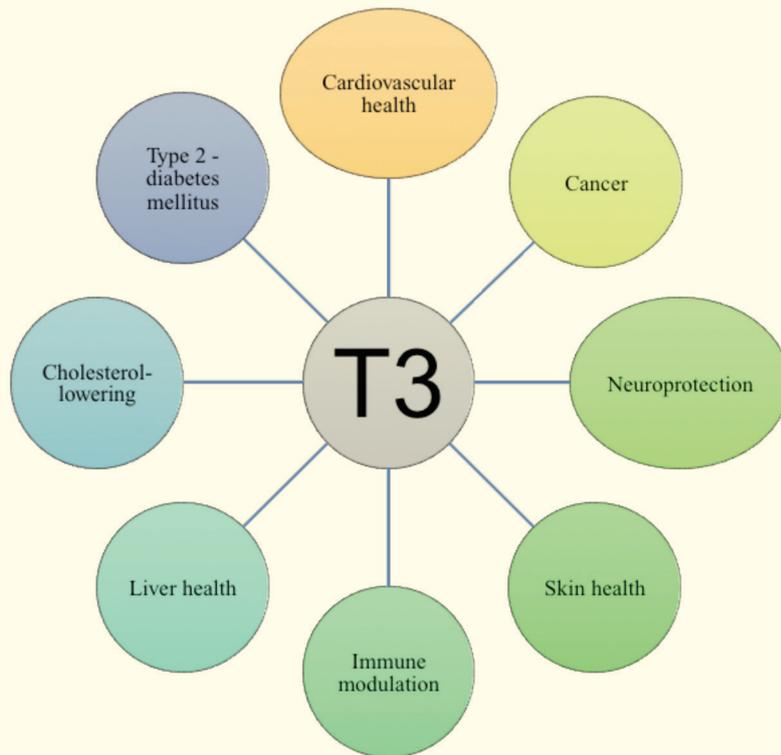


Figure 1. Therapeutic properties of tocotrienols investigated in clinical trials.

by promising evidence from cell and animal studies, a group of eminent researchers from MPOB led by Dr Kalanithi Nesaretnam embarked on a first ever pilot clinical trial on breast cancer patients at the Kuala Lumpur General Hospital. A total of 240 women with early breast cancer were allocated into two groups wherein all of them received the standard care, *i.e.* Tamoxifen, with either the addition of 400 mg of TRF (Tocovid Suprabio®) or placebo capsules, daily for five years. At the end of the five-year study, six women in the placebo group had died as compared with two women in the TRF group. The results from this study, however, were deemed to be clinically insignificant due to the low number of subjects recruited at an early stage of cancer to detect death as a primary outcome (Nesaretnam *et al.*, 2010). Nevertheless, an important outcome suggested by this study was that one out of 30 women could be saved from dying from breast cancer through TRF supplementation (Nesaretnam *et al.*, 2012). This was indeed the finding that attracted the

attention of scientists and health care providers. Eventually five years later, another study was conducted in pre-operative pancreatic cancer patients in Moffitt, USA. Delta tocotrienols of different dosages, ranging from 200 to 3200 mg daily, were supplemented to different groups of patients for two weeks prior to their surgery. Interestingly, delta-T3 supplementation was found to increase apoptosis, which is programmed cell death, in the tumour cells in these patients (Springett *et al.*, 2015).

IMMUNE MODULATION

Immunomodulatory effects of T3 have gained prominence in recent years. In 2009, a study was conducted on healthy subjects to assess the immune parameters such as B and T lymphocytes and natural killer cells following TRF supplementation. However, no significant difference was reported in terms of these immune parameters at the end of the study (Radhakrishnan *et al.*, 2009). A subsequent study was conducted by the same team of researchers

investigating the changes in immune response in healthy volunteers supplemented with TRF and challenged with tetanus toxoid vaccination. Interestingly, following the vaccination, statistically significant levels of immune cells were reported in these subjects, indicating a potential role of tocotrienols in enhancing immune response (Mahalingam *et al.*, 2011).

Another study carried out on TRF-supplemented smokers and non-smokers in Malaysia only showed an elevation of B cells in the non-smokers. The possible reasons for the imperceptible changes in the smokers could be that supplementation was with only 200 mg per day of TRF, and because of the presence of high baseline readings for the measured parameters (Jubri *et al.*, 2013).

NEUROPROTECTION AND COGNITIVE FUNCTION

Tocotrienols have shown potent neuroprotective effects in pre-clinical research, and this led to translational studies in humans. Only a nanomolar concentration of alpha-T3 was required to exert neuroprotection, and therefore the plasma T3 concentrations were found to be adequate in conferring protection (Patel *et al.*, 2012; Meganathan and Fu, 2016). White matter lesions (WML) have been associated with neurodegeneration. Two years of TRF supplementation in patients with WML have shown remarkable reduction in mean WML volume, indicating the therapeutic effect of T3 in providing neuroprotection (Gopalan *et al.*, 2014).

Attention deficit/hyperactive disorder (ADHD) is a behavioural disorder observed in school-going children and has been attributed to oxidative stress. The conventional medication used to manage this condition has been associated with adverse side-effects. The effect of TRF which is a potent antioxidant was investigated in these children.

After six months of supplementation with 200 mg of TRF, no significant findings were reported, and this was probably due to the fact that supplementation was introduced at an older age (Tan *et al.*, 2016).

SKIN HEALTH

One of the common causes of oxidative damage to the skin is exposure to ultraviolet radiation. A formulation containing both tocotrienols and tocopherols was applied to photosensitive individuals before they were subjected to a photoprovocative test. It was notable that a single application was sufficient to endow protection. Moreover, T3 as a natural compound was found to be safe and did not induce any adverse side-effect in these individuals (Pedrelli *et al.*, 2012).

OTHER THERAPEUTIC EFFECTS AND SAFETY OF TOCOTRIENOL SUPPLEMENTATION

Non-alcoholic fatty liver disease (NAFLD) has been reported to be prevalent globally. A team of scientists from the Universiti Sains Malaysia (USM) initiated a study to look at the effects of TRF supplementation on NAFLD patients. TRF supplementation with 400 mg per day over a year showed remarkable improvement in these patients without any worsening of the condition in comparison with the placebo group. Notably, TRF supplementation was also shown to reduce the TC, LDL and TG parameters (Magosso *et al.*, 2013), and was well tolerated by the subjects without any adverse side-effects.

In another study, supplementation with 400 mg TRF daily was found to be tolerable and safe in individuals with metabolic syndrome (Gan *et al.*, 2016). An interesting study conducted on pregnant women supplemented with TRF showed statistically lower blood loss during

delivery. This finding dispels the concerns regarding the elevated risk of bleeding following T3 supplementation (Mahdy *et al.*, 2013).

CONCLUSION

Clinical studies carried out with T3 vary in terms of dose, condition studied and population. Nevertheless, many therapeutic effects of T3 have been established and better understood based on the findings from these studies. Being a nutraceutical compound, T3 has been shown to be safe for consumption. The increasing burden of adverse effects with conventional treatments and their skyrocketing cost have shifted attention to the use of natural compounds. Emerging new findings from larger clinical trials may provide the much needed evidence to health care providers and consumers on the beneficial effects of tocotrienols.

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