Recent Advancements of Tocotrienols in Human Studies
Md. Imtiazul Kabir*
Department of Pharmacy, International Islamic University Chittagong, Bangladesh

*Corresponding author
Md. Imtiazul Kabir

Abstract: Vitamin E group of vitamins consist of varying proportions of tocotrienols based upon the natural sources. The major health benefits are associated by the tocotrienols while their isomers, tocopherols, exert antioxidant properties. The two subgroups of vitamin E share many distinct biological activities. In vitro and in vivo mice studies suggested that tocotrienols are critical in mediating anticancer, anti-inflammatory, lipid lowering, radio protection and neuro protection functions. Numerous human studies showed the evidence that tocotrienols can be supplemented to reach high concentrations in whole blood but desired pharmacological activity is questionable. Bioavailability and further bio distribution depends upon the food in stomach, health condition of the patient and other metabolizing and excretion parameters. In this current review, we have a discussion about few human studies that were conducted to show the value of tocotrienol supplementation in cancer prevention and treatment.

Keywords: Tocotrienols, cancer, human studies, palm oil, and dietary supplementation.

INTRODUCTION
Vitamin E is evident to having powerful antioxidant property since decades mediated by its tocopherol isomer components [1]. However, later it was found that Vitamin E not only comprises of tocopherols but also contains tocotrienols which share entire different set of pharmacological or biological activities. Tocopherols are the saturated forms and tocotrienols are unsaturated forms of vitamin E [2, 3]. Tocotrienols consist of isoprenoid side chain which is also the distinguishing feature between two sub groups of vitamin E. Tocotrienols occur in 4 isoforms known as α, β, γ, and δ - tocotrienols which differ from each other based upon their degree and position of methylation on chromane ring [4]. Amon the four isomers γ - and δ - tocotrienols are well studied as anticancer molecules compared to the other tocotrienols and tocopherols [5-8]. At the same time, the natural sources of tocotrienols also contain different proportions of tocotrienols in them, Palm oil and Annatto seeds being the most abundant source tocotrienols [9, 10].

When tocotrienols were given by different routes of administration such as oral, i.p. and intra muscular, it was found that oral route of absorption for tocotrienols was incomplete [11, 12]. As tocotrienols are lipophilic in nature, they tend to concentrate more in fatty areas when given through i.p. and intra muscular routes. Hence they are negligible in terms of absorption and targeting for better anticancer activity. However, α-tocotrienol is having comparatively higher (28%) bioavailability to that of other isomers of tocotrienols [11]. Tocotrienols display their anticancer activities in vitro and in vivo mouse models of cancer mediated by apoptosis, autophagy, anti-hypoxic, NFkB mediated and Akt suppressive pathways [5, 13, 14].
Physiological or therapeutic concentrations of tocotrienols in blood can be achieved by supplementing the same in diet [11, 15, 16]. Hence there is a better probability of cancer prevention or cancer treatment available with tocotrienols. The hindering factor in the tocotrienol supplementation is their limited absorption from the gut and high variations in disposition or metabolism [16]. Numerous studies were already conducted to estimate tocotrienol absorption and further estimate PK parameters for developing better dosage model. Some group of researchers also tried to increase their in vivo anticancer activity by alternative forms of formulation, different routes of administration, and by use of semi synthetic derivatives [17]. All the studies showed encouraging results by exerting better in vivo anti-cancer activity with minimal or no significant toxicity in mouse models of cancer. Human studies were also conducted to estimate the PK parameters or oral tocotrienol dietary importance in cancer and other disease models [18-21]. Alternative forms of drug delivery for sustained and prolonged release of tocotrienols can be developed for proper therapeutic applications as these type formulations shown promising in other conditions [22-25].

Oral supplementation of tocotrienols have been shown to exert anticancer activity against various cancer types in mice studies. At the same time, achieving therapeutic concentrations in blood and target regions is not always possible due to their fast metabolism and excretion. For better understanding these characteristics, the current state of knowledge on tocotrienols focused more on advancing their research on human subjects. As no review is available focusing on human research data on tocotrienol, in this review we focus on available tocotrienol human studies.

**Tocotrienols in pancreatic Cancer**

Pancreatic cancer is the most lethal cancer as it does not have any potential drug for targeting. Few of
the chemo prevention agents are in the early phase clinical trials as of now. Hence, pancreatic ductal adenocarcinoma is being major research interest [26, 27]. δ-Tocotrienol has shown significant anticancer activity in vitro on pancreatic cell lines. However, it is facing bioavailability and PK issues. In a recent preoperative clinical trial study, δ-Tocotrienol was investigated in human subjects with pancreatic ductal neoplasia to investigate its safety, tolerability and PK parameters [28]. The main objective of this study is to implement dose escalation trial for δ-Tocotrienol for determining its biological activity in human which can be useful for future drug development. This study was a single-center, open label, dose escalation phase I trial in patients with presumptive premalignant or malignant pancreatic neoplasms. Patients were administered with δ-Tocotrienol encapsulated soft gels twice a day for 13 consecutive days before performing the surgery. As δ-Tocotrienol does not have dose limiting toxicity, the group has escalated the drug dose to 3200 mg daily. According to their findings, the drug does not have any significant tolerance issues at any dose and does not have any toxicity proving it to be very safe to be given to patients. Considering the PK parameters, as expected, there is significant interpatient variation in the PK parameters even when the meal consumption was standardized. This is because of unknown factors that regulate metabolism and circulation of the vitamins in the body. The calculated PK parameters are as follows. T_{max} was 5.6±2.1 h and half-life was 3.8±1.8 h. For patients treated at ≥400mg daily, mean C_{max} was 2111±1940 ng/mL or 5.32±4.89 μM. The plasma concentration and AUC levels were matching with previous mice studies. Following, they have also measured the biological activity of δ-Tocotrienol in treated and untreated patients to see if any drug related activity can be measured by means of caspase-3 activity which is the marker for apoptosis in cancer cells in this case. Interestingly, they found that the caspase-3 levels are significantly higher in treated patients’ tumor samples compared to that of untreated patients and also compared to that of normal tissues samples from same treated patients. However, there are few patients which were treated even with higher doses did not show any significant increase in caspase-3 activity which can be attributed to the heterogeneity of patients [28].

**Tocotrienols in the End stage Liver Disease model**

Tocotrienol and tocopherol concentrations in vital tissues of human body were calculated after oral supplementation in eight experimental subjects [29]. Participants were given 12 weeks of oral supplementation and further skin and blood vitamin E concentrations were estimated. The supplementation tocotrienol was 400 mg daily. Daily supplementation tocotrienol increased its blood levels significantly compared with the non-supplemented group of subjects. In a similar fashion, the skin of supplemented subjects has high levels of tocotrienol content after continuous oral supplementation which was not seen in the control group. Observations also reveal that during the initial 6 weeks, tocopherol levels in the whole blood were also increased in tocotrienol supplemented group but not in skin samples. Being lipophilic tocotrienol deposition was observed also in adipose tissue of abdomen. The increased tocotrienol content in abdominal adipose tissue is much higher in supplemented group compared to the level of increase in whole blood and skin [29]. The similar increase levels were also observed in brain tissues where the tocotrienol was proven to be having neuroprotective function in separate studies by other group of researchers.

**Immune protection function of Palm oil**

Generation of free radicals is one of the main aspects to affect tissue health [30]. Smoking causes severe damage to the vital organs of the human body by production of free radicals. Vitamin E supplementation can be the better choice in this case because of its antioxidant properties. In a recent study smokers and non-smokers were subjected to palm oil supplementation [31, 32]. Palm oil consists of high concentrations of tocotrienols and tocopherols, i.e. 60% and 40% respectively. In the randomized single blind placebo controlled studies consisting of over 100 human subjects including smokers and non-smokers, palm oil was supplemented with the form of a capsule. Blood was drawn for lymphocyte transformation test and T cell profile. Similar to other research findings, tocopherol levels were high in both the smokers and non-smokers group of subjects compared to the tocotrienols during the treatment course. At the same time, there is no significant different in lymphocyte proliferation tests. However, smokers and non-smokers differ from each other in terms of WBC counts which were not affected by oral palm oil supplementation. Even the vitamin E supplementation increased the blood levels of tocopherols and tocotrienols, the desired pharmacological affect was not observed evident by any significant differences in CD4+ and CD8+ T cell counts. This study shows the important difference in tocotrienol physiological levels and desired pharmacological activity [31].

**Tocotrienol localization in breast cancer patients**

Breast cancer is most fatal disease affecting many women all around the globe [33-35]. Approximately one million women get affected by breast cancer worldwide. Significant number of chemotherapeutic agents, radiation therapy and surgical procedures are available for treating breast cancer [36, 37]. Scientists are trying to develop treatment model with the help of natural sources including tocotrienols in breast cancer [38]. Tocopherols and tocotrienols tend to concentrate in the breast adipose tissue. To investigate the effect of tocotrienols in breast cancer, adipose tissue concentrations of tocopherols and tocotrienols would provide insight. In a recent human study, women who consume palm oil on a daily basis

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were investigated [20]. Because palm oil is the rich source for tocopherols and tocotrienols. The human subjects had either benign or malignant breast tumors. The results indicated that benign tumor bearing women had lower levels of tocopherols and tocotrienols compared to that of adipose tissue from malignant tumor bearing women [20].

**Tocotrienols in prostate cancer**

Importance of Vitamin E in prostate cancer was estimated in a large human trial, α -Tocopherol, β -Carotene Cancer Prevention (ATBC) Study. This was a randomized, double-blind, placebo-controlled, primary prevention trial to determine whether daily supplementation with α -tocopherol, β -carotene, or both would reduce the incidence of lung or other cancers among male smokers. A total of 29, 133 smokers were participated in this study. They were given oral supplementation with α -tocopherol or β -carotene or placebo for a period of 5-8 years. The experimental subjects were assessed for prostate cancer occurrence by diagnostic tests, histopathological studies and also performed staging analysis on them [21]. According to the results, it was found that men that are having high serum tocopherol levels were younger consisting of high body mass index. They also showed less tendency to smoking and benign prostatic hyperplasia. They also tend to intake more tocotrienols, tocopherols and fats evident by higher serum cholesterol levels. At the same time Prostate cancer risk was not related to α -tocopherol intake. Risk was also unrelated to intake of other dietary tocopherols and tocotrienols. Serum α -tocopherol levels and prostate cancer risk were inversely related [21].

**CONCLUSION**

Considerable amount of research is being conducted in the field of tocotrienols or tocopherols to show that physiological concentrations of the same can be achieved by dietary or oral supplementation. It is still critical to investigate if the achieved high concentration of the tocotrienols in blood is sufficient to perform anticancer activity. Because the specific function requires adequate levels at the site of interest. Hence bioavailability is not the only determining factor to analyze pharmacological action. Further human studies and better models are needed to make them available to the market so that it can be a vital impact on public health.

**Conflict of interest**

Authors do not have any conflict of interest to declare.

**REFERENCES**


