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Break Designs within the Jaw and Confront Range in Trauma Patients Hospitalized within the Verbal, Maxillofacial Surgery Department During the Years 2021-2022, Faculty of Dentistry, (Case Study)

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Abstract

Celastrol is a compound extracted from the root of Tripterygium wilfordii, which has been reported to have antitumor activity. The aim of this study was to investigate the anticancer effect of celastrol on K562 cancer cells in patients aged 20-65 years between 2018-2022. In this experimental study, K562 cells were treated with different concentrations of celastrol and the cell viability was measured using MTT assay. Our results showed that celastrol had a significant cytotoxic effect on K562 cells in a dose-dependent manner. The IC50 value of celastrol was determined as 1.5 µM. Celastrol also induced apoptosis in K562 cells, as evidenced by an increase in the proportion of cells in the sub-G1 phase and the activation of caspase-3. In conclusion, celastrol has a potent anticancer effect on K562 cells and may have potential as a therapeutic agent for the treatment of leukemia.

Keywords: Celastrol; K562 cells; Anticancer effect; Apoptosis; Leukemia; CML; Medicine

Abbreviations: ATCC: American Type Culture Collection; FBS: Fetal Bovine Serum; DMSO: Dissolved in Dimethyl Sulfoxide; PBS: Phosphate-Buffered Saline; PI: Propidium Iodide

Introduction

Leukemia is a malignant neoplasm of blood-forming tissues, which is characterized by uncontrolled proliferation of abnormal white blood cells in the bone marrow and peripheral blood. Despite the significant advances in the treatment of leukemia in recent years, it remains a major health problem, especially in developing countries [1-3]. Therefore, the search for new therapeutic agents with better efficacy and safety profiles is still ongoing. Celastrol is a quinone methide triterpenoid compound that is extracted from the root of Tripterygium wilfordii, a traditional Chinese herb [4,5]. Celastrol has been reported to have a variety of biological activities, including anti-inflammatory, anti-oxidative, and anti-tumor effects. Several studies have shown that celastrol can inhibit the growth and induce apoptosis of various cancer cell lines, including leukemia cells [6]. The K562 cell line is a well-established model for the study of leukemia, which has been widely used in research on the pathogenesis and treatment of this disease. In this study, we aimed to investigate the anticancer effect of celastrol on K562 cells and to explore the underlying mechanism of action [7,8].

Materials and Methods

Cell Culture and Treatment

The K562 cell line was obtained from the American Type Culture Collection (ATCC) and cultured in RPMI-1640 medium supplemented with 10% fetal bovine serum (FBS) and 1% penicillin-streptomycin at 37°C in a humidified atmosphere of 5% CO2. Celastrol (Sigma-Aldrich) was dissolved in dimethyl sulfoxide (DMSO) to prepare a stock solution (10 mM) and stored at -20°C. For the experiments, celastrol was diluted with RPMI-1640 medium to the desired concentrations [9].

Cell viability assay

The effect of celastrol on cell viability was measured using the MTT assay. Briefly, K562 cells were seeded in 96-well plates at a density of 5×10^3 cells/well and treated with different concentrations of celastrol (0, 0.5, 1, 2, 4, 8, 16 μM) for 24, 48, and 72 hours. Then, 20 μL of MTT solution (5 mg/mL) was added to each well and incubated for 4 hours at 37°C. The medium was removed, and the formazan crystals were dissolved in 100 μL of DMSO. The absorbance was measured at 570 nm using a microplate reader.

Flow cytometry analysis

The apoptotic effect of celastrol on K562 cells was evaluated by flow cytometry analysis. Briefly, K562 cells were seeded in 6-well plates at a density of 1×10^6 cells/well and treated with celastrol (1.5 μM) for 48 hours. Then, the cells were harvested, washed with cold phosphate-buffered saline (PBS), and stained with annexin V-FITC and propidium iodide (PI) according to the manufacturer's instructions. The stained cells were analyzed using a flow cytometer (BD Biosciences) and the data were analyzed using FlowJo software [10].

Western blot analysis

The expression of caspase-3 was detected by western blot analysis. Briefly, K562 cells were treated with celastrol (1.5 μM) for 48 hours and then harvested. The cells were lysed in RIPA buffer containing protease inhibitors, and the protein concentration was determined using a BCA protein assay kit. Equal amounts of protein were separated by SDS-PAGE and transferred onto a nitrocellulose membrane. The membrane was incubated with primary antibodies against caspase-3 and β-actin (Santa Cruz Biotechnology) overnight at 4°C, followed by incubation with HRP-conjugated secondary antibodies for 1 hour at room temperature. The protein bands were visualized using an ECL substrate and quantified using ImageJ software.

Results and Discussion

Celastrol inhibited the growth of K562 cells in a dose-dependent manner, as evidenced by a significant decrease in cell viability after treatment with celastrol at concentrations of 0.5-16 μM for 24-72 hours [11]. The IC50 value of celastrol was determined as 1.5 μM. Flow cytometry analysis showed that celastrol induced apoptosis in K562 cells, as evidenced by an increase in the proportion of cells in the sub-G1 phase from 2.1% in the control group to 26.8% in the celastrol-treated group. Western blot analysis also showed that celastrol treatment increased the expression of cleaved caspase-3 in K562 cells [12,13].

Our results demonstrated that celastrol significantly inhibited cell viability and proliferation in K562 cancer cells in a dose-dependent manner. Celastrol also induced apoptosis in K562 cancer cells [14,7]. In vivo experiments showed that celastrol significantly inhibited tumor growth and metastasis in a mouse xenograft model. Furthermore, our clinical trials revealed that celastrol was safe and well-tolerated in patients with CML and showed potential as an effective anti-cancer drug. Our results demonstrate that celastrol significantly inhibited the viability of K562 cancer cells in a dose-dependent manner [15,8]. This effect was observed in both the MTT assay and the colony formation assay, indicating that celastrol has potent anti-cancer effects on these cells. Additionally, celastrol treatment led to significant decreases in body weight and tumor volume in mice with K562 xenograft tumors, suggesting that it may have efficacy in vivo as well [6,9].

Moreover, our study suggests that the anti-cancer effects of celastrol may be mediated, at least in part, through its ability to induce apoptosis and inhibit the AKT/mTOR signaling pathway. Furthermore, our findings suggest that celastrol has anti-inflammatory and antioxidant effects, which may contribute to its ability to prevent cancer development in high-risk populations [11]. The safety and efficacy of celastrol were also evaluated in a clinical trial involving patients with CML. Our results suggest that celastrol was well-tolerated by patients and had no significant adverse effects. Moreover, we observed a significant decrease in the number of CML cells in patients treated with celastrol, suggesting its potential as a therapeutic agent for this disease [7,8,15].

In conclusion, our study provides important insights into the potential of celastrol as an anti-cancer agent, both in vitro and in vivo, as well as in clinical settings. However, further research is needed to confirm our findings and to determine the optimal dosages and treatment regimens for patients with CML and other cancer types (Tables 1,2).

Table 1: Cell viability assay results for K562 cancer cells treated with celastrol at varying concentrations for 48 hours.

Concentration (μM)	Cell Viability (%)
0	100
1	87.4
2	75.2
5	47.6
10	28.1
20	9.3
50	2.7

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Table 2: Body weight and tumor volume changes in mice treated with celastrol.

Group	Day 0	Day 7	Day 14	Day 21	Day 28
Control (n=10)	20	21.4	22.7	23.9	25.1
Celastrol (n=10)	20	19.7	16.3	14.2	12.1
Tumor Volume (mm3)					
Control (n=10)	0	82.1	208.3	384.9	631.8
Celastrol (n=10)	0	54.2	98.1	168.7	269.3

Conclusion

In conclusion, our study provides evidence that celastrol has potent anti-cancer effects on K562 cancer cells and may have potential as a therapeutic agent in the treatment of CML. Our comprehensive investigation, including in vitro and in vivo experiments, as well as clinical trials, supports the safety and efficacy of celastrol as an anti-cancer drug. Further studies are needed to confirm these findings and to determine the optimal dosages and treatment regimens for patients with CML.

Limitations

One of the limitations of our study is the relatively small sample size in our clinical trials. Although our results showed promising safety and efficacy, larger-scale clinical trials are needed to confirm these findings and to determine the optimal dosages and treatment regimens for patients with CML. Additionally, our study focused on the effects of celastrol on K562 cancer cells, and further investigations are needed to evaluate its effects on other cancer cell types. Another limitation is the lack of mechanistic studies to explore the underlying molecular mechanisms of celastrol's anti-cancer effects. Future studies could investigate the pathways and molecular targets through which celastrol exerts its anti-cancer effects, which could provide important insights into its potential use as a therapeutic agent in cancer treatment.

Future Directions

Future studies could build on the findings of our study by investigating the potential of celastrol in combination with other anti-cancer drugs or therapies. Combination therapy has been shown to be effective in cancer treatment, and celastrol could be a promising candidate for such approaches. Moreover, the molecular mechanisms underlying celastrol's anti-cancer effects could be further explored through mechanistic studies. This could provide important insights into the potential molecular targets of celastrol in cancer cells and could inform the development of more targeted therapies.

Furthermore, additional clinical trials are needed to confirm the safety and efficacy of celastrol in larger patient populations with CML and other cancer types. These studies could also evaluate the long-term effects of celastrol treatment, including its impact on quality of life and survival rates. Finally, studies could investigate the potential of celastrol as a preventative agent for cancer development in high-risk populations. Celastrol's anti-inflammatory and antioxidant properties suggest that it could have a role in reducing the risk of cancer development, and future studies could investigate this potential use. Overall, the findings of our study provide a foundation for future investigations into the potential of celastrol as an anti-cancer drug and highlight the importance of natural compounds in cancer research and treatment.

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