Bochemical Society Summer Studentship Report 2024

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Medulloblastoma is the most common malignant brain tumor in children, accounting for nearly 20% of all pediatric brain cancers. Despite significant progress in treatment, typically involving chemotherapy, survivors often face severe cardiovascular complications. These long-term side effects highlight the need for alternative therapeutic approaches that focus on targeting cancer biology more effectively.

One promising strategy involves the use of naturally occurring plant compounds, known as phytochemicals, which have been shown to suppress cancer progression by inhibiting cell proliferation, inducing cell cycle arrest, and promoting apoptosis. Among these phytochemicals, demethylzeylasteral, a compound derived from Tripterygium wilfordii, has shown potential in inducing cancer cell death in vitro, although research is still limited. Preliminary studies suggest that demethylzeylasteral can block the TGF-β signaling pathway in triple-negative breast cancer and may reduce cell migration and proliferation by modulating key pathways such as ERK1/2 and Akt. These promising findings suggest that demethylzeylasteral could serve as a novel therapeutic strategy for improving the treatment of pediatric brain tumors, such as medulloblastoma.

The aim of this project was to evaluate the phytochemical effects of demethylzeylasteral on different medulloblastoma subtypes and its potential cardiac implications. The study specifically focused on assessing the cardiotoxicity of this compound using the HD-MB03 and DAOY cell lines, which are valuable models for investigating signaling pathways involved in cancer cell motility and migration in Group 3 medulloblastoma.

To investigate these effects, the study employed a variety of methods, including flow cytometry, live-cell microscopy, and fluorescent microscopy, to assess the impact of demethylzeylasteral on both cancer cells and cardiac cells. Over the course of a six-week summer internship, the project aimed to analyze time- and concentration-dependent effects of demethylzeylasteral on both the HD-MB03 and DAOY cell lines. Cells were treated for varying time points (24, 48, and 72 hours), followed by cell splitting and analysis using techniques like MTT assays to evaluate cell viability, cytotoxicity, and potential apoptotic effects.

The results of this study demonstrated that demethylzeylasteral has notable chemotherapeutic effects, particularly at concentrations of 5 μM and 50 μM, with EC50 values ranging between 0.128–0.259 μM. These values suggest that demethylzeylasteral is effective at low concentrations in inhibiting cancer cell growth. Furthermore, it was observed that demethylzeylasteral induced irreversible cell damage after 24 hours of treatment, indicating that the compound causes cell death through apoptosis. Importantly, this effect was found to be time-dependent, with significance observed at the later time points (48 and 72 hours), but not at earlier stages. Notably, HD-MB03 cells showed a pronounced response in terms of cell damage, while DAOY cells demonstrated a more gradual onset of cytotoxicity.

Interestingly, the treatment did not significantly affect cell migration, especially in the HD-MB03 cell line, suggesting that demethylzeylasteral does not interfere with tumor cell invasion or metastasis. This is a promising feature, as it indicates that the compound selectively targets tumor cell growth without promoting invasive behavior, which could otherwise lead to more aggressive disease progression.

Further analysis with fluorescent microscopy revealed an increase in Caspase 3/7 activation, which is a key marker of apoptosis, suggesting that the cell death induced by demethylzeylasteral is selective and does not trigger an inflammatory response.

This project has significantly advanced my scientific background, providing hands-on experience with key techniques such as time-lapse live-cell microscopy, flow cytometry, and fluorescence microscopy. Under the guidance of experienced researchers, I developed essential technical and analytical skills for both academic and industry careers. I also gained a strong foundation in experimental design, data collection, and data analysis, deepening my understanding of the research process.

In addition to these technical skills, I honed essential transferable skills such as time management and critical thinking, which are crucial for advancing my research career. I had the opportunity to present my findings at a medical conference attended by clinicians specializing in pediatric oncology, where I emphasized the importance of continued research into the therapeutic potential of phytopharmachemicals. I confidently explained the methodologies and processes behind my project, engaging in thoughtful discussions with clinicians that provided valuable clinical insights. These exchanges highlighted the critical role researchers play in advancing both diagnostic and treatment strategies for pediatric cancers.

During some challenging instances, such as when contamination hindered cell growth, I maintained a positive mindset and implemented alternative strategies to keep the project on track. Through troubleshooting and ensuring a clean environment, I was able to resolve the issue and continue the research. This experience not only enhanced my problem-solving skills but also reinforced my ability to remain adaptable and resilient in the face of unexpected setbacks.

This experience has solidified my commitment to pursuing a career in research, particularly in oncology, and has fueled my passion for discovering novel therapies to improve cancer outcomes. My exposure to both clinical and research environments has demonstrated how research can directly impact patient care and treatment options. Moving forward, I am determined to continue my research with the aim of making meaningful contributions that could improve cancer prognosis and quality of life. The skills and insights gained through this project have strengthened my resolve to pursue innovative solutions for more effective and less toxic cancer treatments.