Abstract of Kandiah Memorial Award for Applied Chemistry - 2022

Improving the Stability of XLAsp-P2 Through Nano conjugation

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Antimicrobial (AMP) and Anti-cancer peptides (ACPs) recently have received significant attention as promising chemotherapeutic agents that avoid the drawbacks of current drugs. Many studies have verified that some synthetic and natural peptides possess a rapid and broad spectrum of anticancer activity towards tumor cells rather than normal cells such as human red blood cells. Moreover, these peptides were also verified to have the ability to overcome the multidrug-resistance mechanism and synergistic effects in combination treatment.

The current study mainly focuses on a peptide known as XLAspP2-RA, a peptide analog (EDLDED) designed based on a novel AMP, XLAsp-P2 (DEDLDE). The natural peptide was initially isolated from the skin tissues of *Xenopus laevis* and has been reported to exhibit moderate antibacterial activity.[1] The analog sequence was designed based on the retro analog concept and possesses a rapid anticancer activity, with the IC_{50} value of 5.36 μg/ml for RD cells. RD was derived directly from biopsy specimens of a pelvic Rhabdomyosarcoma (RMS), a malignant skeletal muscle cancer of pediatric patients.

Emerging evidence has shown that RMS's malignant growth involves a multistep process of signaling protein dysregulation that includes prolonged activation of serine/threonine kinases (Akt). Our *in silico* studies have indicated that peptides exhibited cancer-selective toxicity, mainly because that cancer cells are involved with the hyperactivation of Akt-1 protein. The present study used docking and (un) critical simulation analyses to identify XLAspP2-RA interacting residues of human Akt-1 protein. The results proved that peptide is an allosteric inhibitor of Akt-1 and exerts its inhibitory mechanism by binding to the allosteric site of Akt-1 and engaging the functionally important residues in various interactions. The exact binding mode of the peptide-based on the computational approach is presented, and various interacting residues within the allosteric site of this protein were identified and characterized. The quality of docking was assured by the negative dock score, which was -8.44 kcal/mol, and the identified various molecular interactions between the protein and the ligand. In the docking and (un)binding simulation analyses, the Asn53, Gln59, Trp-80, and Lys268 were identified as the key residues among various important identified residues. The docked peptide-protein conformation is expected to serve as a suitable model for understanding the amino-acid environment mediating molecular interactions and thus, providing details for the inhibitory mechanism of the peptide. In the future, this study will help design novel peptidomimetics for human Akt isoforms, and it will help experimental biologists in testing and designing better inhibitors.

In addition to the cytotoxicity and undergoing inhibitory mechanism of XLAspP2-RA, we proved that it could increase the efficacy of the peptide against RD cells when it is encapsulated with drug carriers such as fHNT. The induced effect is shown to permit the use of relatively low concentrations of peptides and drugs to achieve significant anticancer effects *in vitro*. This dose reduction minimizes drug side effects on normal cells and enables an effective apoptosismediated anticancer effect. Our present study has implications in that XLAspP2-RA peptide may become a promising anticancer therapeutic agent with high anticancer selectivity and a strong induced effect in combination therapy. Our studies mainly illustrate the mechanism of XLAspP2-RA peptide-induced cell death and may be helpful in the design of chemotherapeutics against RMS cell lines.

Furthermore, in the model study, we investigate the potential of GO as an efficient system for sustaining the antibacterial activity of CEF. Upon successful encapsulation of CEF into GO, the anticipated sustained release of CEF was achieved. Moreover, the GO-PEG-CEF composite showed an enhanced antibacterial activity compared to positive control on gram-positive bacteria. GO-PEG-CEF could be an effective nano-based antibiotic system with synergistic antibacterial mechanisms to treat infections caused by gram-positive bacteria.

In the future, the bioavailability of the peptide after release from fHNT-XLAspP2-RA composites can be

confirmed by *in vitro* studies using kinetic assays. The research can be taken further to the next level within *in vivo* studies on different animal models. Additionally, the tubular ends and surface of drug-loaded fHNT can be modified with pH-sensitive polymers, followed by the preparation of oral tablets for gastrointestinal drug delivery. Such aminosilane functionalized nanomaterials have been used in some previous studies, and they displayed no toxicity upon oral consumption.[2,3] These milestones by aminosilane modified nanomaterials indicate the promising usage of the peptide-loaded fHNT.

Contribution

This study, therefore, focused on peptide-nano hybrids, exposing new pathways in therapeutic applications. Ms. B.M. Yasuri D.E. Amarasekara carried out this project in her M. Phil degree. She has completed the work at the Sri Lanka Institute of Nano Technology under the supervision of Dr. Laksiri Weerasinghe. In this project, she managed the methodologies and validated the methods. Further, she did all the formal analysis by herself, and she was able to publish the work in two international journals.

References

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Professor M. U. S. Sultanbawa Award for Research in Chemistry

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Professor M. U. S. Sultanbawa Award for Research in Chemistry - 2022

Ms. Imesha Lakmini Hettige graduated from the University of Sri Jayewardenepura with B.Sc. Honours Degree (First Class Honours) in Chemistry in 2019, becoming the batch-top, and also obtained the Graduateship in Chemistry (First Class Honours) from the College of Chemical Sciences, Institute of Chemistry Ceylon in 2018, ranking third in the batch. During her undergraduate studies, she received several awards such as the Prof. Tuley de Silva Gold Medal for obtaining highest overall marks at the B.Sc. Chemistry Special Degree, Prof. W S Fernando Gold Medal for Physical and Inorganic Chemistry and Prof. A. M. Abeysekara Gold Medal for Organic Chemistry at the University of Sri Jayewardenepura, as well as the Graduate Chemist Silver Jubilee Commemoration Award, Mr and Mrs Gamini Gunasekara and Family Prize, Rasanthika Nayomi Jayathissa Memorial Prize, W.R.O. Fernando Memorial Prize and Professor G.C.N. Jayasuriya Memorial Scholarship and others at the Institute of Chemistry Ceylon. She conducted her research on "Synthesis and characterization of platinum complexes with ethylenediamine and diethylenetriamine sulphonamide ligands towards biological applications" which was selected for the Professor M U S Sultanbawa Award for Research in Chemistry – 2021, under the supervision of Professor Theshini Perera at the University of Sri Jayewardenepura. She just recently started working on her PhD research project for which she was awarded the Postgraduate Research Scholarship from the ARC Industrial Transformation Training Centre for Fragment-Based Design (CFBD) at the Monash Institute of Pharmaceutical Sciences, Faculty of Pharmacy and Pharmaceutical Sciences, Monash University, Australia.