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Human oral bioavailability and pharmacokinetics of tocotrienols from tocotrienol-rich (tocopherol-low) barley oil and palm oil formulations

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ABSTRACT

Tocotrienols are members of the vitamin E family thought to have hypocholesterolaemic, anti-cancer, and neuroprotective properties. We compared the bioavailability and pharmacokinetics of a single oral dose of 450 mg total tocotrienols from α-tocotrienol-rich barley oil and γ-tocotrienol-rich palm oil (both also low in tocopherols) in seven healthy male human subjects 0–24 h post-dose. The maximum α-tocotrienol plasma concentration (22.57 ± 2.84 mg/L, 2.1 ± 0.3 h) was significantly ($p < 0.001$) higher for barley oil than for palm oil (5.25 ± 0.99 mg/L, 2.3 ± 0.6 h). The area under the curve (0–24 h) of total (α-, β-, γ-, δ-) tocotrienols was significantly ($p < 0.001$) (2.6fold) higher in the barley oil group, where the total (0–24 h) urinary metabolites carboxyethyl-hydroxychromans (CEHC) and carboxymethylbutyl-hydroxychromans (CMBHC) were also significantly ($p < 0.05$) (1.2fold) higher (163.9 ± 19.2 μmol). Thus, due to its high proportion of α-tocotrienol, which is known for its preferential absorption, the barley oil formulation was superior to the commercial palm oil formulation. This provides support for the application of tocotrienols from barley oil in the functional foods field.

1. Introduction

The natural vitamin E family comprises eight chemically distinct molecules (Fig. 1): α-, β-, γ-, and δ-tocopherol (α-, β-, γ-, δ-T); and α-, β-, γ-, and δ-tocotrienol (α-, β-, γ-, δ-T3). These tocochromanols contain a polar chromanol head group with a long isoprenoid side chain. Depending on the nature of the isoprenoid chain, a distinction is made between tocopherols (Ts, containing a saturated phytyl chain) or tocotrienols (T3s, unsaturated geranylgeranyl chain) (Dörmann, 2007). The α-, β-, γ-, and δ-vitamers are determined by the number and position of methyl substituents in the chromanol nucleus. Results from human studies suggest that tocotrienols have biological and health effects (Aggarwal, Sundaram, Prasad, & Kannappan, 2010; Chen, Ma, Liang, Peng, & Zuo, 2011); for example, a blood cholesterol lowering effect, anticancer and tumour suppressive activities, and antioxidant properties. Furthermore, numerous animal studies indicate that α-T3 (not γ-T3) exhibits neuroprotective effects at the nanomolar level (Aggarwal et al., 2010). The uptake of T3s into

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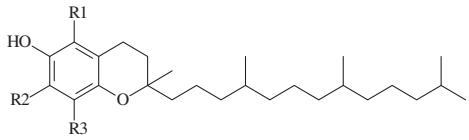
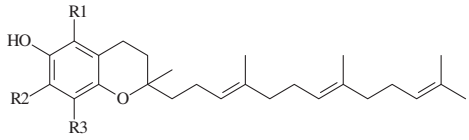
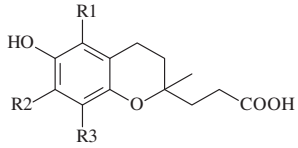


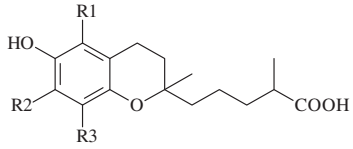
Tocopherols



Tocotrienols



CEHCs (carboxyethyl-hydroxychromans)



CMBHCs (carboxymethylbutyl-hydroxychromans)

	R1	R2	R3
α-	CH_3	CH_3	CH_3
β-	CH_3	H	CH_3
γ-	H	CH_3	CH_3
δ-	H	H	CH_3

Fig. 1 – Structures of the tocochromanols (tocopherols and tocotrienols) and the urinary tocochromanol metabolites CEHCs and CMBHCs.

membranes is faster and higher than that of Ts (Viola et al., 2012), and intramembrane mobility and collision rates with free radicals are higher; these results from *in vitro* studies may partly explain the special biological activities of T3s (Serbinova, Kagan, Han, & Packer, 1991). Moreover, the plasma pyruvate kinase activity of rats fed α-T3 was similar to that of rats fed α-T. These data may indicate that both α-T3 and α-T act as potent antioxidants *in vivo* (Ikeda et al., 2003). Furthermore, studies recently reviewed by Nakamura and Omaye (2009) also indicate that T and T3 function as non-antioxidants, which may help control reactive oxygen species (ROS) by the inhibition of ROS generating enzymes. Therefore, there is great interest in the utilisation and commercialisation of these multiple, disease-preventing functional properties in T3 dietary supplements or functional foods.

Current commercial sources of T3s are palm, rice, and annatto, and the most common source is palm oil from large-scale oil palm plantations. Crude palm (*Elaeis guineensis*) oil (total T3: 364 mg/kg) is particularly rich in γ-T3 (39% of the average total tocochromanol contents of 587 mg/kg) (McLaughlin & Weihrauch, 1979). Rice bran oil, a by-product of the rice milling industry, is a major source of γ-T3 but is low in α-T3 (total T3: 466 mg/kg, total T + T3: 860 mg/kg); and annatto seeds, which are essentially tocopherol-free, naturally contain only δ-T3 (90% of total T3, total T3: 1400 mg/kg) and γ-T3 (10% of total T3) (Aggarwal et al., 2010; Frega, Mozzon, & Bocci, 1998). T3-rich sources endemic to Europe are certain cereals like barley and rye. Barley (*Hordeum vulgare* L.) is unique because it contains all eight vitamers, with T3s contributing about 76% to the total tocochromanols and α-T3 comprising the largest proportion (47%) of the total tocochromanols (Andersson et al., 2008). Recently, dried brewer's spent grain, a barley by-product of the brewing industry available in large volumes, has been shown to be a feasible feedstuff for the production of an α-T3-rich barley oil with more than 700 mg/kg tocochromanol (Bohnsack, Ternes, Büsing, & Drotleff, 2011). Tocotrienols from barley oil can easily be isolated by molecular distillation (Liu, Shi, Posada, Kakuda, & Xue, 2008) for application in highly concentrated food supplements. In this respect, barley oil appears to be an interesting alternative to the market leader, palm oil. Barley oil may thus represent a potentially profitable innovation in the growing European functional foods market (Annunziata & Vecchio, 2011).

The bioavailability of bioactive compounds is a key determinant for their health effects. The different T3-vitamers have been shown to differ considerably in their bioavailabilities. Yap, Yuen, and Lim (2003) gave mixed T3s to rats and found that the absolute oral bioavailability of α-T3 was 28%, while that of both γ-T3 and δ-T3 was 9%. These values were estimated by dividing the total area under the plasma concentration–time curve ($AUC_{0-\infty}$) obtained from intra-gastric administration by that from the $AUC_{0-\infty}$ for intravenous administration. In humans, T3s were detected in postprandial plasma (Fairus, Nor, Cheng, & Sundram, 2006; Fairus, Nor, Cheng, & Sundram, 2012), where they were high mainly in triacylglycerol-rich particles, high-density lipoproteins (HDL), and low-density lipoprotein (LDL) after intervention with the palm T3-rich fraction (with single doses of 526 mg and 1011 mg of the palm T3-rich fraction containing about 32% α-T), although at concentrations significantly lower than α-T. The AUC_{0-8h} for plasma α-T3 was the largest of all T3s: about 60% larger than for γ-T3. T3s were not detected in plasma in the fasted state. The authors of those studies found that bio-discrimination between vitamin E forms influences the rate of T3 absorption, mainly because the affinity of α-T (100%) for the α-T transfer protein (α-TTP), which mediates secretion of vitamers from the liver into the circulating system, is much higher than that of α-T3 (12%) or other T3s. There is presumably interference of dietary α-T on T3 bioavailability, as α-T may out-compete T3s for binding at the α-TTP because of its preferential selectivity for α-T. Moreover, α-T has been reported to attenuate the cholesterol-lowering effect of T3s through activation of the HMG-CoA-reductase activity (whereas T3s have a desirable inhibiting effect) (Khor & Ng, 2000). Therefore, application of T3 preparations with