SYSTEMATIC REVIEW

Pharmacokinetics and bioavailability of tocotrienols in healthy human volunteers: a systematic review

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Abstract

Objectives: To evaluate and compare the pharmacokinetic parameters, especially bioavailability, of annatto-based tocotrienol with palm tocotrienol-rich fraction in healthy human volunteers for better therapeutic outcome.

Method: The systematic review was conducted between April and August 2021 in accordance with the Preferred Reporting Items for Systematic Review and Meta Analysis guidelines, and comprised search on PubMed, Google Scholar, Pakmedinet and Google search engines for open-label or double-blind randomised controlled trials involving healthy human volunteers published till January 2021. Key words used included annatto-based tocotrienol, palm tocotrienol-rich fraction, absorption and bioavailability. Boolean operators were also used, like tocotrienol AND bioavailability, annatto tocotrienol AND pharmacokinetics.

Results: Of the 230 articles identified, 50(21.7%) articles met the eligibility criteria. Of them, 7(14%) were selected for data extraction and detailed analysis. Pharmacokinetic parameters of annatto-based tocotrienol were better than palm-derived tocotrienol. Oral administration of all the isomers of annatto-based tocotrienols resulted in dose-dependent increase in area under curve and plasma levels. Amongst all the isomers of annatto-based and palm-derived tocotrienol, delta isomer of annatto-based tocotrienol had the highest bioavailability with area under curve 7450±89 ng/ml, time to reach peak plasma levels 4 hours, maximum plasma concentration 1591±43 ng/nl and elimination half-life 2. 68 ±0.29 hrs. Pharmacokinetic parameters of delta isomer of annatto-based tocotrienol was greater than palm tocotrienol-rich fraction.

Conclusion: Bioavailability of annatto-based tocotrienol was better than that of palm-derived tocotrienol-rich fraction. Delta isomer of annatto-based tocotrienol had the highest bioavailability amongst all isomers of tocotrienol.

Key Words: Area under curve, Annatto-based tocotrienol, Bioavailability, Palm tocotrienol-rich fraction.

DOI: 10.47391/JPMA.6008

Submission completion date: 24-02-2022
Acceptance date: 24-08-2022

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Introduction

Tocotrienol is a fat-soluble dietary antioxidant and has four isomers alpha (α), beta (β), gamma (ɤ), and delta (δ.) Tocotrienol is mainly found in palm oil, rice bran oil, annatto seeds and barley. Palm oil and annatto seeds are the richest source of tocotrienol.[1,2] Annatto-based tocotrienol contains 90% δ tocotrienols and 10% ɤ tocotrienol. Tocotrienol-rich fraction of palm oil is a mixture of 75% tocotrienols and 25% α-tocopherol. It contains 15% α-tocotrienol, 28% ɤ-tocotrienol, 6% δ-tocotrienol and 15% α-tocopherol.[3,4]

Tocotrienols consist of a chromanol ring and the hydrophobic side chain. They differ in number and location of methyl group in hydrophilic head of 6-chromanol ring which is responsible for the presence of various isomeric forms of tocotrienols. Tocotrienols have unsaturated double bonds so they have better tissue permeation and better lipid phase anti-oxidant potency compared to tocopherols.[5,6]

Annatto-based tocotrienols and palm-derived Tocotrienol-rich supplementations are being widely used for the treatment of cardiovascular diseases, metabolic disorders, Alzhiemer's disease and various carcinomas. Recent research has proven that delta and gamma isomers of tocotrienols due to their unsaturated carbon tail have greater cardioprotective, neuroprotective, antineoplastic, antidiabetic, cholesterol lowering and antiobesity effects.[7] But human evidences have shown that therapeutic implications of tocotrienols are limited due to its variable absorption and poor bioavailability. Palm tocotrienol-rich fraction is the mixture of 75%

tocotrienol and 25% α-tocopherol. Studies have shown that presence of tocopherol prevent the absorption and tissue delivery of tocotrienols. Annatto-based tocotrienols consist of 90% δ tocotrienol and 10% ɤ tocotrienol. In plasma, δ isomer eventually gets converted into other isomers of tocotrienol and tocopherols, leading to variable and poor absorption and bioavailability of tocotrienols. Studies have suggested that inter-individual variability in tocotrienol bioavailability may also be due to presence of variable amount of fat in food, low water solubility, low affinity for α-tocopherol transport protein.[8]

Pharmacokinetic parameters and absolute bioavailability of annatto-based tocotrienols and palm oil-derived tocotrienol-rich fraction has been limited to animal models and cell cultures and human data is insufficient.[9] Systematic review and meta-analyses on pharmacokinetic parameters of these tocoterinols are scarce and comparison of bioavailability of annatto-based tocotrienol and palm tocotrienol-rich fraction is yet to be determined. The current systematic review was planned to compare the bioavailability of annatto-based tocotrienol with palm tocotrienol-rich fraction in healthy human volunteers, and to determine plasma levels of α, β, ɤ, δ tocotrienol and underlying factors which may contribute to their poor bioavailability.

Materials and Methods

The systematic review was conducted between April and August 2021 in accordance with the Preferred Reporting Items for Systematic Review and Meta Analysis (PRISMA) guidelines[10] and comprised search on PubMed, Google Scholar, Pakmedinet and Google search engines for open-label or double-blind randomised controlled trials (RCTs) involving healthy human volunteers published till January 2021. Animal studies, in vitro studies, case reports, case series, abstracts, cross-sectional studies, case-control studies, case cohort studies, review articles and meta-analysis were excluded. Healthy adults using potent cytochrome inducer or inhibitor with documented interaction with tocotrienols or taking anti-oxidants other than tocotrienol were excluded.

Key words used for the search included "Annato-based tocotrienols", "Palm oil-derived tocotrienol-rich fraction". "Absorption", "Bioavailability", "plasma half-life" and "Biotransformation". Boolean operators were used, like "Tocotrienol AND pharmacokinetics", "Tocotrienol AND bioavailability", "Tocoterinol NOT tocopherol", "Annato-based tocotrienol and pharmacokinetics", "Distribution AND tocotrienol-rich fraction".

First author screened all the relevant studies. Research articles were screened in two phases. In the first phase, studies that did not match the inclusion criteria based solely on the title were excluded. In the second phase, abstracts of the remaining studies were screened, and studies that did not meet the inclusion criteria were excluded. Details of studies were extracted and categorised with respect to first author, date of publication, sample size, country of research, study design, and type of tocotrienols used.

Data items or independent variables for which data was retrieved included variable doses of annatto-based tocotrienol and palm tocotrienol-rich fraction, while dependent variables included bioavailability, area under curve (AUC), time to reach peak plasma levels (Tmax), maximum plasma concentration (Cmax), and plasma half-life (T-1/2).

Risk of bias was reduced by including only those studies in which randomisation was done. All data items of each study were cross-checked twice to decrease chances of potential bias.

Results

Of the 230 articles identified, 50(21.7%) articles met the eligibility criteria. Of them, 7(14%) were selected for data

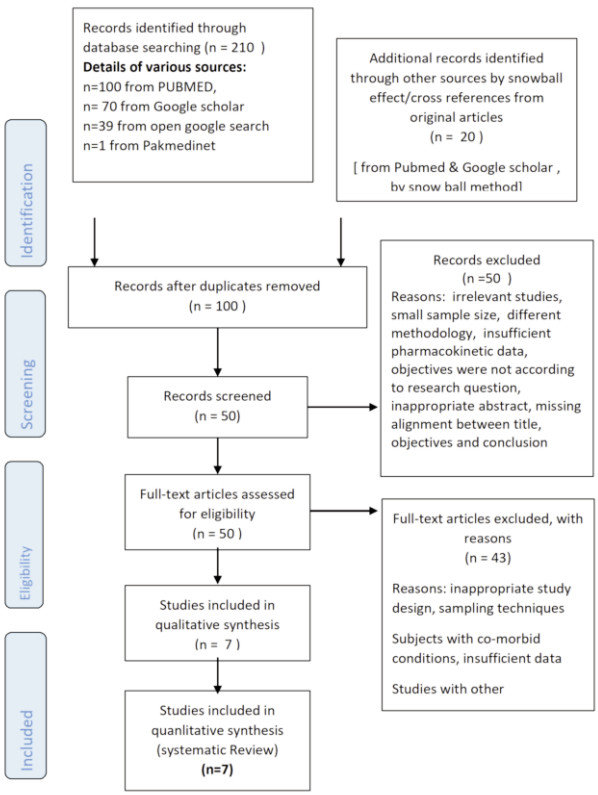

Figure: Preferred Reporting Items for Systematic Review and Meta Analysis (PRISMA) flow diagram showing literature search.

Table-1: Description of pharmacokinetics of different isomers of annatto-based tocotrienols.

s.no	Reference	Study design	Health/diseaseCondition/sample size	Methodology	Intervention withAnnatto based tocotrienol	AUC $_{0\text{-}10h}$ (ng/ml)	Tmax(hours)	Cmax(ng/nl)	Elimination T1/2 (hours)	Inference	Limitations
1	Qureshi et al., 2015.[15]	Open-label randomized clinical study	Healthy human volunteers (n=33)	Participants were randomly divided into 3 groups. Group one received 125mg ,group2 received 250 mg and group 3 received 500 mg annatto based tocotrienol.plasma levels collected at 0, 1, 2, 3, 4, 6, 8 10 hrs for estimation of pharmacokinetic parameters in HPLC	δ tocotrieno (125 mg)	2463.91±191.62	3	828±24.05	1.74±0.36	Pharmacokinetic parameters & bioavailability of δ tocotrienol was better than other isomers of tocotrienol present in annatto seeds. Dose dependent increase in AUC was observed in all isomers of tocotrienols of annatto seeds	Small sample size (n=33), Single dose treatmentBaseline tocotrienol levels were not measured
					δ tocootrienol (250 mg)	5412±274	3	1920±57	1.94±0.05		
					ϒ tocotrienol (125 mg)	1258±126	3	281±21	3.82±0.99		
					ϒtocotrienol (250 mg)	5212±244	3	833±28	2.82±0.99		
					β tocotrienol (125 mg)	1966±129	4	210±79	1.84±0.86		
					β tocotrienol (250 mg)	2077±142	3.46	280±83	1.94±0.90		
					α tocotrienol (125 mg)	869±43.95	2.73±0.65	139±11	2.62±0.72		
					α tocotrienol (250 mg)	1369±26	3	204±9.4	2.89±0.84		
2	Qureshi et al., 2016.[16]	Open-label randomized study	Healthy human volunteers n=6	Participants were randomly divided into 2 groups. Group one received 750 mg ,group 2 received 1000 mg annatto based tocotrienol.plasma levels collected at 0, 1, 2, 3, 4, 6, 8 10 hrs for estimation of pharmacokinetic parameters of tocotrienol isomers in HPLC.	δ tocotrienol (750 mg)	6620±49	4	1444±53	2.74±0.13	Pharmacokinetic parameters & bioavailability of δ tocotrienol was better than other isomers of tocotrienol present in Annatto seeds. Dose dependent increase in AUC was observed in all isomers of tocotrienols of annatto seeds.	Small sample size (n=6), Single dose treatment Baseline tocotrienol levels were not measured
					δ tocootrienol (1000 mg)	7450±89	4	1591±43	2.680.29±		
					ϒ tocotrienol (750 mg)	6262±97.55	4	1352±28	1.96±0.06		
					ϒtocotrienol (1000 mg)	7279±129	4	1386±12	2.12±0.14		
					β tocotrienol (750 mg)	1147±39	4	1185±22	1.020.±0.36		
					β tocotrienol (1000 mg)	1356±44	3	1948±66	2.11±0.03		
					α tocotrienol (750 mg)	197±1.02	3	30±1.06	3.33±.102		
					α tocotrienol (1000 mg)	547±19	4	115±3	2.15 ±0.03		

AUC: Area under curve, T-max: Time to reach peak plasma levels, C-max: Maximum plasma concentration, T-1/2: Elimination half-life.

Table-2: Description of pharmacokinetics of different isomers of palm-based tocotrienol-rich fraction.

3	Fairus et al., 2012.[17]	Open-label randomized study	Healthy human volunteers n=10	Participants received 537 mg palm based tocotrienol. All	δ tocotrienol (526 mg)	22±2.1	5	0.53±0.25 μM	5.16±0.99	Palm tocotrienol rich fraction (526 mg) contain	Small sample size Short duration of therapy Single dose
					ϒ tocotrienol	30±7.6	4	2.73±1.27μM	4.87±0.78		

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				the participants were given tocotrienol free diet for the last 7 days.plasma levels collected at 0, 1, 2, 3, 4, 6, 8 10 hrs for estimation of pharmacokinetic parameters of tocotrienol isomers in HPLC.	α tocotrieno β-tocotrienol	501±42 Not detected	5 -	4.34±1.69μM -	4.99±0.88 -	70% Tocotrienol.T3 were detected only postprandially. Amongst all isomers of T3 Higher plasma levels of α tocotrienol were detected after administration of palm oil derived TRF. Fatty food enhances their absorption.	treatment
4	Drotleff et al., 2014.[18]	Open-label randomized cross over clinical trial	Normal human volunteers (only male subjects were included) (n=7)	Participants were divided into 2 groups. One group received 450 mg barley α tocotrienol and 2nd group received 450 mg ϒ palm tocotrienol. After a wash over period group 1 received ϒ palm tocotrienol and group 2 received barley α tocotrienol.	Barley α- tocotrienol (450mg) Palm ϒ -tocotrienol (450 mg)	3280±28 1159±13	2.1±3 2.3±0.6	22.57±2,8 5.25±0.99	1.25±0.5 1.5±0.7	Barley oil formulation is rich in α-tocotrienol and has better bioavailability than palm ϒ tocotrienol formulation	Small sample size of only 7 healthy subjects Only male subjects were Included Only single dose treatment
5	Meganathan et al., 2015.[19]	Double-blind randomized cross over trials Sample size was 12 n=12	Healthy human volunteers	Study participants were randomly divided into 2 groups. Group 1 received single dose of 600 mg gamma delta tocotrienol while group 2 received 600 mg of palm tocotrienol in terms of gamma	Gamma tocotrienol of new formulation gamma delta tocotrienol(GTD)(600 mg) Delta tocotrienol of new formulation gamma delta tocotrienol(GTD)(600 mg) Gamma tocotrienol from palm oil derived TRF (600mg)	39811.7± 13336.7μg/L 12136±6417. 29μg/L 23312±9804	5.34±0.42 5.18±0.40 4.73±0.90	8406.75±3670μg/L 2693.89±962. 7μg/L 5604±1971	2.97±1.31 5.48±4.75 3.45±2.5	Bioavailability of gamma and delta isomers of new formulation of gamma delta tocotrienol (GDT)was compared with bioavailability of gamma and delta isomer from palm oil rich TRF. It was found that bioavailability of gamma isomers of new formulation was greater than	Small sample size of 12 healthy subjects Single dose treatment

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				and delta tocotrienol						delta isomer of GDT and δ and ϒ isomers of palm oil derived Tocotrienol rich fraction	
6	Springett et al., 2015.[20]	Open label randomized clinical trials	Healthyhuman volunteers Sample size is 19. n=19 duration of therapy is 13 days	Study participants were divided into 3 groups. Group 1,2,3 received 400 mg 800mg &1600mg delta tocotrienol from palm derived TRF for13 days. Blood samples were collected at 1, 2,4,6, 8 hrs for pharmacokinetic parametersin HPLC.	Delta tocotrienol from palm oil derived TRF (400 mg)	13486±9499	4	1299±790	5.3±0.5	In this dose escalation trial, graded dose response relationship was observed. increase in doses of δ-tocotrienol enhanced bioavailability in terms of AUC, Cmax. t1/2.All the doses were well tolerated by healthy human volunteers	Small sample size. Short duration of therapy. Baseline tocotrienol levels were not measured.
					Delta tocotrienol from palm oil derived TRF (800 mg)	15436±9878	5	1882±1505	5.9±0.9		
					Delta tocotrienol from palm oil derived TRF (1600 mg)	27424±16631	5	4141±2717	5.6±1.02		

S. No	Reference	Study design & sample size	Health/ disease status	Methodology	Duration of therapy	Intervention with Palm oil based tocotrienol rich fraction	AUC 0-10h (ng/ml)	Tmax(hours)	Cmax(ng/nl)	Eliminatio nT1/2 (hours)	Inference	Limitations
7	Mahipal et al., 2016.[14]	Open- label randomized control trialSample size n=36	Healthy human volunteers	36 Study participants were divided into 5 groups 1,2,3,4 &5 which received 100, 200 400,800 and 1600 mg palm TRF respectively for 14 days.serial blood samples were collected and pharmacokineticparameters were derived from HPLC	14 days	δ-tocotrienol TRF)(100mg)	1987±741	4±0.5	234±24	1.7±0.4	Study suggested dose-response relationship. Pharmacokinetic parameters in terms of AUC,Tmax, Cmax, $t_{1/2}$ were improved with increasing the doses of δ tocotrienol from palm tocotrienol rich fraction	Small sample sizeShort duration of therapy of 14daysBaseline tocotrienol levels were not measured
						δ-tocotrienol (from palm TRF) (200mg)	2345±741	6.7±1.1	346±78	2.3±0.9		
						δ-tocotrienol (from palm TRF) (400mg)	4518.7±1858.8	7.3 ± 1.2	795±220.37	4.5± 4.5		
						δ-tocotrienol (800mg)	8764.4±6419.6	6.7± 2.3	1299.9±945.2	6.0± 1.8		
						δ-tocotrienol (1600mg)	22171±16485	6.7±1.2	3746±2338	6.9±7.7		

AUC: Area under curve, T-max: Time to reach peak plasma levels, C-max: Maximum plasma concentration, T-1/2: Elimination half-life.

extraction and detailed analysis (Figure). The selected RCTs were published between 2012 and 2019, and 6(85.7%) of them were open-label and 1(14.3%) was double blind (Tables 1-7).

Annatto-based tocotrienol and palm-based tocotrienol-rich fraction is mainly administered through the oral route. Tocotrienols are lipophilic compounds so their oral bioavailability can be greatly enhanced when taken with fat-rich diet. Shen et al. reported that concentrations of tocotrienols in plasma were 0.98, 0.54 and 0.09 μM for α,

ɣ and δ tocotrienol after taking tocotrienol-rich fraction from palm oil.[11]

Tocotrienols are mainly absorbed from small intestines. Tocoterinol due to unsaturated side chain is more lipophilic, and easily permeates through cell membrane compared to tocopherol. Chiroma et al. suggested that absorption of tocotrienols depends on adequate pancreatic function, bile secretion and the formation of micelles in intestines.[12] Short half-lives of tocotrienols is due to low binding affinity for α-tocopherol transfer protein (α-TTP) which maintains plasma levels of tocotrienols. Due to their low affinity with α-TTPs, they stay in liver for prolonged period of time and subjected to excessive degradation and rapid excretion.[13]

Imaging studies with tracking system attached to tocotrienols provided evidence that tocotrienols are almost evenly distributed in body, especially in plasma, liver and adipose tissues. A study conducted on plasma distribution of tocotrienol reported that when variable oral doses of tocotrienol were administered, higher levels of tocotrienol were detected in plasma and adipose tissues, while lower levels were detected in lungs, liver, kidneys and bone marrow.[14]

Bioavailability is the active fraction of drug that reaches the systemic circulation in unchanged form and becomes available at the site of action. A study showed that pharmacokinetic limitations of tocotrienols are due to their poor solubility, presence of phytyl tail in structure, variable absorption, and rapid degradation. Alpha-tocopherol have greater binding affinity (100%) for α-TTP, 9% for α tocotrienol, 12% for δ tocotrienol and 2% for ɣ-tocotrienol. So δ tocotrienol retains in plasma for prolong period of time and has greater bioavailability, slow biotransformation compared to other isomers of tocotrienol. Human evidences have shown that δ tocorrienol has 28%, while ɣ and α isomers have 9% bioavailability. The recommended doses of tocotrienols ranges 125-1000mg/day.[11]

An open-label randomised study established all pharmacokinetic parameters and bioavailability of annatto-based isomers of tocotrienol with three different doses of 125mg/d, 250mg/d and 500mg/d. Results showed dose-dependent increase in AUC and Cmax of all isomers of annatto-based tocotrienol without any toxicity. Moreover, it was demonstrated that δ tocotrienol had the highest AUC, Cmax, Tmax and T-1/2 values compared to other isomers.[15]

Qureshi et al. analysed pharmacokinetics and bioavailability of annatto-based tocotrienols at variable doses of 750mg/d and 1000mg/d. Blood samples were quantified by high-performance liquid chromatography (HPLC). Oral administration of 750mg/d and 1000mg/d of annatto-based tocotrienols resulted in dose-dependent increase in plasma levels of all isomers of tocotrienols in terms of AUC, Tmax, Cmax, T-1/2 and time of clearance. The fed state of human volunteers greatly increased the onset and extent of absorption. Bioavailability was higher for δ tocotrienol amongst all the isomers of annatto-based tocotrienols. Both the doses were well-tolerated by healthy human volunteers, suggesting safe use of higher doses for the treatment of diabetes, Alzhimer's disease and various carcinomas.[16]

An open-label study concluded that after the administration of palm tocotrienol-rich fraction supplementation, α-tocotrienol had the highest bioavailability, while fatty food greatly enhanced the absorption of tocotrienols.[17] Drotleff et al. compared bioavailability of barley oil formulation with palm ɣ tocotrienol formulation, and observed that barley oil formulation was rich in α-tocotrienol and had relatively better absorption than other tocotrienol isomers.[18]

Maganathan et al. manufactured a novel gamma-delta-tocotrienol (GDT) formulation to enhance the bioavailability of ɣ and δ isomers for anticancer activity. They compared bioavailavility of GDT 600mg with δ and ɣ isomers of palm oil-derived tocotrienol-rich fraction, and found that this novel formulation was well-tolerated by healthy volunteers, and bioavailability of gamma tocotrienol of GDT was greater than delta tocotrienol of GDT, and δ & ɣ isomers of palm oil-derived tocotrienol-rich fraction. Both GDT and palm-based tocotrienol-rich fraction were well-tolerated and no adverse effect was observed.[19]

An open-label dose-escalation trial was conducted with variable doses (400mg, 800mg 1600mg) of δ tocotrienol obtained from palm oil tocotrienol-rich fraction. It was observed that by increasing the dose, bioavailability was enhanced proportionately. No adverse effect was observed throughout the period except that only one subject had 2 episodes of drug- related mild diarrhoea. [20]

A multiple-dose trial on healthy human volunteers suggested that multiple doses of palm oil-derived δ tocotrienol (200mg/d, 400mg/d, 800mg/d and 1600mg/d) lead to better bioavailability. All doses were well tolerated by healthy volunteers and no significant dose limiting adverse effects were observed.[14]

Tocotrienols are mainly metabolised in liver. They undergo ώ-hydroxylation by CYP3A4 and CYP4F2,

followed by β-oxidation. Final end-products of tocotrienol metabolism are carboxyethyl-hydroxychromanols (CEHC) and carboxymethylbutyl hydroxychroman (CMBHC) that are readily excreted in urine.[21, 22]

Discussion

The current systematic review demonstrated the comparison of pharmacokinetics and bioavailability of annatto-based tocotrienol and palm tocotrienol-rich fraction. The findings showed that pharmacokinetic parameters and bioavailability in terms of AUC, Tmax and Cmax of annatto-based tocotrienol was much greater than palm tocotrienol-rich fraction.

Dose is not the only factor that affect the plasma concentrations of tocotrienols rather solubility in intestinal lumen and emulsification by bile salts may be major determinants of tocotrienol absorption.[23]

Annatto seeds are the richest source of tocotrienols. A study concluded that after administration of annatto based tocotrienol supplementation, δ-tocotrienol had the highest bioavailability compared to other isomers of tocotrienols, and fatty food greatly enhanced the absorption of tocotrienols.[16] The results were in line with earlier findings.[11,15]

Conclusion

Annatto-based tocotrienols had better oral bioavailability compared to palm tocotrienol-rich fraction, and δ isomer of annatto-based tocotrienol had the highest bioavailability amongst all isomers. Annatto-based tocotrienols may be preferred over palm tocotrienol-rich supplementation in various therapeutic implications due to their better bioavailability.

Disclaimer: None.

Conflict of Interest: None.

Source of Funding: None.

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