

TOCOMIN®
PALM TOCOTRIENOL COMPLEX & CARDIOVASCULAR HEALTH

World Health Organization estimated that, cardiovascular diseases (CVD) cause 12 million deaths in the world each year. It is one of the leading causes of death in the United States(7). More than 2,600 Americans die each day of CVD – an average of 1 death every 33 seconds. Cardiovascular disease (CVD) is a multi-factorial disease involving both genetic and environmental factors. Although, dietary and drug interventions aimed at lowering lipid levels and low-density lipoprotein (LDL) oxidation have reduced mortality rates significantly, the number of individuals inflicted with CVD remains alarmingly high and growing. This has led to an ongoing search for newer alternative and natural preventative methods that could potentially lower the risk of developing CVD.

During the past decade, the health benefits of vitamin E in CVD prevention have been studied extensively. A number of epidemiological studies have shown an inverse association of vitamin E intake and CVD (10-13). Furthermore, vitamin E supplementation was shown to reduce recurrent myocardial infarction by 77% in a recent study (14). Although serum lipid profile generally did not change, it was hypothesized, based on a number of studies, that tocopherol might prevent oxidative modification of LDL, a process believed to be involved in the formation of atherosclerotic plaques (15, 16). However, this theory remains controversial as a number of studies failed to demonstrate any significant association between plasma vitamin E levels and deaths from CVD (17-19).

In recent years, scientists at the University of Wisconsin began to study the relationship between palm tocotrienol complex and CVD in human trials. Palm tocotrienol supplements were shown to lower a number of lipid-related risk factors including cholesterol, LDL-cholesterol, apolipoprotein B, and lipoprotein(a). Moreover, plasma levels of thromboxane B2 and platelet factor 4 were found to be suppressed in these studies suggesting, an anti-thrombotic effect (20, 21, 22). Consistent with tocotrienol's antioxidative effect, other investigators showed that supplemental tocotrienol also reduced blood levels of lipid peroxides (measured as TBARS-thiobarbituric acid reactive substances) with an apparent improved blood flow in patients with carotid atherosclerosis (23). In summary, these studies implicate tocotrienol as a powerful natural phytonutrient with benefits ranging from reduced LDL oxidation, reversal of arterial blockage, reduced cholesterol levels, and reduced platelet adhesion/aggregation.

In this Technical Literature, we will attempt to present the molecular mechanism for each of the proposed properties of palm tocotrienol complex via a vis cardiovascular disease.

Reversal of Arteriosclerosis / Reversal of Arterial Blockage

During the past decade, the health benefits of alpha-tocopherol in CVD prevention have been studied extensively. A number of epidemiological studies have shown an inverse association of vitamin E intake and CVD. However, a number of studies recently (2001) failed to demonstrate any significant association between plasma tocopherol vitamin E levels and deaths from CVD.

Now, scientists say more than one type of vitamin E should be a part of a long-term nutritional or supplement program for reducing the risk of CVD. In fact, vitamin E research has progressed to the point where scientists have identified different forms of vitamin E, especially tocotrienols that confer better protection against the various types of free radical damage as well as having additional unique properties in reducing the risk of cardio vascular disease.

One of the most amazing effects of tocotrienol in preventing CVD is its ability to reverse an arterial blockage. Consistent with tocotrienol's antioxidative effect, other investigators showed that supplemental tocotrienol also reduced blood levels of lipid peroxides (measured as TBARS-thiobarbituric acid reactive substances) with an apparent improved blood flow in patients with carotid atherosclerosis. This 3-year double-blind study was conducted at the Jordan Heart Foundation, New Jersey US with 50 patients with a disease condition called carotid stenosis – blockage of the carotid artery, the main artery that supply blood to the brain. Within 6 months of supplementation 240mg of palm tocotrienol complex per day, 92% of the patients had a regression in their carotid stenosis condition. In comparison, none in the placebo patients had any improvement and in fact 4% of them have had progression in the condition (23).

In the most recent study (Oct 2000, Journal of Nutrition), conducted at the University of North Carolina confirmed the effect of tocotrienols in reversing arteriosclerosis. In this study, genetically modified mice, which were predestined to develop atherosclerosis when fed with diets high in triglycerides and cholesterol, was used. Not only did supplementation with palm tocotrienol complex lowered cholesterol and cholesterol ester by 66%, the size of the atherosclerotic lesions was 92% smaller.

One may very well argues that the normal tocopherol vitamin E does also reduces the risk of cardiovascular. However, once the cholesterol plaque is formed, tocopherol has not been shown to be able to reverse or clear the blockage. The above studies showed that palm tocotrienol complex, besides being a more potent vitamin E in preventing lipid peroxidation (40-60X), has the unique ability to clear arteriosclerotic plaque and hence reduces the lesions.

Hypocholesterolemic Property

The interest in tocotrienol as a hypocholesterolemic compound began when Qureshi *et al.* in 1986 attributed the major cholesterol-lowering action of barley to be at the level of cholesterol synthesis (24). By sequential extraction of barley, α -tocotrienol was identified as the chemical constituent responsible for inhibiting the rate-limiting enzyme of the cholesterol biosynthetic pathway, HMG-CoA reductase (HMGR).

In elucidating the molecular mechanism for this suppression, the effect was ascribed to the side-chain's unique ability to increase cellular farnesol, a mevalonate-derived product, which signals the proteolytic degradation of HMGR (26). This mechanism has been shown to be different from other well known HMGR inhibitors such as lovastatin which tend to be competitive inhibitors to the enzyme.

Subsequent *in vitro* and animal studies confirmed the cholesterol-suppressive action of tocotrienol. Hypercholesterolemic pigs fed a palm tocotrienol complex showed a 44% and 60% decrease in total serum cholesterol and LDL-cholesterol, respectively (27). In isolated human liver cells, α -tocotrienol (10 μ M for 4h) inhibited cholesterol synthesis by 32% (28). Interestingly, delta-tocotrienol, which lacked the 5-methyl substituents present in α -tocotrienol, was shown to possess significantly greater HMGR suppression (28). This structure-activity relationship indicated that in addition to the requirement of the prenyl side chain for HMGR suppression, changes in the methyl substitution on the chromanol ring may also lead to a divergent effect on HMGR activity (29).

These observations heralded a number of small case-controlled human trials to further clarify the role of tocotrienols on blood cholesterol levels (20, 21, 22). These studies used a palm tocotrienol complex, extracted from the fruits of palm, which was administered to hypercholesterolemic human subjects. Participants assigned to the tocotrienol group received four capsules daily, each containing a mixture of α -tocopherol and α , γ , and δ -tocotrienol. It has been noted that α -tocopherol can attenuate the cholesterol suppressive action of tocotrienol (30). Interestingly, those receiving palm tocotrienol supplementation after a controlled dietary regimen experienced significant drops of 15 to 20% in plasma total cholesterol. The major reduction in cholesterol occurred in the LDL fraction, whereas, HDL-cholesterol remained essentially unchanged. A similar reduction was also observed with a tocotrienol preparation composed of pure γ -tocotrienol (21). In another study published in the American Journal of Clinical Nutrition, researchers reported that supplementation with 42mg of pure tocotrienols per day reduced total serum cholesterol by 5.0% – 35.9% and LDL cholesterol by 0.9% - 37.0% (25).

Hypoapolipoprotein B Property

High plasma levels of apolipoprotein B-100 (apoB), the protein moiety of LDL, have been recognized as an independent risk factor for the development of premature coronary artery disease (CAD) (31). Clinical evidence has strongly supported the notion that apoB is a better index of atherogenic risk than total or LDL-cholesterol (32). Furthermore, therapeutic intervention aimed at lowering apoB levels in CAD subjects have resulted in the regression of atherosclerosis (33). Thus, apoB appears to be directly involved in the atherosclerotic process.

Recently, several epidemiological studies (described above) have shown that tocotrienols, both as a palm tocotrienol complex and in the purified γ -tocotrienol form, can reduce the atherogenic apoB plasma levels significantly by 10 to 15% (20, 21, 22). Although the reduction was not as significant as compared to those of commercially available HMGR inhibitors (i.e. many of which ranged from a 30 to 50% reduction) (34), the results nevertheless validate the potential use of tocotrienol as a natural pharmacological agent in reducing plasma apoB levels.

As for its mechanism of action, it is speculated that tocotrienol, as well as other HMGR inhibitors, lowers plasma apoB levels partly by up-regulating LDL receptors in the liver (35). This, in turn, facilitates the clearance of LDL-apoB from the bloodstream. In addition, tocotrienol has been shown in our laboratory to increase the intracellular proteolytic degradation of apoB and alter the assembly process of VLDL (very low density lipoprotein) (36, 37). Without apoB, VLDL, the precursor of LDL, is unable to assemble with core lipids and be secreted from the liver. Thus, the ability of tocotrienol to reduce apoB plasma levels depends largely on both the clearance rate of LDL and the production rate of VLDL.

Hypolipoprotein (a) Property

In the context of other CVD risk factors, lipoprotein(a) (Lp(a)) has been found in numerous studies to be the strongest predictor of CVD (38). Lp(a) is a plasma lipoprotein whose structure resembles that of LDL in which apoB is attached to apo(a) by a disulfide linkage (39).

Like LDL-cholesterol and apoB, elevated plasma levels of Lp(a) is considered atherogenic. It can be modified by lipid peroxidation and thus be taken up by macrophages. This uptake leads to massive deposition of cholesterol into these cells, which are associated with the formation of foam cells within the atherosclerotic lesion (40).

Interest in Lp(a), however, resides mainly in its ability to interfere with plasminogen activation and thus, its association with thrombosis (41, 42). Various epidemiological studies have validated the hypothesis that decreased Lp(a) levels are associated with decreased atherogenesis and thrombosis (43, 44). However, attempts to lower Lp(a) plasma levels have not been easy due to its strong genetic control (45).

Diet and common lipid-lowering drugs including HMGR inhibitors have failed to lower circulating Lp(a) concentration, with the exception of niacin and bezafibrate (46, 47, 48). Niacin has, however, troublesome side effects at the dose levels necessary for the desirable efficacy. Bezafibrate, on the other hand, has mild side effects (49).

In a recent case-controlled study noted above (22), tocotrienol was shown to decrease plasma Lp(a) levels by 17%. This effect was surprising as diet has rarely been shown to have an impact on plasma Lp(a) levels. Should tocotrienols effectively lower Lp(a), it would have important implication in the prevention of atherosclerosis and thromboembolism. Particular attention to the methyl substitution on the chromanol ring of tocotrienol would probably be necessary to fully comprehend its effect on Lp(a) levels.

Anti-Thrombotic Property

A thrombus is said to begin when platelets adhere and aggregate to the vascular endothelium forming a fibrous plaque, which can dislodge and obstruct an artery (50). In recent years, there has been growing interest about vitamin E as a form of treatment against thromboembolic disease. Several cell culture and animal studies have shown that vitamin E supplementation reduced the biosynthesis of eicosanoids involved in platelet adhesion and aggregation (51-53). The reduction was attributed to reduced activity of phospholipase A2, an enzyme that potentiates the release of arachidonic acid from membrane-bound phospholipids to various eicosanoids (54). Alternatively, α -tocopherol has also been postulated to inhibit the transformation of arachidonic acid into prostaglandins by inactivating the cyclooxygenase gene (55). The gene has been shown to possess a redox-sensitive regulatory motif (56). Subsequently, the use of vitamin E as an anti-thrombotic agent has been therapeutically explored in humans. Steiner *et al.* (57) reported a greater reduction in platelet adhesiveness with a concomitant reduction in ischemic events in the patient group who were taking α -tocopherol plus aspirin compared to those taking aspirin alone. Conversely, this anti-thrombotic effect was also demonstrated with tocotrienol.

In recent epidemiological studies, tocotrienol, both as a palm tocotrienol complex and purified γ -tocotrienol, was shown to reduce the synthesis of an eicosanoid, namely thromboxane B2 (20, 21, 22). The mechanism(s) for this effect remains uncertain, but may be similar to that reported for α -tocopherol. Aside from thromboxane B2, supplemental tocotrienol has also been shown to suppress plasma levels of platelet factor 4 (PF4) (20,21, 22).

In summary, the results suggest a probable protective effect on the vascular endothelium and platelet adhesion/aggregation due to vitamin E (both tocopherols and tocotrienols).

Super Antioxidant Property

Vitamin E compounds are well known for their antioxidant property (1). This property depends primarily on the phenolic group in the chromanol ring, rather than the side-chain (58, 59). Tocotrienols, like tocopherols, are capable of scavenging and quenching reactive oxygen species, also known as free radicals.

Their antioxidative activity, however, resides mainly with its “chain-breaking” property, which neutralizes peroxy and alkoxy radicals generated during lipid peroxidation (1, 60). Peroxidation of membrane lipids is known to modify and inactivate cellular components, which can have damaging effects on crucial cellular factors leading to disease. In the case of LDL-lipids, peroxidation has emerged as the initiating step in the pathogenesis of atherosclerosis. Such modification of LDL causes recognition of the particle by the scavenger cell receptor (i.e. a LDL-receptor independent pathway) present on macrophages. This pathway is unregulated and nonsaturable which consequently leads to massive deposition of cholesterol into these cells. This is typically associated with the formation of foam cells in the atherosclerotic lesion (61). Support of this role was found based upon evidence that α -tocopherol could inhibit atherosclerosis in both animal and human models (14, 62, 63).

For many years, α -tocopherol was generally considered the most potent antioxidant against lipid peroxidation in the vitamin E group (64). Recently, however, there has been considerable discrepancy in its relative antioxidant effectiveness when compared to other isomers. On one hand, γ -tocopherol was found to be more potent than α -tocopherol particularly in its interaction with reactive nitrogen oxide species (65). On the other hand, α -tocotrienol was also found to be a better antioxidant than α -tocopherol (66, 67). Notably, Serbinova *et al.* (66), observed a remarkably higher antioxidant activity with tocotrienol against lipid peroxidation in rat liver microsomes than with α -tocopherol.

Kamat and Devasagayam (68) observed similar results with palm tocotrienol complex in rat brain mitochondria and noted a stronger effect with γ -tocotrienol. In an elaborate study, a number of mechanisms were shown to contribute to its higher antioxidant activity compared to α -tocopherol, including: a) a more uniform distribution in the membrane lipid bilayer, b) a more efficient interaction of the chromanol ring with lipid radicals, and c) a higher recycling efficiency from chromanoxyl radicals (66).

Taken together, the recognition that tocotrienol has superior antioxidant activity may have important clinical implication. It may prove to be a more potent inhibitor against LDL oxidation *in vivo*. Serbinova *et al.* (69) noted that tocotrienol was more efficient than α -tocopherol in the protection of the rat heart against oxidative stress induced by ischemia-reperfusion.

Monocytic Adhesion Property

The adherence of monocytes to the vascular endothelium is an important early event in atherogenesis. Monocyte adherence to endothelial cells is mediated by multiple cell adhesion molecules, including ICAM-1, VCAM-1, and E-selectin (70). Enhanced endothelial expression of these surface adhesion molecules has been shown to be a critical step in foam cell formation and the development of atherosclerosis. Many patients with atherosclerosis have been found to have high circulating levels of soluble adhesion molecules (71, 72). The specific mechanism involved in the faulty overexpression of these proteins has largely been associated with the transcriptional activation of NF (nuclear factor)- κ B, a redox-sensitive transcription factor (73). Expression of these proteins is known to be stimulated by oxidants, including oxidized LDL, and downregulated by the presence of antioxidants (74, 75). Interestingly, recent findings by the University of Hawaii have suggested delta-tocotrienol to be the most potent inhibitor of adhesion molecule expression and monocytic cell adherence than α -tocopherol. Considered to be a more potent antioxidant relative to α -tocopherol, these studies support the theory that antioxidants, particularly delta-tocotrienol, represent a potentially important and novel method of controlling atherogenesis.

IN SUMMARY

Collectively known as vitamin E, tocotrienols are identical in structure to tocopherols except for the degree of saturation in their side chain. It is of particular interest that the slight structural differences between tocopherol and tocotrienol can account for the greater and unique physiological activities found with tocotrienol. Although most studies have strongly supported vitamin E supplements as an effective therapeutic agent in the prevention of CVD, not all studies have found an association. This discrepancy has raised concerns about current formulations about the vitamin E composition that would be most beneficial in the prevention of CVD.

These studies implicate palm tocotrienol complex as a powerful natural ingredient with benefits ranging from reversal of arteriosclerosis, reduced LDL oxidation, reduced cholesterol levels, and reduced platelet adhesion/aggregation that collectively reduces the risk of cardio vascular diseases.

For further information, visit the educational website on tocotrienol : www.tocotrienol.org

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<p>The above statement has not been evaluated by the Food and Drug Administration. It is not intended to diagnose, treat, cure or prevent any disease.</p>
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