

Comparative efficacy of tocotrienol and tocopherol (vitamin E) on atherosclerotic cardiovascular diseases in humans

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Abstract

Objective: To compare the efficacy of tocotrienol and tocopherol in the management of patients with atherosclerotic cardiovascular diseases.

Method: The systematic review was conducted in line with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines 2020, and comprised literature search from 2002 till January 5, 2023, on PubMed, Google Scholar, Cochrane Library, Google, Wiley-Inter Science Library, Medline, SpringerLink, Taylor and Francis databases. The search was conducted using key words, such as: "tocopherol", "tocotrienol", "vitamin E", "dyslipidaemia", "cardiovascular diseases" "cardioprotective", "hypercholesterolemia" and "atherosclerosis" along with Boolean operators. Human clinical studies regarding the use of tocotrienol or tocopherol or comparison of its efficacy in patients having atherosclerosis, dyslipidaemia leading to cardiovascular diseases, and studies including details of efficacy of any of the four alpha, beta, gamma, delta isomers of tocopherol or tocotrienol were included. Pertinent data from the eligible studies were retrieved and reviewed.

Results: Of the 516 articles identified, 26 (5%) articles met eligibility criteria. Of them 5(19%) were subjected to detailed analysis. Tocotrienol showed significant anti-oxidant efficacy at (250 mg/d) by decreasing cholesterol and serum inflammatory biomarkers i.e C-reactive protein (40%), malondialdehyde (34%), gamma-glutamyl transferase (22%) ($p < 0.001$). Total anti-oxidant status (TAS) levels raised 22% ($p < 0.001$) and Inflammatory cytokines i.e resistin, interleukin (IL)-1, IL-12, Interferon-gamma were decreased 15-17% ($p < 0.05-0.01$) respectively by tocotrienol. Several microRNA (miRNA-133a, miRNA-223, miRNA-214, miRNA-155) were modulated by δ -tocotrienol. Whereas, tocopherol showed heterogeneity of results by either decreasing or increasing the risk of mortality in atherosclerotic cardiovascular diseases.

Conclusion: Compared to tocopherol, tocotrienol was found to be safe and potential candidate for improving cardiovascular health in the management of atherosclerotic cardiovascular diseases.

Keywords: Cardiovascular diseases, Vitamin E, Atherosclerosis, Tocotrienol, Dyslipidaemia, Tocopherol,

Hypercholesterolemia, Human studies. (JPMA 74: 1124 2024) **DOI:** <https://doi.org/10.47391/JPMA.9227>

Introduction

Atherosclerotic cardiovascular disease (ASCVD), specifically myocardial infarction (MI), have been the most notorious reason of morbidity and increased death rate globally.¹

Among various risk factors related to ASCVD, dyslipidaemia is the predominant factor which is defined as steady rise in serum low-density lipoprotein-cholesterol (LDL-C), total cholesterol (TC), triglycerides (TG) levels, and diminished levels of high-density lipoprotein-cholesterol (HDL-C).^{2,3} hypercholesterolaemia is a cosmopolitan burden that affects the population from young children to the elderly.⁴

Surprisingly, familial hypercholesterolaemia (FH) has also been found prevalent now-a-days.⁵ Pharmacological interventions, together with lifestyle modifications, like regular physical activity and good healthy eating practices, remain the mainstay for ameliorating dyslipidaemia and impeding most cardiovascular events.^{6,7} In the discipline of nutrition, different nutriments have great potential to regulate serum lipid parameters and atherosclerosis.⁵

Vitamin E is mainly composed of tocopherols (TCPs) and tocotrienols (TCTs), each having alpha (α) beta (β), gamma (γ) and delta (δ) isomers based on the position of having methyl groups in its molecular structure. Majorly TCPs are found in oils of almonds, sunflower, nuts, olive, rapeseed oil, linseed, corn and soybean, whereas TCTs are found in annatto oil, barley, hazelnuts, wheat germ, oats, maize, palm and rice bran.^{8,9} Both compounds are structurally similar, having a chromanol ring, but they differ in the side chain with TCP possessing long saturated tail and TCT having short unsaturated tail with three double bonds.⁸

Vitamin E, being fat-soluble antioxidant, is considered a nutriment with anti-atherosclerotic property since long

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due to its effectiveness in reducing oxidation of LDL-C,¹⁰ which is a basic step towards inhibiting atherogenesis. Most surprisingly, vitamin E, mainly α TCP which is the most naturally occurring and active form, has also been found to increase the risk of mortality, acute MI (AMI) and stroke.¹¹ Interestingly, TCTs have also gained wide attention in the management of cardiometabolic diseases, with every isomer showing slightly different characteristics.¹² TCTs have been revealed to have better antioxidant capability compared to TCPs.¹³

In view of cardiometabolic effects, research has shown the role of TCTs as a supplement with cholesterol-lowering properties.¹⁴ Apart from it, many randomised controlled trials (RCTs) have explored the effect of TCT in patients having dyslipidaemia, and different metabolic disorders, like diabetes mellitus (DM) and non-alcoholic fatty liver disease (NAFLD), reporting a range of effects.¹³

In view of dyslipidaemia contributing to ASCVD, and the role of TCPs and TCTs in decreasing serum lipid parameters with varying results, it is necessary to review the available evidence to compare the efficacy of both supplements in the management of CVDs. To the best of our best knowledge, there is no systematic review in literature that has compared the efficacy of TCP and TCT supplements in the management of CVDs. Hence, the current systematic review was planned to fill the gap in literature by comparing the efficacy of TCPs and TCTs in the management of ASCVD.

Materials and Methods

The systematic review was conducted in line with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines 2020¹⁵ and comprised literature search from 2002 till January 5, 2023, on PubMed, Google Scholar, Cochrane Library, Google, Wiley-Inter Science Library, Medline, SpringerLink and Taylor and Francis databases.

The search was conducted using key words, such as: "tocopherol", "tocotrienol", "vitamin E", "dyslipidaemia", "cardiovascular diseases" "cardioprotective", "hypercholesterolaemia" and "atherosclerosis". Boolean logic was applied, such as "tocotrienol AND cardiovascular diseases", "tocopherol atherosclerosis OR dyslipidaemia", "tocotrienol human atherosclerosis NOT animals", "Tocotrienol OR tocopherol AND hypercholesterolaemia in humans only", and "Tocopherol AND cardioprotective in

Table-3: Pedro quality assessment for randomised controlled trials (RCTs).

Studies	Eligibility	Random Allocation	Concealed allocation	Baseline comparability	Blind Subjects	Blind therapists	Blind assessors	Adequate follow up	Intention to treat analysis	Between group comparison	Point estimated variability	Total Score
Slivka et al., 2020 ²²	1	1	1	1	1	1	1	1	0	1	1	10/11
Qureshi, et al., 2015 ²³	1	1	1	1	1	1	1	1	0	1	1	9/10
Muid et al., 2018 ²⁴	1	1	0	1	0	0	0	1	0	1	0	5/11

1: Yes, 0: No.

Table-1: Newcastle-Ottawa Quality Assessment for case-control and cohort studies.

Studies	Selection (max.5 stars)	Comparability (max.2 stars)	Outcome (max.3 stars)	Total score (max.10 stars)
Prentice., et al., 2019 ²⁰	3	2	2	7
Huang., et al., 2019 ²¹	3	2	3	8

Table-2: Assessment of risk of bias in randomised controlled trials (RCTs).

Studies	Random Sequence generation	Allocation concealment	Blinding of outcome assessment
Slivka et al., 2020 ²²	+	-	+
Qureshi, et al., 2015 ²³	+	+	+
Muid et al., 2018 ²⁴	-	-	-

?: Unclear, +: Low risk, -: High risk.

humans only". Articles were also retrieved by open google search and snowball technique from reviews and meta-analyses. RCTs, case-control and cohort studies were included.

The inclusion criteria comprised human clinical studies regarding use of TCT or TCP, studies comparing their efficacy in patients having atherosclerosis and dyslipidaemia leading to CVDs, studies having details of efficacy of any of the four α , β , γ and δ isomers of TCP or TCT, original articles, RCTs, case-control, cohort and cross-sectional studies written in English language and published in impact factor journals.

The exclusion criteria comprised animal studies, editorials, letters to editor, cell-line studies, grey literature, like conference papers, dissertations and patents, case reports, systematic reviews, commentary, news, case series and short communications.

Eligibility of study was based on the Patient/Problem-Intervention-Comparison-Outcome (PICO) format.¹⁶

Data recorded from the research papers included the year of publication, research design, place of study, health/disease status of patients, sampling technique, methodology, duration of intervention, outcome effect, conclusion and limitations. Data was reviewed and analysed.

Newcastle-Ottawa Scale (NOS) was used for risk of bias assessment in case-control and cohort studies (Table 1).¹⁷ while RCTs were assessed by using the 11-point Pedro scale, with higher score showing good quality of research.¹⁸ Assessment of risk of bias was evaluated by three researchers by using Cochrane risk of bias tool (Table 2,3).¹⁹

Results

Of the 516 articles identified, 5(1%) were subjected to detailed analysis (Figure).²⁰⁻²⁴ There were 2 (40%) studies regarding TCP effects on cardiovascular system and they showed heterogeneity (Table 4). One cohort study showed increased cardiovascular risk with higher intake of αTCP in post-menopausal women in the United States.²⁰ On the contrary, a 30-yr prospective cohort study in Finland showed decreased CVD mortality with higher baseline serum αTCP among men.²¹

Among the 3 (60%) studies²²⁻²⁴ done regarding TCT effects on cardiovascular system, 1(20%) showed decreased inflammatory biomarkers along with improved lipid profiles. TCTs also modulated micro ribonucleic acid (miRNAs) expression related to CVD, including miRNA-155, 133a, 223 and 214.²² Further, 1(20%) study in the US reported decreased frequency of resistance to aspirin in patients on dual antiplatelet regimen, like aspirin and clopidogrel.²³ Similarly, an RCT (20%) in Malaysia on non-familial hypercholesterolaemia (NFH) patients using combination of TCT-rich fraction (TRF) and statin reported that TRF decreased LDL-C level in NFH patients, but to a lesser extent compared to statins (Table 5).²⁴

Despite extensive and frequent search on multiple database search engines, no data was found revealing comparative analysis of TCT and TCP in ASCVD management. Also, no data was found regarding TCT efficacy directly on different CVDs. Only studies regarding TCT effects on hypercholesterolaemia and platelet function in transient ischaemic attack (TIA) patients were available.

Table-4: Summary of studies on effects of tocopherol (TCP) on the cardiovascular system.

References (Harvard Style)	Type of study/Trial Registration No.	Health/ Disease condition	Methodology	Duration of intervention (years/weeks)	Tocotrienol intervention		Outcome Effect	Conclusion	Limitations
					Treatment group	Control Group			
1) Prentice, et al., 2019 ²⁰	Cohort NCT01858311	Post-menopausal women	Serum concentrations of α-tocopherols along with other micronutrient were routinely measured in Women's Health Initiative (WHI) cohorts in US & correlated with incidence of cardiovascular & other diseases. N= 5488	11 years	α-tocopherol	Placebo	Approximated HRs (95% CIs) for a doubling α-tocopherol are above 1 for CABG/PCI, which was associated with rise in CABG/PCI.	α-tocopherol caused increase cardiovascular outcomes in (CABG/PCI) with higher doses	Confounding factors could not be avoided as being observational study. Efficacy of α-tocopherol could be influenced by interaction of other micronutrients.
2) Huang, et al., 2019 ²¹	30-years Prospective Cohort study	Male Smokers	Serum α-tocopherol was estimated at baseline by using HPLC in ATBC (AlphaTocopherol, Beta-Carotene Cancer Prevention) Study and during a 30-year follow-up to determine the association b/w serum α-tocopherols levels & over all cause specific mortality in Finland. M= 29133	30 years	α-tocopherol (50 mg/d)		Male with greater serum α-tocopherol showed significant less mortality (p< 0.0001) from cardiovascular disease & heart disease.	High baseline serum α-tocopherol has potential to decrease cardiovascular disease mortality.	Inclusion of male smokers may limit generalizability of findings to other populations including females. Any information regarding blinding is not mentioned in article.

RCT: Randomised controlled trial, N: Total number of patients, M: Male, F: Female, Int: Intervention, Con: Control, PCI: Percutaneous coronary intervention, CABG: Coronary artery bypass graft, CI: Confidence interval, HR: Hazard ratio, IU: International units, CVD: Cardiovascular disease, HPLC: High-performance liquid chromatography.

(Tables 4,5).²²⁻²⁴

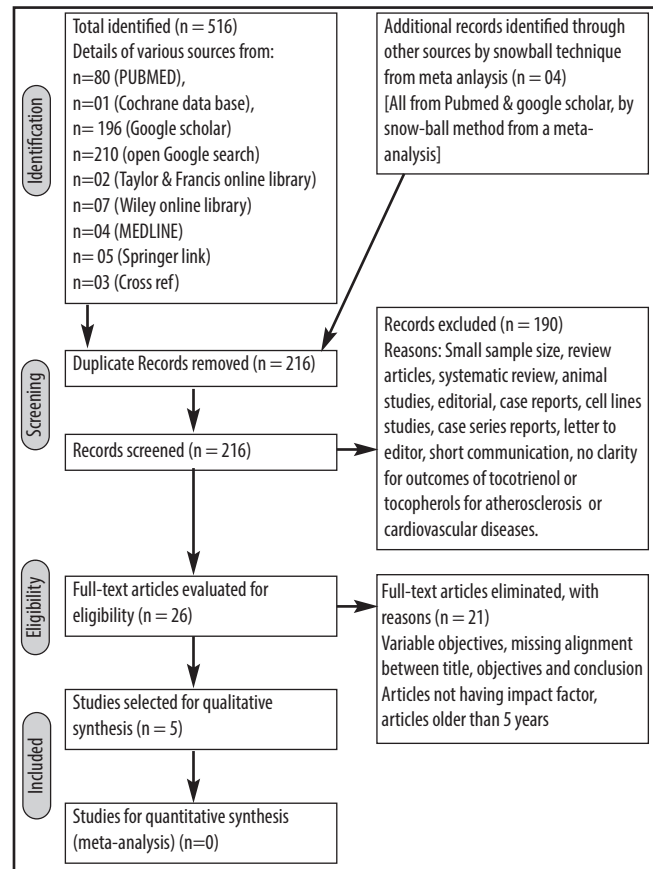


Figure: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart.

Table-5: Summary of randomised controlled trials (RCT)s dose-response studies on the effects of tocotrienol (TCT) on the cardiovascular system.

References (Harvard Style)	Type of study/Trial Registration No.	Health/ Disease condition	Methodology	Duration of intervention (years/weeks)	Tocotrienol intervention		Outcome Effect	Conclusion	Limitations
					Treatment group	Control Group			
1) Slivka et al., 2020 ²²	Double blind RCT (NCT00000611)	Transient ischaemic attack/stroke	Comparison of placebo and TCT (400 & 800 mg) daily on platelet function in transient ischaemic attack (TIA) patients in last 24 weeks in USA N= 150 Int (400 mg TCT) = 51 Int (400 mg TCT) = 50 Con= 49	24	400 mg TCT 800 mg TCT	Placebo (PBO)	Results have shown decline in resistance of aspirin in patients on combine regimen of TCT, aspirin & clopidogrel ($p=0.03$).	TCT significantly decreased frequency of resistance to aspirin in patients on dual antiplatelet therapy with aspirin & clopidogrel.	Small no of patients Number of females was large in proportion to males.
2) Qureshi, et al., 2015 ²³	Dose-response study Forced titration design, DB study	Hyper- cholesterolaemia	δ -tocotrienol in increasing doses were given to Hypercholesterolaemic subjects with age (50-71 years) & serum cholesterol > 5.1 mmol/L from Pakistan. Serum lipid levels, various plasma cytokines, cDNA & miRNAs were estimated. N = 31 M=26 F= 5	16	δ - tocotrienol (125, 250, 500,750 mg/d)		Decrease in lipid parameters serum TC (15%), LDL-cholesterol (18%), TG (14%) with maximum effects on 250 mg/d dose ($p < 0.001$). Doses greater than 500 mg/d resulted in increase in levels of all lipid parameters, except HDL cholesterol. Cytokines (Interleukins & TNF- α ,) were down-regulated ($p < 0.01$). Anti-angiogenic miRNA-(7a, 15a, 20a), Skeletal muscle regeneration miRNA-(21, 29a, 92a, 200, 206) were up-regulated as compared to baseline ($p < 0.01$).	δ -tocotrienol showed significant decrease in serum lipid parameters & various cytokines (TNF- α , interleukins) at low dose (250 mg/d) which can contribute a major part in future management of cardiovascular diseases	Small no of patients Unequal ratio of male & female Short span study Lack of placebo group
3) Muid et al., 2018 ²⁴	RCT	Non-familial hyper- cholesterolaemia (NFH)	Patients were randomized to either (Palmvitee/ NFHe) group (60 mg/day TRF) or (Atorvastatin / NFHs) group (10 mg/day) to compare their effects of TRF on serum lipids & oxidative stress biomarkers in comparison with statin treatment in Malaysian population. N=37 M=24 F=13 C (NFHs) = 25 Int (NFHe) = 12	???	RCT	Non- familial hyper- cholester- olaemia (NFH)	Patients were randomized to either (Palmvitee/ NFHe) group (60 mg/day TRF) or (Atorvastatin / NFHs) group (10 mg/day) to compare their effects of TRF on serum lipids & oxidative stress biomarkers in comparison with statin treatment in Malaysian population. N=37 M=24 F=13 C (NFHs) = 25 Int (NFHe) = 12	TRF possess significant potential in prevention of incidence of atherosclerosis due to its potent antioxidant & cholesterol lowering activity.	RCT

N: Total number of patients, M: Male, F: Female, Int: Intervention, Con: Control, TNF- α : Tumour necrosis factor-alpha, LDL-C: Low-density lipoprotein cholesterol, TC: Total cholesterol, hsCRP: High-sensitivity C-reactive protein, HDL-C: High-density lipoprotein cholesterol, γ -GT: Gamma glutamyl, IL-6: Interleukin 6, NO: Nitric oxide transferase, TG: Triglycerides, miRNA: Micro-ribonucleic acid, δ -tocotrienol: Delta tocotrienol, γ -tocotrienol: Gamma tocotrienol, PDGF: Platelet-derived growth factor, MDA: Malondialdehyde, FGF-b: Fibroblast growth factor-b, TRF: Tocotrienol-rich fraction CC-60 palm carotene, NFH: Non-familial hypercholesterolemia

Discussion

Atherosclerosis, being a chronic inflammatory disorder, leads to increased deposition of plasma lipoprotein on arterial intima, resulting in hyperplasia of connective tissue,

thickening and stiffening of the arterial wall. Infiltration of lipoproteins in the arterial wall is a basic initiation step that starts an inflammatory response and promotes the development of atherosclerosis.²⁵ It is broadly considered

that healthy eating habits can have an inhibitory role to some extent in the development of atherosclerosis. Vitamins, being anti-oxidants, can stabilise atherosclerotic plaque by reducing the level of inflammatory biomarkers.²⁶

As the link of oxidative stress to ASCVD came into evidence, more clinical trials were conducted with natural anti-oxidant α TCP in the management of these diseases. A recent 30-year prospective cohort study in Finland claimed decreased cardiovascular mortality in men with increased baseline serum α TCP.²¹ Similar results were obtained by another collaborative cohort study in Japan which covers a period of 19.3 years by taking high dietary supplements of fat-soluble vitamins K, E and D, showing decreased risk of heart failure among females but not males.²⁷ Another prospective population-based study in Hong Kong, showed reduced risk of adverse cardiovascular risk outcomes by taking anti-oxidant vitamins A, C and E in combination.²⁸ But these studies had the limitations of not clearly mentioning the source regarding TCP or TCT component of vitamin E.

Regrettably, the beneficial role of α TCP in the reduction in CVD events reported in early epidemiological studies were not observed in a large number of recent trials. Increased risks of cardiovascular outcomes were observed with higher α -tocopherol intake.²⁰

Most of the studies carried out in the US and Pakistan regarding TCT's effects showed decreased inflammatory biomarkers, improved lipid profiles and total antioxidant status (TAS) and modulating miRNA expression related to CVDs, including miRNA -223, 133a, 155 and 214.^{23,24} So far, TCTs have shown no increased risk of mortality in patients as TCP has demonstrated.

The current systematic review has its limitations, as despite detailed search across multiple databases and finding more than 500 articles, the review could not find any data regarding the comparison of TCT and TCP efficacy in cardiovascular patients. Also, there was lack of conclusive evidence on the efficacy of TCT directly on different CVDs because only a few studies regarding TCT effect on hypercholesterolaemia were available. There was a lot of data available on animals and cell lines, but recent human clinical trials of TCP on dyslipidaemias, hypercholesterolaemia and atherosclerosis were not available. There was no comprehensive data available regarding the comparison of individual isomers of both TCP and TCT on CVDs. Besides, only a few dose-response studies of TCP and TCT could be found. Finally, the systematic review was registered with Prospective Register of Systematic Reviews (PROSPERO) retrospectively.²⁹

Future researchers should keep these limitations in mind, and plan prospective, double-blind RCTs on individual CVDs, like angina, MI and heart failure, and more comprehensive studies regarding the potency of individual isomers of TCT and TCP in humans. The need is to conduct forced titration design, double-blind studies as well as studies to explore the basic molecular mechanisms involved in cardioprotective activity of different isomers. A long follow-up would add great value to future studies.

Conclusion

TCTs, compared to TCPs, were found to be safe and potential candidates in improving cardiovascular health by having better anti-oxidant effects and without any reported mortality risk in the management of ASCVD patients.

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Author Contribution:

SR: Concept, design, data analysis, interpretation, agreement to be accountable for all aspects of the work.

DAK: Concept and design.

KF, MS: Final approval.

MAK: Drafting and revision.

MN: Agreement to be accountable for all aspects of the work.