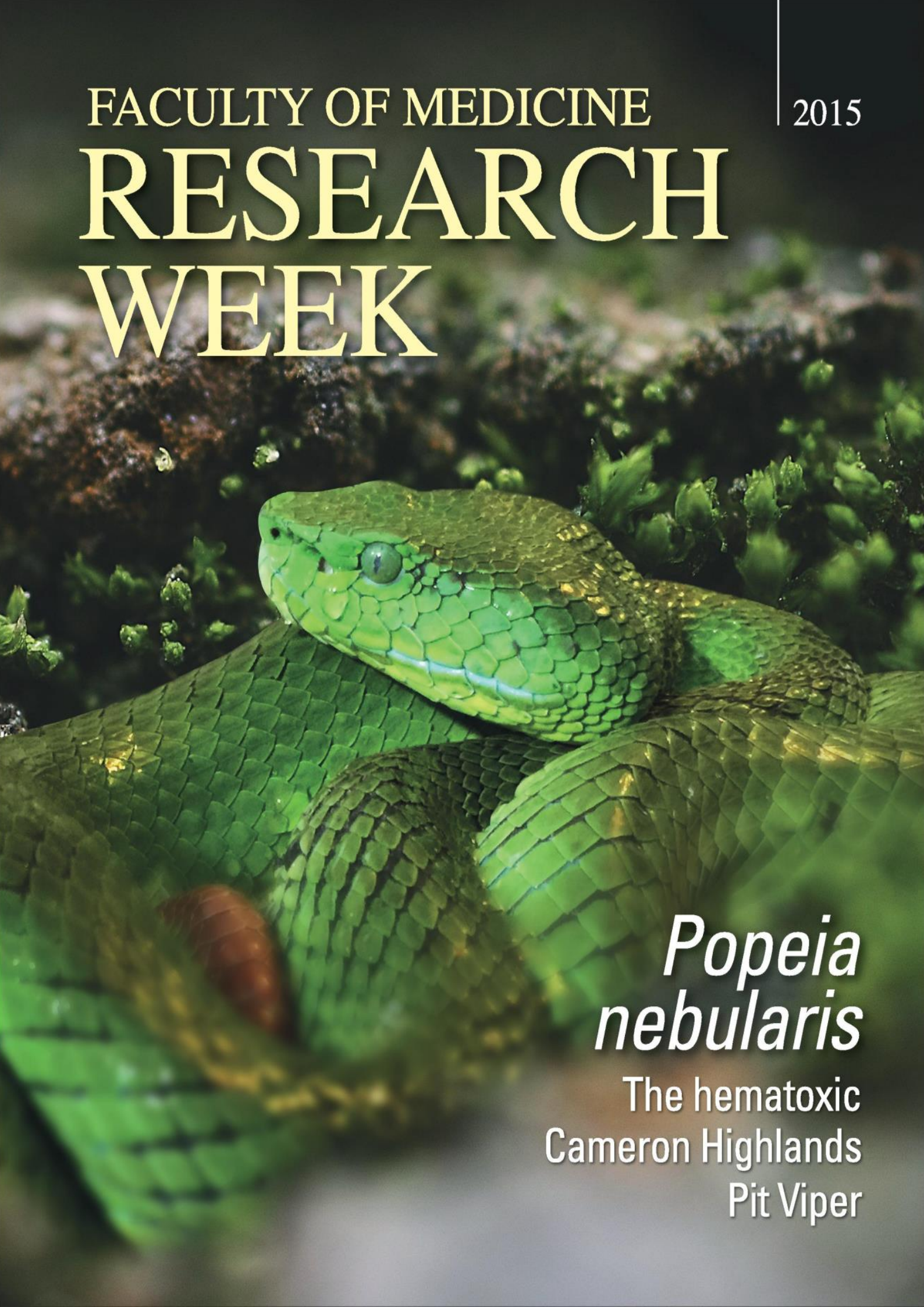
FACULTY OF MEDICINE

RESEARCH WEEK

2015



Popeia nebularis

The hematoxic Cameron Highlands Pit Viper

Cover Art for Faculty of Medicine Research Week 2015

By Dr. Tan Choo Hock, Department of Pharmacology, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia, Email: tanch@um.edu.my

Description:

The cover page depicts the Cameron Highlands pit viper (*Popeia nebularis*, syn: *Popeia inornata*), a beautiful endemic species with venom that can cause coagulopathy and hemorrhagic syndrome. Studies on venom toxin profiling, antivenom neutralization and potential drug discovery are undertaken at the Venom and Toxin Research Laboratory, Faculty of Medicine, UM. The photo was taken on a specimen of author's personal collection with a smart phone and displayed using Illustrator software.

Foreword: Faculty of Medicine Research Week (FOMRW) 2015

The ***Research Week*** is a prestigious annual event of the Faculty of Medicine, University of Malaya. Throughout the years, research undertaken at the Faculty of Medicine in UM continues to achieve national and international impact, making constructive changes that benefit the society. The Faculty of Medicine Research Week celebrates these achievements through a series of activities that cultivate the passion in research and foster networking among researchers from within and without the university.

The year 2015 has marked the third annual Research Week of the Faculty of Medicine. This year, the Department of Pharmacology and the Department of Pharmacy hosted the event from 11th (Monday) to 15th May (Friday) at the Faculty of Medicine. The Faculty of Medicine Research Week 2015 carried the theme "From Powder to Pill & Pill to Heal", and it aims to create awareness among the stakeholders about the diverse research programmes currently going on in the Faculty, in particular the two departments. Specifically, the event was launched with the following objectives:

1. To showcase ongoing research activities in the Faculty of Medicine, particularly from the Department of Pharmacology and the Department of Pharmacy
2. To encourage and establish inter-disciplinary collaboration amongst researchers within the University of Malaya and with other institutes of higher learning so as to achieve excellence in research
3. To recognise academic staff, post-doctoral researchers and students who are actively engaged in quality research
4. To enhance external visibility of the research through attendance of invited local and international speakers, participants from other institutes of higher learning, and representatives from industries, foundations and healthcare centres.

This year, the Faculty of Medicine Research Week was open to all from the campus and invited external guests. There was a series of research lectures, symposia, workshops, poster exhibitions, forum discussion and cover art competition throughout the week. The participants have found the event activities very relevant and beneficial to the development of their research career.

FOMRW15 Organizing Committee

Abstracts

Plenary Speaker

PS01

Targeting STAT3 signaling pathway in cancer: Pharmacological inhibitors and clinical implications

Gautam Sethi

Department of Pharmacology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, 117597

STATs comprise a family of cytoplasmic transcription factors that transmit signals, mediate intracellular signaling usually generated at cell surface receptors and transmitted to the nucleus. Numerous studies have demonstrated constitutive activation of STAT3 in a wide variety of human tumors. There is a strong evidence to suggest that aberrant STAT3 signaling promotes development and progression of human cancers by either inhibiting apoptosis or inducing inflammation, cell proliferation, angiogenesis, invasion, and metastasis. Suppression of activation of STAT3 results in the induction of apoptosis in tumor cells, and accordingly its inhibition by approaches such as tyrosine kinase inhibitors, antisense oligonucleotides, decoy nucleotides, dominant negative proteins, RNA interference and chemopreventive agents have been employed to suppress the proliferation of various tumor cells and tumorigenicity in vivo. However, the development of novel drugs for the targeting STAT3 that is both safe and efficacious remains an important scientific and clinical challenge. My talk will provide the evidence for critical roles of STAT3 in oncogenesis and discusses the potential for development of novel cancer therapies based on mechanistic understanding of STAT3 signaling.

PS02

Visualization of tableting process based on self-organizing map and finite element analyses

Kozo Takayama

Department of Pharmaceutics, Hoshi University, Japan

Tablets are widely used dosage form for the oral administration of drugs. To design a tablet formulation, the formulator must consider a wide range of characteristics, such as the disintegration time, dissolution rate, hardness, stability, and so on. In most cases, the relationships between the formulation factors, process variables and the tablet properties are complex, and the effects of the causal factors are substantially changed by the changing physicochemical properties of the active pharmaceutical ingredients (APIs). We have successfully created the tablet dataset composed of over 1,000 formulations including several different compounds as APIs. To visualize the internal structure of the tablet dataset, the self-organizing map was applied and the analysis clearly revealed the latent activity of the tablet dataset. The feature mapping suggested the involvement of physicochemical properties of APIs on the critical pharmaceutical characteristics. Various stresses remain in tablets after tableting process, because of the induction of elastic recovery. This type of stress, the residual stress distribution, affects tablet characteristics and often causes tableting problems. The Drucker-Prager Cap (DPC) model is one of the continuum mechanical models, in which the powder is considered as a porous medium. Several studies have reported using the finite element method, in which the powder is modeled using the DPC model. We have demonstrated that the residual stress distribution of tablets was affected by formulation and process variables, and was closely related to the characteristics of the tablets.

PS03

Biased activity of soluble guanylyl cyclase and vasospasm

Paul Vanhoutte

State Key Laboratory of Pharmaceutical Biotechnology and Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, University of Hong Kong, Hong Kong

In coronary arteries, hypoxia causes an acute augmentation of vasoconstrictor responses that is dependent on the presence of nitric oxide (NO) and activation of soluble guanylyl cyclase (sGC). This hypoxic effect is accompanied by increases in the intracellular level of inosine 5'-triphosphate (ITP) and in the synthesis of inosine 3',5'-cyclic monophosphate (cIMP) by soluble guanylyl cyclase (sGC). The hypoxic augmentation due to increased activity of Rho kinase (ROCK), indicating that cIMP may mediate the hypoxic effect by sensitizing the myofilaments to Ca2+ via ROCK. Hypoxia is implicated in exaggerated vasoconstriction in the pathogenesis of coronary artery disease, myocardial infarction, hypertension and stroke. Similar endothelium-dependent, NO-dependent and sGC-dependent contractions can be evoked with thymoquinone, which also augments the levels of cIMP. The understanding of the role of this non-canonical cyclic nucleotide may help in identifying novel therapeutic targets for certain cardiovascular disorders.

PS04

Interrupting the renin angiotensin aldosterone system; the good, not so good and the dicey

Abdul Rashid Abdul Rahman

Malaysian Institute for Graduates and Higher Training, Kuala Lumpur, Malaysia

The importance of the Renin Angiotensin Aldosterone System (RAAS) in pathophysiology came to the forefront 81 years ago with the Goldblatt Hypertension model. It not only propelled Harry Goldblatt to international scientific stardom, but also brought renin and the RAAS into scientific prominence. The next big leap forward was not made in the laboratory but in the sugar cane plantations in Brazil. Workers in the plantation were observed to collapse after being bitten by the viper (*Bothrops jararaca*), which eventually lead to the discovery of orally active Angiotensin Converting inhibitor (ACEI), captopril, almost exactly 40 years ago. By the late 70s and early 80s ACE inhibitors were approved for the treatment of hypertension mainly by virtue of its action of the tissue RAAS system. The next big leap with the RAAS in general and ACEI specifically came in the mid 80s when the role of circulating RAAS in pathophysiology of heart failure was better characterised. This lead to seminal animal experiments and clinical trials, which established the role of ACE inhibitors as the cornerstone in the treatment of systolic heart failure by the late 80s. By the early 1990s the role of circulating RAAS was demonstrated in the post myocardial infarction experimental model followed by a series of landmark clinical trials, which confirmed the important clinical benefits of ACEI post myocardial infarction. By the mid 1990s, ACEIs are established treatment for hypertension, systolic heart failure and post myocardial infarction. By the late 1990s and early 2000s, the benefits of ACEI were further enhanced with clinical trials confirming its benefits in high risk cardiovascular patients and in diabetics, with or without nephropathy. Pharmacologically, there are other and potentially better ways to interrupt the RAAS. Angiotensin II Receptors Blockers (ARBs) was approved in the mid 1990s but for all its theoretical benefits with a more targeted mode of action, it did not live up to its reputation of being superior to ACEI. It now remains a drug to be considered in ACEI intolerant patients. Orally active Direct Renin Inhibitors (DRIs), which came to the market less than a decade ago, also promises a better approach to interrupt the RAAS. It however stumbled almost at the first hurdle when important clinically outcome trials published over the last 5 years failed to show benefits but instead unmasked potential harm. The RAAS however continue to intrigue us. Interrupting the RAAS at the aldosterone level has shown surprising benefits in both severe systolic heart failure and more recently in mild systolic heart failure and diastolic heart failure. Very recently, a drug with a combined action of angiotensin receptor and neprilysin inhibitor (LCZ 696) has shown potential as the next major advancement in hypertension and heart failure in two decades. The next few years will either confirm or refute this. Interrupting the RAAS has been one the most rewarding story in all of medicine over the last century and the final chapter has certainly not been written yet. It has been a success story of ‘from bench to bedside ‘, and a classic example of “from powder to pill and from pill to heal”.

Symposium Speakers

SS01

Harnessing Tumor-Stromal Cell Interaction for Cancer Drug Discovery

Ivy Chung

Department of Pharmacology, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia

Cancer was once thought to be a 'stand-alone' malignancy where we treat patients with drugs that target only cancer cells. Recently, more evidence is showing that cancer cells do not thrive alone, they rely on their environment to maintain their survival and to progress into an aggressive state. The tumor microenvironment is made up of endothelial cells, adipocytes, mesenchymal cells, mesenchymal stem cells, macrophages and fibroblasts. It is now uncontested that these components are very important in supporting the growth of tumor and impacting the outcome of therapy. Interestingly, these niche cells are endowing chemoresistance through distinct mechanism including cell-cell and cell-matrix interactions influencing the cancer cell sensitivity to apoptosis, local release of soluble factors enhancing survival and tumor growth and direct cell-cell interactions with tumor cells. Our laboratory primarily interested in understanding how the microenvironment surrounding cancer cells can be explored in designing better therapy for cancer patients. In particular, we are interested in a special type of fibroblast cells, known as cancer-associated fibroblasts. There is abundant data showing that these fibroblasts actively communicate with cancer cells and such interaction has affected the behavior of many cancer types, including breast, prostate and pancreatic cancer. In this talk, I will discuss some evidence we obtained recently from an endometrial cancer model, that demonstrate the importance of cancer-associated fibroblasts in tumor progression, and how we can harness their biology when developing new therapy for this disease.

SS02

Can we rely on natural products for cancer prevention and therapy?

Looi Chung Yeng

Department of Pharmacology, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia

Conventional cancer therapies (e.g. radiotherapy) cause serious side effects and, at best, merely extend the patient's lifespan by a few years. Thus, there is a need to utilise alternative concepts or approaches for cancer treatment. Phytochemicals derived from fruits, vegetables and other plants are potential therapeutic agents. In addition to their cancer preventive effects, they are relatively non-toxic and inexpensive. With the advent of medicinal chemistry, researchers are now looking at small molecules, proteins, inorganic and organomethallic compounds as potential anti-cancer drugs. However, there is also a great need to investigate the potential benefits and risks of administering *synthetic* or biologic/chemical *agents* to reverse, suppress, or prevent carcinogenic progression. *We have* recently *attempted* to identify *synthetic* or biologic/chemical *agents* that act through the apoptotic pathway to kill cancer cells. Although the search for *synthetic* or biologic/chemical compounds with few or no adverse effects is challenging, it will remain as a top priority in our drug discovery research.

SS03

Polymer conjugate as nanosized medicine in anticancer chemotherapy

Kiew Lik Voon

Department of Pharmacology, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia

The development and use of nano-medications for anticancer therapy has grown tremendously in the past three decades. This follows the breakthrough discovery in the 1980's on the enhanced permeability-retention (EPR) effect, a phenomenon that bestow tumour homing capabilities to the nano-medications. Using nano-sized polymer-therapeutics, a fast growing subclass of nano-medication as the model, this talk will review the basic working principles of the nano-medications and their advantages over the conventional small molecular size drugs in cancer treatment. This talk will also introduce to the audience recent advances in the anticancer polymer-therapeutics research in the international arena; related research that is currently ongoing in the Faculty of Medicine, University of Malaya; as well as the current concerns and future perspective of the polymer-therapeutics R&D.

SS04

Halal pharmaceutical

Amrahi bin Buang

Deputy Director (Clinical), University Malaya Medical Centre, University of Malaya, 50603 Kuala Lumpur, Malaysia

Halal pharmaceuticals are a relatively new subject in the pharmaceutical industry. Even though it is meant to fulfil the needs of the Muslim patients, it is suitable for all patients. Halal is considered a new value in the supply chain of medicines. Various efforts are done to define halal so that it can be accepted as a new and added value in the pharmaceutical industry. Previously, the major challenge to produce halal pharmaceutical products, both locally and globally is the non-existence of an internationally accepted manufacturing standard. However in 2011, various stakeholders in Malaysia, comprising of the National Pharmaceutical Control Bureau (NPCB), Standard Department Malaysia, Malaysian Religious Affairs Department (JAKIM), Halal Development Corporation (HDC), professionals and academicians have come together and finally established the Halal Pharmaceuticals – General Guideline in 2012 (MS 2424:2012). Currently, this is the only internationally accepted standard for the production of halal pharmaceuticals. The availability of this standard has lead to new opportunities for both local and international drug manufacturers to move forward in the challenging markets. The government of Malaysia has given immense support for local manufacturers to produce halal pharmaceuticals under the New Key Economic Areas. It has also been proposed to be in the 11th Malaysian Development Plan – 2016 to 2020. Under the National Medicines Policy, the promotion of halal pharmaceuticals for the various stakeholders is one of the three key performance indicators under the chapter of "Access to Medicines". The first halal vaccines for umrah and hajj pilgrims will be in the global market in 2017.

SS05

Snake venom: the bite that kills and heals

Tan Choo Hock

Department of Pharmacology, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia

Snake venoms are complex bioactive compounds with diverse pharmacological activities. Distinct from poisons, they are produced in specialized glands of certain animals and are delivered through specialized envenoming systems into the recipient tissues. In envenomation cases, venoms cause deleterious health effects; nonetheless, the pharmacologically diverse toxins in snake venoms constitute a valuable repertoire for drug discoveries. The two somewhat dichotomous values of snake venoms have been the centre of toxicology research over the past decades for the improvement of snakebite management and the innovation of therapeutic agents. In Malaysia, the *Venom and Toxin Research Group* (VTRG) at the University of Malaya has been studying venoms based on a translational research-orientated approach. The studies involve multidisciplinary methodologies, ranging from the classical biochemical and pharmacological assays to modern immunological and molecular technologies. More recently, the technique of functional transcriptomics and proteomics has assisted the group to unveil the complexity of many venoms in the region, providing deep insights into the compositional variation, pathophysiology as well as neutralization profiles of venom toxins. The outcomes are significant as they began to show positive impact on the medical practice. Besides, the continuous detailed characterization of toxins provides a platform for molecular manipulation of those natural bioactive compounds, opening the door to novel drug design in the future.

SS06

Potential anti-obesity assessment of selected medicinal plants in obese animal model

Mohammed Abdullah Mahdi Alshawsh

Department of Pharmacology, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia

Obesity is considered a significant health challenge in medicine. It has a negative impact on blood pressure, cholesterol, triglyceride and insulin sensitivity. Obesity has been associated with cardiovascular disease, diabetes mellitus and cancers. Despite the increasing public health preventive measures, obesity is on the rise in developed and developing countries. Factors that lead to obesity are modifiable and non-modifiable. Modifiable factors are diet, life style, physical activity and environmental factors while non-modifiable factors include genetics and ethnicity. Therefore, to assess the anti-obesity effects of medicinal plants, it is necessary to choose a suitable animal model. This will allow the study of the molecular mechanisms of obesity. A variety of natural products, including crude extracts and isolated compounds from plants, is expected to prevent diet-induced obesity and to reduce body weight by targeting various important pathways related to energy homeostasis. The mechanisms of action of medicinal plants in obesity could be by stimulating thermogenesis, enhancing lipolysis, lowering lipogenesis, decreasing lipid absorption, modulation of fat and suppressing appetite. Even though some medicinal plants showed promising anti-obesity activity in animal models, reports on their safety and efficacy in humans are still not established.

SS07

Genetic and epigenetic mechanisms linking diabetes and Alzheimer's disease

Batoul Sadat Haerian

Department of Pharmacology, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia

Diabetes mellitus (DM) is a group of metabolic disorders characterized by high blood glucose levels resulting from defects in insulin secretion, insulin action or both. Type 2 DM (T2DM) is one of the most common types of DM, accounted for 90-95% of the diabetic cases worldwide. Chronic high blood glucose levels in T2DM can damage several major organs leading to disabling or life-threatening complications. Evidence suggested that T2DM is also linked to development of Alzheimer's disease (AD). AD is a neurodegenerative disorder of the brain characterized by the presence of neuritic amyloid plaques and neurofibrillary tangles. Both T2DM and AD are aging-dependent diseases, contributed by an interaction between genes and environment. Many environmental factors (e.g., overweight, obesity, and inactivity) can modulate T2DM-AD related genes through epigenetic markers. Epigenetic mechanisms reversiblely change gene expressions at the molecular level without altering DNA sequence. DNA methylation, histone modification, microRNA (miRNA), and their interactions are the most frequently studied epigenetic mechanisms. Altered expression of certain miRNA molecules relevance to the T2DM-AD suggests that miRNAs could have a crucial regulatory role linking these disorders.

SS08

Endoplasmic reticulum stress: Their importance in metabolic related diseases

Dharmani Devi Murugan

Department of Pharmacology, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia

The endoplasmic reticulum (ER) is the key cell organelle responsible for protein translation, folding and trafficking. The maintenance of calcium homeostasis, and production and storage of glycogen as well as other macromolecules take place in the ER which is also the early site responding to cellular stress. Disruption in ER homeostasis or its function associated with oxidative stress, inflammatory reaction, high glucose or calcium deprivation, and the exposure to chemicals such as thapsigargin or tunicamycin leads to misfolding and aggregation of proteins within ER lumen; a process known as ER stress, leading to activation of a complex signalling network called the unfolded protein response (UPR), which coordinates adaptive and apoptotic responses to restore normal ER function. Accumulating evidences implicates prolonged ER stress in the development and progression of many diseases, including diabetes, hypertension, cardiac hypertrophy, atherosclerosis and ischemic heart disease. A detailed understanding of the mechanisms and consequences involved during ER stresses may provide promising therapeutics approaches for the treatment of human metabolic diseases.

SS09

Synergistic effects of flavonoids in experimental diabetes

Aditya Arya

Department of Pharmacy, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia

The traditionally used anti-diabetic plants that contain phytochemicals such as flavonoids are recently getting more attention and privilege in treating diabetes and its related complications. Our findings on different plants and their extracts enriched with polyphenolics and flavonoids have shown potential role in the management of diabetes and its associated complications in mouse pancreatic ß-cells as well as on the streptozotocin (STZ)-induced and STZ-nicotinamide-induced diabetic rat models. The role of flavonoids is probably by the enhancement of glucose metabolism or peripheral insulin sensitivity or insulin release in the islets cells, as we know the whole-body glucose homeostasis is regulated by the glucose transporter (GLUT) proteins, GLUT-2 and GLUT-4, which enhances the glucose uptake and insulin secretion by translocating the insulin-regulated glucose into the cells. The presence of flavonoids and polyphenolic compounds in plant extracts triggers the glucose ingestion by modulating the glucose transporter proteins and improving the insulin-signaling cascade. Thus, our findings support the synergistic effect of flavonoids in the management of hyperglycaemia and insulin resistance in diabetic rat models and therefore, open a new window of research on the combinatorial use of flavonoids in treating diabetes.

SS10

Research activities in biological product development

Yvonne Khoo

National Pharmaceutical Control Bureau, Ministry of Health, Selangor, Malaysia

Biological product development is highly encouraged by scientific discoveries through advances in the fields of molecular biology, proteomics and genomics. Some biotechnology-manufacturing giants today have started as spin-offs of academic research laboratories and are contributing extensively to the creation of novel biotherapeutics. This talk aims to provide an overview of past, present and future research activities supporting development and commercialisation of biological products. A history of some blockbuster biological product development is provided. The audience will be briefly walked through current biological technologies and the pipeline of biological products to come. The future of biological products is bright with a great anticipation of novel products as a result of rapid research progress. Examples include therapeutic vaccines and nanotechnology-based therapies. In the local front, a strong political will exists to gear up the local industry in the quest for made-in-Malaysia biological products. Some success stories will serve as motivation to our local researchers. The take home message is that basic research findings can lead to commercialisation of new technologies in biological drug development. Every researcher, big or small has good opportunity to contribute in this area. One only needs to identify a research niche pertaining to improving a product's delivery and safety, then work towards translating bench discoveries to bedside applications. An arduous but potentially rewarding path lies ahead.

SS11

Pharmacoeconomics

Fatiha Hana Shabaruddin

Department of Pharmacy, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia

The costs of health care have increased significantly in the past decade. Providing health services in a condition where rising costs are accompanied by the continuous emergence of new, innovative and often expensive treatment is a challenge to health care providers. Every health care budget has a limit and it is the responsibility of health care policy makers to decide how this budget is spent. Economic evaluation offers a framework to compare the cost and outcomes of a new treatment to current practice. The results of an economic evaluation can quantitatively describe whether a treatment is considered cost-effective. Many policy makers across the world now use data from economic evaluations to inform health care decision making. This talk will illustrate how adopting treatments that are cost-effective can optimise patient outcomes and the overall health of a nation.

SS12

A statin a day to keep the cardiologist away: Lessons from clinical trials and observational studies

Nur Lisa Zaharan

Department of Pharmacology, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia

In recent years, the public has become markedly more interested in assuring the safety and effectiveness of their prescribed medicines. Appropriate and valid pharmacoepidemiology methods are central to evaluating the safety and effectiveness of medicines and their use. Statins, a cholesterol lowering drug has been promoted strongly for prevention of cardiovascular diseases. The ability of statins to reduce cardiovascular events as evidenced by results from various randomized clinical trials (RCT) and the advice to initiate statins in those with high cholesterol levels by many clinical guidelines has lead this drug to assume the spot as the most widely prescribed drug in the world. The prescribing of statins in the population is expected to increase significantly with the latest American Heart Association (AHA) and the American College of Cardiology (ACC) guideline which advocate the early use of statins in those with cardiovascular risk factor, with less emphasis on their baseline cholesterol levels. The adverse effects of statins have also garnered wide attention both in the scientific community and the public media. Besides the commonly known adverse effects of myopathy, myositis and abnormal liver functions, interests have emerged on the risk of statins to induce new-onset diabetes, which in itself is also a cardiovascular risk factor. Meta-analyses of RCTs have shown increased risk of diabetes with the use of statins with different types and doses of statins showing different risks of diabetes. Large population based pharmacoepidemiological studies have consistently supported these findings. These pharmacoepidemiological studies utilized data from cohorts of different population such as the Women's Health Initiative study (US), the UK general practice research database, the Canadian hospital population and the Irish pharmacy claims database. In a cohort of hypertensive Malaysian population, use of simvastatin was associated with higher HbA1c in those with and without diabetes (adjusted OR=1.29, 95% CI 1.01, 1.65 (p=0.04). Long-term studies are needed to determine if the increased risk of diabetes with statin therapy may undermine the beneficial cardiovascular disease risk outcomes in different population. The case of statins and risk of diabetes illustrated how pharmacoepidemiological studies are important in providing supporting evidence of the risk of a drug in the general population in addition to data obtained from the gold standard RCTs.

Posters

P01

A Retrospective Analysis of the Medication Error in University Malaya Medical Centre

[1]Zakaria, MI; [3]Faridzatul Syuhada AR; [2]Che Zuraini S; [2]Buang, A; [3]Mokhtarudin, R

[1]Academic Unit Trauma and Emergency, University of Malaya, Lembah Pantai, Kuala Lumpur, 50603, Malaysia, [2]Department of Pharmacy, University Malaya Medical Centre, Jalan Universiti, Kuala Lumpur 59100, Malaysia, [3]Department of Quality, University Malaya Medical Centre, Jalan Universiti, Kuala Lumpur 59100, Malaysia

E-mail: idzwan@ummc.edu.my

Introduction: Medication error is defined as any preventable error occurring during the process of prescribing to administering of medication resulting in injuries. The objectives of this study were to determine and quantify the phases of medication errors and analyze the factors that contributed to the errors.

Materials & Methods: This was a retrospective study on the incidents of medication error reported using the EZFORM online incident reporting system in University Malaya Medical Centre (UMMC) from 2011 to 2014. A multidisciplinary Medication Safety Committee pioneered by UMMC was established. It conducted risk management strategies and developed policies and procedures which includes analyzing the rates of prescribing, dispensing and administration errors, evaluating the degree of severity and conducting root cause analysis (RCA) on the errors causing harm or death (serious safety events). Data were analyzed using Microsoft Excel 2010.

Results: Data analysis from 2011 to 2014 showed an increase in medication errors in 2012 due to the introduction of EZFORM that year. Then, it showed a steady decline in the subsequent years with a reduction of 68.7% from 2012 to 2014.

Prescribing error was the main cause of medication error followed by dispensing and administration errors. Common causes of dispensing error were failure to adhere to work procedure (21%), look and sound alike (LASA) medication related errors (32.36%), inexperienced personnel (13.6%) and working at peak hours (9.56%).

Discussions: The EZFORM has improved the rate of incident reporting. The subsequent years showed a steady decline of errors to 68.7% in comparison to Mc Clead RE et al which was 76.5%. One of the methods to reduce prescribing errors was the introduction of the integrated hospital based pharmacy information system with proper clinical decision support module.

Conclusion: The three main phases of medication errors were prescription, dispensing or administration errors and prescription error has the highest rate.

P02

The Role of CYP3A5 Polymorphism on Trough and Dose-Adjusted Trough Levels on Two Different Tacrolimus Formulations in Malaysian Post-Renal Transplant Patients

[1]Guad, RM; [1]Zaharan, NL; [1]Chik, Z; [1]Zahurin, M; [2]Ng KP, [2]Wan Md Adnan, WAH

[1]Department of Pharmacology, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia; [2]Department of Medicine, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia

E-mail: rhanyeguad@yahoo.com

Introduction: A once-daily formulation of tacrolimus has just been recently available in Malaysia in addition to the previously used twice-daily formulation. Variability of blood trough concentration (C0) in different formulations of tacrolimus due to CYP3A5 polymorphisms have been reported. We aimed to examine the role of CYP3A5 polymorphisms on the within-patient variability of trough and dose-adjusted trough levels of the different tacrolimus formulations in the Malaysian post-renal transplant patients. **Materials & Methods:** Ethics approval was granted by UMMC Ethics Committee #989.7). Post-renal transplant patients (n=28, 79% males) who were switched from twice-daily Prograf® (Tac-BID) to once-daily Advagraf® (Tac-OD) were recruited from University Malaya Medical Centre. Patients' trough levels and concomitant tacrolimus doses at 1st month, 2nd month, 3rd month, 4th month and 6th months; both pre- and post-conversion were examined. Blood samples were collected from venous blood and DNAs were isolated using Qiagen DNA purification kit according to manufacturer's instructions. Genotyping of CYP3A5 was performed using reverse transcriptase polymerase chain reaction. Tacrolimus levels and exposure indices within the different genotype groups were compared using Mann-Whitney U test. Comparison between groups was examined using one-way ANOVA.

Results: The majority of patients (54%) had low-expressive genotype (CYP3A5*3/*3), whereas only 32% and 14% of patients had intermediate or high-expressive genotypes (CYP3A5*1/*3 and CYP3A5*1/*1) respectively. There was no significant differences in the mean trough levels of both Prograf® and Advagraf® between the different genotypes. The average dose-adjusted trough level of the once-daily Advagraf® was significantly higher in patients with low-expressive genotype (156.94±50.81 ng.kg.day/mg.ml) compared to intermediate (87.52±47.73) and high-expressive genotypes (77.81±27.55) (p=0.002). **Discussions:** The pharmacokinetics of tacrolimus is influenced by several factors which include polymorphism of CYP3A5.

Conclusion: Polymorphisms of CYP3A5 may play an important role in predicting the within-patient variability of the once-daily tacrolimus levels in the Malaysian post-renal transplant population.

P03

Metabolic Changes on Obese Rats Treated with *Piper betle* Leaves Extract Based on Biofluids ^{1}H NMR-Based Metabolomics.

[1,2] Abdul Ghani, ZDF; [2]Husin, JM; [2]Ab Rashid, AH; [3]Shaari, K, [1] Chik, Z

[1]Department of Pharmacology, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia, [2] Industrial Biotechnology Research Centre, Sirim Berhad, 40700 Shah Alam, [3] Institute of Bioscience, Universiti Putra Malaysia, 43400 Serdang.

E-mail: zuleen@siswa.um.edu.my / zuleen@sirim.my

This study was performed to evaluate the correlation of food intake, body weight with serum and urine metabolite profile from *Piper betle* leaf extracts using ***metabolomics*** approach. 70% ethanolic extract of *P. betle* was filtered and the solvent was removed under reduced pressure and then finally freeze-dried and stored at -80^{o}C prior study. Four of the five groups of animals were introduces to the High-fat Diet for 16 weeks to gain obesity weight and another one group will remain to give Standard Diet to be a comparison as a normal diet. After 12 weeks, the animal then treated with water for the control group, 10mg/kg of Phentermine for drugs control group and *P. betle* for 100 and 500 mg/kg for the *P. betle* treatment group until the end of the study. At the end of the studies, urine and blood serum sample of the experimental animal were analysing using ^{1}H-NMR. From the animal studies, HFD animals treated with Phentermine (10mg/kg) give a significant decrease in food intake and body weight from 1st weeks until the end of the studies. While, HF/PB (100mg/kg) act in maintaining body weight without giving an effect on the food intake even though the animals were consumed with HF diet continuously until the ends of the studies. The H^{1}-NMR data analysing with Principle Component Analysis (PCA) separations of serum samples show a major change of glucose and lipid metabolism. While PCA of urine samples show a major changes of creatine, lipid and amino acid metabolism. The entire treatment group also gives a good separation metabolite in PCA analysis thus suggest there were significant metabolite changes. To conclude the metabolic changes we will be analysing the H^{1} NMR data with OPLS-DA to compare each of the treatment group with the control group of individual metabolite changes.

P04

VDR Polymorphisms and its Association with Obesity Parameters, Cardiometabolic Risk Factors and Vitamin D Status in Malaysian Urban Adolescents

[1]Zaharan, NL; [1]Hamidi, A; Fauzi, F; [2]Singh, S; [2]Jalaludin;MY; [1]Mohamed, Z

[1]Department of Pharmacology [2]Department of Paediatrics, Faculty of Medicine, University of Malaya, Lembah Pantai, Kuala Lumpur, 50603, Malaysia

E-mail: lisa@ummc.edu.my

Introduction: Vitamin D receptor (VDR) gene plays an important role in regulating the synthesis of vitamin D receptors. We assessed the association between polymorphisms of the VDR rs15444410 with obesity traits, cardiometabolic profiles and vitamin D status in multi-ethnic adolescents in Malaysia.

Materials & Methods: 1,118 adolescents were recruited from 23 randomly selected secondary schools in Kuala Lumpur, Malaysia.

Obesity parameters included were body mass index (BMI), waist (WC) and hip circumference, waist and hip ratio (WHR) and percentage of body fat (BF%) (inBody 230). Cardiometabolic profiles examined were blood pressure (Omron-HEM907), fasting glucose, insulin and lipid. Of these, 698 students were included in this case-control study according to their BMI classifications (n=99 obese (BMI>95th centile), n=599 normal weight (BMI 5th-85th centiles). DNAs were isolated using GeneAll^{R} DNA purification kit. Genotyping for VDR gene polymorphism (rs15444410) was performed using Sequenom MassARRAY. Vitamin D status was classified as sufficient (>20 ng/mL) and nonsufficient (≤20 ng/mL). Association of allele with parameters was performed using adjusted logistic regression. Spearman's correlation was used to examine the relationship between VDR gene and obesity parameters. One way ANOVA and Kruskal Wallis test were conducted for comparison of means between alleles.

Results: The mean and standard deviations for obesity parameters in our Malaysian adolescents were as follows: BMI 20.6±5.1, WC 68.9±12.2cm, WHR 0.8±0.3, and BF% 29.6±10.7. VDR rs1544410 was not associated with obesity parameters in this population.

Those with AA genotype of VDR rs1544410 were associated with higher insulin (p=0.04) and lower Vitamin D (p=0.002) levels compared to those with GG and GA genotypes.

Carriers of A allele were associated with increased risk of vitamin D nonsufficiency (adjusted odds ratio: 0.65(95% Confidence intervals 0.44-0.97) (p=0.04)

Conclusion: Carriers of A allele of VDR rs1544410 were associated with increased risk of vitamin D insufficiency in our Malaysian adolescent population. P05

Orthogonality of Separation in Two Dimensional Chromatography of *Plectranthus Amboinicus*

Abu Bakar Ameera Adeeba [1]; Saad Rasha [2]; Daud Mohd Zahedi [1]

[1]Department of Health Science, Faculty of Health & Life Science, [2] Department of Pharmaceutical Chemistry, School of Pharmacy, Management and Science University, University Drive, Off Persiaran Olahraga, Section 13, 40100 Shah Alam, Selangor Darul Ehsan, Malaysia

Email: ameeraadeeba92@yahoo.com

Plectranthus amboinicus which from family Lamiacae and genus Plectranthus is traditionally used for the treatment of coughs, sore throat, asthma and disease affected by virus and bacteria. This plant is reported to have many biological activities such antiepileptic, anti-mutagenic, anti-inflammatory, anti-fungal and anti-tumor activity. Major chemical of this plants are carvacrol, thymol, a-terpineol, caryophylene oxide and B-seline. Although the plant showed an interesting bioassay, on the other hand, the extract was extremely complex for further purification. Thus the purpose of this research is to separate the complex extract and identify the active components with desired antioxidant activity. Two dimensional chromatography which refers to different selectivity between separation can improve the purification throughput complex mixtures. The plant was first extracted and then proceeds with column chromatography. By using column chromatography this plant was fractionated into ten fractions by using methanol, methanol:chloroform and chloroform as mobile phase. Then, antioxidant activity was carried out for each of the fractions and extract using 1,1-diphenyl-2-picrylhydrazyl (DPPH) reagent. Finally all the fractions and extract were screening using Thin Layer Chromatography (TLC). The antioxidant activity of some fractions showed greater than the antioxidant activity of the extract. From the thin layer chromatography and HPLC, we found that they were possibly seven compounds. Three of them in the area of highly polar, two in the area of moderate polar and two of them in the area of low polar.

P06

GABRA1 Polymorphism and Susceptibility to Epilepsy in Malaysian Population

[1]Nozaka, Yuka; [1]Haerian BS; [1]Mohamed Z; [1]Sha'ari HM; [2]Tan HJ; [2]Raymond AA; [3]Tan CT

[1]Pharmacogenomics Laboratory, Department of Pharmacology, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia, [2]Division of Neurology, Department of Medicine, Faculty of Medicine, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia, [3]Division of Neurology, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia

Email: yuukaym2007@yahoo.co.jp

Introduction: Epilepsy is one of the most common neurological disorders characterized by unprovoked seizures. Several polymorphisms in gamma-aminobutyric acid A receptor, alpha 1 (GABRA1), a ligand-gated chloride channels, have been reported to be associated with susceptibility of juvenile myoclonic epilepsy and childhood epilepsy. In this study, we evaluated the association of GABRA1 rs4367330, rs4554269, rs2279020, rs1457701 and rs35166395 with the risk of epilepsy in Malaysian population.

Materials & Methods: Genomic DNA of 1789 Malaysian subjects (1088 healthy-declared population and 701 epilepsy patients consisting of 41% cryptogenic, 26% idiopathic and 33% symptomatic epilepsy) was genotyped by using Sequenom MassArray technique.

RESULTS: Our results showed no significant association between the GABRA1 rs4367330, rs4554269, rs2279020, rs1457701 and rs35166395 polymorphisms and susceptibility to epilepsy.

Discussions: Significant association between GABRA1 rs2279020 polymorphisms and the risk of epilepsy in the Malay population was observed. However, following Bonferroni test for multiple comparisons, no statistically significant differences were found in both allele and genotype results.

Conclusion: Results of this study suggest that GABRA1 polymorphisms do not contribute to the risk of epilepsy in the Malaysian populations.

P07

Effect of Sodium Lauryl Sulphate (SLS) and Tween 80 on the drug release from paracetamol suppositories of palm kernel base

Lim, SS; Phoon, MF*; Lau, CL, Nyamathulla, S

Department of Pharmacy, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia
Email: foong324@gmail.com

Introduction: Suppositories are one of the frequently used dosage forms prescribed through rectal route when oral route is not feasible. However, suppositories have the limitation of poor drug release from suppository base. Surfactants are usually added into the suppositories to increase the drug release and aid in absorption. Sodium lauryl sulphate (SLS) and Tween 80 was used in this study to examine their effect on the drug release from paracetamol suppositories prepared using HAMIN® base.

MATERIALS & METHODS: Suppositories without any surfactant, with the addition of surfactant SLS and Tween 80 at concentrations of 0.25, 0.5, 0.75 and 1% w/w respectively were prepared using double casing method.

Results: Results of *in vitro* dissolution showed 26.6, 28.9, 37.4 and 84.6% increase in drug release from suppositories with SLS at concentration of 0.25, 0.5, 0.75 and 1% w/w respectively. Nevertheless, at the same concentrations, Tween 80 exhibited higher percentage of increase in drug release than that of SLS, by 79.5, 891.1, 1032.5 and 1032.5% respectively.

Discussion: Tween 80 significantly enhanced the drug release (Student T-test, $p<0.001$), which can be attributed to its wetting property that might have made the suppositories to absorb more water into the hydrophilic base and enhanced the diffusion of drug to the surrounding medium. SLS has high hydrophilic-lipophilic balance, theoretically it should be able to increase the hydrophilicity of the HAMIN® base. In contradiction, our study showed a poor drug release with it. However, SLS enhanced the drug release when compared to blank suppositories but the result is not significant ($p> 0.05$). The higher the concentration of SLS in the suppositories, the higher the cumulative percentage of drug release observed.

Conclusion: SLS and Tween 80 facilitated the drug release from prepared HAMIN® base paracetamol suppositories. However, SLS was not as effective as Tween 80 at the same concentration.

P08

Elucidating the Mechanistic Action of MBIC as a Potential Antitumor Agent

[1]Mohadeseh Hasanpourghadi; [1]Chung Yeng Looi; [2]Piyush Trivedi; [1]Mohd Rais Mustafa

[1]Department of Pharmacology, Faculty of Medicine, University of Malaya, Lembah Pantai, Kuala Lumpur, 50603, Malaysia. [2]University of Technology of Madhya Pradesh.462636, India

Email: mohadeseh_hasanpour@yahoo.com

A novel synthetized agent, Methyl 2-(5-fluoro-2-hydroxyphenyl)-1H-benzo[d]imidazole-5-carboxylate (MBIC) is a benzimidazole derivative that appeared to have antitumor activity against breast cancer cells MCF-7. Aim of our study was to determine mechanistic action of MBIC against MCF-7. Cytotoxicity of MBIC was evaluated 24 & 48 hours after treatment. MBIC-induced apoptosis was detected using flow cytometry. Tubulin polymerization assay was performed to determine microtubule dynamics after MBIC treatment. Paclitaxel and colchicine were selected as positive controls. Cell cycle arrest stage after treatment, was determined by flow cytometry. Experiments were carried out in triplicates. Data were mean $\pm$ SD. MBIC inhibited MCF-7 cell viability at IC_{50}: 0.69μM$\pm$0.08 and 0.21μM$\pm$0.05, 24 & 48 hours after treatment. Apoptosis detection declared distribution of apoptosis among MBIC-treated cells. Tubulin polymerization assay determined that MBIC with Vmax:<4mOD/min interfered with tubulin which was similar to colchicine's Vmax:<4mOD/min compare to paclitaxel with Vmax:>30mOD/min and control group with Vmax:12mOD/min. Cell cycle analysis declared MBIC-treated MCF-7 cells were arrested in G_2-M phase. In our study, MBIC perturbed microtubule dynamics through tubulin binding and interfered with tubulin polymerization. Further, G_2-M phase arrest demonstrated that MBIC caused mitotic arrest by suspending tubulins that are involved in mitotic spindle assembly. Consequently, cells were arrested in mitosis by spindle assembly checkpoints and finally entered apoptosis during mitotic arrest. This event seems to be through mitotic catastrophe wherein it is assumed to be related to caspase cascade activation. Our study introduced a novel antitumor agent, MBIC as a potentially compatible drug with conventional chemotherapeutic agents.

P09

FTO polymorphisms and its association with obesity-related traits and cardiometabolic risk factors in multi-ethnic Malaysian adolescents

Muhamad, NH; Zaharan, NL; Hamidi, A; Fauzi, F; Mohamed, Z

Department of Pharmacology, Faculty of Medicine, University of Malaya, Lembah Pantai, KualaLumpur, 50603, Malaysia
Emsil: hanisah_seven@yahoo.com

Introduction: Fat mass and obesity-associated (FTO) gene plays an important role in controlling feeding behavior and energy expenditures. We examined the association of three FTO polymorphism; rs1421090, rs7186521, and rs7204609 with obesity-related parameters and cardiometabolic risk factors among multi-ethnic adolescents across the city of Kuala Lumpur, Malaysia.

Materials & Methods: 1118 adolescents (13 yo) were recruited from 23 randomly selected secondary schools in Kuala Lumpur. Anthropometric measures included body mass index (BMI), waist and hip circumference and waist hip ratio (WHR). Percentage of body fat (BF%) was assessed using bioelectrical impedance analysis (inBody 230). Cardiometabolic profiles included systolic and diastolic blood pressure, fasting glucose, insulin, and lipid. 698 students were included in this case control study according to their BMI classifications (n=99 obese (BMI > 95th centile, n=599 normal weight (BMI < 85th centiles). Venous bloods were collected and DNAs were isolated using GeneAll^{R} DNA purification kit. Genotyping of the FTO genes polymorphisms was performed using Sequenom MassARRAY. Association of allele with obesity related-traits was performed using multiple logistic regression adjusting for gender, ethnicity and puberty stages. Spearman's correlation was used to examine the relationship between FTO and obesity parameter and cardiometabolic risk factors. SPSS 22 was used for analysis.

Results: The mean and standard deviations for obesity parameters were as follows: BMI 20.6±5.1, WC 68.9±12.2cm, WHR 0.8±0.3, and BF% 29.6±10.7. Significant but weakly negative correlations were found between FTO rs1421090 and WC (r=-0.07, *p*=0.04), BF% (r=-0.08, *p*=0.02), fasting insulin (r=-0.08, *p*=0.02) and LDL (r=-0.08, *p*=0.03) respectively. Weak positive correlation was observed between FTO rs7186521 and WHR (r=0.08, *p*=0.02) while significant negative correlations were observed with WC (r=-0.07, *p*=0.04), WHR (r=-0.08, *p*=0.02) and fasting insulin (r=-0.09, p=0.04)

Conclusion: These three FTO SNPs were not found to be strongly associated with obesity parameters and cardiometabolic risk factors in our adolescent population.

P10

Neutron-activated ^{153}Sm as an Alternative Radionuclide to ^{111}In for Gastrointestinal Transit Assessment

[1,2]Yeong, CH; [1,2]BJJ, Abdullah; [1,2]KH, Ng; [3]Chung, LY; [4]Goh, KL; [1,2]Sarji, SA; [5]Perkins, AC

[1] *University of Malaya Research Imaging Centre, University of Malaya, 50603,*

[2] Departments of Biomedical Imaging, [3] Pharmacy and [4] Medicine, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia

[5] Radiological and Imaging Sciences and Nottingham Digestive Diseases Biomedical Research Unit, University of Nottingham, Nottingham, NG7 2UH, United Kingdom

Email: *chyeong@um.edu.my*

Introduction: In is a commonly used radionuclide in nuclear medicine primarily for long hour study such as whole GI transit examinations. However this cyclotron produced radionuclide is not commonly available and the cost is relatively high. This study aimed to produce a safe and viable capsule formulation containing neutron activated ^{153}Sm-labelled resin as an alternative radiopharmaceutical to assess whole GI transit.

Materials & Methods: Medical-grade size 1 capsules were filled with 150 mg non-radioactive ^{152}Sm-labelled resin and sealed before coating with a pH sensitive biocompatible polymer. The capsules were then sent for neutron activation using a research reactor at the Malaysian Nuclear Agency. *In vitro* disintegration tests mimicking the gastric and intestinal environments were performed to investigate the disintegration behaviour of the enteric-coated capsules prior to *in vivo* study. A clinical scintigraphic study was carried out in ten healthy volunteers. Static images were acquired every 30 min for 9 h with a final image at 24 h after ingestion of the formulation. Blood and urine samples were collected to monitor for any ^{153}Sm excretion through the urinary tract or absorption into blood plasma.

Results: Both *in vitro* and *in vivo* data demonstrated that all the capsules met the required properties of remaining intact in stomach and disintegrating in the small intestine before dispersing in the colon. The scintigraphic images obtained with the ^{153}Sm-labelled formulation provided satisfactory image quality suitable for clinical use. No radioactivity was detected in the urine or blood samples of all the volunteers. The total whole body effective dose per subject = 0.88 ± 0.16 mSv.

Conclusion: We have successfully developed a safe and practical oral capsule formulation suitable for whole gut transit scintigraphy using neutron activated ^{153}Sm-labelled resin. This provides an alternative to ^{111}In-labelled resin and does not require hospital radiopharmacy manufacturing facilities and minimises radiation exposure to radiopharmacy staff.

P11

Evaluation Of Scattered Dose Reduction Of Occupational Exposure In Interventional Radiology Using Lead Free Protection Drape

[1,2]Khamizah Taharim, N; [1,2]Yeong, CH; [1,2]Ng, KH; [1]Abdullah, BJJ

[1]Department of Biomedical Imaging, Faculty of Medicine, University of Malaya [2]Medical Physics Unit, University of Malaya Medical Centre, Kuala Lumpur, Malaysia

Email: chyeong@um.edu.my

Introduction: Occupational radiation dose in interventional radiology (IR) has become a concern due to increasing complexity of the procedures and fluoroscopic time. A lead-free protection drape has been introduced to absorb scattered radiation during IR procedures. To ensure the safety of medical personnel working with radiation, it is imperative that the efficacy of protection equipment meets the required standards. This research aimed to establish the physical characteristics and assess the efficacy of the protection drape, RadPad, in reducing scattered dose to the personnel, in comparison to a typical lead shield.

Methods: The physical characteristics of RadPad were assessed by establishing its attenuating and backscattering properties and its dose reduction profile. The percentage attenuation was measured using two calibrated semiconductor detectors, each placed before and after the protection drape, which was placed on a phantom and exposed at varying X-ray energies. Backscatter properties of RadPad were studied by measuring the entrance surface air kerma on a phantom. RadPad's dose reduction profile was established by analysing exposed radiochromic films partially covered by the protective drape. Additionally, the films were sandwiched between sheets of 2cm thick Perspex phantom to simulate dose distribution at different depths within the patient body. RadPad's efficacy in dose reduction was further assessed through scattered radiation dose mapping during a simulated fluoroscopy-guided procedure, in which phantoms were used to simulate a radiologist and a patient. RadPad was placed over the patient phantom and exposure was made using routine fluoroscopy settings.

Results & Conclusion: RadPad significantly reduces scattered radiation dose to staff during prolonged fluoroscopy-guided procedure. RadPad Orange (90% attenuation) shows similar attenuation to 0.25 mm lead-equivalent shield at 90 kVp. However, empirical results show deviation from manufacturer specifications. Backscattered radiation was detected, indicating possible increase in patient skin dose. 0.25 mm lead-equivalent produces higher backscatter radiation compared to RadPad, suggesting that RadPad is advantageous in reducing patient skin dose. RadPad has potential as additional radiation shielding, however its lower linear attenuation coefficient compared to lead suggests that it would not be an ideal replacement for lead as the primary personal radiation protection for medical staff.

P12

Accuracy of Tissue Elasticity Measurement using Shear Wave Ultrasound Elastography: A Comparative Phantom Study

[1]Ting, CE; [1,2]Yeong, CH; [1,2] NG, KH; [1,2] Abdullah, BJJ; [1]Ting, HE

[1]Department of Biomedical Imaging, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia, [2]University of Malaya Research Imaging Centre, University of Malaya, Kuala Lumpur, Malaysia

Email: chyeong@um.edu.my

Introduction: There is a strong correlation between tissue elasticity and pathological state. The information of tissue elasticity superimposed to any anatomical image provides great diagnostic value. Shear wave elastrography (SWE) is a new imaging technique using ultrafast ultrasound to measure tissue elasticity. The objectives of this study were to verify the accuracy of tissue elasticity measured using SWE compared to the gold standard (electromechanical microtester) and to investigate several factors that might affect the accuracy of SWE measurement.

Materials & Methods: A tissue-mimicking phantom with acoustic and shear elasticity properties similar to the human breast was developed using animal hide gelatine. Each inclusion was made in pair, one for *in vivo* measurement using a commercial SWE scanner and the other for destructive *in vitro* measurement with the microtester. The measurements using both methods were compared statistically using the paired-sample t-test with 95% confidence interval. To investigate the possible factors affecting SWE measurements, the phantom was also designed to encompass inclusions with varying diameters and elasticity values, embedded at different depths in the phantom. SWE measurements were obtained for each inclusion.

Results: Despite a strong linear correlation, a statistically significant difference ($p<0.05$) was found between the elasticity values measured using SWE and the gold standard, whereby the SWE overestimated the elasticity by a mean of 22.79±15.00 kPa. This overestimation might be due to artefacts caused by wave interferences between the elasticity boundaries. Shear wave reflection at boundaries could cause either constructive or destructive interference, consequently causing underestimation or overestimation of the actual elasticity values. Due to shear wave reflection, an increase in contrast between elasticity boundaries was also shown to reduce reproducibility of consistent measurements. A spatio-temporal directional filter has been suggested as a means to reduce the artefacts in the reconstructed shear modulus map. Size and depth of inclusions did not affect SWE measurements.

P13

Accuracy of Tumour Targeting of A Commercial CT-Compatible Robotic System

[1]Yeong CH, [1]Abdullah BJJ, [1]Ng KH, [2]Prakash B

[1]Department of Biomedical Imaging and University of Malaya Research Imaging Centre, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia

[2]Perfint Healthcare Pvt Ltd, Chennai 600017, India

Email: *chyeong@um.edu.my*

Introduction: A new CT- or PET-CT-compatible robotic system, MAXIO™ was developed by Perfint Healthcare, USA to assist tumour targeting in biopsy and interventional procedures. This study aimed to evaluate the accuracy of the robotic system in tumour targeting.

Materials & Methods: Watermelon, with aluminum seeds (1x1 mm) implanted at 30, 50, 70 and 90 mm depth, was used as a phantom. The implanted seeds were identified and targeted in the treatment plan. The orbital angulations of the needle insertion were varied at 0^o, 30^o, 45^o, 60^o, -30^o, -45^o and -60^o, whereas the cranio-caudal angulations were varied at 0^o, 30^o, 45^o, -30^o and -45^o. After needle insertion, CT check scans were done to determine the deviation in X, Y and Z axis of the needle tip and target.

Results & Discussions: A total of 120 needle trajectories were assessed using 4 watermelons. The depth of target from the surface did not show significant difference in affecting accuracy of needle positioning. The orbital and craniocaudal angulation alone also did not affect the accuracy. The highest deviation of needle tip from the target was 2±1 mm, occurred more frequently in the combination of orbital and cranio-caudal angulations, e.g. $(45, 45)^0$, $(-45, 45)^0$, $(45, -45)^0$. Higher accuracy was noted with the robot docked at the right compared to the left side of the scanner.

Conclusion: The MAXIO™ robotic system achieved high accuracy of ±2 mm in tumour targeting. It showed great potential to improve accuracy and minimize radiation exposure during CT-guided biopsy or interventional procedures.

P14

Venom variation and Impact: Insights into the Proteome, Mechanism and Neutralization of the Venom of Monocled Cobra (*Naja kaouthia*) from Three Geographical Areas

Kae Yi Tan[1], Choo Hock Tan[2,*], Shin Yee Fung[1], Nget Hong Tan[1]

[1]*Department of Molecular Medicine, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia,* [2] *Department of Pharmacology, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia*

Email: kytan_kae@yahoo.com; tanchoohock@gmail.com

Snake venoms can vary tremendously even within a same species, leading to discrepancies in clinical severity and effectiveness of antivenom treatment. Monocled cobra (*Naja kaouthia*) is a dangerous species widespread in many parts of Asia; previous studies implied that the venoms of this species from Peninsular Malaysia and Thailand varied in their lethal potencies while the mechanism is poorly understood. Here, we elucidated the intraspecific venom variation of *N. kaouthia* from Malaysia (NK-M), Thailand (NK-T) and Vietnam (NK-V) using reverse-phase HPLC, SDS-PAGE and mass spectrometry; involving correlation to neuromuscular depressant, lethal activities, and antivenom effectiveness in neutralizing the toxic effect. The results showed NK-M, NK-T and NK-V venoms each comprises 13 toxin families with three-finger toxins (3FTxs) being the most diversified (11-18 subtypes) and the most abundantly expressed (63-77%). Neurotoxins are the lethal principles that show remarkable differences in the three populations: NK-T has the highest content of neurotoxins (50%), followed by NK-V (28%) and NK-M (18%). On CBCNM preparation, the venoms time-dependently inhibited the indirect twitches of muscle, with t_{90} values (time to inhibit 90% of twitches) increased in the order of NK-T<NK-V<NK-M. The strong neuromuscular depressant and lethal effects of NK-T venom were consistent with the predominance of neurotoxins (long chain subtype - potent post-synaptic curarimimetic) in its proteome. In mice, NK-T venom is the most lethal (lowest LD_{50}) followed by NK-V and NK-M venoms. Despite the proteomic and functional variations, Thai *N. kaouthia* monovalent antivenom (NKMAV) was able to neutralize the neurotoxic and lethal effects of all three venoms. From the clinical standpoint, NKMAV indicated for use in Thailand would be useful and life-saving for cases in Malaysia and Vietnam. Proper distribution and appropriate use of this antivenom is promising to overcome the issue of shortage and wrong choice of antivenom common in this region.

P15

Orchiectomy Reduces Mean Arterial Pressure (MAP) in Male Spontaneous Hypertensive Rat (SHR)

[1]Loh, SY; [1]Gholami, K; [1]Hoe, SZ; [1]Lam, SK; [2]Mustafa MR; [1]Salleh, N*

[1]Department of Physiology, Faculty of Medicine, University of Malaya, Lembah Pantai, Kuala Lumpur, 50603, Malaysia.
[2]*Department of Pharmacology, Faculty of Medicine, University of Malaya, Lembah Pantai, Kuala Lumpur, 50603, Malaysia.*

Email: suyi91189@hotmail.com

Sex hormones not only act on the reproductive organs, but could exert other actions on the non-reproductive tissues and contribute to the increased incidence of cardiovascular diseases. In this study, we investigated the effect of orchiectomy and ovariectomy on mean arterial pressure (MAP) and correlate these changes to the levels of testosterone. Wistar Kyoto (WKY) and spontaneous hypertensive rats (SHR) were used in this study. Animals from each strain were divided in to 4 groups, eg. intact male, orchiectomized (ORX) male, intact female and ovariectomized (OVX) female. All procedures were carried out at 8 weeks of age. The MAP was measured via the carotid artery at 16 weeks of age and blood serums were collected for testosterone measurements. As anticipated, all SHR exhibited higher MAP as compared to normotensive WKY. Our findings were in consistent with the previous studies in which male rats were shown to possess higher MAP as compared to female rats of both strains. Ovariectomy was found to lower the MAP in WKY and SHR which is in contrast with the previous reports that estrogen deficiency could lead to no changes or increased blood pressure in females. The MAP of ORX male was shown to be significantly reduced as compared to intact male of WKY and SHR. In addition, a reduction in the testosterone levels caused by orchiectomy was observed in both strains. In overall, orchiectomy was found to attenuate testosterone levels and prevent the development of high blood pressure in male SHR rat whereas ovariectomy which resulted in low estrogen levels might not accelerate the development of hypertension and could be multifaceted.

P16

Preparation and Evaluation of Gastroretentive Matrix Tablets of Ciprofloxacin HCl Using Salep, a Natural Polymer

Harun, M A H, Lee, Y C, Tan, G H, Nyamathulla, S.

Department of Pharmacy, Faculty of Medicine, University of Malaya, 50603-Kuala Lumpur, Malaysia.
Email: har_peace92@yahoo.com

Introduction: Ciprofloxacin HCl is a fluoroquinolone antibiotic which has short elimination half-life, narrow absorption window and is mainly absorbed in proximal areas of gastrointestinal tract. The aim of this study was to formulate and evaluate floating matrix tablets of Ciprofloxacin HCl by using *salep* as the swelling natural polymer to enable floating of tablets and sustain the drug release at the site of its absorption.

Materials & Methods:: Natural polymer *salep* was purchased, characterized for physical appearance, viscosity, pH and for polymer-drug compatibility by DSC and FTIR. Five formulations (CS1 to CS5) were prepared using different concentrations of *salep* between 10 to 18% w/w. The final formulations were evaluated for uniformity of weight, hardness, thickness, diameter, friability, floating lag time, floating time and *in vitro* drug release.

Results: CS2 was considered the best formulation as it exhibited relatively shorter floating lag time than other formulations and was able to float, sustain drug release for more than 10 hours. All the prepared formulations exhibited good tableting characteristics.

Discussion: Formulations CS1, CS2, CS3, CS4 and CS5 that were prepared using 10, 12, 14, 16 and 18% w/w of *salep* gave floating lag times of 2, 8, 21, 16 and 14 minutes respectively. Except CS1 all formulations sustained release of drug more than 10 hours. CS1 could able sustain drug release for 6 hours. The drug release for CS2, CS3, CS4 and CS5 were 90%, 60%, 75% and 60% respectively after 10 hours.

Conclusion: *Salep* was able to sustain release drug over 10 hours due to the viscous gelly layer formed. Due to strong gelling ability and cheap cost, *salep* is considered as a potential polymer to be used in developing floating sustains release matrix tablets. Further studies on bioequivalence with commercially available sustained release formulation and *in vivo* biopharmaceutical evaluation are needed.

P17

High Value of Plant Extract Using Chromatographic and Spectroscopic Method as a Fast Identification Tool

Megaleswary N, Mariam-Aisha F.

Faculty of Health Sciences, Management & Science University (MSU)

Email: mizzmega90@yahoo.com

Phenolic compounds are phytochemical constituents that are found in all types of plants. They consist of simple phenols , benzoic , cinnamic acid , coumarins , tannins, and flavonoids. Spectrophotometric and chromatographic techniques are utilized regularly to identify and quantify individual phenolic compounds. Spectrophotometric analysis is to measure the concentration of solutes in solution by the amount of light that is absorbed by the solution, while chromatographic technique involves the separation of a mixture by distributing its components between two phases. The extracts used in this study are from *Lawsonia inermis*, *Garcinia mangostana* rind and *Nephelium lappaceum* seed Xanthone and 2-Hydroxy-1,4-naphthoquinone (HNQ) are used as a standards. The main aim of this study was to investigate the presence of these active compounds using ultra-violet visible spectrophotometer, Fourier transform infrared spectroscopy and thin layer chromatography methods. The results obtained showed suggestively xanthone presence in liquid mangosteen rind and rambutan seed extracts with signature peaks at 450cm-1,460 cm^{-1} and 470 cm^{-1}. Henna can be confirmed to contain HNQ at 500 cm^{-1}. In Thin layer chromatography, two spots were detected of henna aqueous extract with retention factor of 0.82 and 0.98. While in HNQ is 0.82. This shows that henna contains HNQ. These active compounds can also be quantified in these extracts.

P18

Effect of Ethyl Acetate and Aqueous Fractions from Methanolic Extract of Morinda citrifolia Fruit on Conditioned Place Preference in Rats

Narasingam Megala[1], Pandy Vijayapandi[1], Mohamed Zahurin[1]

[1]Department of Pharmacology, Faculty of Medicine, University of Malaya, Lembah Pantai, Kuala Lumpur, 50603, Malaysia
Email: meg.megala@gmail.com

Noni fruit (*Morinda citrifolia* L.) has been used in Polynesia as a traditional folk medicine to treat a wide variety of health ailments including drug addiction. However, there is no direct scientific report published till date. Thus, the objective of the present study was to evaluate the de-addiction potential of *Morinda citrifolia* L. fruit fractions on heroin-induced conditioned place preference in rats. Among the behavioural animal models of addiction, conditioned place preference (CPP) is widely used and considered a model of environmental stimuli's ability to acquire incentive motivational properties by virtue of being paired with drug exposure[1]. The animals are subjected to CPP paradigm individually for twelve days. CPP was induced in rats by escalating doses of heroin as a 10-day conditioning schedule. The effect of ethyl acetate (EA) and aqueous (AQ) fractions from the methanolic extract of noni fruit on the rewarding properties of heroin was tested in rats receiving oral administration, 1h prior to the CPP test on 12thday (Test day). Intraperitoneal administration of heroin in escalating doses for five alternative days produced significant increase in place preference to the heroin-paired compartment when compared to saline control. Acute oral gavage of EA 25 and AQ 10 mg/kg fractions, 1h prior to the CPP test on the 12th day significantly reversed the heroin-induced place preference. The present study results suggest EA and AQ fractions could suppress the rewarding properties of heroin. However, further studies using other animal models of addiction are warranted to confirm de-addiction potential of noni fruit.

P19

L-Arginine as a Hydrotropic Agent for the Novel 5-Phenylaminouracil Derivatives: Evaluation of Cytotoxic Effect in Vero 76 Cell Cultures

[1]Omar Ahmad, NF; [1]Abu Hanipah, NF; [2]Tripathy, M; [3]Gureeva, E; [1]Krasinilkova, AV; [1]Wang, SM

[1]Faculty of Medicine, Universiti Teknologi MARA (UiTM), Sungai Buloh Campus, 47000 Sungai Buloh, Selangor, Malaysia; [2]Faculty of Pharmacy, Universiti Teknologi MARA (UiTM), Puncak Alam Campus, 42300, Puncak Alam, Malaysia; [3]Department of Pharmaceutical & Toxicological Chemistry, Volgograd State Medical University, Pavshikh Borsov Sq. 1, 40131, Volgograd, Russia.

E-mail: *noorfarahomarahmad@yahoo.com*

Introduction: Novel 5-phenylaminouracil derivatives have shown inhibitory activity against several viruses. Due to their highly lipophilic and poorly water-soluble properties, these limit their solubility in aqueous cell culture media for *in vitro* studies. Solvents such as DMSO and methanol help in dissolving the compounds at high cytotoxic dose. L-arginine is an essential amino acid that serves as a precursor for many important molecules in cellular physiology and widely used as a hydrotropic agent. Our data indicated that 5-phenyl-aminouracil derivatives solubilized in a concentration of ≥700mM L-arginine. In this study, we aimed to determine the cytotoxicity of L-arginine against Vero cell culture.

Materials & Methods: Vero 76 cells were seeded (1×10^4/well) into a 96 wells plate and incubated overnight at 37°C with CO_2. Two-fold serial dilutions of L-arginine (concentration ranging from 0.0016mM to 860mM) were then added into each well and further incubated for 72 hours. MTS assay (Promega) was then carried out in accordance to the manufacturer's protocol.

Results: L-arginine did not exhibit significant cytotoxicity on Vero cells. Vero cells showed an average cell viability of 103%±0.06 compared to non-treated cells at concentration from 0.0016mM to 107.5mM. At concentration of ≥215mM, L-arginine appeared to enhance cell growth, with concentrations at 215mM, 430mM and 860mM showed a cell viability of 167%, 235%, and 203% respectively.

Discussions: Our study showed that L-arginine enhanced cell proliferation at concentrations from 215mM to 860mM, but able to maintain ~100% cell viability at ≤107.5mM. As 5-phenylaminouracil derivatives only solubilized at a concentration of ≥700mM L-arginine, indicating it is not suitable to use as a hydrotropic agent. Ideally, a cell viability of ~100% is required for testing the cytotoxicity of drugs against cell culture.

Conclusion: L-arginine is not suitable to use as a hydrotropic agent for 5-phenylaminouracil derivatives in cytotoxicity assays against Vero cells.

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The Effects of Bone Marrow Stromal Cells on Dermal Fibroblast Wound Healing

[1]Savatey, Hak; [1]Sik Loo, Tan; [1,2]Tunku, Kamarul

[1]Tissue Engineering Group, Department of Orthopaedic Surgery, NOCERAL, University of Malaya, 50603 Kuala Lumpur, Malaysia. [2]Clinical Investigative Centre (CIC), University Malaya Medical Centre, Kuala Lumpur, Malaysia

E-mail: hak_savatey@yahoo.com

Bone marrow stromal cells (BMSCs) have been known to promote repair when applied to cutaneous wound. However the mechanism behind this remains largely unknown. This study aims to investigate the effect of BMSCs (at difference ratios) on human dermal fibroblasts (HDFs) response in wounding. Firstly, the effect of BMSCs in HDFs wound closure was determined with a scratch wound assay of mixture culture of RFP-labelled BMSCs and GFP-labelled HDFs at different BMSC:HDF ratios: 0:4(Group1), 1:3(Group2), 2:2(Group3), 3:1(Group4), 4:0(Group5). A semi-quantitative analysis of wound closure based on the fluorescence microscope images captured by at 0, 12, 24, 36, 48 and 60h showed significantly (p<0.05) enhanced wound closure in Group4 throughout the experiment. The transwell system and AlamarBlue assay were used to evaluate cells proliferation in HDFs co-cultured with BMSCs. Group4 showed the most significant (p<0.05) cell proliferation. In Cultrex 96 Well Cell Migration Assay, HDFs showed significant (p<0.01) cell migration after 24h co-cultured with BMSC condition-medium, compared to its control (BMSCs fresh medium or HDFs growth-medium). At 48h co-cultured with/without BMSCs, the mRNA gene expression levels of HDFs was analyzed with RT2 Profiler PCR arrays. The mRNA expression levels of CDH2, COL1A2, F11R, GSK3B, KRT7, MAP1B, PTK2, TSPAN13, VIM, CCL11, CTGF, and TGFBR2 were significantly down regulated (p<0.05). Whereas, genes that significantly (p<0.05) up-regulated were THBS2, DCN, ENG, HGF, IL13RA2, ITGA2, ITGB3, JUN, MMP1, RGS2, and TFPI2. In conclusion BMSCs exert paracrine signaling which enhanced cell proliferation and migration in the target cells (HDFs). These promote tissue regeneration but prevent scar formation.

P21

Discontinuation of Dabigatran Therapy in Patients with Atrial Fibrillation

[1]Beshir, SemiraAbdi.;[2] Chee, Kok_Han,; [1]Lo,Yoke_Lin,,

[1]Department of Pharmacy, [2]Department of Medicine , Faculty of Medicine, University of Malaya, Kuala Lumpur, 50603, Malaysia.

Email: Semiraabdi@gmail.com

Maintenance on oral anticoagulant (OAC) therapy is essential for effective prevention of stroke or other thromboembolic events. Discontinuation of OAC is associated with an increased risk of thromboembolic events. The objectives of this study are to determine the likely reasons for discontinuation of dabigatran therapy and to estimate dabigatran discontinuation rates in patients with atrial fibrillation. The clinical and demographic data of 192 patients who were initiated with dabigatran between 2010 and 2012 at the University Malaya Medical Centre (UMMC) were reviewed and collected until the date of death, the date of discontinuation of dabigatran, or 31 December 2013. All patients who discontinued dabigatran for reasons other than transient disruption of therapy due to surgery were included. The median follow up period for all 192 patients is 20 (interquartile range 15-26) months. The median period between the initiation and the discontinuation of dabigatran therapy in 30 patients (17%) is 6 (interquartile range 2-10) months. The cited reasons for discontinuation include bleeding events (17%), high acquisition cost (17%), successful cardioversion (17%), renal impairment (13%), deaths (12%), gastric upset (3%), patient's refusal (7%), general practitioner's decision (7%) or increased bleeding risk (7%). Dabigatran discontinuation rate in this study is comparable to RELY trial which reported a 20% discontinuation during a 2-year follow-up. The rate of cessation of dabigatran was higher in younger patients or during the first 6 months of therapy. Adverse drug events such as bleeding and gastric upset contribute to 20% of the causes of discontinuation. The rate of discontinuation of dabigatran in patients with atrial fibrillation at UMMC is similar to that previously reported. Adverse drug events contribute significantly to discontinuation of dabigatran. Hence, identification of patients at risk of these adverse events is important for effective stroke prevention.

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Effect of α-asarone in apomorphine-induced climbing behaviour in mice

[1]Vijeepallam, Kamini; [1]Pandy, Vijayapandi

[1]Department of Pharmacology, Faculty of Medicine, University of Malaya, Lembah Pantai, Kuala Lumpur, 50603, Malaysia.

Email: Kamini88@hotmail.com

α-asarone is known to be one of the active compound which is identified to be responsible for therapeutic benefits of Acorus species. In previous work, it has been revealed that *Acorus calamus* leaf extract exerted the neuromodulatory effects on nigro-striatal dopaminergic system. Thus, the present study aimed to evaluate the potential effect of the active compound, α-asarone on the dopaminergic system using a mouse model. Experiments were performed using swiss albino male mice (bodyweight 25-30g). In acute study, α-asarone at different doses 1, 10, 30, 50, and 100 mg/kg, were administered orally one hour prior to apomorphine (5mg/kg, i.p) injection respectively. Immediately after injection of apomorphine, the mice were placed into cylindrical individual cages (12 cm in diameter and 17 cm in height) with the floor and wall consisting of vertical metal bars and recorded for climbing time and climbing behaviour. The climbing behaviour was scored as 0 = four paws on the floor, 2 = two paws on the wall of the cage, 4 = four paws on the wall of the cage. Acute oral treatment of α-asarone at 1, 10, 30, 50, and 100 mg/kg exhibited inverted bell-shaped dose-response in cage climbing behaviour. α-asarone at 30 and 50 mg/kg significantly decreased the apomorphine-induced cage climbing time and climbing behaviour in mice. These observed effects might be attributed to dopaminergic antagonistic and/or the reduction of dopamine availability in the brain. Antagonism of dopamine D2 receptors may be a common feature of most clinically effective antipsychotic drugs, especially active against hallucinations and delusions. Overall, the present study revealed the antidopaminergic activity of α-asarone; thereby α-asarone exhibited the antipsychotic-like activity in mice. However, further neurochemical studies are warranted to explore the actual mechanism of action of α-asarone as a promising novel antipsychotic agent.

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Essential Oils of Ocimum sanctum Inhibit MMP-9 Gene Expression and Cancer Cell Proliferation

[1,2]MS, Kanthimathi; [1]R, Jayakumar; [1,2]M, Thamilvaani

[1]Department of Molecular Medicine, Faculty of Medicine, [2]CENAR, University of Malaya, 50603 Kuala Lumpur, Malaysia
Email: kanthi@ummc.edu.my

Inflammatory cells release matrix metalloproteinases (MMPs) which are involved in the development and progression of human cancers such as breast, colon and ovarian cancers. *Ocimum sanctum* essential oil (OSEO) was tested for its effect on the inhibition of the proliferation of breast cancer cells, MCF-7, and reducing the expression of MMP-9 in human lymphocytes. OSEO was extracted and treated on MCF-7 to determine the effect on proliferation using the MTT assay. Genes involved in proliferation/apoptosis were assessed using RT-PCR. The effect of OSEO on MMP-9 gene expression was analyzed on inflammation-induced lymphocytes using gelatin zymography and real-time reverse transcriptase PCR. OSEO inhibited proliferation (IC_{50}= 170 µg/ml) of MCF-7 cells in a dose-dependent manner. Gene expression analysis showed that OSEO upregulated the expression of apoptotic genes, p53 and Bid, in MCF-7 cells. Gelation zymography showed that MMP-9 expression was completely inhibited by the essential oil at a concentration of 250 g/ml. The real-time reverse transcriptase PCR analysis showed a dose-dependent decrease in the expression of MMP-9. OSEO inhibited the proliferation of MCF-7 cells dose-dependently with an IC_{50} of 170 µg/ml. The oil showed better cytotoxic effect over the positive control, resveratrol. The essential oil also increased the expression of p53 and Bid in a dose-dependent manner. Hence, OSEO has the ability to induce apoptosis in MCF-7 cells. Our results indicate that OSEO has anti-inflammatory potential by suppressing MMP-9 expression in LPS-induced cells. Studies have shown that inhibition of MMP-9 activity could reduce inflammation and prevent cancer progression and metastasis as well. The results of our study indicate that OSEO has the ability to express both anti-inflammatory and anticancer activities.

P24

Evaluating the Purity and Activities of a Long-Expired Taiwan Bivalent Antivenom

[1]Liew, Sin Teng; [2]Tan, Choo Hock; [2]Sim, Si Mui; [3]Tan, Nget Hong

[1]Department of Biomedical Sciences; [2]Department of Pharmacology; [3]Department of Molecular Medicine, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia

Email: debrasim@um.edu.my

Introduction: Antivenom is the most important and specific treatment for snake envenomation that can help to reduce its morbidity and mortality. However, the supply of antivenoms is limited worldwide. Therefore, it is important to consider the potential use of expired antivenoms when fresh antivenoms are not available. However, the effect of expiry on the effectiveness of antivenoms remains to be investigated since there is limited published information on the activity of antivenoms over a long period of time. This study examined the purity, immunological reactivity and neutralisation effectiveness of a long-expired lyophilised Taiwan bivalent antivenom (expired for 17 years) that acts against *Viridovipera stejnegeri* and *Potobothrops mucrosquamatus* venoms.

Materials & Methods: The purity and composition of the long-expired Taiwan bivalent antivenom was examined by SDS-PAGE under reducing and non-reducing conditions. Its immunological reactivity to venoms was assessed using indirect ELISA, while its effectiveness in neutralising haemorrhagic, procoagulant and lethal activities was examined by toxicity and neutralisation studies. The most recent Taiwan bivalent antivenom was used as the reference-control.

Results & Discussion: The long-expired antivenom showed similar banding patterns as the reference-control antivenom in both reducing and non-reducing SDS-PAGE. Long expiry did not cause aggregation of proteins in the antivenom, which has retained similar purity and composition as the reference-control antivenom. The long-expired antivenom still retained comparable immunological reactivity (83.9-87.0%) as the reference-control antivenom. Furthermore, it was still effective to neutralise the toxic activities (haemorrhagic, procoagulant and lethal activities) of both *V. stejnegeri* (77.6%, 48.2% and 69.8%) and *P. mucrosquamatu* (88.4%, no procoagulant activity and 100.0%) venoms since the difference in effectiveness between the reference-control and long-expired antivenoms was not remarkable.

Conclusion: The long-expired Taiwan bivalent antivenom was more robust than indicated by its expiry date and it may still be effective in function for neutralisation of both *V. stejnegeri* and *P. mucrosquamatus* venoms.

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Expired and Room Temperature-stored Antivenoms: Are They Still Effective?

[1]Tan, Qian Yi, [2,*]Tan, Choo Hock, [2]Sim, Si Mui, [3]Tan, Nget Hong

[1]Department of Biomedical Sciences; [2]Department of Pharmacology; [3]Department of Molecular Medicine, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia

Email: tanch@um.edu.my

Introduction: Antivenom is the only specific treatment for snake envenomation. However, there has been a shortage of antivenom worldwide as many manufactures have stopped producing antivenoms due to the low profit margin and high production cost. Thus, it is important to make good use of available antivenoms and to minimize wastages globally. This study aims to answer the research questions surrounding the effect of expiry and room temperature storage on antivenom.

Materials & Methods: Expired Hemato Polyvalent Antivenoms (HPAV) of two storage conditions (expired and kept at 4 °C, EXP-4C; and expired but kept at room temperature for 5 years, EXP-RT) were tested for their ELISA immunoreactivity and effectiveness in neutralizing the lethal effect of Malayan pit viper (*Calloselasma rhodostoma*) venom. Non-expired HPAV stored at 4 °C (N-4C) was used as the reference control.

Results and Discussion: EXP-4C, EXP-RT and N-4C showed significantly higher immunoreactivity towards *Calloselasma rhodostom*a venom compared to *Naja kaouthia* venom (negative control). The expired HPAVs, regardless of storage temperature, remained immunoreactive to bind *Calloselasma rhodostoma* venom antigens. In neutralization study, the expired antivenoms were shown to be able to neutralize the lethal effect of *C. rhodostoma* venom in mice. The relative effectiveness of EXP-4C, EXP-RT and N-4C appeared comparable (90-110%).

Conclusion: We showed that expiry and storage at room temperature did not affect the performance of HPAV in terms of its immunoreactivity and neutralization effectiveness against *Calloselasma rhodostoma* antivenom. The results suggest that the expired and room temperature-stored HPAVs can be still useful in neutralizing the venom of *Calloselasma rhodostoma*. It is hoped that the findings provide clues to the optimization of antivenom distribution and use in the region.

Appendix:

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