SYSTEMATIC REVIEW

COMPARATIVE ANALYSIS OF BIODISPOSITION OF DIFFERENT ISOMERS OF TOCOPHEROLS

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Tocopherols are indicated as adjuvant therapy in metabolic disorders, various types of carcinomas and as neuroprotective and cardioprotective agents. Their use is limited due to poor water solubility, variable absorption and low bioavailability. This study was undertaken to compare the biodisposition or pharmacokinetic parameters of different isomers of tocopherol. This systematic review explored the possible underlying causes of poor bioavailability of tocopherols. A computerized database search was done till 11th January 2022 through Pubmed, Google Scholar, PakMediNet, and open Google Search by using MeSH keywords: pharmacokinetics, biodisposition, bioavailability and tocopherol. Boolen operators were also used to retrieve original articles like tocopherol AND bioavailability, tocopherol AND pharmacokinetics. Only original research articles that provided information about pharmacokinetics of tocopherol in healthy human volunteers were included. This systematic review was carried out following the Preferred Reporting Items for Systematic Review and Meta Analysis (PRISMA) guidelines, and 510 original research articles were retrieved from literature. After eliminating the duplicate studies, 20 articles fulfilled the eligibility criteria, 6 original articles were selected for data extraction. Pharmacokinetic parameters of α-tocopherol in terms of area under curve, time to achieve peak plasma levels, maximum plasma concentration and elimination half-life were found to be better than β, ɤ and δ isomers of tocopherols. Bioavailability of α-tocopherol was highest amongst all the isomers of tocopherols. In various clinical implications α-tocopherol may be preferred over other isomers due to its greater bioavailability for better therapeutic response.

Keywords: Absorption, Area under curve, Bioavailability, Plasma half-life, Tocopherols, Vitamin E isomers

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INTRODUCTION

Vitamin E belongs to lipid soluble compounds and exists in two forms, tocopherol and tocotrienol collectively known as tocochromanols. Tocopherols are preferred over tocotrienols as adjuvant therapy in various clinical conditions due to their relatively better permeation and bioavailability as compared to tocotrienols.[1] Tocopherols have four isomers including α, β, γ, and δ, which are highly lipophilic. Alpha and γ tocopherol are the most commonly occurring form of vitamin E and is mainly found in almonds oil, nut oils like wheat germ oil, corn oil and soybean oil.[2]

Tocopherols have chromanol ring and saturated phytyl side chain in their structure. The chromanol ring can donate a hydrogen atom to reduce free radicals thus accounts for its anti-oxidant effects. While a hydrophobic side chain allows easy permeation through cell membranes.[3] Four isomers of tocopherols differ in their structure due to variable number and position of methyl group on chromanol ring. Alpha isomer has 3 methyl groups, while β and ɤ isomers contain 2, and δ isomer has one methyl group on chromanol ring. These variable numbers and position of methyl groups accounts for their differences in extent of absorption, biotransformation and bioavailability.[4,5]

All the isomers of tocopherol are orally active agents. But they differ in absorption, biotransformation and bioavailability due to different number and positions of methyl group in their structures. Absorption of tocopherols in intestine varies from 20% to 80% due to their poor water solubility.[6] Peak plasma levels of α-tocopherols are achieved after 3–4 hours while that of ɤ and δ tocotrienol are achieved within 5 hours of ingestion.[7] Among all isoforms only α-tocopherol attains high levels in plasma and tissues due to its greater binding affinity with hepatic α-tocopherol transfer protein (αTTP) so it retains in plasma for prolong period of time to exert its pharmacological effects while other isoforms of tocopherols are rapidly metabolized and excreted in faeces.[8,9]

Tocopherols are widely used as adjuvant therapy for the treatment of metabolic disorders, diabetes mellitus, obesity atherosclerosis, Alzhiemer's disease, Parkinson's disease and various carcinomas due to their well-known antioxidant and anti-inflammatory properties.[10,11] But their therapeutic uses are limited due to variable absorption and low bioavailability. Human evidence has shown that therapeutic response of different isomers of tocopherols are highly variable amongst individuals due to variable bioavailability of

tocopherols which may be due to their poor water solubility, presence of variable content of fat in food and variable incorporation of tocopherols into miscelles involved in tocopherol absorption and metabolism.[12,13]

Pharmacokinetics of different isomers of tocopherol has not been extensively studied and to date no human data is available showing comparative analysis of pharmacokinetics of 4 isomers of tocopherols.[14] The objective of this review was to present an overview and comparison of pharmacokinetic parameters of four isomers of tocopherols in terms of area under curve (AUC), maximum plasma concentration (C_{max}), time to reach maximum plasma concentration (T_{max}) and elimination half life ($t^{1/2}$) and possible underlying factors that may cause poor bioavailability.

METHODOLOGY

Original research articles of randomized control trials having details of pharmacokinetics of any isoform of tocopherols in any dose or dosage form, administered through any route of administration published in English language until January 2022 were included in this review. *In vitro* studies, cross sectional studies, case control, case cohort studies, review articles and meta-analysis, were excluded from this systematic review. Original articles containing information about pharmacodynamics were excluded. Studies involving children and pregnant and lactating women were excluded from this systematic review.

Data base literature search was done from October 2021 till January 2022 through PubMed, Google scholar, Open Google Search and PakMediNet. Latest literature about pharmacokinetics of tocopherols was retrieved by using Medical subject headings (MeSH) key words like tocopherol, absorption, bioavailability, and plasma half-life. Boolean operators/search strings were used like tocopherol AND absorption, tocopherol AND bioavailability. Restriction was set in relation to English language and date of publication.

Selected articles were screened by first two authors in three phases before they were included for this review article following the PRISMA guidelines. In the first phase, studies that did not fulfil the inclusion criteria were excluded. In the second phase, abstracts, title and full text of original articles were screened. Data collection and extraction was performed independently by first author. Details of studies were extracted and categorized according to first author, date of publication, study design, methodology and type of tocopherol isomer taken by participants. Data about pharmacokinetics of tocopherols was collected and compiled in tables. Quality assessment of studies were performed by first two authors.

Data item or variables for which data was retrieved includes variable doses of tocopherol (independent variable) while dependent variables includes bioavailability in terms of area under curve.

Before data extraction, all information of original article was crosschecked two times to decrease the chances of potential bias. We included all studies with positive as well as negative findings to decrease the chance of bias across the studies.

RESULTS

Original articles were selected by first two authors in four steps, i.e., identification, screening, eligibility and inclusion by following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram. From literature search 490 relevant articles were identified from PUBMED, Google Scholar, PakMediNet and Open Google Search. Additional 20 articles were searched from PubMed by snowball references. Two-hundred research articles were left after excluding the duplicate articles. One-Hundred-Eighty-Five articles were also excluded due to irrelevance to our topic, different methodology and insufficient data. Twenty articles were assessed for eligibility. Out of them, 14 were excluded due to inappropriate study design, insufficient pharmacokinetic data and concomitant use of other drugs with documented interactions with tocopherols. Finally, 6 articles were eligible for data extraction to be included for this review article. Figure-1 shows PRISMA flow diagram for finally selected 6 articles.

Only randomized clinical trials were selected for this systematic review. All these studies were carried out on human volunteers. Only those original articles were selected in which pharmacokinetic parameters especially bioavailability was assessed after administering of tocopherol. All pharmacokinetic parameters were measured by using high performance liquid chromatography (HPLC).

Despite broad therapeutic efficacy of tocopherols, their implications are limited due to poor oral bioavailability which may due to their poor water solubility, variable absorption, and rapid degradation.[15] Six original articles were selected to compare pharmacokinetics of all the four isomers of tocopherols in terms of area under curve (AUC), maximum plasma concentration C_{max}, time to reach C_{max} (T_{max}) and elimination half life ($t^{1/2}$). (Tables 1–5)

A study conducted by Fairus *et al* revealed that after administration of same dose of α-tocopherol from corn oil and palm based tocotrienol rich fraction, higher plasma levels of α-tocopherol from corn oil were detected due to greater intestinal absorption as compared to tocotrienol rich fraction (TRF) because TRF is a mixture of α-tocopherol and tocotrienols and in the presence of tocotrienols absorption of α-tocopherol was decreased due to competition with the same α-tocopherol transport protein.[16] (Table-1)

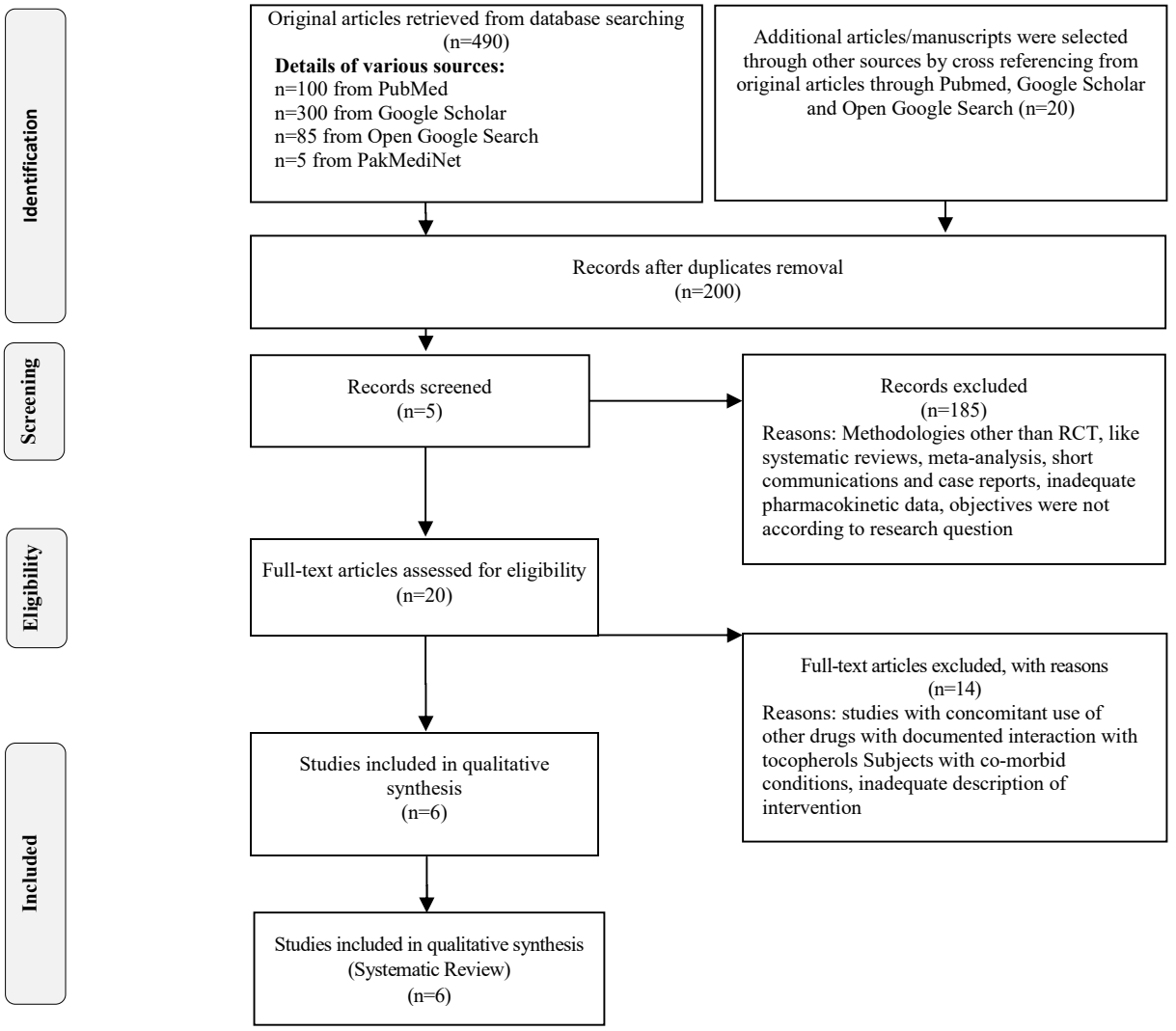

Figure-1: PRISMA flow diagram showing literature search for systematic review

A randomized cross over double blind trial conducted by Mah *et al*[17] revealed that absorption and bioavailability of α and ɤ-tocopherol was less in patients of metabolic syndrome as compared to healthy subjects due to reduced absorption and less hepatic uptake of tocopherols in patients of metabolic syndrome due to atherosclerosis. Bioavailability of α-tocopherol was higher in healthy as well as in patients of metabolic syndrome as compared to ɤ-tocopherol.[17] Results are tabulated as Table-2.

Another open label randomized study was carried out to assess the pharmacokinetic parameter of all the isomers of tocopherol by using HPLC. It was concluded that α-tocopherol has the highest bioavailability as compared to other isomers of tocopherols. Dose dependent increase in AUC and increased C_{max} was observed with variable increasing doses 125 and 250 mg of tocopherols.[18] The results are summarized in Table-3.

Consistent with these results is another randomized study that revealed that oral administration of higher doses 750 and 1,000 mg/d of tocopherols resulted in dose-dependent increase in plasma levels of all isomers. All the doses were well tolerated by healthy human volunteers. Bioavailability was highest for α-tocopherols amongst all the isomers of tocopherols.[19] Results are shown in Table-4.

In another study[20] when same doses of ɤ- and δ-tocopherol were administered, bioavailability of delta tocopherol was found to be higher. A phase 3 cross over trial was done which for the first time revealed that absorption and bioavailability of deuterium labelled intravenous α-tocopherol was much higher than deuterium labelled oral α-tocopherol on healthy human volunteers.[21] Results are summarized in Table-5.

Table-1: Comparison of pharmacokinetic parameters of four isomers of tocopherols

Study design and sample size	Methodology	Intervention with tocopherol	AUC (µmol/L)	T_{max} (hrs)	C_{max} (µmol/L)	Elimination $T^{½}$ (hrs)	Inference	Reference
Open-label randomized cross over study, n=10 (5 males and 5 females)	Participants were divided into 2 groups. One group received α-tocopherol while other group received α-tocopherol from Tocotrienol rich fraction. Therapy continued for 7 days followed by one week wash out period. Both isomers were switched over to other groups. Plasma levels of tocopherols were measured by HPLC.	α-tocopherol (537 mg).	353.52 ±30.40	8	37.8 ±3.59	10 ±2.5	Higher plasma levels were detected after α-tocopherol administration (due to greater intestinal absorption) as compared to α-tocopherol obtained from tocotrienol rich fraction. Fatty food enhanced their absorption	Fairus *et al,* 2012
		α-tocopherol from Tocotrienol rich fraction (TRF) (526 mg)	286.16 ±19.85	6	30.13 ±2.9	9 ±1.7		

Table-2: Comparison of pharmacokinetics parameters of four isomers of tocopherols

Study design and sample size	Methodology	Intervention with tocopherol (15 mg)	AUC (µmol/L)	T_{max} (hrs)	C_{max} (µmol/L)	Elimination $T^{1/2}$ (hrs)	Inference	Reference
Randomized, cross over double blind trial, n=10/group	Participants were divided into two groups. First group comprised of healthy subjects while second group comprised of patients of metabolic syndrome. Both groups received α- and ɤ-tocopherol (15 mg)	α-tocopherol (15 mg). (Healthy subjects)	106 ±7	12.4 ±0.4	2.73 ±0.18	30.6 ±1.1	Bioavailability of α- and ɤ-tocopherol was less in patients with metabolic syndrome as compared to healthy subjects due to atherosclerosis leading to reduced absorption and less hepatic uptake of tocopherols. Bioavailability of alpha tocopherol was higher in healthy and patients of metabolic syndrome as compared to ɤ-tocopherol.	Mah *et al*, 2015
		α-tocopherol (15 mg) (metabolic syndrome)	84 ±6	12 ±0.00	2.04 ±0.14	36.6 ±19		
		ɤ-tocopherol (15 mg) (healthy subjects)	18.2 ±1.1	11.7 ±0.3	0.47 ±0.03	31.4 ±1.5		
		ɤ-tocopherol (15 mg) (metabolic syndrome)	12.3 ±1.1	11.7 ±0.3	0.29 ±0.03	37.3 ±2.1		

Table-3: Comparison of Pharmacokinetics Parameters of four isomers of tocopherols

Study design and sample size	Methodology	Intervention with tocopherol	$AUC_{0-10\ h}$ (ng/ml)	T_{max} (hrs)	C_{max} (ng/nl)	Elimination $T^{1/2}$ (hrs)	Inference	Reference
Randomized control trial (n=33)	Study subjects were randomly divided into 2 groups. Group 1 received 125 mg tocopherols while group 2 received 250 mg tocopherols. Plasma levels were measured from HPLC.	δ-tocopherol (125 mg)	1971.91 ±197.62	6	341 ±62.05	3.25 ±0.36	Pharmacokinetic parameters of α-tocopherol was better than other isomers of tocopherol. Increase in dose proportionately increased the bioavailability of all isoforms of tocopherols	Qureshi *et al,* 2015
		δ-tocopherol (250 mg)	5007 ±164	4.18	756 ±57	5.22 ±0.05		
		ɤ-tocopherol (125 mg)	3564 ±126	5.46	507 ±24	2.45 ±0.99		
		ɤ-tocopherol (250 mg)	3575 ±154	3	643 ±37	5.17 ±1.06		
		β-tocopherol (125 mg)	6410 ±195	5.18	695 ±70	1.82 ±0.23		
		β-tocopherol (250 mg)	5973 ±403	3.09	949 ±126	3.97 ±0.66		
		α-tocopherol (125 mg)	14754 ±218	6	1822 ±48	5.99 ±0.69		
		α-tocopherol (250 mg)	15852 ±518	6	1931 ±92	5.91 ±0.84		

Table 4: Comparison of pharmacokinetics parameters of four isomers of tocopherols

Study design and sample size	Methodology	Intervention with tocopherols	AUC (ng/ml)	T_{max} (hrs)	C_{max} (ng/nl)	Elimination $T^{1/2}$ (hrs)	Inference	Reference
Randomized contol trial (n=6)	Healthy human volunteers were randomly divided into 2 groups. Group 1 received 750 mg tocopherols while group 2 received 1000 mg tocopherols. Plasma levels were measured by using HPLC	δ-tocopherol (750 mg)	7766 ±192	3.33 ±1.16	1353 ±79	2.44 ±0.13	Bioavailability of α-tocopherol was better than other isomers of tocopherol Increase in dose proportionately increased the bioavailability of all isoforms of tocopherols	Qureshi *et al,* 2016
		δ-tocopherol (1,000 mg)	8305 ±216	4	1472 ±71	2.58 ±0.22		
		ɤ-tocopherol (750 mg)	3066 ±187	4	547 ±11	2.92 ±0.21		
		ɤ-tocopherol (1,000 mg)	3107 ±147	4	589 ±39	2.83 ±0.19		
		β-tocopherol (750 mg)	4623 ±81	4	704 ±28	3.02 ±0.32		
		β-tocopherol (1,000 mg)	7220 ±183	4	1325 ±55.6	2.94 ±0.19		
		α-tocopherol (750 mg)	18282 ±275	3.33 ±1.16	2754 ±83	4.33 ±0.01		
		α-tocopherol (1,000 mg)	18531 ±96	6	2914 ±39	5.28 ±0.03		

Table-5: Comparison of Pharmacokinetics parameters of four isomers of tocopherols

Study design and Sample size	Methodology	Intervention with tocopherol	$AUC_{0\text{-}10\,h}$ (µM)	T_{max} (hrs)	C_{max} (ng/nl)	Elimination $T^{1/2}$ (hours)	Inference	Reference
Randomized controlled study (n=30)	There were 2 study groups. First group received ɤ- while second group received δ-tocopherol	ɤ-tocopherol	207.6	4.0 ±0.0	25.6 ±5.2	6.4 ±0.3	Bioavailability of δ-tocopherol was better than ɤ-tocopherol	Liu *et al*, 2019
		δ-tocopherol	489 ±8.1	2.7 ±0.7	8.64 ±0.20	4.3 ±0.2		
Open label randomized controlled cross over trial (n=27)	A phase 3 cross over design was used. No randomization and blinding was done. Participants were divided into two group. 1st group received deuterium labelled oral tocopherol while second group received IV deuterium labelled tocopherols.	Oral deuterium labelled α-tocopherol (30 mg/d)	147 ±17	12	4.1 ±0.4	30.02 ±2.1	First ever study which used IV α-tocopherol in healthy volunteers and established that IV absorption and bioavailability was more than oral formulation.	Teraber *et al,* 2019
		IV deuterium labelled α-tocopherol (30 mg/d)	272 ±25	8	7.1 ±0.6	32.7 ±1.4		

DISCUSSION

This systematic review for the first time compiled the results of original articles to compare the pharmacokinetics and bioavailability of different isomers of tocopherols. To date no human data was available showing comparative analysis of pharmacokinetics of four isomers of tocopherols. Our study revealed that bioavailability of α-tocopherol was highest amongst all the isomers of tocopherols.

Our results have shown that administration of equal doses of α-tocopherol from corn oil and from palm oil based tocotrienol rich fraction, led to higher plasma levels of α-tocopherol from corn oil due to its greater intestinal absorption as compared to tocotrienol rich fraction (TRF). TRF is a mixture of α-tocopherol and tocotrienols and in the presence of tocotrienols, absorption of α-tocopherol was decreased due to competition with the same α-tocopherol transport protein.[13] Author also revealed that absorption of tocopherols were greatly enhanced in the presence of fatty food.[16] Our results are in accordance with a human trial which revealed that 24-hour area under curve of tocopherol was increased two times in fed state compared with fasting state probably due to increased triglycerides and bile secretion after a high fat meal. Peak plasma levels of tocopherols are achieved earlier in healthy fed volunteers as compared to the fasting.[8] These postprandial studies indicated that food consumption greatly enhanced the absorption and hence improved the bioavailability of orally administered tocopherols.[22]

A randomized cross over double blind trial revealed that absorption and bioavailability of α- and ɤ-tocopherol was less in patients of metabolic syndrome as compared to healthy subjects due to reduced absorption and less hepatic uptake of tocopherols in patients of metabolic syndrome due to atherosclerosis of blood vessels indicating that disease conditions can affect bioavailability of tocopherols. Bioavailability of alpha tocopherol was higher in healthy as well as in patients of metabolic syndrome as compared to ɤ-tocopherol.[17] An open labelled randomized study conducted by Qureshi *et al* concluded that α-tocopherol has the highest bioavailability as compared to other isomers of tocopherols. Author suggested that better pharmacokinetic parameters of α-tocopherol may be due to its relatively increased water solubility and greater binding affinity for α-tocopherol transport protein, so it remains in plasma for prolong period of time to exert its pharmacological effects. Dose dependent increase in AUC and increased C_{max} was observed with variable increasing doses of all the isomers of tocopherols (125 mg/d and 250 mg/d).[18] These results were consistent with another randomized control trial which revealed that oral administration of still higher doses of 750 and 1,000 mg/d of tocopherols resulted in dose-dependent increase in plasma levels of all isomers. All the doses were well tolerated by healthy human volunteers. Bioavailability was highest for α-tocopherol amongst all isomers of tocopherols.[19] In contrast to these findings there was a study in which when higher doses of tocopherols were given, peak plasma concentrations did not increase proportionately So author suggested that dose is not the only determinant that affect the plasma concentrations of tocopherols rather solubility of tocopherols in intestinal fluids and emulsification by bile salts may also be involved in their absorption.[23]

In another study when equal doses of ɤ- and δ-tocopherol were administered, bioavailability of delta tocopherol was found to be higher than ɤ isomer.[20] A phase 3 cross over trial was done in which it was revealed that absorption and bioavailability of deuterium labelled intravenous α-tocopherol was much higher than deuterium labelled oral α-tocopherol on healthy human volunteers. Author also observed that fatty food greatly enhanced oral bioavailability of deuterium labelled oral α-tocopherol.[21] Consistent with our results is a randomized control trial which revealed faster rate of absorption and greater bioavailability of intravenous tocopherols (T_{max} 1 hr) as compared to oral formulation (T_{max} 4 hrs).[22]

Our study inferred that pharmacokinetic parameters and bioavailability of α-tocopherol was

highest amongst all the isomers of tocopherols followed by δ, ɤ, and β isomers. It may be due to its relatively better water solubility and greater affinity for α-tocopherol binding protein, so it retains in plasma for prolong period of time.

CONCLUSIONS

Alpha tocopherol has the highest oral bioavailability followed by δ, ɤ, and β isomers. Enhanced bioavailability of α-tocopherol may be due to due to its increased water solubility, enhanced affinity to bind with α-TPP, slow degradation and excretion. Due to better pharmacokinetic parameters and bioavailability, we recommend that α-tocopherol may be preferred to other isomers of tocopherols in various clinical implications as adjuvant therapy.

STUDY LIMITATIONS

The limitations of this study include small sample size, shortage of high quality studies, and non-assessment of baseline tocopherol levels in these studies which may be a potential cofounder for this study. We used few research engines for literature search and mainly included randomized control trials conducted on human volunteers. So we are restricted to extrapolate the outcome of this study on different populations.

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MS: Literature search, write up and drafting manuscript
DAK: Topic selection, supervising the entire write up of manuscript
KF: Data extraction and analysis, finalizing article
MN: Critical review of manuscript and assists in drafting manuscript
MAK: Assists in literature searching and data compilation
SR: Assists in data collection and extraction, compilation

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