ANTI-CANCER STUDY OF 1'-S-1'-ACETOXYCHAVICOL ACETATE EXTRACTED FROM MALAYSIAN *Alpinia conchigera*

Currently, there is no approved anti-cancer drugs in Malaysia despite its abundant natural resources and initiatives on potential drugs such as tocotrienol from oil palm and silvestrol from a rainforest tree. In our efforts to contribute, we started with the chemical investigations of the Malaysian ethno-medicinal Zingiberaceae plant *Alpinia conchigera* and isolation of its active compound, 1'S-1'-acetoxychavicol acetate (ACA). The chemical structure of ACA with a terminal double bond and an acetoxyl group at position C-1' is responsible for the cytotoxic effect or cell killing effect against human cancers (Fig. 1) (Awang et al., 2010).

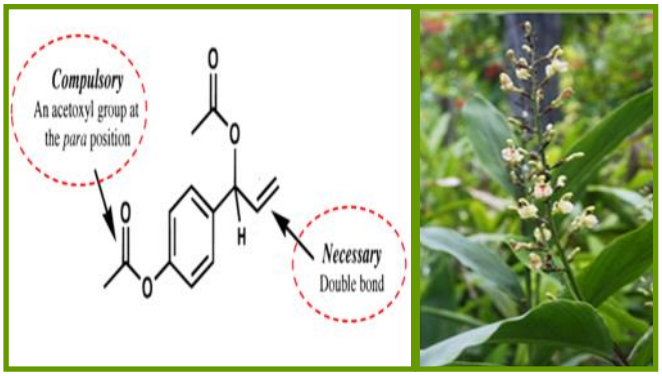

Fig. 1: Chemical structure of the Malaysian isolate, ACA from *Alpinia conchigera* Griff. (Zingiberaceae)

Previous cell culture and animal model analyses showed ACA induces apoptotic cell death in cancer cells and reduces physiological side effects on normal cells (In et al., 2012). In spite of the high anti-cancer efficacy of ACA, various clinical development drawbacks were anticipated, such as, poor solubility, depreciation of biological activity and non-specific targeting of tumour cells. In a collaborative study with Institute of Engineering Immunology, Russia, these problems were addressed using their novel drug conjugation technology involving a recombinant human alpha fetoprotein (rhAFP) and ACA. Synergism was observed due to the ability of ACA to induce apoptosis effectively together with rhAFP as a result of specific recognition of tumour cells that express AFP-receptors (Fig. 2)(Norhafiza et al., 2015).

To study the synergistic effect of ACA and rhAFP on human prostate and lung cancer grafts, athymic (with no cell-mediated immunity) mice were treated with stand-alone and combination regimens. The combined treatments displayed higher reductions in tumour volume (Fig. 3) with milder signs of systemic toxicity, such as, minimal loss in

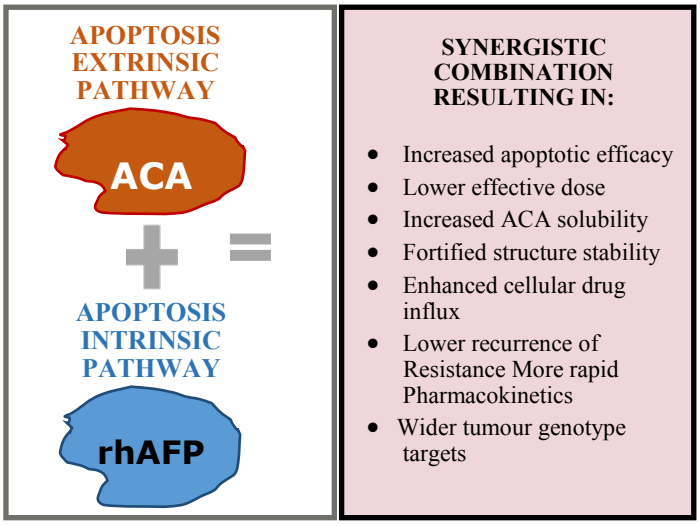

Fig. 2: Synergistic effects of ACA and rhAFP via extrinsic and intrinsic apoptosis-mediated pathways

body weight and reduced inflammation of vital organs compared to stand-alone agents (Fig.4) (Norhafiza et al., 2015).

Tumour marker levels were consistent for all ACA/rhAFP treatment groups where levels of cancer biomarkers, carcinoembryonic antigen (CEA) and prostate specific antigen (PSA) were elevated at the start of the treatment and consecutively reduced as the tumour bulk volumes decreased (Fig. 5) Also, the combined treatments showed reduced levels of all important cancer-associated and inflammatory proteins (Norhafiza et al., 2015).

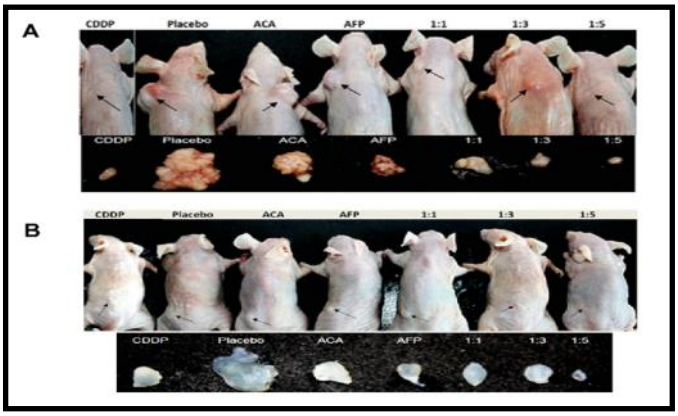

Fig. 3: Tumour reduction effects of various rhAFP/ACA treatment regimens on athymic mice. Location of all surface tumour sites are indicated by closed arrows, and representative photographs (n=6) of tumours harvested 35 days post-implantation for (A) Human lung A549 tumour grafts and (B) Human prostate PC-3 tumour grafts. Saline solution 0.9% (w/v) sodium chloride was used as placebo, while cisplatin (CDDP) (10.0 mg/kg) was used as a positive control reference

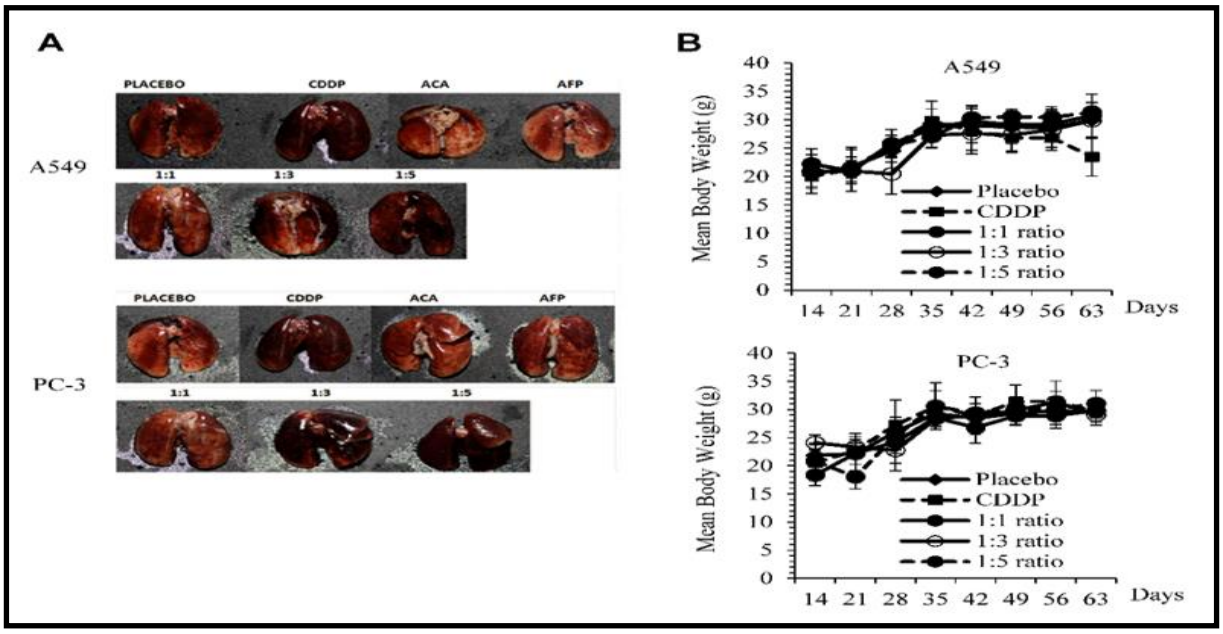

Fig. 4: Physiological side effects of rhAFP/ACA in mice. **(A)** Signs of pulmonary inflammation and capillary haemorrhaging in cisplatin (CDDP) treated groups and at high rhAFP/ACA molar ratio regimens (≥1:3) compared to placebo in A549 human lung and PC-3 human prostate tumour grafts. **(B)** Assessment on mean ± S.D. body weight loss between various combined rhAFP/ACA treatment groups on A549 lung and PC-3 prostate grafts. Placebo denotes groups treated with 0.9% (w/v) sodium chloride solution while concentration of CDDP was set at 10.0 mg/kg once per week

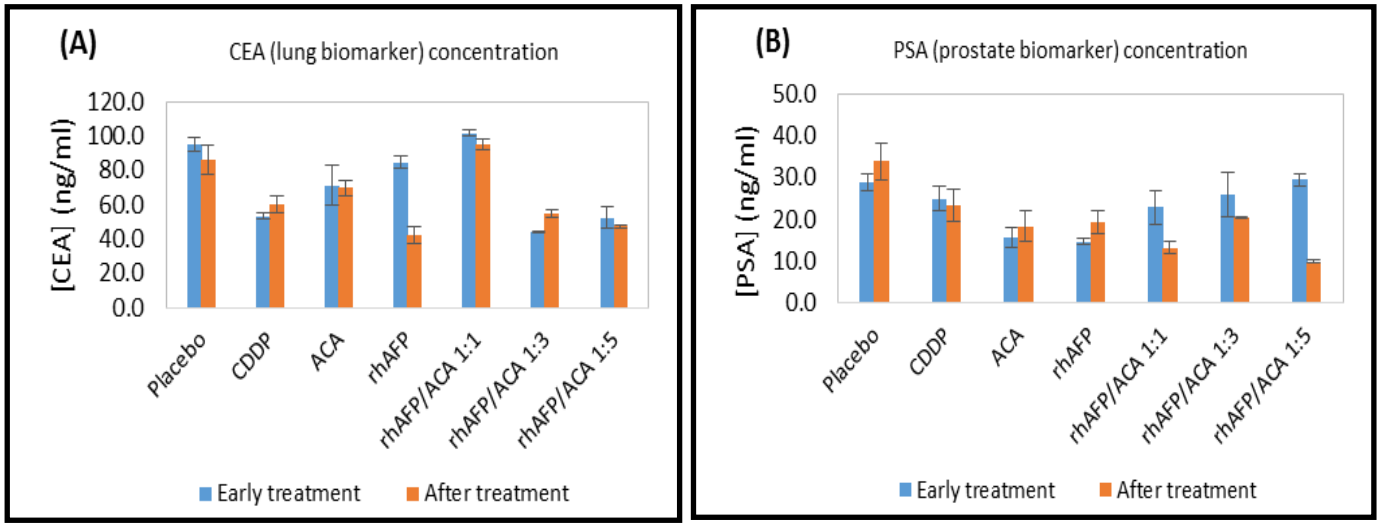

Fig. 5: CEA (lung) and PSA (prostate) tumour antigen marker levels. CEA and PSA tumour antigen marker levels from blood sera of athymic mice with **(A)** A549 human lung tumour grafts and **(B)** PC-3 human prostate tumour grafts upon treatment with rhAFP/ACA complex at various molar concentration ratios in comparison to placebo, stand-alone and CDDP controls

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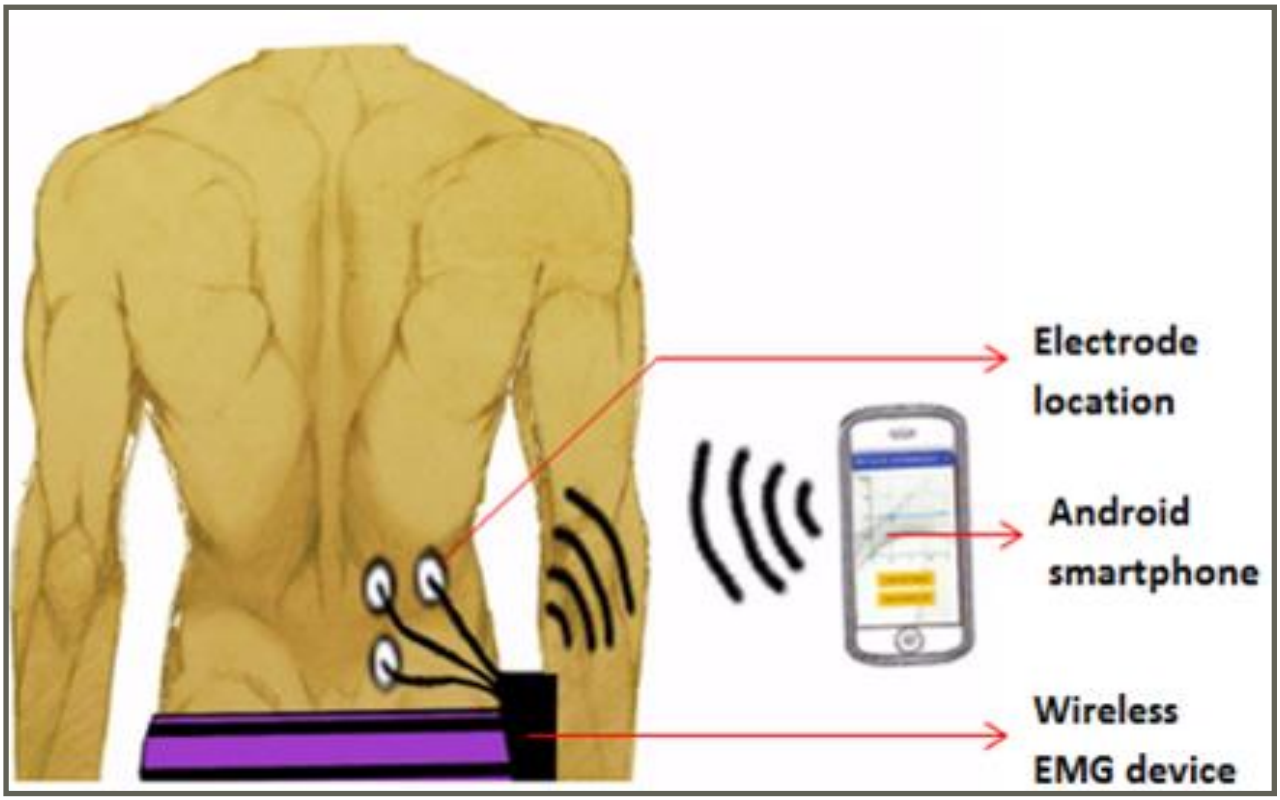
This research is exemplary of a fusion between traditional medicinal knowledge with the present advanced modern technology of protein conjugation. It has great therapeutic potential and is a pioneer for the basis of future anti-cancer drug developments. This project has graduated 2 PhDs, filed 1 patent, published 6 ISI Q1/Q2 papers and 3 on-going PhD research studies in toxicity, toxicokinetic, pharmacokinetic, pharmacodynamic and nanodelivery of ACA.

SMART WEARABLE DEVICE FOR MONITORING LOW BACK PAIN (MyEMG)



Wearable device for monitoring low back pain rehabilitation (MyEMG)

Low back pain (LBP) is a common discomfort that usually occurs among adults aged between 30 and 60 year olds. According to Institute for Health Metrics and Evaluation Malaysia, LBP is the leading cause of disability since 2005 and the number has been increasing over the past 12 years. LBP is identified as most common cause of work disability. World Health Organization estimated 60% to 70% common LBP in industrialized countries, approximately 20.5 million Malaysian has encountered LBP at least once in their life time. LBP usually caused by strained muscle or ligaments, results from abrupt movement and muscle spasm. The current assessment and evaluation of low back pain is based on questionnaires on patient's level of pain and discomfort such as the modified Roland-Morris Disability Questionnaire (MRMQ), a simple verbal pain severity scale, a modified pain symptoms frequency and bothersome-ness indices, Fear-Avoidance beliefs Questionnaire (FABQ), Baecke Physical Activity Questionaire (BPAQ) and work satisfaction scale. However, the accuracy of this questionnaire assessment is limited because the degree of pain and discomfort suffered by patients are described qualitatively without any measurement performed to the low back pain muscle. This qualitative assessment can be highly subjective and has limited accuracy in accessing progress of rehabilitation. Thus, there is a necessary to develop an Electromyography (EMG) instrumentation system that can monitor the progression of low back pain muscle. A smart wireless EMG, MyEMG device integrated with smartphone based application is developed to monitor the progression of low back pain rehabilitation. The system consists of EMG acquisition hardware in conjunction with signal processing and analysis software application on Android smartphone. The device acquires EMG signals from erector spinae (ES) muscles at L4 and L5 lumbar region. The signals are then processed, amplified and sent to microcontroller for analog-digital conversion. Real time EMG signals are sent wirelessly to smartphone based application for calculation of muscle signal activities. The performance of EMG device has been verified and tested on ES muscle of a healthy subject. Real time EMG data can be sent to Android smartphone wirelessly through Bluetooth communication. Clinical application developed in Android smartphone is able to display real time EMG signals and calculate the muscle values to analyse progress of rehabilitation. The transmitted EMG signals of ES muscles are stored in the application and use to perform the muscle signal calculation. To analyse the improvement of muscle, muscle

signals are compared before and after interventions. These values quantified the improvement in LBP after rehabilitation. The integration of MyEMG device with smartphone application can be used to monitor the progress of LBP rehabilitation.

Currently, there is no diagnostic equipment available for LBP assessment in the market. MyEMG is a low cost, non-invasive, portable, wearable and wireless device. It is in the commercialization process to target rehabilitation clinics/hospital, commercial vehicle drivers, NIOSH, PERKESO and personal care.

MyEMG research is led by Prof. Ir. Dr. Fatimah Ibrahim along with team members: Prof. Jong Man Cho, Assoc. Prof. Dr. Mazlina Mazlan (UMMC), Dr. Anwar Suhaimi (UMMC), Aung Thiha, Karunan Joseph, Siti Hajar and Nor Amirah Mohd Noh. Due to its novelty and high impact potential, MyEMG has achieved a brilliant track record in various competitions.

MyEMG has won several awards such as the 11th International Convention on Rehabilitation Engineering & Assistive Technology 2016 (i-Create 2016) under merit award that was held in Thailand, first prize in the IEEE Final Year Project Online Competition 2016 and gold award in University of Malaya Final Year Project 2016. MyEMG was also presented to the Guest of Honour, Her Royal Highness Princess Maha Chakri Sirindhorn of Thailand. At present, MyEMG has been chosen as one of the UM's special products for Malaysia Commercialization Year (MCY) 2017. This programme is held to acknowledge the progress of commercialization by Research Institutes and Research Universities in Malaysia. In addition, MyEMG has been featured in several local newspapers, such as Kosmo, Berita Harian and Utusan Malaysia.

info

MyEMG rawatan sakit belakang

MyEMG

→ **Penyelidikan** bermula 2013
→ **Siap** sepenuhnya tahun lalu
→ **Memberi** maklumat aktiviti isyarat otot secara kuantitatif
→ **Membantu** perawat pemulihan memantau perkembangan pesakit secara lebih dekat dan berkesan
→ **Kajian** Pertubuhan Kesihatan Dunia (WHO) pada 2010 menunjukkan 60 hingga 70 peratus kebarangkalian untuk seseorang mengalami sakit belakang dalam hayatnya
→ **Berikutan** peningkatan peratusan golongan berusia di seluruh dunia, masalah sakit belakang dilihat akan meruncing pada masa hadapan
→ **Kaedah** rawatan untuk sakit belakang lazimnya memerlukan pesakit melakukan senaman fizikal, dan keberkesanan kan dipantau perawat pemulihan atau hli fisioterapi dari emasa ke semasa

Oleh Basir Zahrom
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Kuala Lumpur

Pusat Inovasi Kejuruteraan Perubatan (CIME) di Jabatan Kejuruteraan Bioperubatan, Fakulti Kejuruteraan, dengan kerjasama Fakulti Perubatan, Universiti Malaya (UM), berjaya membangunkan sistem mudah alih lengkap untuk pengurusan rawatan sakit belakang dinamakan MyEMG.

Ketua Penyelidik CIME, Prof Ir Dr Fatimah Ibrahim, berkata inovasi penyelidikan sejak 2013 dan siap sepenuhnya tahun lalu itu dilengkapi komponen penderia isyarat otot atau Electromyography (EMG) yang ditempatkan pada permukaan kulit pesakit menyelaputi otot 'erector spinae'.

Katanya, ujian awal melalui kaedah 'motosikal statik' dijalankan ke atas 50 penunggang lelaki dan wanita dengan tahap kesihatan otot masing-masing diukur menggunakan alat EMG, selain soal selidik.

Beliau berkata, otot yang selari dengan tulang belakang itu memainkan peranan amat penting dalam mengekalkan kestabilan tulang belakang manusia, dan isyarat elektrik aktivitinya boleh dijadikan sandaran kepada korelasi keberkesanan rawatan pemulihan sakit belakang melalui senaman fizikal.

Penilaian subjektif

"Penderia yang mengesan isyarat EMG otot akan menghantarnya pula ke bahagian pemancar (transmitter) khas yang boleh dilekatkan pada seluar pesakit atau diletakkan di dalam poket.

"Unit ini seterusnya akan berkomunikasi dengan aplikasi mudah alih Android pada telefon mudah alih pesakit menggunakan capaian teknologi Bluetooth.

"Algoritma khusus bagi menentukan keberkesanan rawatan pemulihan turut dimuatkan dalam aplikasi ini, selain membenarkan pemantauan terhadap prestasi dan kadar 'keletihan' (fatigue) otot pada ketika dan selepas melakukan senaman," katanya.

Mengulas lanjut, Prof Fatimah berkata, idea menghasilkan sistem itu tercetus apabila beliau dimaklumkan bahawa kaedah pengurusan rawatan sakit belakang adalah bersandarkan penilaian subjektif terhadap pesakit semata-mata.

Beliau berkata, keadaan itu agak menyukarkan perawat untuk menentukan kadar keberkesanan rawatan pemulihan, terutama yang membabitkan pesakit berusia.

Kaedah kuantitatif

"Berbekalkan kemahiran pembangunan peranti dimiliki penyelidik CIME dan kepakaran klinikal di Fakulti Perubatan UM, kami berjaya membangunkan sistem mudah alih ini.

"Melalui kaedah kuantitatif sebegini, pemantauan rawatan pemulihan sakit belakang boleh dilakukan oleh perawat pemulihan secara lebih sistematik, malah pesakit membuat pemantauan kendiri dan memaklumkan sebarang perubahan dengan lebih baik tanpa bergantung kepada penilaian subjektif," katanya.

Inovasi MyEMG *yang dihasilkan untuk membantu pengurusan rawatan sakit belakang.*

Gambar rajah *menunjukkan cara MyEMG berfungsi.*

Prof Fatimah

i-Create 2016

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