

## Review Article

# Tocotrienols and its impact in cardiovascular health

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**Received:** 10 November 2014

**Accepted:** 29 November 2014

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### ABSTRACT

Tocotrienols are members of the vitamin E family essential for human nutrition. It has four isomeric forms i.e.,  $\alpha$ ,  $\beta$ ,  $\gamma$ ,  $\delta$ . Palm oil and rice bran oil represent two major nutritional sources of natural tocotrienols. Taken orally, tocotrienols are bioavailable to all vital organs. Apart from tocotrienols antioxidant, anti-inflammatory, antineurodegeneration, antimicrobial, anticancer properties it also has antihypercholesterolemic and antiangiogenic properties. During the last 7 years, tocotrienol research has gained substantial momentum. More than 75% of the entire PubMed literature on tocotrienols has been published on or after 2000. This represents major swing in the overall direction of tocotrienol research. The objective of this review is to highlight the potential significance of the tocotrienol in cardiovascular diseases, mainly anti hypercholesterolemic and anti hyperlipidemic properties along with its efficacy and safety.

**Keywords:** Tocotrienols, Cardiovascular diseases, TRF, Oxidative stress, Anti hyperlipidemic

### INTRODUCTION

Tocotrienols are members of the vitamin E family. An essential nutrient for the body, vitamin E is made up of four tocopherols ( $\alpha$ ,  $\beta$ ,  $\gamma$ ,  $\delta$ ) and four tocotrienols ( $\alpha$ ,  $\beta$ ,  $\gamma$ ,  $\delta$ ). Tocotrienols are natural compounds found in selected vegetable oils, wheat germ, barley, saw palmetto and certain other types of seeds, nuts, and grains. Palm oil and rice bran oil represent two major nutritional sources of natural tocotrienol. This variant of vitamin E typically only occurs at very low levels in nature.<sup>1-3</sup>

The natural vitamin E family includes eight chemically distinct molecules:  $\alpha$ ,  $\beta$ ,  $\gamma$ ,  $\delta$  tocopherols and  $\alpha$ ,  $\beta$ ,  $\gamma$ ,  $\delta$  tocotrienols. Tocochromanols contain a polar chromanol head group with a long isoprenoid side chain. Depending on the nature of the isoprenoid side chain, tocopherols (containing a phytol chain) or tocotrienols (geranyl chain) can be distinguished.<sup>4</sup> Chemically, vitamin E in all its

forms functions as an antioxidant. All the tocotrienols and tocopherol isomers have this antioxidant activity due to the ability to donate a hydrogen atom (a proton plus electron) from the hydroxyl group on the chromanol ring, to a free radical in the body. This process inactivates (quenches) the free radical by effectively donating a single unpaired electron (which comes with the hydrogen atom) to radical.<sup>5</sup>

Tocotrienols are named by analogy to tocopherols; but with this word changed to include the chemical difference that tocotrienols are trienes, meaning that they share identical structure with the tocopherols except for the addition of three trans double bonds to their hydrocarbon side chains. Because of these unsaturations in the isoprenoid side chain, tocotrienols are thought to assume a unique conformation<sup>6</sup> while the proposed curved structure has not been confirmed by NMR,  $\alpha$ -tocotrienol is very likely much more flexible in the side chain and it puts a greater curvature stress on phospholipid

membranes. This is dynamic issue and has been confirmed in scanning calorimetry data. Indeed tocotrienols possess numerous functions that are not shared by tocopherol. For example oral supplementation of tocotrienol protects against stroke.<sup>7</sup> Nanomolar concentrations of  $\alpha$ -tocotrienol uniquely prevent inducible neuro degeneration by regulating specific mediators of cell death.<sup>8-10</sup> Micromolar amounts of tocotrienol suppress the activity of 3-hydroxy - 3-methyl glutaryl coenzyme A (HMG-CoA) reductase, the hepatic enzyme responsible for cholesterol biosynthesis.<sup>11,12</sup> In animal cells also T3 inhibits production of cholesterol by liver cells by suppressing 3-Hydroxy 3-Methyl Glutaryl coA Reductase enzyme (HMGR), a key enzyme in the stereogenic pathway.<sup>13</sup> Tocopherols do not share the cholesterol properties of Tocotrienol.<sup>14</sup> Since the 1980s, there have been more studies proving tocotrienols are more potent in their antioxidants<sup>15</sup> and anticancer effect<sup>16</sup> than the common forms of tocopherol due to their chemical structure. Unsaturated side chain in tocotrienols causes them to penetrate tissues with saturated fatty layers more efficiently<sup>17</sup> making them ideal for anti-aging oral supplements and skin care range.<sup>18</sup>

Tocotrienols are better able than tocopherols at combating oxidative stress of skin that had been exposed to U. V rays of the sunlight.<sup>19</sup> Since 2000, scientists have suggested tocotrienols are better antioxidants than tocopherols at preventing cardiovascular diseases.<sup>20</sup>

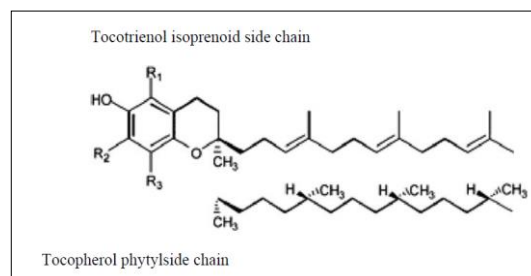
Heart disease or cardiovascular diseases are the class of diseases that involve the heart or blood vessels (arteries & veins). While the term technically refers to any disease that affects the cardiovascular system, it is usually used to refer to those related to atherosclerosis (arterial disease). These conditions usually have similar causes, mechanism and treatments.<sup>21</sup> Cardiovascular diseases remain the biggest cause of deaths worldwide, through over the last two decades cardiovascular mortality rates have declined in many high income countries but have increased at an astonishingly fast rate in low and middle income countries. The percentage of premature death from cardiovascular disease range 4% in high income countries to 42% in low income countries. In recent years, cardiovascular risk in women has been increasing and has killed more women than breast cancer.<sup>22</sup>

Diets designated to lower cholesterol and improve multiple metabolic risk factors can lower the risk of coronary artery diseases. There are real benefits to an emphasis on solid nutritional principles. Cholesterol lowering diets & supplements may allow therapeutic goals for LDLc to be reached without additional medication.<sup>23</sup> The available data support the hypothesis that oxidation of LDL by cells in the arterial wall is a pivotal step in the initiation of early lesions seen in coronary atherosclerosis. Thus, there has been a heightened interest in antioxidants which may work to prevent or retard this process. This may work to prevent or retard this process. Several lines of evidence support

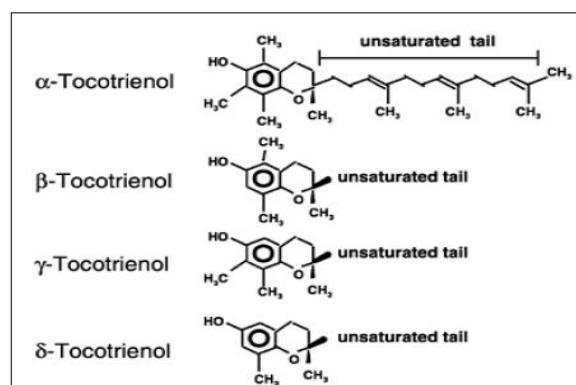
an important role for vitamin E ( $\alpha$ -tocopherol), which is carried on LDL and is a potent lipid soluble antioxidant.<sup>24</sup> Apart from tocotrienols antioxidant, anti-inflammatory, anti angiogenic, anti neurodegeneration, antimicrobial properties, anti-cancer activity, it has also antihypercholesterolemic and anti-cardiovascular disease properties.<sup>25,26</sup>

## CHEMISTRY AND BIOLOGICAL ACTIVITY OF TOCOTRIENOLS

Vitamin E consists of a group of 8 molecules belonging to 2 classes designated as tocopherols and tocotrienols. Both tocopherols and tocotrienols possess 4 structurally similar forms designated  $\alpha$ ,  $\beta$ ,  $\gamma$  and  $\delta$ . Tocotrienol differs from tocopherol by having 3 double bonds in the carbon side chain of the molecule.<sup>6</sup> This unique structure makes this tocotrienol a potent antioxidant with many health benefits. The tocotrienol molecule looks like a tadpole, with a head and a tail. The head with polar chromanol ring and tail with a long isoprenoid side chain. Tocopherols containing a phytyl chain while tocotrienols with geranyl farnesyl chain. The head of T<sub>3</sub> is designated as  $\alpha$ ,  $\beta$ ,  $\gamma$  and  $\delta$  depending on the amount of substituted methyl groups. Tocotrienols (T<sub>3</sub>) have only a single chiral centre, which exist at the 2' chromanol ring carbon, at the point where the isoprenoid tail joins the ring. Tocotrienols extracted from natural sources always consist of dextrorotatory enantiomers only. These naturally occurring dextrorotatory stereoisomers are generally abbreviated as the "d" forms, for example "d-tocotrienol" or "d alpha-tocotrienol".<sup>5</sup>



**Figure 1: Chemical structure of tocotrienol.**



**Figure 2: Four different forms of tocotrienol.**

## NATURAL SOURCES OF TOCOTRIENOLS

Tocotrienols are the primary form of vitamin E in the seed endosperm of most monocots, including agronomically important cereal grains such as wheat, rice and barley. Palm oil contains significant quantities of tocotrienol.<sup>27</sup> Crude palm oil extracted from the fruits of *Elaeis guineensis* particularly contains a high amount of tocotrienols (upto 800 mg/kg), mainly consisting of  $\gamma$ -tocotrienol and  $\alpha$ -tocotrienol. Compared to tocopherols, tocotrienols are considerably less widespread in the plant kingdom.<sup>28</sup>

The identification of  $\alpha$ -tocotrienol as a cholesterologenesis-inhibitory factor derived from barley (*Hordeum vulgare* L.) represents a landmark early discovery highlighting the unique significance of tocotrienols in health and disease.<sup>29</sup> Palm oil represents one of the most abundant natural sources of tocotrienols.<sup>30</sup> The distribution of vitamin E in palm oil is 30% tocopherols and 70% tocotrienols.<sup>27</sup>

$\alpha$ -tocotrienol is the predominant form of tocotrienol in oat (*Avena sativa* L.) and barley (56 and 40 mg/kg of dry weight, respectively).  $\beta$ -Tocotrienol is the major form of tocotrienol found in hulled and dehulled wheats (from 33 to 43 mg/kg of dry weight).<sup>31</sup> Although tocotrienols are present in edible natural products, it is questionable whether these dietary sources could provide sufficient amounts of tocotrienol to humans. For example, the processing of 1000 kg of crude palm oil is necessary to derive 1 kg of the commercial product Tocomin® 50% (Carotech, NJ).<sup>32</sup>

## FUNCTIONS & HEALTH EFFECTS OF TOCOTRIENOLS

Indeed,  $\alpha$ -tocotrienol possesses numerous functions that are not shared by  $\alpha$ -tocopherol.<sup>33</sup> For example, nanomolar concentrations of  $\alpha$ -tocotrienol uniquely prevent inducible neurodegeneration by regulating specific mediators of cell death.<sup>8-10</sup> Oral supplementation of tocotrienol protects against stroke.<sup>7</sup> Micromolar amounts of tocotrienol suppress the activity of 3-Hydroxy-3-Methyl Glutaryl coenzyme A (HMG-CoA) reductase, the hepatic enzyme responsible for cholesterol synthesis.<sup>11,12</sup> Tocopherols do not share the cholesterol-lowering properties of tocotrienol.<sup>14,29</sup> Sterol-regulated ubiquitination marks HMG-CoA reductase for Endoplasmic Reticulum (ER)-associated degradation by 26S proteasomes. This degradation, which results from sterol-induced binding of reductase to ER membrane proteins called Insigs, contributes to the complex, multivalent feedback regulation of the enzyme. Recently it has been demonstrated that  $\delta$ -tocotrienol stimulates ubiquitination and degradation of reductase and blocks processing of Sterol Regulatory Element-Binding Proteins (SREBPs), another sterol-mediated action of Insigs. The  $\gamma$ -tocotrienol analog is more selective in enhancing reductase ubiquitination and degradation than

blocking SREBP processing. Other forms of vitamin E neither accelerate reductase degradation nor block SREBP processing.<sup>34</sup> Tocotrienol but not tocopherol, suppresses growth of human breast cancer cells.<sup>35</sup>

In the peer-reviewed stroke journal (Oct 2005), oral supplementation of a natural full spectrum palm tocotrienol complex to spontaneously hypertensive rats led to increased tocotrienol levels in the brain. The rats, supplemented with tocotrienols, showed more protection against stroke-induced injury compared to controls (non-supplemented group). This study demonstrated that oral supplementation of the palm tocotrienol complex acts on key molecular checkpoints (c-Src and 12-Lipoxygenase) to protect against glutamate- and stroke-induced neurodegeneration and ultimately protect against stroke *in vivo*.<sup>7</sup>

In a 2009 *in vitro* study, scientists at department of nutrition and food sciences, Texas Woman's University evaluated the impact of  $\delta$ -tocotrienol, on human MIA PaCa-2 and PANC-1 pancreatic carcinoma cells and BxPC-3 pancreatic ductal adenocarcinoma cells. They concluded suppression of mevalonate pathway activities, be it by modulators of HMG CoA reductase (statins, tocotrienols, and farnesol), farnesyl transferase (farnesyl transferase inhibitors), and/or mevalonate pyrophosphate decarboxylase (phenylacetate) activity, have a potential in pancreatic cancer chemotherapy.<sup>36</sup>

In a 2009 study at the Li Ka Shing Faculty of Medicine, The University of Hong Kong, scientists found reduction in skin cancer cells when treated with  $\gamma$ -tocotrienol with chemotherapy drugs. For the first time, researchers recorded the anti-invasion and chemosensitization effect of  $\gamma$ -tocotrienol against human malignant melanoma cells.<sup>37</sup>

The human body makes cholesterol from the liver, producing about 1g of cholesterol each day or 80% of the needed total body cholesterol. The remaining 20% comes from what we eat. Excessive cholesterol is a health risk because gradual fatty deposits clog up the arteries. This will cause blood flow to the brain, heart, kidneys and other parts of the body to become less efficient.

Cholesterol, though needed metabolically, is not essential in diet. Tocotrienols can decrease the liver's capacity to manufacture cholesterol. They do so by dialing down HMG-CoA reductase, the enzyme in the liver responsible for cholesterol synthesis.<sup>3</sup>

## EFFECTS OF TOCOTRIENOL ON CARDIOVASCULAR SYSTEM

### *Hypercholesterolemic effects*

Hypercholesterolemia is a recognized risk factor for atherosclerotic disease.<sup>38</sup> Studies have demonstrated that with very few exceptions, populations that consume

large quantities of saturated fat and cholesterol have relatively high concentration of serum cholesterol and correspondingly high mortality rates from coronary heart disease.<sup>39</sup>

Purification of an oily, non-polar fraction of high protein barley flour by high pressure liquid chromatography yielded ten major components. Two of these components were identified as potent inhibitors of cholesterologenesis both in vivo as well as in vitro. Addition of the purified inhibitor I (2.5-20 ppm) to chick diets significantly decreased hepatic cholesterologenesis and serum total and low density lipoprotein cholesterol and concomitantly increased lipogenic activity. The high resolution mass spectrometric analysis and measurement of different peaks of inhibitor I gave a molecular ion at m/e 424 (C<sub>29</sub>H<sub>44</sub>O<sub>2</sub>) and main peaks at m/e 205, 203, and 165 corresponding to C<sub>13</sub>H<sub>17</sub>O<sub>2</sub>, C<sub>13</sub>H<sub>15</sub>O<sub>2</sub>, and C<sub>10</sub>H<sub>13</sub>O<sub>2</sub> moieties, respectively. Based on these results, d- $\alpha$ -tocotrienol was identified as the active principle. This identification was confirmed against synthetic samples.<sup>29</sup> That the  $\alpha$ -tocotrienol form of natural vitamin E, not tocopherol, may have significant cholesterol - lowering properties represents one of the early findings describing the unique biological properties of tocotrienol that was reported two decades ago.<sup>29</sup> The endoplasmic reticulum enzyme 3-Hydroxy-3-Methyl Glutaryl (HMG-CoA) CoA reductase produces mevalonate, which is converted to sterols and other products. It is proposed that tocotrienols are effective in lowering serum total and LDL-cholesterol levels by inhibiting the hepatic enzymic activity of HMG-CoA reductase through a post-transcriptional mechanism.  $\alpha$ -Tocopherol, however, had an opposite effect (induces) on this enzyme activity.<sup>14</sup> This contrast is of outstanding significance and requires further characterization. Evidence that the Tocotrienol-Rich Fraction (TRF) of palm oil may indeed lower plasma cholesterol in mammals came from a study of normolipemic and genetically hypercholesterolemic pigs of defined lipoprotein genotype.<sup>40</sup> The pigs were fed a standard diet supplemented with 50 micrograms/g TRF isolated from palm oil. Hypercholesterolemic pigs fed the TRF supplement showed a 44% decrease in total serum cholesterol, a 60% decrease in LDL-cholesterol, and significant decreases in levels of apolipoprotein B (26%), thromboxane-B2 (41%), and platelet factor 4 (PF4; 29%). It was also noted that TRF had a marked protective effect on the endothelium and platelet aggregation. The effect of the lipid-lowering diet persisted only in the hypercholesterolemic swine after 8 week feeding of the control diet.<sup>40</sup> These interesting observations were quickly put to test in humans by means of a double-blind, crossover, 8-week study.<sup>41</sup> The goal was to compare effects of the tocotrienol-enriched fraction of palm oil (200 mg palmvitee capsules/day) with those of 300 mg corn oil/d on serum lipids of hypercholesterolemic human subjects (serum cholesterol 6.21-8.02 mmol/L). Concentrations of serum total cholesterol (-15%), LDL cholesterol (-8%), Apo B (-10%), thromboxane (-25%), platelet factor 4 (-16%), and glucose (-12%) decreased

significantly only in the 15 subjects given palmvitee during the initial four weeks. Results from the crossover study established that the noted beneficial effects were indeed caused by palmvitee. A carry-over effect of palmvitee was also reported. Serum cholesterol concentrations of seven hypercholesterolemic subjects (>7.84 mmol/L) decreased 31% during a four-week period in which they were given 200 mg  $\gamma$ -tocotrienol/d. These results suggest that  $\gamma$ -tocotrienol could be the active principle cholesterol inhibitor in palmvitee capsules.<sup>41</sup> Experimental data from the study of hamsters are in agreement.<sup>42</sup> What added to the interest in tocotrienol as a cholesterol-lowering nutrient in humans was a concurrent independent study reporting the hypocholesterolemic effects of palmvitee.<sup>43</sup> Each palmvitee capsule contained approximately 18, 42, and 240 mg of tocopherols, tocotrienols, and palm olein, respectively. All volunteers took one palmvitee capsule per day for 30 consecutive days. Overnight fasting blood was recorded from each volunteer before and after the experiment. Palmvitee lowered both serum total cholesterol and low-density-lipoprotein cholesterol concentrations in all subjects. The magnitude of reduction of serum total cholesterol ranged from 5.0% to 35.9% whereas the reduction of low-density-lipoprotein cholesterol values ranged from 0.9% to 37.0% when compared with their respective baseline values.<sup>43</sup>

Tocotrienol, not only of palm oil origin, but also isolated from rice bran show cholesterol lowering properties.<sup>44,45</sup> Amaranth oil, containing tocotrienol, possesses hypocholesterolemic properties as well.<sup>46</sup> A human study with 28 hypercholesterolemic subjects has been executed in 5 phases of 35 days each. The goal was to check the efficacy of a TRF preparation from rice bran alone and in combination with lovastatin. After placing subjects on the American Heart Association (AHA) Step-1 diet (phase II), the subjects were divided into two groups, A and B. The AHA Step-1 diet was continued in combination with other treatments during phases III to V. Group A subjects were given 10 mg lovastatin, 10 mg lovastatin plus 50 mg TRF, 10 mg lovastatin plus 50 mg  $\alpha$ -tocopherol per day, in the third, fourth, and fifth phases, respectively. Group B subjects were treated exactly according to the same protocol except that in the third phase, they were given 50 mg TRF instead of lovastatin. The TRF or lovastatin plus AHA step-1 diet effectively lowered serum total cholesterol (14%, 13%) and LDL-cholesterol (18%, 15%), respectively. The combination of TRF and lovastatin plus AHA step-1 diet significantly reduced the lipid parameters by 20-25%. Especially significant were the increase in the HDL/LDL ratio to 46% in group A and 53% in group B. None of the subjects reported any side-effects throughout the study of 25 weeks.<sup>47</sup> Consistent results were obtained using rice-bran derived TRF in another human study.<sup>14</sup> A dose of 100 mg/day of TRF decreased the level of serum total cholesterol, LDL-cholesterol, apolipoprotein B and triglycerides compared with the baseline values. The work led to the suggestion that a dose of 100 mg/day TRF plus AHA step-1 diet

could control the risk of coronary heart disease in hypercholesterolemic humans.<sup>14</sup>

### Clinical studies of TRF for lipid profile

In general, the palm TRF lowered blood cholesterol concentrations without showing any adverse effects in healthy volunteers and subjects with hypercholesterolemia or NIDDM. For example, administration of 60 mg palm TRF in 22 healthy Malaysian subjects (with no age limitation) for 30 d lowered both serum total cholesterol (TC) and low-density-lipoprotein cholesterol (LDL-C) concentrations. The magnitude of reduction of serum TC ranged from 5 to 35.9% whereas the reduction of LDL-C values ranged from 0.9 to 37.0% when compared with their respective starting values. No adverse effects were reported.<sup>45</sup>

The palm TRF was tested in 16-25 hypercholesterolemic Malaysian subjects aged 30-60 year at a dose of 200-300 mg/d over a 4-8 week period.<sup>41,48</sup> Significant reductions in serum total cholesterol, LDL cholesterol, apolipoprotein B, thromboxane B2, and platelet factor were observed.

Ajuluchukwu et al. (2007)<sup>49</sup> studied the effect of palm oil TRF on the serum lipid profiles of 28 individuals aged 18-80 year with mild hypercholesterolemia and another cardiovascular risk factor. Subjects were randomly assigned to consume tocotrienols as TOCOVIDTM Suprabio™ capsules (consisting of 15.38 mg  $\alpha$ -T3, 28.20 mg  $\gamma$ -T3, 6.42 mg  $\delta$ -T3 and 22.90 mg  $\alpha$ -T) or 500 mg or

1000 mg vitamin E ( $\alpha$ -T) capsules per day or every other day (n=16) for 4 weeks. Compared to the T supplement, the T3 supplement significantly decreased total cholesterol and LDL-cholesterol, but not HDL-cholesterol or triglyceride concentrations.

Qureshi et al. (2002) investigated the effect of 4 doses (25, 50, 100, and 200 mg/d) of a TRF (8.7 %  $\alpha$ -T, 15.5 %  $\alpha$ -T3, 1.6%  $\beta$ -T3, 39.4 %  $\gamma$ -T3, 5.2 %  $\delta$ -T3, and 4.4 %  $\delta$ -T, 20.9% Ddesmethyl (D-P21-T3), plus D-didesmethyl (D-P25-T3) T3, 4.3 % unidentified tocotrienols) extracted and purified from rice bran oil on the suppression of serum cholesterol in Malaysian adults.

### Oxidative stress and biomarker test

In a randomized, placebo-controlled study, 50 subjects (aged 49-83 year) with carotid atherosclerosis received palm TRF (240 mg T3 and 90 mg T/d) or placebo in addition to standard medical therapy over 18 months.<sup>50</sup> Serum measures of oxidative stress (TBARS) showed a significant decrease with no appreciable change in serum lipids or other biochemical markers. Both T3 and placebo groups displayed attenuated collagen-induced platelet aggregation responses (P <0.05) as compared with entry values. Serum total cholesterol, low density lipoprotein cholesterol, and triglyceride values remained unchanged in both groups, as did the plasma high density lipoprotein cholesterol values.

### SAFETY & EFFICACY OF TOCOTRIENOLS

**Table 1: Human clinical studies reporting no adverse effects of rice bran TRF.**

| Number and status of subjects | Dose of T3  | Ratio of T3: $\alpha$ -T                                | Duration  | Reference                |
|-------------------------------|---|---|-----------|--------------------------|
| 28 hypercholesterolemic       | 3 mg/day T3;<br>0.04 mg/kg<br>BW/day;                   | T3: $\alpha$ -T: $\delta$ -T=86.9:8.7: 4.4              | 35-70 d   | Qureshi et al. 2001      |
| 36 hypercholesterolemic       | 0.33 mg/kg<br>BW/d from a<br>processed rice<br>bran oil | 25 mg $\alpha$ -T, 42 mg $\gamma$ -T, 20 mg $\delta$ -T | 4 week    | Qureshi et al. 1997      |
| 90 hypercholesterolemic       | 25, 50, 100, and<br>200 mg/d                            | T3: $\alpha$ -T: $\delta$ -T=86.9:8.7: 4.4              | 5 week    | Qureshi et al. 2002      |
| 25 carotid atherosclerosis    | 112 mg/d  | T3: $\alpha$ -T=52:60                                   | 3 year    | Kooyenga et al. 2001     |
| 19 NIDDM                      | 3 mg/kg BW/d  | T3: $\alpha$ -T=92.5: 7.5                               | 60 d      | Baliarshingh et al. 2005 |
| 23 familial dysautonomia      | 100 mg/d  | NA  | 3-4 month | Rubin et al. 2008        |

As shown in above table, several studies reported no adverse effects with the supplementation of TRF or processed oil extracted from rice bran oil. Qureshi et al. (1997)<sup>51</sup> performed a randomized double blind placebo controlled trial in which 41 hypercholesterolemic Malaysian subjects were first placed on the low fat diet for 4 week and then given 200 mg/d of TRF from rice

bran oil or corn oil as placebo. No adverse effects due to T3 ingestion were observed.

Qureshi et al. (2001)<sup>47</sup> investigated the efficacy of TRF of rice bran alone and in combination with the cholesterol lowering drug, lovastatin. The TRF consisted of 8.7%  $\alpha$ -T, 4.4%  $\delta$ -T, and 86.9% T3. The combination of TRF and



lovastatin significantly reduced lipid metabolites by 20-25% ( $P < 0.001$ ) in these subjects. The authors stated that subjects reported no side effects during the 25-week study.

Baliarsingh et al. (2005)<sup>52</sup> reported the therapeutic impacts of palm TRF (3 mg palm TRF/kg BW/d, 60 d) on serum lipoprotein lipid levels in 19 Indian subjects with NIDDM. The composition of tocopherols in palm TRF was 7.5%  $\alpha$ -T, 14.6%  $\alpha$ -T3, 2.2%  $\beta$ -T3, 38.8%  $\gamma$ -T3, 4.6%  $\gamma$ -T, and 29.9%  $\delta$ -T3. No adverse effects were reported.

## CONCLUSION

Our study revealed an age related increase in cardiovascular disorders such as hypercholesterolemia, atherosclerosis, vascular oxidative stress, myocardial infarction, stroke, C.H.D etc. are the prominent cause for human health hazards and mortality. Long term lack of tocotrienol in the diet may repress any putative tocotrienol transport mechanism in vivo. Thus, long term supplementation studies are needed. To our best of knowledge, tocotrienol rich supplementation has not yet been very well studied in relation to oxidative stress and cardiac markers in healthy older and cardiac disordered individuals. Our review study shows that the TRF supplementation in relation to lipid profiles is beneficial to prevent the cardiovascular diseases. Furthermore it is need to study the TRF supplementation in relation to prevention of CVD on parameters such as cardiac enzyme markers (SGOT, SGPT), antioxidant enzymes (SOD, CAT, GPx), oxidative stress (TBARS), CRP and lipoproteins to know the clinical role of TRF in relation to diagnosis, treatment, prognosis and prevention of cardiovascular disorders.

## ACKNOWLEDGEMENTS

This study was supported by Director, DMSRDE, DRDO (Defense Research and Development Organisation), Kanpur and Chairman, Research and Development Unit of Mayo Institute of Medical Sciences, Barabanki, Uttar Pradesh, India.

*Funding: No funding sources*

*Conflict of interest: None declared*

*Ethical approval: Not required*

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DOI: 10.5455/2349-3259.ijct20141102

**Cite this article as:** Mishra BP, Badade ZG, Lingidi JL, Jaiswal S, Anand BK. Tocotrienols and its impact in cardiovascular health. *Int J Clin Trials* 2014;1:87-94.