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Enhanced Bioavailability and Anticancer Activity of Vitamin Analogs

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Abstract

There is increased evidence to show that dietary supplementation of vitamins contributes to cancer prevention and also therapy. This paper explains the anticancer activity of few vitamins and the necessity of preparing their analogs to enhance their bioavailability. While the vitamin supplementation is needed in various health disorders, over supplementation of the same may not be effective due to failure to reach over maximal concentrations in the body. Vitamin mediated anticancer activities include cell cycle progression inhibition, targeting cell survival, inducing autophagy or apoptosis, inhibiting hypoxia, eradication of oxygen free radicals and immune modulation. As the in vitro data seems sufficient to support vitamin biological effects, advanced research is needed to support their in vivo activity and long-term treatment.

Keywords: Vitamin; Bioavailability; Tocotrienols; Cancer

Introduction

Being lipophilic, tocotrienol sub group of Vitamin E compounds face difficulties in reaching optimum concentration in blood and further at target site [1,2]. This is because of poor water solubility that is limiting their absorption via gut. Further, they are metabolized rapidly resulting in excretion in urine [3,4]. In order to enhance their bioavailability and natural limitations, they were subjected to synthesis of derivatives [5-7].

The active form of vitamin D3, 1, 25-dihydroxy vitamin D3 has many functional roles including cell growth regulation, differentiation, proliferation, apoptosis and immune responses [8-10]. But, it can be given directly to the patient due to problems arising of hypercalcaemic side-effects at pharmacological doses [11,12]. This leads to calcium deposition in various organs. Hence analogs were prepared for vitamin D3 that has minimal side effects. These analogs can be used in cancer and other inflammatory diseases [13-15].

Vitamin K is also known for its anticancer activity [16]. Initially it was known for its nutritional activities that mediate clotting mechanisms in human beings [17,18]. However, vitamin K1, K2 and K3 were shown anticancer potential [19]. Research evidence is available to show the anticancer activity of vitamin K mediated by acting on tyrosine kinases and phosphatases, modulating various transcription factors such as Myc and Fos [16].

As the natural compounds have difficulty in achieving pharmacological concentrations in blood, numerous nano formulations, sustained release dosage forms, targeting delivery and other approaches need to be used. They have been shown significant efficiency in cancer and also in other forms of diseases [20-25]. Formulation type can alter their biological activity in favor of cancer treatment [26-29].

Intake of Vitamins and Cancer Risk

Early research is available, where scientists studied the correlation between intake of vitamins in diet and women breast cancer risk [30]. The analysis was conducted in a total of 121, 700 women in multiple regions. The study participants were provided with a questionnaire. In that they have to answer questions regarding their menopausal status, suspected risk of cancer and cardiovascular diseases, parity and any known risk factors regarding cancer or other diseases. They were also asked about their diet to estimate the impact of dietary constituents in cancer occurrence. The diet was calculated to measure their vitamin content, apart from calculating any multivitamin supplements they have been taking. Vitamin A intake had inverse relation with the breast cancer incidence. At the same time, there was no inverse relation between vitamin C and E to the breast cancer incidence. This can be because of failure to reach therapeutic levels in the body. Moreover, when the dietary vitamin A levels are sufficient enough, the separate supplementation of the same does not have any significant effect on breast cancer risk [30,31].

Vitamin D Analogs

To overcome the limitations associated with vitamin D ($1,25(OH)2D_3$) mediated *in vivo* anticancer activity, the analogs of vitamin D were tested for their anti-proliferative activity [32]. *In vitro* metabolic activity was calculated for the vitamin D analogs by incubating them with microsomal proteins. Liver microsomes from different species such as human, mouse, rat, dog and monkey were used in the study to see the variations of activity. Results indicated that $20S(OH)D_3$ and $20R(OH)D_3$ both have good metabolic stability irrespective of variations between them against multi species microsomes. The half-life for $20S(OH)D_3$ was 50 min, and $20R(OH)D_3$ was just 30 min. When compared with in the species, the human microsomes were favorable in terms of half-life with a value of 30-60 min. As the main purpose of the study is to lower the *in vivo* toxicity of hypercalcemia, mice studies were conducted. The two analogs were given to mice in intra peritoneal route for three weeks ant fixed doses. Following, blood chemistry and pathological analysis were conducted in them. Organs were separated after the conclusions of experiment and fixed on slides for analysis. Even at high dose of 60 µg/kg, the analogs of vitamin D did not exert any hypercalcemia unlike their parent compounds which are known for their hypercalcemic affects [32]. At the same time, the mice lost body weight in parent compound treated group but not in the analogs treated group and control group confirming the safety of the analogs *in vivo*.

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Liver injury or damage markers including alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, and cholesterol were tested revealing no analogs treatment associated unwanted toxic effects. Histological analysis indicated no calcification in analogs treated group of mice organs including liver, heart and kidney. Other than toxicity studies, anti-proliferative studies showed similar or higher effect of analogs compared to their parent compounds. Analogs, $20S(OH)D_3$ and $20R(OH)D_3$, also translocated the vitamin D receptor (VDR) to the nucleus from cytoplasm which can be effective to make gene regulation mediated anti-proliferative activity [32].

Oxazine Derivatives of Tocotrienols

While parent compounds g- and d-Tocotrienols do not have significant *in vivo* anticancer activity in mouse model of mammary tumor, their oxazine derivatives were shown promising results [26]. Subjecting the chromane ring of parent tocotrienols to the electrophilic substitution reactions, namely, Mannich and Lederer-Manasse procedures resulted in 42 new products. These included the 3,4-dihydro-1,3-oxazines 3-29 and 35-44, Mannich bases 30-31, and the hydroxymethyl analogs 32-34 [33].

After the oxazine derivatives of g- and d- tocotrienols were prepared, they were tested on +SA cell lines. These are estrogen receptor independent mammary tumor cell lines that were derived from spontaneous adenocarcinoma of BALB/c mice [34]. The cells were treated with oxazine derivatives, compound 26, 31, 39, 40 and 44, for 4 days period to measure cell viability and estimate further anticancer activity. From the results, it is clear that IC50 values of the oxazine derivatives was similar or lower to that of their respective parent compounds [33]. Ensuring the *in vitro* anticancer activity led to the formulation of nanoemulsions with them. Nano emulsions were prepared by various concentrations of phospholipids and hydrophilic surfactants. Aqueous and lipophilic phase were prepared separately and passed through homogenizer to get the emulsions. They were tested for droplet size and size distribution using zeta potential, and microscopic studies. Parent compounds were also subjected to nanoemulsions preparation along with the oxazine derivatives. Following, mammary tumor was developed in the mice and started the treatment with nanoemulsions. Even the IC50 values for *in vitro* treatment were similar to their parent compounds, all the oxazine derivatives showed significant tumor growth delay compared to their parent compounds in 11-day treatment period. Tumors were isolated at the end and protein analysis revealed that, g- and d-tocotrienols mediated decrease in tumor growth was due to lowering of cell cycle regulatory proteins cyclin D1, CDK2, CDK4 and CDK6 [33]. However, this decrease was not very significant compared to the a-tocopherol containing nanoemulsions. At the same time, oxazine derivative containing nanoemulsions resulted in significant decrease in the cell cycle progression proteins. Moreover, their anticancer activity was mediated by decreased phosphorylation of cell survival protein Akt and inflammatory mediator, NFkB. Moreover, compound 44 that is derivative of d-tocotrienol showed antihypoxic activity *in vitro* and *in vivo* [35].

Conclusion

Natural compounds in colon cancer migration

In a recent study, a total of 75 compounds including alkaloids, phenylpropanoids, flavonoids, steroids and terpenoids were tested for their anticancer activity against 26-L5 cells that are murine adenocarcinoma cell line having high liver metastatic potential [36]. Tumor metastasis leads to the death of patient due to poor response to the treatment. Metastasis greatly changes the genotype of the cancer cells due to multiple mutations leading to more aggressive form [37-41]. It is not easy to track the metastatic cells during the process and further making it difficult to target. However, 23 of the 75 compounds that were tested in this research showed potent anti-migratory activity against the highly metastatic colon cancer cells. Five compounds, evodiamine, corydaline, papaverine, magnolol, and kaempferol, had lower IC50 values in inhibiting the migration but had higher IC50 in regard to the proliferation inhibition. Evodiamine was the most potent with IC50 of 1.25 ug/mL. When compared with the standard chemotherapy drug, Paclitaxel, Evodiamine also showed dose dependent effect on migration inhibition [36].

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