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Effect of Tocotrienols isomers on the Viability of Oral Cancer Cells (ORL-48): An MTT Assay Study

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ABSTRACT

Objectives: This study aimed to conduct an *in vitro* investigation to evaluate the viability of tocotrienol isomers (α, β, γ, δ) on human oral squamous cell carcinoma (OSCC), specifically targeting the ORL-48 cell line, using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay.

Methods: The MTT assay is a widely used colorimetric assay for measuring the cytotoxic effects of potential medicinal or active compounds. Technical triplicates were employed in this study to ensure the reliability and reproducibility of the results.

Results: Among the tocotrienol isomers tested, γ-tocotrienol demonstrated significant viability inhibition, with an IC_{50} of 5.2 ± 1.4 µg/mL on the ORL-48 cell line. In contrast, the IC_{50} values for α, β, and δ tocotrienols were not determinable (ND), as their percentage of inhibition was less than 50%, indicating a lack of significant effect at the tested concentrations.

Conclusions: These findings suggest that γ-tocotrienol has potential as an antiproliferative agent against oral cancer cells (ORL-48). Its significant activity underscores the need for further functional studies to better understand its mechanisms of action and potential therapeutic roles in future cancer treatment. Future research should focus on elucidating the molecular pathways effects of γ-tocotrienol and exploring its.

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1. INTRODUCTION

In 2022, there were approximately 20 million new cancer cases globally and about 9.7 million deaths due to cancer. By 2050, the annual number of new cancer cases is expected to reach 35 million due to the aging and growth of the population, assuming current incidence rates remain unchanged (American Cancer Society, 2024; International Agency for Research on Cancer, 2024). In Malaysia, oral cancer ranks among the top 20 most common cancers, with a five-year prevalence of 2,199 cases. Alarmingly, the incidence is expected to double by 2040 due to population growth and age-specific trends (Ferlay et al., 2021).

Despite advancements in technology for the diagnosis and treatment of cancer, the lack of effective drugs and sensitive diagnostic methods means cancer remains one of the deadliest diseases worldwide. Current treatments, including surgery, radiation, and chemotherapy, are often inadequate, costly, and associated with significant post-treatment morbidity and mortality due to recurrences (Sailo et al., 2018). Therefore, discovering a novel therapy that is safe, effective, and affordable are indispensable for the better care of this disease. Nutraceutical is one of the important resorts for scientists and researchers in finding cure for cancer (Sailo et al., 2018). Dietary supplements like fruits and vegetables are rich in phytochemicals and provide a variety of antioxidants such as vitamin A, C, E. Tomatoes (lycopene), Turmeric (curcumin), and some medicinal mushrooms are also used as chemo-preventive and chemotherapeutic agents (Aggarwal et al., 2019).

Tocotrienols (T3), the unsaturated vitamin E analogues, is easily accessible from the nature such as palm oil, rice bran and annatto seeds. It exists in different isoforms such as alpha (α), beta (β), gamma (γ) and delta (δ). The abundance of α-tocopherol as antioxidant in the human body caused an oversight to the properties of tocotrienols that are often not exhibited by tocopherols (Sailo et al., 2018). This is because only 3% of the studies are conducted for tocotrienols isoforms. Studies showed that tocotrienols were more effective than α-tocopherol (Sailo et al., 2018; Aggarwal et al., 2019). In 2010, it was discovered that α-T3 and γ-T3 were more potent than δ-T3 and α-tocopherol in impeding proliferation in human cervical cancer HeLa cells by up-regulation of interleukin 6 (IL-6) and down-regulation of cyclin D3, p16, and CDK6 expression (Sailo et al., 2018; Aggarwal et al., 2019).

Considering the fact that studies showed role of tocotrienol is not amplified by the presence of tocopherol but rather aggravates it. Therefore, manufacturers should formulate with δ- and γ-tocotrienols, with the least amount or none of α -tocopherol possible in order to fully appreciate the wonders of tocotrienol (Tan, 2017). Substantial research over the past several years has proven that tocotrienols effectively prevent/inhibit the growth of different types of cancers (Wu & Ng, 2010; Abubakar et al., 2017; Husain et al., 2017; Rajasinghe et al., 2018; Narimah et al., 2009; Kani et al., 2013). Furthermore, rising lines of evidence verified that tocotrienols can sensitize cancer cells to chemotherapeutic agents (Sailo et al., 2018). Delivering tocotrienols combined with chemotherapeutic agents can show notable inhibition of growth effects via check-point regulators (Aggarwal et al., 2019). Tocotrienols are chosen for various cancer studies due to their multitargeted actions against cancer cells, including inducing apoptosis, inhibiting angiogenesis, and preventing metastasis. These natural compounds can promote cancer cell death through apoptosis, a mechanism by which they exhibit anti-cancer activity. Specifically, γ-tocotrienol has been shown to trigger significant apoptosis in tumour cells by downregulating the expression of several oncogenic genes (Musa, 2021). However, it is important to acknowledge that cancer cells from different tissues may respond differently to the same treatment due to their unique genetic and molecular profiles. For instance, while tocotrienols have shown promising effects in other cancer types, the response in oral cancer cells might be distinct due to variations in cell signaling, resistance mechanisms, or differences in the tumour microenvironment.

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To the best of our knowledge, the study of tocotrienol isomers on specifically on ORL-48 has never been reported elsewhere. Therefore, this study aimed to investigate the viability of α, β, γ, δ tocotrienols on ORL-48.

2. Materials And Methods

2.1 Preparation of cell lines

The OSCC cell lines, ORL-48 obtained from Cancer Research Institute and Foundation, Subang Jaya Medical Centre (CARIF, Malaysia) was developed from an Asian female patient with gum tumour. The cell line was grown using complete culture media–DMEM (Dulbecco's modified Eagle medium) F-12 medium (Gibco, Gaithersburg, MD, USA) supplemented with 10% Foetal Bovine Serum (FBS) (Gibco, USA / Capricorn, Germany) and 1% penicillin (Gibco, USA / Capricorn, Germany) and streptomycin (Gibco, USA / Capricorn, Germany). The cell line was incubated at 37°C with 5% CO_2 (Thermo Forma, Gaithersburg, MD, USA) for approximately three to four days to reach 70–80% confluency.

2.2 Preparation of Test Compounds

The material was in viscous liquid form and required dilution to the desired concentrations for used in the experiments. Tocotrienol (DavosLife, Malaysia) compounds were diluted in <0.1% dimethyl sulfoxide (DMSO) (Thermofisher, USA). Different tocotrienols concentrations of 0.1, 1.0, 2.5, 5.0, 7.5 and 10.0 µg/ml were prepared using DMEM F-12 supplemented with 10% fetal bovine serum 2 mL of penicillin-streptomycin.

2.3 Cells counting (haemocytometer)

A haemocytometer was used to determine the number of viable and non-viable cells. 10 µl of ORL-48 cell suspension was placed on a parafilm along with 10 µl of trypan blue (Sigma Aldrich, USA) and resuspended for about 10 times. Trypan blue is a dye that distinguishes between living and dead cells. From the mixture, 10 µl was pipetted on the haemocytometer. A piece of glass slide was placed on the haemocytometer and the mixture was pipetted on the edge of glass slide and spread evenly to avoid air bubbles. After that, the haemocytometer was placed under the microscope. Under the microscope, each chamber was divided into a grid pattern, consisting of 9 large squares of the same dimension. The viable cells were counted in the 4 large corner squares. The concentration of viable cells was calculated and used in formula (M1V1=M2V2) to get the volume of complete media that needs to be added to achieve cell molarity of 3×10^4 cells/cm^2.

2.4 MTT assay

The MTT assay (Thermofisher, USA) was used to assess cell viability by detecting the reduction of the yellow MTT dye to a dark purple formazan product, which occurs only in viable cells. This calorimetric assay will measure the reduction of yellow 3-(4,5-dimethythiazol2-yl)-2,5-diphenyl tetrazolium bromide (MTT) by mitochondrial succinate dehydrogenase. The dye enters mitochondria of the cell where it will be reduced into dark purple coloured formazan product. Viable cells can take up the dye via active transport and passes into mitochondria but not for the non-viable cells. As a result, after washing, viable cells released the incorporated dye in under acidified-extracted conditions.

The MTT assay provides a quantitative measurement of the number of viable cells and can be measured at OD 590 nm using a spectrophotometer or an absorber reader (ELISA reader). For this assay, the sub-

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cultured cell lines were plated in a 96-well culture plates. In separate wells, a stock of tocotrienols were diluted into several different concentration of T3 for each isomer, which will be 0.1, 1.0, 2.5, 5.0, 7.5, and 10.0 µg/mL and prepared using DMEM supplemented with 10% fetal bovine serum, 2 mL of penicillin-streptomycin. A blank control was also included. These cultures were incubated in an incubator for 72 hours at 37°C and 5% CO_2. After incubating the cells for 72 hours at 37°C and 5% CO2, 100 µL of 1% MTT dye was added to each well and incubated for an additional 2 hours. The medium was then replaced with MTT solvent, and the cells were incubated for 15 minutes at room temperature. The absorbance of the purple formazan product was measured at 570 nm using a microplate reader. The experiment was repeated three times in triplicate (n=3).

$$\text{Percent of Inhibition} = \frac{\text{(OD control} - \text{OD sample)}}{\text{OD control}} \times 100\%$$

2.5 Statistical analysis

All results were computed and expressed as mean ± standard deviation (SD) from three determinations performed in triplicate (n=3).

3. RESULTS

Table 1. Cytotoxic activity of tocotrienol isomers of OSCC (ORL-48) measured by the concentration required to inhibit 50% of cell proliferation. (*ND: Not Determinable)

Treatment	**IC_{50} (µg/mL)**
α-tocotrienol	ND
β-tocotrienol	ND
γ-tocotrienol	5.2 ± 1.4
δ-tocotrienol	ND

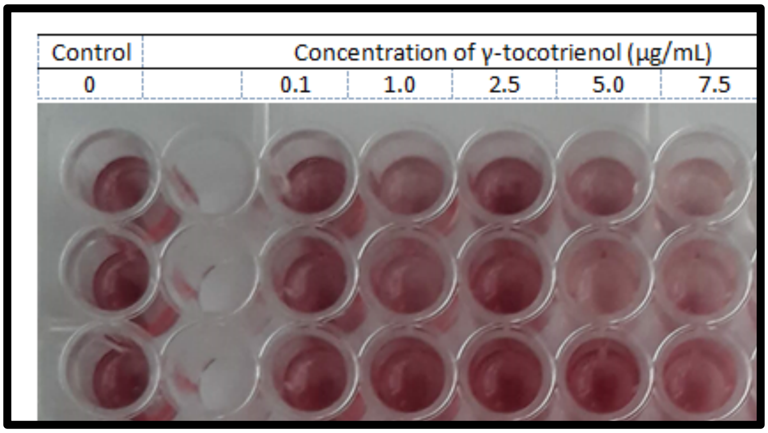

Fig. 1. 96-well plate of γ-tocotrienol after 72 hours incubation with MTT reagent shows different colour intensity of cell viability with concentration of γ-tocotrienol.

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γ-tocotrienol demonstrated an IC_{50} of 5.2 ± 1.4 µg/mL on ORL-48 cells, whereas α-, β-, δ-tocotrienol did not exhibit cytotoxic activity at the tested concentration (0.1-10 µg), resulting in non-determinable (ND) IC_{50} values. Additionally, γ-tocotrienol caused noticeable colour changes in the media (Figure 1) after the addition of MTT reagent, in contrast to α-, β-, and δ- isomers. Following 72 hours of incubation, wells displayed varying intensities of purple, due to the reduction of MTT to insoluble dark purple formazan. The intensity of the purple colour, which was quantified using an ELISA reader by measuring optical density (OD), decreased from 0 µg/mL to 10 µg/mL (Figure 1). The highest intensity of formazan and OD values were observed at 0 µg/mL, reflecting the absence of treatment. Higher intensities of formazan indicate the presence of viable cells, as viable cells reduce the MTT reagent to purple formazan, resulting in higher OD values. Conversely, lower OD values and reduced formazan intensity suggest fewer viable cells. Thus, the data shows that higher concentrations of γ-tocotrienol (5, 7.5, and 10 µg/mL) resulted in lower intensities of purple formazan and lower OD values, indicating reduced cell viability, while lower concentrations of γ-tocotrienol maintained higher cell viability.

4. DISCUSSION

In the treatment and eradication of early oral squamous cell carcinoma (OSCC), chemotherapy and radiotherapy have proven to be highly effective (Kani et al., 2013). Cisplatin, a widely prescribed immunotherapeutic agent used against tumour, has been reported to affect tumour antigenicity *in vitro*. In consensus with *in vitro* studies on ORL-48 reported by Zulkapli et al. (2009), the IC_{50} for cisplatin was found to be <1.0 µg/mL on ORL-48. However, concern over the use of many chemotherapeutic drugs is that they are not selective on cancer cells only and tends to kill normal cells and tissues as well (Husain et al., 2017). The toxicity of cisplatin on human epidermal keratinocytes is an evident at the lowest concentration (<0.1 µg/mL), despite its anti-proliferative effects on OSCC (Zulkapli et al., 2009). Thus, the identification of chemopreventive agents from nutritional sources is worth further investigation.

Emerging suggests that vitamin E has potential anticarcinogenic properties and could be a promising candidate for adjuvant cancer treatment. Vitamin E is a vital micronutrient essential for preserving the balance between antioxidant and prooxidant reactions in tissues (Rajasinghe et al., 2018). It is relatively nontoxic and well tolerated by humans, existing in nature as 8 isomers: 4 tocopherols (abbreviated as α-TOC, ß-TOC, γ-TOC, and δ-TOC) and 4 tocotrienols (abbreviated as α-T3, ß-T3, γ-T3, and δ-T3) (Musa, 2021). Zulkapli et al. (2009) extensively discussed the antitumor activities of α-TOC on ORL-48; however, the cytotoxic effect of tocotrienol isomers towards ORL-48 has yet to be reported. Hence, in this *in vitro* study, the investigation of cell viability for each tocotrienol isomers denoted by prefixes of α, β, γ and δ respectively, towards oral cancer cell lines (ORL-48).

γ-tocotrienol showed the highest viability activity with an IC_{50} of 5.2 ± 1.4 µg/mL, whereas the $IC_{50\ value}$ for α, β and δ were ND. This result aligns with other studies indicating that γ-tocotrienol is more effective than the other isomers. Inhibitory concentration (IC_{50}) is a tool to stipulate the concentration of tocotrienol compounds that is needed to inhibit the oral cancer cell viability by half. A larger IC_{50} value indicates that tocotrienol compounds reacted less efficacious with the sample of ORL-48 compared to compounds with smaller IC_{50} values (Abubakar et al., 2017). Cell cytotoxicity was assessed by measuring the growth inhibitory concentration for 50% of the cell population in a standard MTT assay.

A study by Sen et al. (2010) suggests that between all four isomers of tocotrienols, γ and δ-tocotrienols exhibit the most potent anticancer properties, while α-tocotrienol turns out to be potent in neuroprotection. One of the earliest studies in regard to tocotrienols against neoplastic disorders, on sarcoma 180, Ehrlich carcinoma, and invasive mammary carcinoma was done by Komiyama et al. The study was conducted by injecting α and γ-tocotrienols intraperitoneally in mice and the cytotoxic effects were observed. Both tocotrienols were effective antitumor activity but γ-tocotrienol exhibited a higher effect than α-tocotrienol.

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Furthermore, both α and γ isomers appeared to display growth inhibition of human and mouse tumour cells when incubated for 72 hours (Sen et al., 2010).

Additionally, Kani et al. (2013) found that γ-tocotrienol slightly inhibited nuclear p65 protein expression in human oral cancer B88 cells. Previous studies confirm that tocotrienols, but not tocopherols, presented potent antiproliferative and apoptotic activities against neoplastic mammary epithelial cells, which displayed little or no effect on normal cell growth. For instance, γ-tocotrienol has been shown to suppress the activation of NF-κB in a diverse cancer cell line. Results established that γ-tocotrienol inhibited the proliferation of human oral cancer cells, enhanced docetaxel-induced apoptosis, and inhibited activation of NF-κB. Similar studies also reported that γ-tocotrienol portrayed antiproliferative activity in gastric and pancreatic cancer cells.

According to the guideline stated in the Cell Culture Screening Protocol 1.600 (1972), any pure compound with an IC_{50} of less than 4.0 µg/mL would be considered active as an antitumour agent against the tested cancer cells. However, although γ-tocotrienol possessed the highest inhibitory percentage in our study compared to other tocotrienol isomers, the IC_{50} is 5.2 µg/mL is above the 4.0 µg/mL which indicated the lower effectiveness of γ-tocotrienol compared to α-tocopherol which reported to possess IC_{50} less 2.5 ± 0.4 µg/mL(< 4.0 µg/mL). This discrepancy may be due to the to the presence of three double bonds in the side chain of tocotrienols, whereas tocopherol has a saturated side chain. Further research is needed to explore these factors that may contribute to the antiproliferative effects of vitamin E.

5. CONCLUSION

Our study focused on the effect of tocotrienols on the viability of ORL-48 cells, and the results indicate a reduction in cell viability, suggesting potential anticancer activity. Compared to other isomers, γ-tocotrienol is the most potent among the tocotrienol isomers compared to α-T3, ß-T3, γ-T3, and δ-T3. However, it did not fully demonstrate activity as an antitumor agent against ORL-48 cells. However, to fully understand whether oral cancer cells respond differently compared to other cancer cell lines, further comparative studies would be necessary. These studies could involve testing tocotrienols on multiple cancer cell lines under the same experimental conditions, assessing differences in response, and exploring the underlying mechanisms.

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CONFLICT OF INTEREST

There are no conflicts to declare.

AUTHORS' CONTRIBUTIONS

Rahayu Zulkapli conceptualized the study and led the project supervision and funding acquisition. **Rahayu Zulkapli** and **Khor Goot Heah** jointly supervised the research work and provided critical guidance. **Nur Shahinaz Mahadi, Wan Fatimah Wan Fatul**, and **Atiqa Syazwani Ridzuan** were responsible for data collection, investigation, and performing the MTT assay.

Nur Shahinaz Mahadi, Wan Fatimah Wan Fatul, and **Rahayu Zulkapli** contributed to manuscript drafting and initial writing. All authors reviewed, approved the final manuscript, and agreed to its publication.

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6. APPENDIX

A. About the authors

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