Newsletter

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Greetings from Faculty of Science, the home of established researchers and bright students. This issue present research activities from September to December 2021 which highlights the latest research findings and activities by the Faculty members. We're happy to share our newsletter with community, alumni, and friends.

HIGHLIGHTS

- Enhanced cancer treatment
- Optimizing radiomics technique
- A new class of two derivative Runge-Kutta type methods
- Pyrrolylated-chalcone scaffold
- ITEX 2021 – Award Achievement

SYNERGISTIC COMBINATION OF A RUTHENIUM(II) POLYPYRIDYL COMPLEX AND PARP INHIBITOR FOR ENHANCED CANCER TREATMENT

Report by: : Assoc.Professor ChM. Dr. Haslina Ahmad,
Department of Chemistry, Faculty of Science, Universiti Putra Malaysia
e-mail: haslina_ahmad@upm.edu.my

Cancer remains as one of the primary causes of death associated with a high number of reported global incidences annually. Despite chemotherapy being the most common option for cancer treatment with some have had high successful rates, current chemotherapy utilizing single-drug treatment remains clinically limited. This is because single-drug treatment may not lead to sufficient tumour suppression and with very few exceptions, single-drug treatment had not been successful in prolonging patient survival due to drug resistance. In this regard, our ambition is to introduce new successful combination strategy to combat these issues.

This work explores new combination comprising of ruthenium(II) polypyridyl complex $[Ru(dppz)_2(PIP)]^{2+}$ (Ru-PIP) and poly(ADP-ribose) polymerase (PARP) inhibitor Olaparib. Ruthenium complexes in particular have been extensively studied as single agents and they have shown higher efficacy with lower systemic toxicities. To the best of our knowledge, this drug-drug combination is significant and distinct from other related combination studies with the use of emerging ruthenium anti-cancer candidates of Ru-PIP which was synthesized in our lab that consists of an unusual molecular geometries and useful luminescent properties. The fundamental concept of this work is the pharmacological rationale for the selection of Ru-PIP/Olaparib as the ideal pairing as they target key pathways of DNA damage response (DDR) of the highly proliferative cancer cells in a characteristically synergistic manner. Compared to single-agent conditions, this synergistic combination improves cancer cell killing through the induction of G2/M cell cycle arrest and apoptotic cell death. Most importantly, minimal cytotoxicity towards non-malignant cells was observed. Our findings provide evidence of significant superiority of Ru-PIP/Olaparib combination, thus showing its potential to address current challenges of intolerable side effects and can circumvent resistance while simultaneously improve overall response rates. The demonstration that this drug synergy can show exquisite activity in several cancer cell lines including breast, lung and bladder cancers further implying that this approach may offers activity towards numerous cancer types.

This work was the Master research of Nur Aininie Yusoh under a supervisory team comprising Assoc. Prof. Dr Haslina Ahmad in the lead, Prof. Dr. Mohd Basyaruddin Abdul Rahman and Assoc. Prof. Dr Chia Suet Lin as co-supervisors. International counterparts for sharing knowledge and findings include the collaboration withDr. Martin R. Gill from Swansea University, Wales, United Kingdom.

This work has received several recognitions including two Gold medals at both international and local exhibitions and has also resulted in 2 peer-reviewed journal papers of high impact (Q1/ Q2).

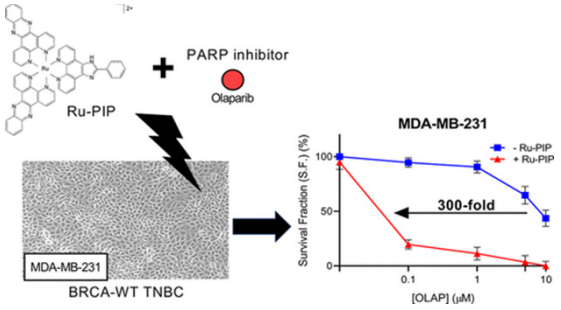

Figure 1: Low dose Ru-PIP renders MDA-MB-231 cells hypersensitive to Olaparib (OLAP), with a >300-fold increase in Olaparib potency. Figure adapted from Yusoh et al. (2020a).

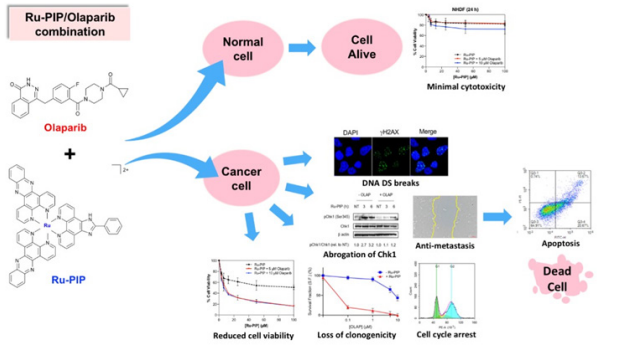

Figure 2: Representation of the mechanism of action for the anti-cancer activity of Ru-PIP in combination with Olaparib in cancer cells.

References:

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Yusoh, N. A., Ahmad, H., Gill, M. R. (2020). Combining PARP inhibition with Platinum, Ruthenium or Gold Complexes for Cancer Therapy. ChemMedChem. 15(22), 2121-2135.

OPTIMIZING RADIOMICS TECHNIQUE AS POTENTIAL RADIOGRAPH BIOMARKER VIA REPRODUCIBILITY STUDY

Report by: Dr. Muhammad Khalis Abdul Karim,
Department of Physics, Faculty of Science, Universiti Putra Malaysia.
e-mail: mkhalis@upm.edu.my

Since its introduction, radiomics features has been acknowledge for its fundamental methods for machine learning development in the medical imaging field. Basically, radiomics technique is a high throughput analysis that applies advanced computational approaches to convert image data from the selected region into high dimensional feature data, assuming the data provide information that could be used as a potential predictive biomarker. The quantitative features from the technique have been utilized extensively in cancer research and incorporate with machine learning to improve breast cancer prognosis. These features which originate from various sources of diagnostic information also overcomes the limitation of observer. However, the most critical parts in radiomics technique are reproducibility. Reproducibility describes the performances of radiomics measurements using different techniques or observers, or even from different diagnostic centers. To obtain accurate and precise results, the extracted features should be optimized to estimate patient survival analysis and boost treatment selection and monitoring for each patient.

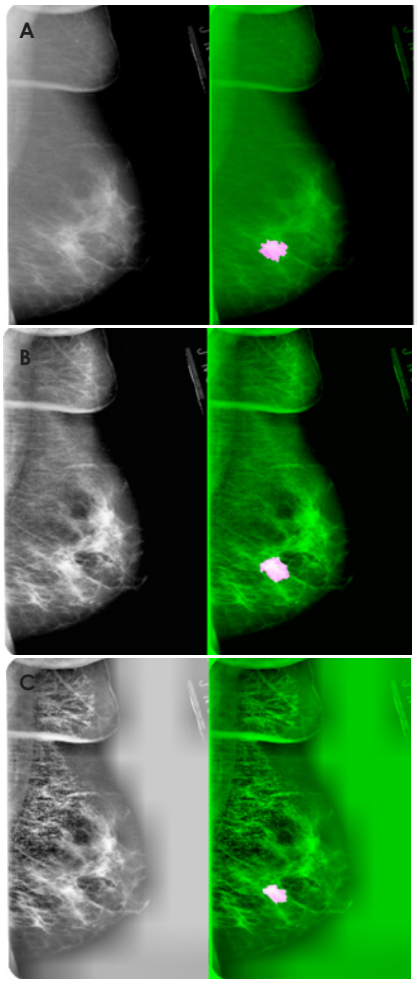

Figure 1: Mammogram radiograph with A) no image enhancement B) AHE enhancement C) CLAHE enhancement and segmented tumor for each dataset.

Hence, this work focuses the reproducibility of tumor segmentation during quantitative image extraction. Although physicians commonly use manual segmentation, this method is a time-consuming process that has more substantial inter-observer variability. To ensure higher accuracy in semiautomatic segmentation, pre-processing image enhancement is vital (Fig.1). Therefore, we assessed the robustness reproducibility of radiomics features of breast cancer through 2D mammograms. As illustrate in Fig 2, 37 radiomics imaging features were included and classified into three main features (6 tumor intensity histogram-based features, 22 textural features and 9 shape-based features). We found three quantitative imaging features were robust and had higher reproducibility when semiautomatic tumor segmentation with enhancer, Contrast Limited Adaptive Histogram Equalization (CLAHE) and Adaptive Histogram Equalization (AHE) techniques ($p<0.05$) were applied. The CLAHE set had higher reproducibility for most GLCM-based features and shape-based features compared to AHE techniques. The results showed that most of these features achieved high reproducibility scores when contrast enhancement and semi-automatic segmentation were applied to the image dataset. This work shows the existence in variation for the radiomics features extracted from tumor region and differed significantly with the image enhancement techniques. Semiautomatic segmentation with image enhancement using CLAHE algorithm gave the best result and was a better alternative than manual delineation as the first two techniques yielded reproducible descriptors.

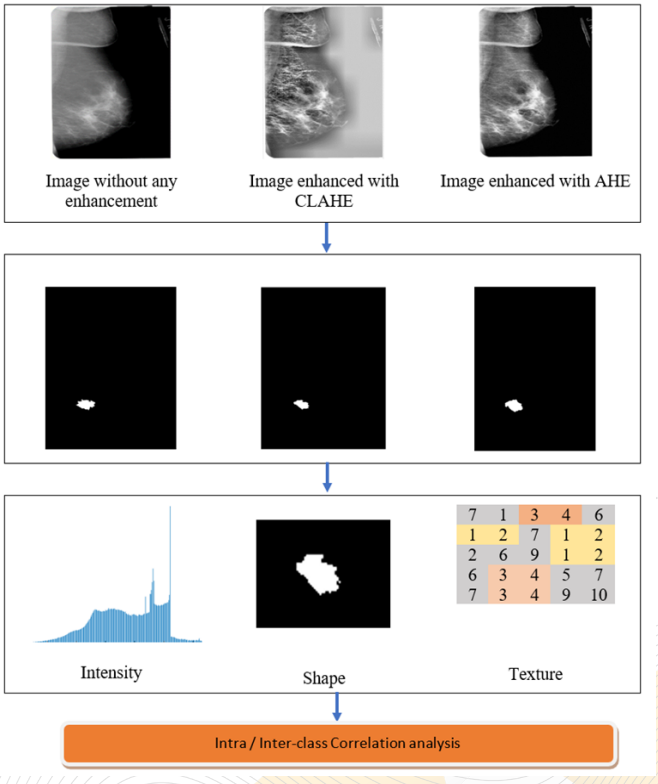

Figure 2: Reproducibility analysis of radiomics features in the 2D mammograms. (a) Three datasets were selected in our study with different image enhancement. (b) Three datasets were segmented using semi-automatic segmentation and manual delineation. Intensity, shape and textural transformed features were extracted from every dataset. The reproducibility of the radiomics features was measured by different indicators.

A NEW CLASS OF TWO DERIVATIVE RUNGE-KUTTA TYPE METHODS FOR SOLVING THIRD-ORDER ODES WITH APPLICATION TO THIN FILM FLOW PROBLEM

Report by: Assoc. Prof. Dr. Norazak Senu,
Department of Mathematics and Statistics, Universiti Putra Malaysia.
e-mail: norazak@upm.edu.my

This study introduces new special two-derivative Runge-Kutta type (STDRKT) methods involving the fourth derivative of the solution for solving third-order ordinary differential equations. In this regards, rooted tree theory and the corresponding B-series theory is proposed to derive order conditions for STDRKT methods. Besides, explicit two-stages fifth order STDRKT method is derived. Accuracy and effectiveness of the proposed techniques are validated by a number of various test problems and compared to existing methods in the literature. Initial value problems of third order ordinary differential equations (ODEs):

$$\begin{cases} u'''(x) = f(x, u(x), u'(x), u'(x)), (1) \\ u(x_0) = \alpha, \quad u'(x_0) = \beta, \quad u'(x_0) = \gamma, \quad x \in [x_0, x_{end}], \end{cases}$$

where

$$u \in \Re^N, f := \Re \times \Re^N \times \Re^N \times \Re^N \to \Re^N$$

is a continuous vector functions.

A s-stage special two derivative Runge-Kutta type method for third-order IVPs is prescribed as follow:

$$\begin{aligned} u_{n+1} = \quad & u_n + hu'_n + \frac{h^2}{2}u''_n + \frac{h^3}{6}f(x_n, u_n, u'_n, u'_n) + h^4\sum_{i=1}^{s} b_i\, g(x_n + c_i h, U'_i, U'_i), \\ u'_{n+1} = \quad & u'_n + hu''_n + \frac{h^2}{2}f(x_n, u_n, u'_n, u''_n) + h^3\sum_{i=1}^{s} b'_i\, g(x_n + c_i h, U_i, U'_i, U''_i), \\ u''_{n+1} = \quad & u''_n + hf(x_n, u_n, u'_n, u''_n) + h^2\sum_{i=1}^{s} b''_i\, g(x_n + c_i h, U_i, U'_i, U''_i), \end{aligned}$$

All the rooted trees for STDRKT methods up to order seven and selected rooted trees comprised of all order conditions for STDRKT methods with order eight and nine are shown in Lee et al. (2020). The order conditions for u,u' and u'' up to order five (see Lee et al. (2020)):

$$\begin{aligned} & b^T e = \frac{1}{24}, b^T c = \frac{1}{120}, b'^T e = \frac{1}{6}, b'^T c = \frac{1}{24}, b'^T c^2 = \frac{1}{60}, b'^T \bar{A} e \\ & = \frac{1}{120}, b''^T e = \frac{1}{2}, b''^T c = \frac{1}{6}, b''^T c^2 = \frac{1}{12}, b''^T \bar{A} e = \frac{1}{24}, b''^T c^3 \\ & = \frac{1}{20}, b''^T \hat{A} e = \frac{1}{120}, b''^T \bar{A} c = \frac{1}{120}, b''^T c \bar{A} e = \frac{1}{40} \end{aligned}$$

Parameters of the new method are given in Butcher tableau and denoted by STDRKT2(5) shown in Figure 1:

$$\begin{array}{c|cccccc} 0 & & & & & & \\ \frac{1}{2} & \frac{1}{384} & 0 & \frac{1}{40} & 0 & \frac{1}{8} & 0 \\ \hline & \frac{1}{40} & \frac{1}{60} & \frac{1}{12} & \frac{1}{12} & \frac{1}{6} & \frac{1}{3} \end{array}$$

Figure 1: The Butcher tablue for STDRKT2(5) method

Thin film flow problem

$$u''' = f(u), f(u) = u^{-2},$$
$$u(0) = u'(0) = u''(0) = 1, \qquad [0,5]$$

Problem 1:

$$u''' = u'' - u' + u + e^x, u(0) = 1, u'(0) = 1, u''(0) = 0,$$
$$x \in [0,2]$$

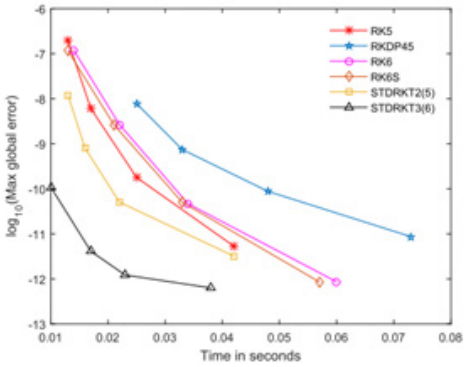

Figure 2: Maximum global error versus time of computation curves for problem 1.

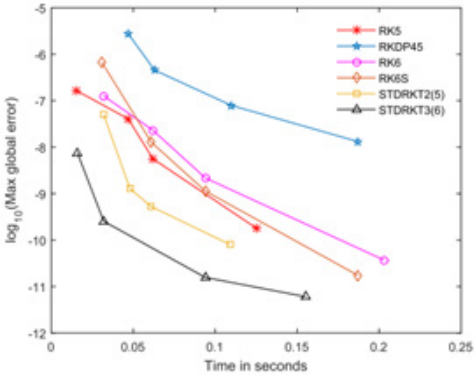

Figure 3: Maximum global error versus time of computation curves for thin film flow problem.

From the figures above, it is evident that these new Runge-Kutta methods are more proficient than traditional Runge-Kutta methods in term of maximum global error versus time of computation. STDRKT methods with same amount of stages acquired higher accuracy rate due to their ability to reach higher algebraic order compared to traditional Runge-Kutta methods.

References:

K.C. Lee, N. Senu, A. Ahmadian, S.N.I. Ibrahim, D. Baleanu, (2020). Numerical study of third-order ordinary differential equations using a new class of two derivative Runge-Kutta type methods, Alexandria Engineering Journal,Volume 59, Issue 4, 2449-2467. https://doi.org/10.1016/j.aej.2020.03.008

EXPLORING PHARMACOLOGICAL SIGNIFICANCE OF PYRROLYLATED-CHALCONE SCAFFOLD

Report by: Dr. Siti Munirah Mohd Faudzi
Department of Chemistry, Faculty of Science, Universiti Putra Malaysia.
e-mail: sitimunirah@upm.edu.my

Chalcones are generally originated from plants and serve as precursor in the biosynthesis of flavonoids and natural biocides. Traditionally, plants-containing chalcones have been consumed as herbal medicines to treat various illnesses. With scientific advancement in drug discovery and increased medicinal chemistry knowledge, the unique properties of these natural products-based molecules are further diversified chemically and therapeutically through synthetic approach. Concurrently, pyrrole-containing small molecules are widely used clinically with high potency and better safety profile. Based on this information, we incorporated the pyrrole scaffold into a chalcone structure by replacing one of the aromatic rings (Figure 1) and evaluated its potential in multiple diseases. Until recently, we discovered approximately ten hits of the pyrrolylated-chalcone scaffold from the in-house compound library with significant antiinflammation, anti-seizure, and anti-MRSA properties, respectively.

The experimental data show that the various pharmacological activities of the studied chalcones depend on their specific substitution, as summarize in Figure 1. These drug-like compounds were also reported with no toxic effects in the normal embryonic development, blood vessel formation, and apoptosis in the zebrafish model, reflecting its significant safety profile. These overall preliminary results suggest that the new pyrrolylated-chalcones could be a promising drug-candidate for the treatment of various disorders and can serve as a basis for further studies involving hit-to-lead optimization, *in vivo* efficacy and safety assessment in in bigger mammalian models and mechanism of action to speed up the discovery of new medications for the respective target diseases.

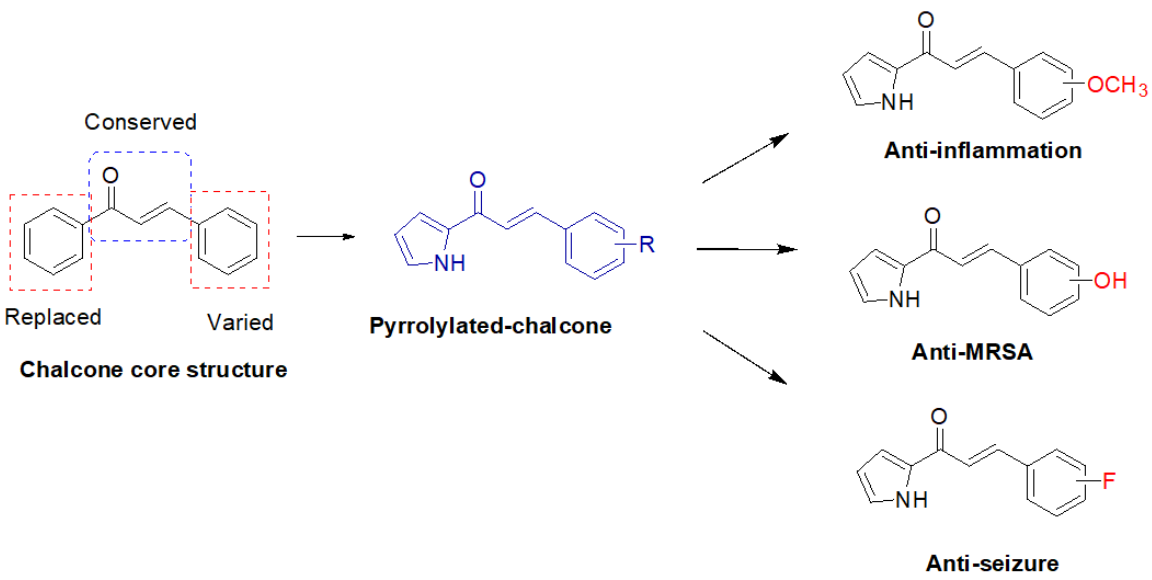

Figure 1: Schematic conversion of chalcone to pyrrolylated-chalcone and its pharmacological properties

References:

Siti Munirah Mohd Faudzi, Maryam Aisyah Abdullah, Mohd Rashidi Abdull Manap, Ahmad Zaidi Ismail, Kamal Rullah, Mohd Fadhlizil Fasihi Mohd Aluwi, Aizi Nor Mazila Ramli, Faridah Abas, Nordin H. Lajis (2020). 'Inhibition of nitric oxide and prostaglandin E2 production by pyrrolylated-chalcones: Synthesis, biological activity and molecular docking studies'. Bioorganic Chemistry, 94, 103376.

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ITEX 2021 - Gold Medal

Report by: Prof. Dr. Janet Lim Hong Ngee
Department of Chemistry, Faculty of Science, Universiti Putra Malaysia
e-mail: hongngeel@upm.edu.my

ITEX is a prestigious international exhibition of innovations held annually, organised by the Malaysian Invention and Design Society (MINDS) and C.I.S Network Sdn. Bhd. that provide the platform and market for the latest innovations and ideas globally.

Prof. Dr. Janet Lim Hong Ngee from the Faculty of Science won a gold medal for her innovation called GrafinTok™. It provides the benefits of patented graphene technology for engine oil. It is compatible with all types of vehicles. It revives cars by unleashing dormant horsepower, providing bulletproof protection, extending oil life, providing cooler engine and saving fuel. It is able to improve engine combustion efficiency, and revive sluggish engine with reduction in noise and vibration for a smoother, silent drive.

Figure 1: GrafinTok™ displayed at ITEX 2021.

Figure 2: The gold medal won for her innovation at ITEX 2021.

Her research on graphene spans for over a decade and has been employed for various applications, one of which as a lubricant for transportation. She also utilizes graphene for energy storage devices such as supercapacitor and battery, sensor, glove, drug delivery, adsorbent and many more. She won the Research Entrepreneur Award of the Malaysia Commercialization Year 2018 organized by MOSTI, then MESTECC, for her research in graphene.

GO Advanced Solutions Sdn. Bhd. licensed the lubricant technology through Putra Science Park. The startup company was incorporated under the Innohub initiative.

Figure 3: Prof. Dr. Janet (5th from left) with her colleagues and organizers.

Figure 4: Prof. Dr. Janet (2nd from right) with her colleagues and Deputy Vice-Chancellor (Research and Innovation), Prof. Dr. Nazamid Saari (4th from left).

Figure 5: Prof. Dr. Janet with GrafinTok™.

ITEX 2021 - Silver Medal

ViVac UPM Aquafeed Vaccine: Oral feed-based vaccine for vibriosis in aquaculture

Report by: Assoc. Prof. Dr. Mohammad Noor Amal Azmai,
Department of Biology, Faculty of Science, Universiti Putra Malaysia.

Aquatic Animal Health and Therapeutics Laboratory, Institute of Bioscience,
Universiti Putra Malaysia.

e-mail: mnamal@upm.edu.my

ViVac UPM Aquafeed Vaccine is a feed-based vaccine against vibriosis in fish, particularly marine fishes. It comprises of an antigen, which is the inactivated *V. harveyi* strain VH1 mixed with 10% palm oil before being incorporated into commercial fish feed. The vaccine is administered orally via feeding at 4-5% bodyweight and the vaccination regimen consist of three phases of vaccination. The first vaccination is by feeding of the feed containing the vaccine, the second phase is a booster dose at week 2, and the third is the last booster on week 6.

This vaccine confers high protection in fish with relative percentage survival (RPS) of 70-85% post-infection with virulent *Vibrio* spp. under experimental conditions. The oral vaccine was later tested for field efficacy and showed 70-80% survival in farmed hybrid grouper *Epinephelus fuscoguttus* × *E. lanceolatus* and Asian seabass *Lates calcarifer*.

This oral vaccine is unique in terms of its cost-effectiveness, easy delivery and safe to the environment. Rather than applying antibiotics that are unsustainable to prevent bacterial diseases, this oral vaccine can stimulate both mucosal and systemic immune responses that prevent infection by *Vibrio harveyi*, *V. parahaemolyticus* and *V. alginolyticus*. Generally, from the existing technologies, all vaccines are targeting *V. harveyi* with slight modifications of the preparation methods, while the administration is by injection, either intramuscular or intraperitoneal. However, injectable vaccines require trained personnel, handling that stressed the fish and time-consuming. Since most of the aquaculture products are from Asia and Asian farmers are small to medium-sized holders, injectable vaccines are not their favour. Not only that, all existing vaccines against warm water vibriosis are actually monovalent that are effective against only *V. harveyi* and not against other *Vibrio* spp. Besides, some of these vaccines use commercial adjuvants, which contributes to the high cost of vaccine preparation and vaccine price.

To solve the problems, our vaccine is a feed-based vaccine, which is administered orally through feeding. In other words, vaccination is done while the farmers are feeding their fish. Therefore, trained personnel are not needed, no fish handling is required, and the fish could be vaccinated in a short period of time. Moreover, the vaccine uses palm oil as an adjuvant. Locally abundant palm oil contains a high level of Vitamin E that is essentials in enhancing the efficacy of this feed-based vaccine. The cheap palm oil will eventually result in a cheaper vaccine.

This newly developed feed-based vaccine uses locally isolated *V. harveyi* strain VH1 as the antigen. It has been shown that the strain used in this vaccine provides cross-protection against other species of *Vibrio*, including *V. harveyi*, *V. parahaemolyticus*, and *V. alginolyticus*. Thus, with one vaccine application, infection by almost all-important *Vibrio* spp. in this region is controlled or could significantly reduced.

ITEX 2021 - Silver Medal

PATENTED QVID-X SOLUTION AS ECO-FRIENDLY, NATURAL AND NON-TOXIC GERMICIDE AGENT

Report by: Dr. Nur Kartinee Kassim,
Department of Chemistry, Faculty of Science, Universiti Putra Malaysia.
e-mail: kartinee@upm.edu.my

MALAYSIA PATENT APPLICATION NO. PI 2020004195
INTERNATIONAL PCT APPLICATION NO. PCT/MY2021/050066

CURRENT ISSUES

The COVID-19 pandemic has led to a rise in hospital-onset resistant infections such as Methicillin-resistant Staphylococcus aureus (MRSA). COVID-19 patients admitted in ICUs are coinfected with multidrug-resistant bacteria such as Acetinobacter baumannii. For the infection control, alcohol-based hand sanitisation is widely considered to be effective to reduce or eliminate bacterial/viral load.

WHO recommended alcohol based hand sanitisers which are made up of ethanol, isopropyl alcohols and hydrogen peroxides in different combinations (WHO, 2020). However, these chemicals have known toxic and hazardous impact on human health and environment when misused. It is recognised that ingestion of low concentration of hydrogen peroxide (3% solution) is responsible for minor gastrointestinal tract irritation (Moon et al., 2006) and in a few cases it is also responsible for portal vein embolism (Sung et al., 2018) and mild mucosal irritation and vomiting (ATSDR, 2014)

BRIEF TECHNOLOGY, INVENTION AND NOVELTY

Patented Qvid-X solution is a non alcoholic, natural and non toxic germicide agent which can decrease the infectivity, morbidity, and rate of mortality associated with pathogens and microorganisms. The product formulation is made from 100% food grade ingredients and thus biodegradable. The invention is a plant-based nano emulsion solution with the size less than 200nm. The operational process is green synthesis, simple and affordable. The nano delivery system improves the efficacy, stability and ease of handling.

In vitro antibacterial and antiviral study of the Qvid-X solution at the Medical Faculty of UPM has shown that it can kill hospital acquired bacteria particularly MRSA and Acinetobacter baumannii , which is a common threat to public health but with limited therapeutic options. The solution also has antiviral activity when tested on human coronavirus OC43 (HCoV-OC43) which is a beta coronavirus under the same group as the SARS-COV-2. It also exhibited good antioxidant properties and the activity is comparable to Vitamin E. The cytotoxicity test conducted on a few cell lines showed low IC_{50} values.The invention is unique which can be used as dual therapy in managing bacteria and viral infections. The product is suitable to be used as surface decontaminant in hospitals, health care services even as a household cleaning agent and also as hand sanitisers. The alcohol free and antioxidant properties of the Qvid-X solution give minimum toxicity, safer and kind to the skin. The lemon scented of the product deodorise the treated area or skin and leave it as fresh, clean and bright. This novel and natural formulation containing terpenes as active ingredient offers greater safety as a sustainable alternative, effective and lower production cost which has a high chance of turning into profitable business products

The invention is the outcome from the collaborative research between Faculty of Science and Faculty of Medicine. The team members include Dr Nur Kartinee Kassim as a project leader (Natural Product Chemist), Dr Norazlinaliza Salim (Colloid Chemist), Professor Dr Rukman Awang Hamat (Consultant Microbiologist) and Assoc. Professor Dr Chee Hui Yee (Virologist).

Science is much more than just a body of KNOWLEDGE. It is a way of THINKING.

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Farah Syakila Mohd Raziff

FACULTY OF SCIENCE, UNIVERSITI PUTRA MALAYSIA, 43400 UPM SERDANG, SELANGOR DARUL EHSAN, MALAYSIA
+603 97696601/6602/6603 www.science.upm.edu.my fs_tdps@upm.edu.my