Palm-Derived Tocotrienols and Inflammatory Diseases

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INTRODUCTION

Diet plays a major role in the prevention of chronic non-communicable diseases (NCDs) including obesity, diabetes mellitus, cardiovascular diseases (CVD), hypertension and stroke, and some types of cancer. Extensive scientific investigation has been carried out on diets to discover the possible functional properties and in particular, the role of antioxidants in preventing degenerative diseases. One such antioxidant is vitamin E, which made up of two classes of compounds: Tocopherols (Toc) and tocotrienols (T3) (*Figure 1*).

Palm oil is the richest source of natural tocotrienols (Palm-T3), an antioxidant that is several times more powerful than the tocopherols. This fat-soluble vitamin is in fact an essential nutrient for the body. There are four types of tocotrienols present in palm oil: namely α-, β- , γ- and δ-tocotrienol. Each individual tocotrienol has unique beneficial properties of its own. The Malaysian Palm Oil Board (MPOB) has produced individual tocotrienols from palm oil in high purity via green and environmental friendly processes (Han *et al.,* 2004).

In addition to vitamin E, other types of phytonutrients are found in palm oil, and these include the vitamin A (carotenes), sterols, squalene, coenzyme Q10, phospholipids and polyphenol (Choo *et al.,* 1996; Ong., 2002). Although these phytonutrients account for less than 1% of the oil's constituents together with tocotrienols, they play a significant role in preventing chronic diseases. Palm vitamin E is a mixture of tocopherols (Toc) (18%-22%) and tocotrienols (T3) (78%-82%) and is found in the tocotrienol-rich fraction (TRF) from palm oil. T3 can be extracted from crude palm oil (CPO), and it is a mixture of α-, γ-, δ-T3 (70%-75%) and α-tocopherols (5%-30%). The major forms of T3 that can be found in palm oil are α-T3 (22%), γ-T3 (46%) and δ-T3 (12%) (Puah *et al.,* 2007). It was the powerful antioxidant activity exhibited by palm-T3 that stimulated laboratory-based and clinical research on the importance of

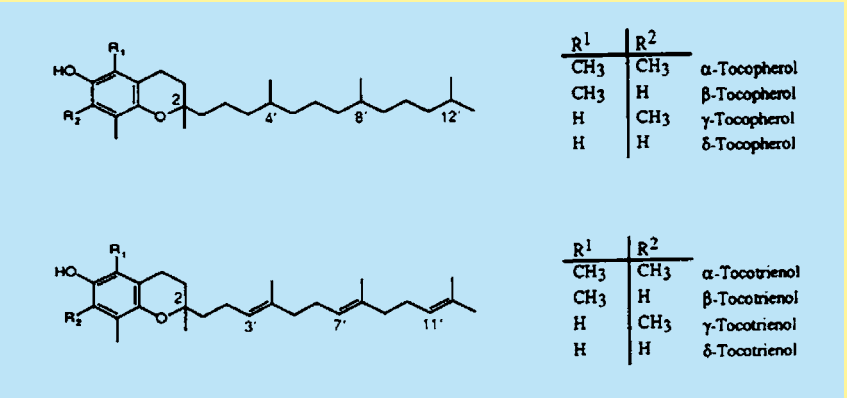

Figure 1. The structure of vitamin E correlates with a range of antioxidant benefits.

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palm-T3 in human health (*Figure 2*). Numerous scientific investigations have been done on the role of palm tocotrienols, in the prevention of degenerative diseases using *in vitro, in vivo* and clinical studies.

In this article, we have reviewed some of the recent literature on the health-enhancing effects of a palm-tocotrienols in suppressing inflammation and in alleviating several pathological conditions such as cancers (breast, prostate), metabolic diseases (osteoporosis, diabetes, arthritis), cardiovascular diseases, neurological diseases (cognitive function, Alzheimer's disease) and autoimmune diseases (psoriasis).

INFLAMMATORY DISEASES

Inflammatory diseases are a complex biological phenomenon in which the insufficiency of the nutritional status related with the presence of chronic inflammation and oxidative stress. This enhancement to the many age-related diseases and commonly onset of some chronic diseases. Cardiovascular and neurodegenerative diseases, diabetes, cancer, infections, are closely related to a deficiency in the nutritional status and to the presence of a chronic inflammatory situation. Oxidative stress produced the free radicals can lead to a destruction of DNA, lipids and proteins with later changed cellular homeostasis and integrity. Dietary supplements with palm-T3 can restore the balance and protect against the deteriorating effects of oxidative stress, progression of degenerative diseases, and aging. Current experimental studies in cell cultures and in animals have obviously revealed that palm-T3 has a essential role as antioxidant agent against the lipid peroxidation on cell membranes and thus, preserving the tissue cells from the oxidative damage.

PALM-T3 IN TREATING CANCER

Research has revealed that palm-T3 have anti-cancer activities. A number of studies *in vivo*, *in vitro* and human clinicals have found palm-T3 to be powerful antioxidants that possess potent anti-cancer effects in prostate cancer, colon cancer, breast cancer, pancreatic cancer, stomach cancer, lung cancer, and skin cancer (Abdul Hafid *et al.*, 2013; Patacsil *et al.*, 2012). Studies on breast cancer *in vitro* and *in vivo* using palm tocotrienols showed that tocorienols act as anti-estrogen in killing cancer cell (Guthrie *et al.*, 1997; Nesaretnam *et al.*, 2004; Selvaduray *et al.*, 2011). Palm-T3 was reported to inhibit proliferation of tumour cells as well as to induce the death of these cells through activation of the apoptosis pathway (Yap *et al.*, 2010). On-going human clinical trials in cancer studies using palm-T3 are being conducted all over the world (Zhihong *et al.*, 2010; Luk *et.al.*, 2011).

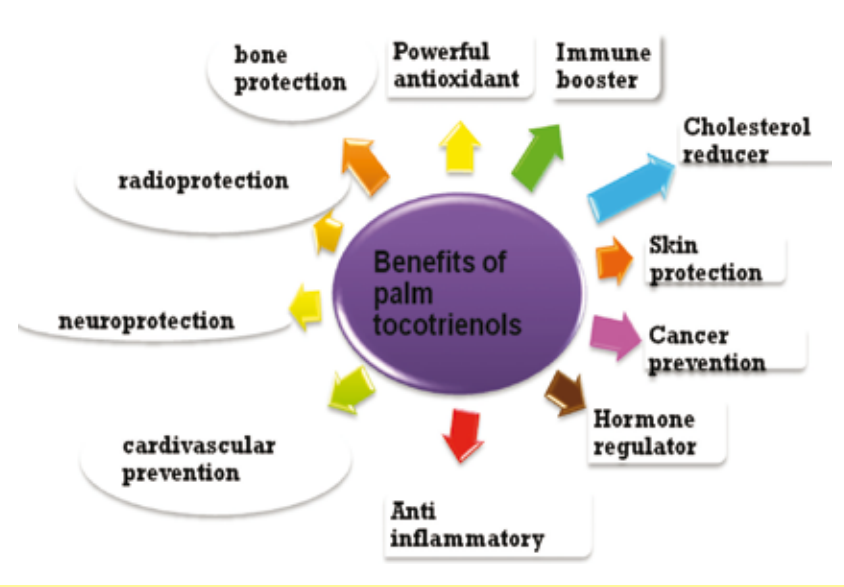

Figure 2. Health-enhancing effects of palm tocotrienols in inflammation and diseases.

PALM-T3 PREVENTING CARDIOVASCULAR DISEASES

Many studies have revealed that palm-T3 have given more cardioprotection than those of tocopherols. Palm-T3 demonstrated that it can protect the heart from ischemia-reperfusion injury (Das *et al.*, 2005). Furthermore, palm-T3 exhibit their cardioprotection properties via lipid-lowering (Vasanthi *et al.*, 2012), anti-atherosclerotic (Qureshi *et al.*, 2011), anti-ischaemic (Esterhuyse *et al.*, 2006) and anti-thrombotic activities (Aggarwal *et al.*, 2010). It inhibits cholesterol production in the liver, thereby lowering total blood cholesterol. More recently, it was reported that the lipid-lowering property of tocotrienols was found to be through the down-regulation of hepatic HMG-CoA reductase activity (Chao *et al.*, 2002), whilst the anti-ischemic property was through the modulation of the nitric oxide pathway (Vasanthi *et al.*, 2012).

PALM-T3 AS ANTI-DIABETES

Palm-T3 can have an anti-diebetic effect as it ameliorates oxidative stress in Type 1 Diabetes Mellitus patients and improves antioxidant defence system (Nazaimoon *et al.*, 1996). Research by Fang *et al.*, (2010) proved that palm-T3 helps to reduce blood glucose levels in human subjects and preclinical animals. A study carried out by Muharis *et al.*(2010) and Budin *et. al.* (2009) in rats found that palm-T3 improve vascular endothelials functions in diabetes and reduced serum glucose and glucated haemoglobin concentrations.

PALM-T3 IN PREVENTING OSTEOPOROSIS

Bone loss or osteoporosis is a common disease that affects the majority of the older adults and tobacco smokers. It has been reported that palm vitamin E supplementation can reverse nicotine-induced bone loss and stimulate bone formation in humans (Hermizi *et al.,* 2005) and in a rat model (Norazlina *et al*., 2007). Studies have shown that palm-T3 exhibit protective effects against osteoporosis. Ima-Nirwana's group had carried out intensive studies on the effect of palm-T3 on bone metabolism or osteoporosis (Ima-Nirwana *et al.,* 2012). They found that palm-T3 had prevented and reversed osteoporosis in rats. The γ-T3 is most effective as an anti-osteoporotic medication.

PALM-T3 AS ANTI-INFLAMMATORY - ARTHRITIS

Palm-T3 is effective in treating and preventing arthritis. Palm-T3 fractions down- regulated COX-2 enzyme in macrophage cells stimulated with lipopolysaccharide (LPS) (Yam *et al.,* 2009) and in bovine chondrocytes with γ-T3 inhibited the IL-1a induced expression of COX-2, IL-1B and IL-6, which are classical markers of inflammation and cartilage degradation in arthritis joints and as well as increasing of glycosminolgycan (GAG) (Zaida *et al.,* 2013). The γ-T3 also inhibited the NF-κB activation pathway and down regulated various gene products involved in the inflammatory process.

PALM-T3 IN PREVENTION OF STROKE AND BRAIN DISEASE

A number of neurodegenerative conditions in the human brain are associated with disturbed PUFA metabolism of AA such as acute ischaemic stroke. Palm-T3 has been shown to be a potent inhibitor of lipid peroxidation and protein oxidation in rat brain mitochondria (Kamat *et al.*, 1995). In another pre-clinical study, it was found that α-T3 but not γ-Toc protected neurons from the glutamate challenge (Khanna *et al.*, 2010). More recently, it was reported that palm α-T3 at nanomolar concentrations can attenuate both enzymatic and non-enzymatic mediators of AA metabolism and neurodegeneration, and helps prevent stroke-induced injuries to the brain in rats (Sen *et al.*, 2010).

The clinical study published in the *American Heart Association Journal*, Stroke, recently, showed palm T3 can protect brain cells and the nervous system as well as help minimise brain cell injuries, especially during a stroke. This two year human clinical study carried out in Universiti Sains Malaysia, shows the palm-T3 support white matter health by weakening the progression of white matter lesions (WML) or oxygen-starved brain cells. About 50% of human brain is made of white matter and brain WMLs have been reportedly linked to the development of other neurodegenerative diseases, such as Alzheimer's and Parkinson's (Gopalan *et al*., 2013).

PALM-T3 IN PREVENTION OF SKIN DISEASES (PSORIASIS)

Palm-T3 was reported to have a higher efficacy in protecting the skin against UV-induced damage in animals fed with palm TRF (Yamad *et al.*, 2008). In another study, it was found that palm-T3 could reduce the expression of UV-induced inflammatory genes and proteins such as COX-2, IL-6 and monocyte chemotactic protein-1 (MCP-1) (Shibata *et al.*, 2010). Pedrelli and co-workers (2012) also found that palm-T3 helps to maintain a healthy level of Toc in the skin as this is essential for preventing skin damage. In addition, the authors found that skin treated with TRF (palm tocotrienol mix with tocopherol at 70:30) showed very high concentrations of vitamin E, which is beneficial to skin health (Pedrelli *et al.*, 2011). It was recently reported that low doses of δ-T3 can reduce the melanin content by decreasing the levels of tyrosinase-related protein-1 (TRP-1) and -2 (TRP-2), which are responsible for the biosynthesis of melanin in cultured melanoma cells (Michihara *et al.*, 2010).

CONCLUSION

Palm-T3 is a potent antioxidant, which is able to neutralise free radicals, and this is the key fac-

tor in inflammation. It can help to eliminate the body of free radicals and defend it from many types of inflammatory diseases. Research on palm-T3 (as anti-inflammatory) has been extensively studied in cell systems, animal models and few in human studies. Palm-T3 has proven to exhibit excellent anti-oxidative, anti-hypercholesterolemia, neuroprotective, anti-aging, anti-obesity, anti-diabetes, anti-cancer activity *etc*. In conclusion, future experiments in clinical studies are important to understand both the molecular basis of inflammatory diseases and the protective actions of palm-T3 in human health. Outcome studies designed in light of such information would yield worthwhile returns.

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