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Natural Sources of Tocotrienols: A Note on Absorption

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Abstract

Tocotrienols are the major interest of research for their various biological potentials including anticancer activity. They belong to the Vitamin E group of compounds consisting of four isomers. They are obtained from various natural sources including palm oil, rice bran oil, and annatto. However, consuming these sources through diet cannot achieve the desired therapeutic effect due to the poor absorption and distribution of the tocotrienols through gut. It is being challenging since years to increase the bioavailability of tocotrienols so that they can be efficiently taken in the diet. Being lipophilic, they can be absorbed considerably well in the presence of food. Several human and *in vivo* animal studies indicated the potential of tocotrienols in various medical conditions such as cancer, neuro protection and inflammation. Rigorous research is needed to make them available for the public consumption with proper formulating techniques.

Keywords: Tocotrienol; Vitamin E; Cancer; Absorption; Natural sources

Introduction

Since many years natural sources of foods have been studies intensively to investigate their role in prevention and treatment of many health disorders including cancer [1-5]. Caner is the most lethal disease in humans with very low survival rate [6,7] because of the cancer associated mutations in cells, and metastasis [8,9]. Vitamins and their sources have their key role as they have shown to have potent anticancer effect against various types of cancer with minimum toxicity [6,10-14]. Several *in vivo* and human studies indicated the role of Vitamin E, especially γ-tocotrienol, being the potent anti-cancer agent against variety of cancers compared to other isoforms [15-17]. Natural including palm oil and rice bran oil are the richest source of Vitamin E [18,19]. Vitamin E family of compounds comprise of eight naturally occurring compounds that can be grouped into two subgroups called tocopherols and tocotrienols [20,21]. Even the two subgroups share similar structure; tocotrienols have an unsaturated phytyl chain, a distinguishing factor between the two members of the vitamin E family (Figure 1) [21]. At the same time, tocotrienols differ from tocopherols in their biological activity and have many health benefits [22,23].

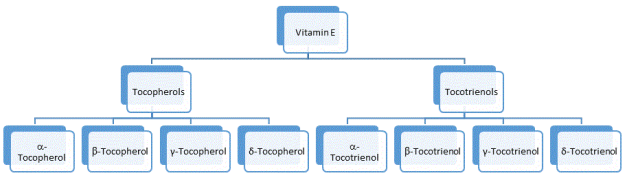

Figure 1: Sub groups of vitamin E.

The ratio of tocopherols and tocotrienols in the Vitamin E can be the important factor for determining its biological property. Tocopherols are known for their anti-oxidant property, while γ- and δ-tocotrienols are known for their anti-cancer activity [14,23]. Tocotrienols exert their anticancer activity through targeting various intracellular signaling pathways that affect cellular proliferation, differentiation, and survival [13,24,25]. *In vivo* and human studies indicated that tocotrienols when given in diet cannot be absorbed completely unlike tocopherols. However, there are some solubility and transportation issues regarding the oral administration of tocotrienols limiting their bio-availability and anti-cancer activity [26-28].

Health Benefits of Tocotrienols

Other than anticancer or specific pharmacological activity, tocotrienols along with tocopherols are also playing an important role in health and ageing [29]. In ageing, the human body organs or cells decrease in their functional capacity in time which leads to death. Several nutrients are considered to be the best dietary substances to delay process of ageing working synergistically with ageing biomarkers [29,30]. Tocotrienols also have the similar function on ageing delay. They are powerful antioxidants especially in lipid systems. Tocotrienols also have similar functions including cellular

protection, neuro protection, anti-inflammatory, and anti-osteoporotic. In a human study consisting experimental subjects have Alzheimer's disease (AD), cognitive function was tested using valid tools which shows that tocotrienol has delaying effect of AD patients [31]. In other words, serum tocotrienol levels were maintained at high levels when compared to the AD subjects. Highest tocotrienols levels were associated with almost 95% lower odds of having AD as compared with lowest tocotrienols subjects. This is possible by tocotrienol mediated prevention of cell death and further neuro degeneration [31].

In another study consisting of 232 adults, circulating tocotrienol levels were measured to associate the results with risk of developing AD [32]. The study showed that if tocotrienol levels are maintained high in blood, it reduces the risk of AD development in a 6 year follow up analysis. At the same time, there is no significant association between different tocotrienol levels and AD risk (HR for tocotrienol=0.70, 95% CI: 0.44–1.11, HR for beta-tocotrienol=0.69, 95% CI: 0.45–1.06). This can be due to the fact that the mixture of tocopherols and tocotrienols at various concentrations is necessary for the protective action and can affect cell metabolism [32].

Natural Sources of Vitamin E: Tocotrienols

Vitamin E can be obtained from various natural food sources such as leafy vegetables, nuts, fish and etc. (Figure 2). However, obtaining tocotrienols from various natural sources is challenging as they are present in only few sources at low concentrations [33,34]. Annatto is a rich natural source of 100% tocotrienol (90% of δ-tocotrienol and 10% of γ-tocotrienol), extracted from the seeds of achitoe tree (*Bixa orellana* L.) [35,36]. Palm oil is another rich source of tocotrienol (up to 0.8 g/kg) it is extracted from the fleshy orange-red mesocarp (reddish pulp) of fruits of the palm tree (*Elaeis guineensis*), consisting mainly of 46% of γ-tocotrienol and 22% of α-tocotrienol [37]. Annatto and Palm oil are used various food preparations due to their stability under high heat. Recent studies have shown that palm oil can protect against many common health problems including Alzheimer's, vitamin A deficiency, cancer, and cardiovascular diseases [11,38,39].

Cereals such as barley, oat, and rye contain small amounts of tocotrienols in them. Fruits such as Cranberries and blueberries contain 0.33 mg, and 0.08 mg of γ-tocotrienol per 100 g of edible weight respectively. Other fruit sources of tocotrienols include plum, coconut and kiwi. Tocotrienols are synthesized both as edible as well as nonedible plant products [40]. For instance, rubber latex represents a major non-food natural source of tocotrienols. Extraction of tocotrienols depends upon the natural source from which it needs to be extracted [18]. Several methods are available including solvent extraction, Supercritical Fluid Extraction (SFE), column chromatography, thin layer chromatography, normal and reversed High-performance Liquid Chromatography (HPLC), Soxhlet extraction, etc.

Figure 2: Natural sources of Tocotrienols.

We can also select the method based upon the efficiency required at the end stage, economical limits, and purity of the compound. In Soxhlet extraction procedure, the source is minced well and packed into the Soxhlet apparatus with solvent of interest such as petroleum ether. Final sample extracted will be diluted in hexane and filtered for qualitative testing using HPLC [41]. In alternative way, tocotrienols can be isolated in saponification method. This method involves use of alkaline digestion to extract unsaponifiable elements with hexane as solvent. Saponification of the sample is carried out at 60°C for 20 min [42]. Another way of extraction is the chromatography technique in which various ratios of solvents is used to separate tocotrienols from the crude constituents of the natural source [43].

Absorption and Disposition

Vitamin E group of compounds are lipophilic nature. Hence their absorption in the intestine depends upon the secretion of bile and transporters such as α-tocopherol transfer protein (α-TTP). Unless properly absorbed, they cannot reach therapeutic levels in the body to exert their anticancer activity. Even though γ- and δ- tocotrienols are potent anti-cancer agents *in vitro*, it is challenging to see their activity *in vivo*. This is because of their poor absorption and bio-availability limitations [44-46].

Similar to any other fatty substances, efficient absorption of tocotrienols can be dependent upon presence of food in intestine [47]. *In vivo* studies showed that the presence of food greatly increased absorption of tocotrienols from gut compared to fasted state [47]. However, absorption potential of tocopherols and tocotrienols are not same, due to their structure and further binding variations to the transporters in the gut. Moreover concentration levels of tocotrienols in plasma when given in fasted state are negligible, with exception of δ-tocotrienol as its concentration is doubled in platelets. Moreover, presence of food in gut favors the extent of absorption of different isomers of tocotrienols to reach maximum concentrations in plasma but does not affect the rate at which they are absorbed [26].

In separate set of studies, isolated segments of rat jejunum and ileum were perfused with various concentrations of γ-tocotrienol [44]. They have found that intestinal permeability of γ-tocotrienol decreased at concentration more than 25 µM indicating that the intestinal uptake of the same is saturable and carrier mediated process. They also suggested that Niemann-Pick C1-like 1 (NPC1L1) transporter is partly responsible for intestinal uptake of γ-tocotrienol. After absorption from intestine, γ-tocotrienol is secreted into lymph where it is incorporated into triglyceride-rich chylomicrons and some part is transported to the adipose tissue [47].

In Vivo Studies

Several *in vitro* and *in vivo* studies indicated the potential of tocotrienols against different cancer types. Tocotrienols showed significant *in vivo* anticancer activity in breast cancer, pancreatic cancer and melanoma. Their anticancer activity is mediated by apoptosis, autophagy, and NFkB mediated pathways [48-52].

Few studies were also conducted to make semi synthetic derivatives of tocotrienols to make their anticancer activity enhanced in mouse model of breast cancer [11,15]. For this, γ and δ tocotrienols were subjected to Mannich based reactions to prepare oxazine derivatives. The derived semisynthetic derivatives displayed enhanced anticancer activity *in vivo* with lower IC50 values compared to their parent compounds. Further they have also shown to be having anti hypoxic activity. Similar to their parent compounds, oxazine derivatives display their pharmacological activity by inhibiting the PI3K activity and further reducing the levels of phosphorylated Akt. Also they have inhibited the activation of NFkB pathway which is essential in generation of inflammation to support aggression and further metastasis [11,15].

In a recent epidemiological study which was conducted as a joint project between the national public health of Finland and the US national cancer institute showed that Finnish male smokers (the study was conducted on 29,133 recruited patients) between 50-69 years, and 1,732 were diagnosed with incident prostate cancer from 1985 to 2004. In this study, the dietary intake of tocopherol and tocotrienol were not directly related to prostate cancer risk or subgroup of intervention, follow-up period, or disease stage, with the exception of a significant inverse association between γ-Tocotrienol and advanced prostate cancer [53]. Tocotrienol is currently in phase I clinical trials as a chemotherapeutic agent against prostate cancer, and the preliminary results showed that it is well tolerated at doses up to 800 mg daily [54].

Besides potent anticancer activity, tocotrienols are so far tested positive with various diseases and disorders including Alzheimer's disease [55], neurotoxicity suppressive action, Parkinson's disease [56], osteoporosis and immune modulatory conditions [57].

Conclusion

Being the major biological activity regulators, Tocotrienols exert various activities such as anticancer, neuroprotection, radio protection, lipid lowering, and anti-inflammatory. Reaching the biological active concentrations is critical for Tocotrienols. Instability of the bioavailability tocotrienols is also the major concern which is limiting its usage in the medicine. Tocotrienols have multiple targets in cancer and can affect progression of cancer at every step. Considering the potential benefits of Tocotrienols, it is very important for rigorous studies to be conducted for usage. Therapeutic efficacy can be achieved by properly formulating the tocotrienols.

Conflict of Interest

Authors do not have any conflict of interest to declare.

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