

## Abstracts of Theses Approved for the PhD/MMed/MSc at the School of Medical Sciences, Universiti Sains Malaysia, Kubang Kerian, Kelantan, Malaysia

### BE KIND: DEVELOPING AND PILOTING A POSITIVE PSYCHOLOGY INTERVENTION TECHNIQUE TO REDUCE STRESS AND PROMOTE PSYCHOLOGICAL WELL-BEING OF NURSES IN PAEDIATRIC SETTING

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**Introduction:** The present study aimed to develop and pilot a protocol of positive psychological intervention techniques focusing on kindness as the main component which was named as BE KIND intervention. This study aimed to examine the effects of BE KIND intervention on perceived stress and psychological well-being of paediatric nurses when they were subjected into intervention or active control group at pre and post-intervention levels. A protocol was developed as a self-help intervention in the form of a manual which includes instructions, study timeline and activity templates needed to guide the participants in completing the activities accordingly.

**Methods:** Present study is an interventional study with active control. Nurses from paediatric department were invited to participate in the study and then randomly assigned according to the briefing slots attended into either intervention group ( $n = 16$ ) or to active control group ( $n = 16$ ) by using cluster randomisation.

**Results:** The BE KIND intervention shown a significant,  $P = 0.005$  results in reducing perceived stress level among intervention group. However, there were no significant increase,  $P = 0.075$  found in participants psychological well-being level at post-test.

**Conclusion:** Overall, the BE KIND intervention seems to be a feasible self-help intervention and results suggests that the BE KIND seems promising in reducing paediatric nurses' perceived stress level. There is a need to further test the effectiveness of the BE KIND intervention as a self-help intervention to promote well-being.

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### THE EFFECTS OF AN EMOTIONAL COMPETENCY MODULE AT IMPROVING EMOTIONAL COMPETENCY AMONG MALAYSIAN ADOLESCENTS FROM LOW-INCOME HOUSEHOLDS IN KELANTAN

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**Introduction:** The aim of this study was to test the effects of the Emotional Competency Module (ECM) at improving emotional competency (EC) among Malaysian adolescents from low-income households.

**Objectives:** Previous literature has consistently demonstrated the importance of EC in promoting healthy youth development while preventing negative influences on wellbeing, yet EC intervention programmes have not been sufficiently explored within the Malaysian context.

**Methods:** To further investigate the potential effectiveness of the ECM, particularly with low-income adolescents, 56 Form 4 students aged 15 years old to 16 years old from within the B40 community in Kelantan were recruited. Among them, 30 were placed in the intervention group and 26 in the control group, where those in the intervention group participated in a two-day programme in which the ECM was administered. Baseline and post-intervention measures were obtained using the USM Emotional Quotient Inventory.

**Results:** Two-way mixed analysis of variances (ANOVAs) were conducted to examine differences in overall EC score and EC domain scores from baseline to post-intervention with comparing the intervention and control group. The results postulated that there were no significant changes in EC at post-intervention from baseline measures in the intervention group participants, as compared to the control group participants.

**Conclusion:** This study suggests that the ECM did not lead to improvements in EC among Kelantanese adolescents from low-income households. Nevertheless, possible confounding variables of the study were identified, including quality of programme implementation, competence of facilitators, degree of rapport and structure of the intervention. Future research will be necessary to clarify the

influence of extraneous variables and further establish the effectiveness of the ECM.

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## ALPHA, BETA, THETA-ALPHA POWER RATIO AND COGNITIVE FUNCTIONS ASSESSMENTS IN HEALTHY AGEING IN KLANG VALLEY, MALAYSIA

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**Introduction:** Population ageing is happening worldwide which urges the practice of healthy ageing lifestyle as pathological ageing is debilitating at multiple aspects which includes cognitive functioning. This study aims to determine the brainwave characteristics including Theta-Alpha Power Ratio (TAR) and cognitive functions in Malaysian urban healthy ageing group while examining the relationship with age and gender.

**Methods:** Data from 32 healthy middle-aged people (18 females and 14 males) were included for this cross-sectional study. Data was collected in the electroencephalogram (EEG) laboratory of Universiti Sains Islam Malaysia. EEG recording (32-electrodes EEG cap) was done on participants during resting-state and two cognitive tasks (Stroop-colour-word-task [SCWT] and N-back task). SCWT assesses executive functions such as cognitive control and N-back task measures working memory. Due to invalid results, N-back results were excluded. Behavioural performance was evaluated using paired-sample testing and independent-sample testing. Spearman correlation analysis was used to correlate EEG changes and behavioural performance while Fisher's  $Z$  test compares correlation coefficient between genders.

**Results:** Results showed that positive correlations between Alpha Stroop effect and the behavioural Stroop effect in occipital (right:  $r_s = 0.568$ ,  $P = 0.001$ ; midline:  $r_s = 0.497$ ,  $P = 0.004$ ; left:  $r_s = 0.357$ ,  $P = 0.045$ ), centroparietal (right:  $r_s = 0.495$ ,  $p = 0.004$ ; midline:  $r_s = 0.369$ ,  $P = 0.038$ ; left:  $r_s = 0.358$ ,  $P = 0.044$ ) and other right-hemispheric regions. Whereas, Beta had widespread correlational results with reaction time across the brain, strongest at occipital midline ( $r_s = 0.523$ ,  $P = 0.002$ ). Elevated TAR in occipital midline ( $r_s = 0.413$ ,  $P = 0.019$ ), right occipital ( $r_s = 0.355$ ,  $P = 0.046$ ) and right frontocentral ( $r_s = 0.393$ ,  $P = 0.026$ ) was accompanied by smaller Stroop effect. As for gender differences, females performed better in SCWT. They exhibited significant correlations in left centroparietal area between EEG activities and accuracy scores which

were significantly different from males (Delta:  $Z = 3.016$ ,  $P = 0.003$ ; Theta:  $Z = 3.056$ ,  $P = 0.002$ ; Alpha:  $Z = 2.318$ ,  $P = 0.020$ ). Besides, gender differences were evident in age-related correlations with  $r_s$ -EEG, especially at left brain regions.

**Conclusion:** We can conclude that Alpha contributed in successful conflict resolution in SCWT while Beta played a general role in interference control and selective attention which aided in efficient neural processing to overcome cognitive conflict introduced by incongruent stimuli. With stronger correlational results in occipital and centroparietal regions, cognitive control might be modulated by bottom-up guidance more than top-down executive control. In contrast with pathological study results, TAR showed to behave differently in the healthy ageing context and increased with better cognitive control. Females might have more efficient cognitive information processing due to their higher reliance on the left centroparietal than males. Caution should be addressed in future studies about gender effect as this study proved that there are gender differences in both behavioural and neurophysiological level and age-related alterations in brainwave activities.

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## A STRUCTURAL EQUATION MODEL OF MENTAL HEALTH LITERACY, PSYCHOLOGICAL FACTORS AND MENTAL HEALTH HELP-SEEKING INTENTION AMONG UNDERGRADUATE STUDENTS IN HEALTH CAMPUS, UNIVERSITI SAINS MALAYSIA

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**Introduction:** The rate of mental health help-seeking from formal sources such as doctors, social workers, counsellors, psychologists or psychiatrists is low in undergraduate students, despite reports of worsening mental health in recent years. Using intention to as gauge for behaviour, this study looks into the effects of mental health literacy and psychological factors (attitude, perceived public stigma, self-stigma and psychological distress) on mental health help-seeking intention.

**Objective:** The main aim of this study is to determine the structural relationship between mental health literacy, attitude, perceived public stigma, self-stigma and psychological distress with mental health help-seeking intention among undergraduate students in Health Campus, Universiti Sains Malaysia (USM).

**Methods:** A cross sectional study using self-administered questionnaire was conducted among undergraduate students in Health Campus, USM. Study participants were selected by means of convenience sampling. Confirmatory factor analysis was performed to ensure the questionnaires used were valid and reliable to measure the study variables, and structure equation modelling was performed to determine the path relationships between the variables.

**Results:** A total of 755 undergraduate students participated in this study. For the measurement model of mental health literacy, the final model which consisted of 21 items fit the data well based on the fit indices (comparative fit index (CFI) = 0.949, Tucker-Lewis index (TLI) = 0.942, weighted root-mean-square residual (WRMR) = 1.091, Root mean square error of approximation (RMSEA) (90% CI) = 0.027 (0.021, 0.033), RMSEA *P*-value = > 0.950). As for the attitude towards seeking professional psychological help-short form (ATSPPH-SF), the second-order two factor scale showed relatively good model fitness (CFI = 0.936, TLI = 0.913, standardised root-mean-square residual (SRMR) = 0.039, RMSEA (90% CI) = 0.045 (0.033, 0.057), RMSEA *P*-value = 0.752). The perceived devaluation-discrimination (PDD) scale showed good model fitness (CFI = 0.968, TLI = 0.948, SRMR = 0.024, RMSEA (90% confidence intervals [CI]) = 0.056 (0.038, 0.074), RMSEA *P*-value = 0.200), after removing three items from the original scale and adding correlations between items. The 8-item self-stigma of seeking help (SSOSH) scale with correlated items had excellent model fitness (CFI = 0.969, TLI = 0.950, SRMR = 0.029, RMSEA (90% CI) = 0.042 (0.025, 0.059), RMSEA *P*-value = 0.770). The Kessler psychological distress scale (K10) showed acceptable model fitness (CFI = 0.955, TLI = 0.935, SRMR = 0.034, RMSEA (90% CI) = 0.080 (0.68, 0.091), RMSEA *P*-value < 0.001). The final structural model had an excellent fit based on the fit indices (CFI = 0.946, TLI = 0.939, SRMR = 0.063, RMSEA (90% CI) = 0.038 (0.034, 0.042), RMSEA *P*-value > 0.950). The final structural model supported eight hypotheses showing direct and indirect relationship between the study variables. The variables attitude, perceived public stigma and self-stigma have interrelationship between each other to predict help-seeking intention. Meanwhile, mental health literacy has direct effect on help-seeking intention, and indirectly through attitude and self-stigma.

**Conclusion:** Findings of this study suggest that help-seeking intention may be enhanced (directly and indirectly) by improving mental health literacy. Therefore, it is vital that accurate and complete information about mental disorders and treatment resources, and reinforcement of positive attitude or beliefs are provided to the undergraduate students.

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## ASSOCIATION BETWEEN SECOND-HAND SMOKE EXPOSURE AT HOME AND COGNITIVE PERFORMANCE AMONG RURAL PRIMARY SCHOOLS CHILDREN IN KUALA KRAI, KELANTAN

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**Introduction:** Children are most likely to be exposed to second-hand smoke (SHS) at home. Passive smoking is linked to many serious health problems, such as asthmatic attacks, respiratory infections and ear infections. SHS exposure may impair children's cognitive development. The data was collected by using self-administrated questionnaires and Wechsler intelligence scale for children fourth edition (WISC-IV).

**Objective:** This study aimed to determine the association between SHS exposure at home and cognitive performance among school children, and the prevalence of SHS exposure at home among rural primary school children in Kuala Krai, Kelantan.

**Methods:** A multi-stage sampling was conducted among rural primary schools in Kuala Krai, Kelantan where the data was collected by using self-administrated questionnaires. A sampling frame listing all the rural primary schools in Kuala Krai were obtained from Kuala Krai District Education office. There is a formation of 34 clusters since there are 34 rural primary schools in Kuala Krai district. Based on the sample size calculation, four schools were randomly selected using simple random sampling (SRS). Then, a list of name for primary four, and primary five was obtained from each selected schools. After obtaining the list of names, the 78 schools' children were randomly selected from each school by SRS using a random number generated by computer software. A sample of 312 school children was selected in four primary schools.

**Results:** The prevalence of SHS exposure at home among rural primary school children was 55.8% where 11.9% of children lived with one smoker while 43.9% of children lived with two or more smokers. There was a significant mean difference in cognitive tests in combination between exposed and non-exposed children to the SHS; Pillai's Trace = 0.092, *F*-statistic (df) = 7.738 (4,307), *P* < 0.001. After adjustment for sex, parents' educational levels, family income and academic performance, there was a significant mean difference in cognitive tests in combination between exposed and non-exposed children to the SHS; Pillai's Trace = 0.084, *F*-statistic (df) = 6.803 (4,302), *P* < 0.001.

**Conclusion:** More than half of the primary school children in Kota Bharu were exposed to second-hand smoke from at least one smoker in the house. There was an association between SHS exposure at home and cognitive

performance in combination among rural primary school children in Kuala Krai, Kelantan.

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## ASSOCIATED FACTORS OF STROKE SEVERITY AMONG YOUNG ADULT STROKE PATIENTS IN MALAYSIA FROM NATIONAL NEUROLOGY REGISTRY 2014–2018

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**Introduction:** Stroke ranks second in overall global mortality and stroke severity is a well-established predictor of stroke outcome.

**Objective:** To estimate the proportion of young adult stroke patients and to determine the factors associated with stroke severity (mild, moderate, and severe stroke) by the National Institute of Health Stroke Scale [NIHSS] (classification) among young adults' stroke patients.

**Methods:** This was a cross-sectional retrospective secondary data analysis from the National Neurology Registry (NNR). Consecutive young stroke patients who were registered from January 2014 to December 2018 with the first stroke event aged between 18 years old and 49 years old were recruited. Socio-demographic characteristics, stroke subtype classification, comorbidities characteristics, cardioembolism characteristics, prior treatments, lifestyle habits characteristics and other risk factors were extracted from NNR database. The outcome measure was stroke severity which evaluated with NIHSS and categorised as mild, moderate or severe. Ordinal logistic regression was used to analyse and quantify the odds ratio (OR) and 95% confidence interval (CI).

**Results:** A total of 1,421 patients with a mean age of  $41 \pm 7.64$  years old were recruited. There were a larger proportion of male patients with a ratio of 1.7 to 1. The overall proportion of young adult stroke patients was 6.22%. The proportion of mild, moderate and severe were 50.8% (95% CI: 0.48, 0.54), 40.7% (95% CI: 0.38, 0.44) and 8.6% (95% CI: 0.07, 0.10). In multivariable analysis, ischaemic stroke (OR = 2.15, 95% CI: 1.43, 3.23), atrial fibrillation (OR = 3.94, 95% CI: 2.08, 7.47) and alcohol drinking (OR = 1.93, 95% CI: 1.06, 3.50) were factors that influenced higher odds of having a more severe stroke.

**Conclusion:** This study highlighted there were a higher proportion of mild stroke followed by moderate and severe among young adult stroke patients in Malaysia.

Multiple ordinal logistic regression analysis revealed that stroke classification, atrial fibrillation and alcohol drinking were factors that influenced in having a more severe stroke.

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## ELUCIDATION OF SERUM LEVELS OF IL-17, IL-23 AND THEIR RECEPTORS IN SYSTEMIC LUPUS ERYTHEMATOSUS PATIENTS: ASSOCIATIONS WITH SEROLOGICAL PARAMETERS AND DISEASE ACTIVITY

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**Introduction:** Interleukins (ILs) are a group of cytokines, mainly synthesised by  $CD4^+$  T helper cells, as well as by endothelial cells, monocytes and macrophages. ILs bind to their interleukin receptors and this is one of the pivotal factors in the development and progression of systemic lupus erythematosus (SLE).

**Objectives:** This study aimed to determine the serum levels of IL-17, IL-23 and their receptors; IL-17RA and IL-23R, in SLE patients compared with healthy controls. In addition, the associations of these interleukins and their receptors were associated with serological parameters and disease activity, specifically SLEDAI-2K score.

**Methods:** SLE patients and healthy controls ( $n = 50$  in each group) were recruited in this study. The serum levels of IL-17 and IL-23 were evaluated using pre-coated specific antibody via human IL-17/IL-23 ELISA test. PBMCs were isolated from the peripheral blood using histopaque-1077 density centrifugation and stained with fluorochrome-labelled antibodies for staining of surface IL-17RA and IL-23R, and their levels determined by flow cytometry analysis.

**Results:** SLE patients showed significantly elevated levels of IL-17RA and IL-23R ( $P < 0.001$ ) compared with healthy controls. Significant downregulation of serum IL-17 ( $P < 0.001$ ) while no significant difference ( $P = 0.73$ ) in IL-23 levels were observed in SLE patients compared with healthy controls. In addition, no significant associations between IL levels with SLEDAI-2K and serological parameters. Interestingly, IL-17RA levels were significantly associated with antinuclear antibodies (ANA) ( $P = 0.024$ ) and IL-23R levels were significantly associated with higher SLEDAI-2K scores ( $P = 0.011$ ). However, the decreasing level of serum IL-17 might need further work as the relation with its receptor where the elevated IL-17RA expression is expected to take up most of the circulating serum IL-17 resulting in its reduced levels.

**Conclusion:** We suggest that therapeutic inhibition of IL-17RA and IL-23R represents a potential treatment option for SLE patients.

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## THE ROLE OF OESTROGEN IN ANTIBODY PRODUCTION BY IL-27 STIMULATED-B CELLS

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**Introduction:** Systemic lupus erythematosus (SLE) is an autoimmune disease involving multiple organs and this disease can lead to tissue damage and diverse clinical manifestations. Serum level of interleukin (IL)-27 was reported to be elevated in SLE patients compared to healthy donors. In addition, serum level of IL-27 plays a role in B cell development and autoantibody production. Since most SLE patients are women of child-bearing age, oestrogen has been suggested to play an important role in SLE pathogenesis.

**Objectives:** Thus, this study aimed to compare the serum level of IL27 from SLE patients and healthy donors, and also to investigate the potential effects of oestrogen particularly on the antibody production by IL-27 stimulated-B cells in normal and SLE condition.

**Methods:** Serum was isolated from 39 healthy donors and 39 SLE patients using centrifugation technique. Serum level of IL-27 from both healthy donors and patient groups were measured using ELISA. The data were analysed using GraphPad Prism, version 5.01. Comparison between SLE patients and healthy donors groups was done using Mann Whitney test. To investigate the role of oestrogen in antibody production by IL-27 stimulated-B cells, 20 mL of blood was collected from three healthy donors and three SLE patients. B cells were isolated from peripheral blood mononuclear cells (PBMCs) of both groups using magnetic separation technique. The purity of B cells was checked using flow cytometry. Purified B cells were stimulated with anti-IgM, CD40 ligand, and recombinant IL27, then treated with 1000 nM of 17 $\beta$ -oestradiol (oestrogen) before cultured for 48 h in 37 °C in CO<sub>2</sub> incubator. The supernatants of the cultured cells were collected to measure total IgG ELISA for both healthy donors and SLE patients.

**Results:** The serum level of IL-27 in SLE patients was higher compared to healthy donors. In healthy donors and SLE patients, total IgG concentration was lower when IL-27 stimulated-B cells treated with 17 $\beta$ -oestradiol compared with untreated condition.

**Conclusion:** In normal and SLE condition, oestrogen does have an effect on IL-27 stimulated-B cells through the antibody production and has a critical role in SLE pathogenesis.

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## RELATIONSHIP BETWEEN OBESITY, PRIMARY KNEE OSTEOARTHRITIS AND OTHER MEDICAL COMORBIDITIES AMONG PATIENTS VISITING ORTHOPEDICS OUTPATIENT CLINIC OF HOSPITAL UNIVERSITI SAINS MALAYSIA (HUSM)

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**Introduction:** Obesity is increasingly a pervading chronic illness, globally expressed as BMI >30 kg/m<sup>2</sup> and rising to over 1 billion overweight adults, amongst includes about 400 million adults who were obese. Osteoarthritis is a disabling degenerative joint disorder characterised by pain, stiffness, decreased mobility and negative impact on the quality of life that is highly associated with obesity. Comorbidities are defined as diseases or medical conditions unrelated in etiology or causality to the principal diagnosis that coexists with the disease of interest.

**Objectives:** The aim of the study is to show the effect of obesity on the increased predisposition of patients to primary knee osteoarthritis. A prospective cross sectional design that uses a convenience sampling method.

**Methods:** Total of 86 patients were examined to determine the association of obesity with primary knee osteoarthritis among patient visiting orthopedic surgery clinic of HUSM. The data was analysed using descriptive and inferential statistics Descriptive statistics describe demographic variables by percentage, mean, mode, median, and standard deviation and Inferential statistics: *t*-test and chi-squared test were used to determine the association between obesity and knee osteoarthritis, obesity and medical comorbidities and obesity with pattern of dietary intake.

**Results:** The association between obesity and primary knee osteoarthritis revealed that there is a significant mean association of BMIs,  $t(84) = -3.47$ ,  $P$ -value = 0.001 between the osteoarthritis group, the mean BMI of patients in the knee osteoarthritis –YESI group 40.97 (SD = 3.59) was higher than the mean BMI of patients in the group without knee osteoarthritis –NOI groups: 31.29 (SD = 0.71). On obesity and comorbidities association, the result showed that there was no significant mean difference of BMI between the comorbidity groups,  $F(3, 82) = 0.82$ ,  $P$ -value = 0.489, however, the mean BMI of patients in Severe group

34.86 (SD = 4.66) was higher than the –None group (mean = 32.10, SD = 12.38). Among all the various types of food items, only consumption of rice, sugar, cordial drinks, evaporated milk, prawns and anchovies showed a significant association with obesity (*P*-values are 0.001, 0.022, 0.027, 0.020, 0.019 and 0.029), respectively, even at this, the relationships remained inconsistent. From FFQ, fruits (92.4%), green leafy vegetable (91.0%), rice (88.4%), fresh fish (85.8), condiments/spices (83.5%) and poultry (81.4%) were the food items in the highly consumed food category, sugar, eggs, palm oil, snacks and noodles are moderately consumed while carbonated drinks, cheese and yogurt are the least consumed. Obesity was shown to be significantly associated with primary knee osteoarthritis, although no significant associated was noted between obesity and medical comorbidity, however, the trending revealed that higher BMI patients were more in the severe comorbidity category indicating a positive link. These findings will help healthcare providers and policymakers in understanding and promoting measures toward reducing obesity rise.

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## FUNCTIONAL BRAIN ACTIVATION AND CONNECTIVITY OF WORKING MEMORY IN MODERATE TRAUMATIC BRAIN INJURY: A PRELIMINARY ADAPTIVE PLASTICITY USING fMRI

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**Introduction:** The aim of this study is to investigate functional brain activation and functional connectivity (FC) during n-back working memory (WM) tasks in the first visit or otherwise known as the initial study in which composed first, visit moderate traumatic brain injury (TBI) (within four weeks at time injury) compared to healthy control (HC) and preliminary adaptive plasticity the study is otherwise known as the follow-up study among moderate TBI of the first visit compared to the one year visit from the duration of the first visit. Participants were age and years of education matched. Moreover, participants were gender specific, males and applied convenience sampling approach.

**Methods:** Moderate TBI participants were acquired from road traffic accidents (RTAs) with closed head injury. Functional brain activation and FC patterns during WM tasks were assessed using the functional magnetic resonance imaging (fMRI) with a total sample size of 16 participants with an allocation of eight participants for each group (first visit moderate TBI and HC group) for first visit (initial) study.

In addition, preliminary adaptive plasticity (follow-up) study that targeted moderate TBI participants with a sample size of two participants for each group (first visit and one year visit group). Every participant performed the n-back alphabetical tasks during fMRI scan. The neuropsychological assessment data were analysed using a parametric independent *t*-test for first visit study and non-parametric, Mann-Whitney U for the preliminary adaptive study. In addition, random field analysis (RFX) was used to determine brain activations using the SPM12 and regression region of interest (ROI) to ROI in FC analysis was measured using the CONN toolbox.

**Results:** Based on functional brain activations and FC during WM n-back task results, the first visit moderate TBI in initial and preliminary adaptive plasticity studies were observed to use different brain regions and pathways that highly involved the subcortical and ventral cortical that may perhaps serve as a compensatory mechanism. One-year group in the preliminary adaptive plasticity study was observed to activated brain regions and used pathways involved four lobes including the frontoparietal system regions in which were also found to be activated in the HC group in the initial study. These observations were postulated to serve as recovery from injury.

**Conclusion:** Hence, with our result findings, it may serve as a biomarker to differentiate TBI severities and it may provide a better understanding of the underlying activities of moderate TBI.

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## ROLE OF *Heterotrigona itama* BEE BREAD ON REPRODUCTIVE SYSTEM IN MALE RATS FED WITH HIGH-FAT DIET

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**Introduction:** Obesity has been reported to cause testicular oxidative stress, inflammation and apoptosis thereby resulting in impaired male reproductive function while bee bread, on the other hand, exhibits antioxidant, anti-inflammatory and anti-apoptotic properties as seen in other tissues. However, to date, the role of *Heterotrigona itama* bee bread on male reproductive system in obesity has not been reported.

**Objectives:** Therefore, the objectives of this study were: i) to assess pH, composition and antioxidant properties of *Heterotrigona itama* bee bread and ii) to determine the role of *Heterotrigona itama* bee bread on anthropometric parameters, sperm parameters, testicular oxidative stress, inflammation, apoptosis, sexual behaviour as well as reproductive performance in male rats fed with high-fat diet (HFD).

**Methods:** Thirty-two adult male Sprague Dawley rats weighing between 250 g and 300 g were randomised into four groups ( $n = 8/\text{group}$ ), namely normal control (NC), HFD, HFD plus bee bread (HFD+B) and HFD plus an anti-obesity drug, orlistat (HFD+O) groups. Bee bread (0.5 mg/kg/day) and orlistat (10 mg/kg/day) were suspended in distilled water and given by oral gavage for 12 weeks. During the tenth week, each male rat was cohabited with a fertile female rat to assess male sexual behaviour and reproductive performance. At the end of 12 weeks, male rats were anaesthetised and blood, as well as the reproductive organs, were removed for the determination of reproductive functions.

**Results:** Bee bread was acidic, had in vitro antioxidant properties and nine phenolic compounds. Bee bread significantly improved the anthropometric parameters and lipid profile in rats fed with HFD. Similarly, bee bread also significantly ameliorated testicular oxidative stress, inflammation, apoptosis and germ cell proliferation in rats fed with HFD. Furthermore, bee bread significantly enhanced sperm count, viability, motility, and reduced abnormal sperm morphology as well as fragmented nDNA. In addition, bee bread significantly increased the levels of reproductive hormones and penile cyclic guanosine monophosphate, and decreased leptin level, thereby increasing the number of rats with improved intromission and ejaculation as well as mating and fertility indices.

**Conclusion:** Bee bread significantly improved the reproductive system in male rats fed with HFD by attenuating testicular oxidative stress, inflammation, apoptosis and improving testicular germ cell proliferation. However, further studies are needed to further investigate the molecular mechanism of action of bee bread and to determine its safety via toxicity study before it is used as a complementary treatment among obese patients.

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## ELUCIDATION OF TOLL-LIKE RECEPTOR 4 ANTAGONIST ON LEARNING AND MEMORY FUNCTIONS OF MICE FOLLOWING CHRONIC STRESS

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**Introduction:** Learning and memory functions are severely impacted by chronic stress due to Toll-like receptor 4 (TLR4)-mediated microglial upregulation and dopaminergic (DA) neuronal imbalance. Although lipopolysaccharide-*Rhodobacter sphaeroides* (LPS-Rs), a TLR4 antagonist,

can inhibit TLR4 activation pathway, its role in alleviating chronic stress-induced learning and memory impairments is still elusive.

**Objectives:** This study primarily aimed to elucidate the potential role of LPS-Rs in preserving learning and memory functions of mice following chronic stress.

**Methods:** Learning and memory performances of Swiss albino male mice underwent 21 days of chronic stress paradigm (restraint stress with social isolation) were assessed using Morris water maze (MWM) test. Immunohistochemistry (IHC) analysis was done to measure the expression levels of TLR4 protein, microglia and DA neurons in the dentate gyrus (DG) of hippocampus, prefrontal cortex (PFC) and ventral tegmental area (VTA).

**Results:** Twenty-one mice were included in this study. Stressed mice treated with LPS-Rs performed better than untreated mice in MWM test (latency: 9.30 s versus 16.79 s,  $P\text{-value} = 0.041$ ; path length: 217.40 cm versus 396.80 cm,  $P\text{-value} = 0.045$ ). IHC analysis showed significantly lower expression level of TLR4 protein in LPS-Rs treated compared to untreated groups in all the three brain regions (mean OD DG: 0.10 versus 0.24,  $P\text{-value} = 0.022$ ; PFC: 0.09 versus 0.20,  $P\text{-value} < 0.001$ ; VTA: 0.17 versus 0.27,  $P\text{-value} = 0.003$ ). Similar findings were observed on microglial expression level (mean OD DG: 0.14 versus 0.33,  $P\text{-value} < 0.001$ ; PFC: 0.10 versus 0.31,  $P\text{-value} < 0.001$ ; VTA: 0.15 versus 0.31,  $P\text{-value} < 0.001$ ). For DA neuronal expression level, both LPS-Rs treated and untreated groups exhibited significantly higher expression than control in the VTA (mean OD LPS-Rs treated: 0.14 versus 0.07,  $P\text{-value} = 0.016$ ; untreated: 0.17 versus 0.07,  $P\text{-value} = 0.001$ ) while no differences on DA neuronal expression were observed in hippocampal DG and PFC.

**Conclusion:** LPS-Rs improved MWM performance as well as reduced TLR4 and microglial activation in the hippocampal DG, PFC and VTA of stressed mice. Nevertheless, lack of effect of LPS-Rs was observed on DA neuronal expression. This study concluded that LPS-Rs has the potential to intercept chronic stress-induced TLR4-dependent neuroinflammation pathways.

*Supervisor:*  
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*Co-supervisors:*  
Professor Dato' Dr Jafri Malin Abdullah  
Dr Sangu Muthuraju

## ATTENTION CUES FOR GAME-BASED LEARNING IN XYZ: AN EYE TRACKING STUDY ON DIGITAL GAME

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**Introduction:** Attention cueing has been widely discussed in multimedia learning but studies focusing on

game-based learning (GBL) are still very limited. Attention cue and GBL were both contribute to enhance learning outcome but cueing effect in GBL is still subtle. Eye tracking methodology helps in examining the cueing effect in GBL and learning performance which were examined through the knowledge transfer test.

**Objectives:** This study primarily aims to examine how the cueing effect in game-based learning influences eye movements and knowledge transfer performance. Eye movements and knowledge transfer performance of 34 first-year medical students (cue group,  $n = 17$ ; no cue group,  $n = 17$ ) were assessed using eye tracking methodology and knowledge transfer test. The observed eye movement parameters was time to first fixation, first fixation duration, average fixation duration, fixation count, saccade count and average saccade duration during the game-based learning. A pre-test and post-test were used to examine the knowledge transfer performance. Eye movement parameters and knowledge transfer test scores were compared among cue and no cue groups.

**Results:** Eye movement results showed that the time to first fixation for size cue group had a statistically significant difference from no size cue group while first fixation, average fixation duration, fixation count, saccade count, average saccade duration showed no statistically significant differences between the two groups. All of the eye movement parameters revealed no statistically significant differences between the colour cue and no colour cue groups. A statistically significant difference was found only in no cue group instead of cue group for knowledge transfer performance, and only no size cue group revealed the statistical improvement in knowledge transfer score. Reaction time to AOI also showed no statistically significant differences between both groups.

**Conclusion:** Utilising eye tracking method can help researchers to understand learner's cognitive processes during the game-based learning. Implementation of salient size cue could guide learner's attention to relevant information but is unnecessarily improve the learning outcome. This study concluded that proper cue may guide learner's attention and game-based learning has the potential to improve learning outcome.

Supervisor:

Professor Dato' Dr Jafri Malin Abdullah

Co-supervisor:

Associate Professor Ts Dr Tan Wee Hoe

## EFFECTS OF STINGLESS BEE PROPOLIS ON OXIDATIVE STRESS AND STRUCTURAL INTEGRITY OF HEART IN STREPTOZOTOCININDUCED DIABETIC RATS

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**Introduction:** Diabetes mellitus (DM) is a concerning non-communicable disease worldwide that has great socio-economic impact especially in Malaysia where the prevalence beats global figure. Type 1 DM is a chronic metabolic disorder characterised by persistent hyperglycaemia leading to overproduction of oxidative stress that causes diabetic cardiomyopathy. Stingless bee propolis is rich in phenolic compounds that is made of resins from plant exudates and stingless bee's saliva. It has antihyperglycaemia, antioxidative and anti-ischaemic potential. Nevertheless, no previous study reported the effect of stingless bee propolis on diabetic heart.

**Objectives:** Thus, this study aims to determine the effect of supplementation of stingless bee propolis on oxidative stress and histopathology of heart in streptozotocin-induced diabetic rats.

**Methods:** The polar antioxidative compounds was extracted from raw stingless bee propolis using ethanolic extract. Adult male Sprague Dawley rats was divided into five groups ( $n = 8$ ): normoglycaemia (non-DM), untreated DM, diabetic treated with 300 mg/kg/day metformin (DM+Metformin), diabetic treated with 300 mg/kg/day propolis (DM+propolis), diabetic treated with both 300 mg/kg/day metformin and 300 mg/kg/day propolis (DM+combined) and treatment was given on daily basis. Single dose of 60 mg/kg streptozotocin was administered intraperitoneally to induce type 1 diabetes mellitus. Treatment was given for four weeks duration following successful induction of diabetes mellitus via oral gavage. Body weight, fasting blood glucose, water intake and food intake were taken every week. The rats were sacrificed after four weeks using 300 mg/kg of sodium pentobarbital. Serum and heart were collected for determination of colourimetric assays (oxidative stress markers and antioxidative enzymes) and histopathology.

**Results:** Diabetic rats experienced manifestation of hyperglycaemia such as polydipsia, polyphagia and weight loss. Their heart contains higher oxidative stress markers and alteration in antioxidative enzymes. Heart of DM rats showed features of diabetic cardiomyopathy including cardiomyocyte hypertrophy, cardiac fibrosis and perivascular fibrosis. Metformin or propolis supplementation reversed the clinical manifestation of DM but propolis alleviated histopathology and biochemical alteration of diabetic cardiomyopathy better than metformin. However, combination of metformin and propolis supplementation observed better improvement than metformin alone.

**Conclusion:** In a nutshell, this study of stingless bee propolis managed to produce positive data on diabetic cardiomyopathy in rats through its antihyperglycaemic and antioxidative properties.

Supervisor:

Dr Norsuhana Omar

Co-supervisors:

Associate Professor Dr Mahaneem Mohamed

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Dr Rozaziana Ahmad



## INVESTIGATING THE EFFECTS OF BRIEF MINDFULNESS INTERVENTION ON MINDFULNESS, PERCEIVED STRESS AND EMOTIONAL INTELLIGENCE IN MEDICAL STUDENTS: A PILOT STUDY

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**Introduction:** Medical students experience heightened stress levels which may affect their psychological wellbeing. Nonetheless, researchers have identified high levels of mindfulness and emotional intelligence (EI) to buffer stress, which in turn protect the psychological health of individuals.

**Objectives:** The aims of this study were to: i) develop and validate a four-weeks' brief mindfulness-based intervention (b-MBI) and ii) evaluate the effects of this b-MBI on the levels of mindfulness, perceived stress and EI in medical students.

**Methods:** Fifty-nine medical students studying in Years 1–3 at Universiti Sains Malaysia participated in this study. Participants were randomly allocated to intervention ( $N = 30$ ) or waitlist control ( $N = 29$ ) groups. The intervention group attended four weekly group-based sessions and performed daily home-based practices. All participants completed measures of mindfulness (mindful attention awareness scale [MAAS]), perceived stress (perceived stress scale [PSS-10]) and emotional intelligence (USM emotional quotient inventory [USMEQI]) at pre- and post-intervention.

**Results:** At baseline, all participants reported low stress and high EI levels. Results from mixed-factorial ANOVA revealed significant cross-over interactions, but no significant main effects of treatment conditions and time, on mindfulness and perceived stress. Post-hoc analyses indicated that intervention group experienced significant increase in mindfulness ( $P = 0.012$ ) and significant reduction in perceived stress ( $P = 0.003$ ) from baseline to post-intervention; these effects were not observed in the controls. For EI, significant main effect of time was observed ( $P = 0.001$ ). However, only intervention group reported significant increase in overall EI ( $P = 0.004$ ), self-management ( $P = 0.011$ ) and relationship management ( $P = 0.008$ ).

**Conclusion:** The lack of between-group treatment effects could be justified as a result of low stress and high EI for intervention and control groups at baseline. Nonetheless, within-group findings provided preliminary evidence that b-MBI might be beneficial in improving mindfulness, perceived stress and EI. This brief intervention

may be adapted into the medical curriculum to improve psychological wellbeing of medical students.

*Supervisor:*  
Associate Professor Dr Azizah Othman

*Co-supervisor:*  
Associate Professor Dr Muhamad Saiful Bahri Yusoff  
Dr Phang Cheng Kar

## A QUALITATIVE EXPLORATION OF THE LIVED EXPERIENCES OF HOMELESS PARENTS IN MALAYSIA IN RELATION TO MENTAL HEALTH

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**Introduction:** In addition to the stigma and discrimination attached to homelessness, homeless parents are responsible for the upbringing of their child in a high-risk environment, thereby placing them at a greater risk for developing mental illness.

**Objectives:** The study aimed to explore the lived experiences of homeless parents in Malaysia in relation to their mental health.

**Methods:** A total of nine homeless parents were recruited through purposive and snowballing method. Semi-structured, face-to-face interviews were conducted. Data were transcribed verbatim and analysed manually using thematic analysis.

**Results:** Four major themes emerged from the analysis, each consisted of several subthemes namely self-perceptions (parenting, locus of control and social comparison), hardships (family problems, living condition, financial instability and, stigma and discrimination), vulnerability (shame, fear, uncertainty, helplessness, rumination and upward comparison) and coping (personal and social). The results of the study showed that the participants are vulnerable to mental health problems, due to constant exposure to stress.

**Conclusion:** This study showed that the respondents are susceptible to mental health problems, which resulted from the multiple forms of hardship. In spite of this, the coping mechanisms used by the participants were shown to be effective in mitigating the adverse effects of homelessness.

*Supervisors:*  
Dr Mohd Nasir Che Mohd Yusoff  
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## HANDEDNESS AND SCHIZOTYPY PERSONALITY TRAIT ASSOCIATION AMONG NON-CLINICAL POPULATION

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**Introduction:** Schizotypy is shown to have correlation with the pattern of handedness which might be due to the brain lateralisation process. However, literature on the pattern of handedness association with schizotypy has a bigger gap. Hence, this research is to close the gap in the literature by looking on the pattern of handedness association with schizotypal personality trait.

**Objectives:** To find out the correlation between the pattern of handedness and schizotypal personality trait.

**Methods:** Survey questionnaire method has been used in order to gain information from 162 participants. Only 117 participants are valid for data analysis. Convenient sampling and quantitative research method have been used to analyze the correlation between schizotypal personality questionnaires (SPQ) and laterality quotient (LQ) score based on Edinburgh handedness inventory (EHI). SPQ has been used in order to measure the schizotypal personality traits, and EHI is being used to measure the score of the pattern of handedness by calculating the LQ score.

**Results:** There is a significant weak correlation between the SPQ total score and LQ score. There is also significant weak correlation between the cognitive perceptual, negative, and paranoid domain of the SPQ with the LQ Score. Disorganised domain has no correlation with the pattern of handedness. Multilinear regression result shows that only paranoid is only the best predictor on the LQ score.

**Conclusion:** There is a weak correlation between pattern of handedness and schizotypal personality trait. All the domains of the schizotypal personality have association with the pattern of handedness except for disorganised domain. Paranoid domain is the strongest predictor of the pattern of handedness. This finding of paranoid as the best predictor for pattern of handedness can be added into the literature which found disorganised is the best predictor.

Supervisor:

Dr Mohamed Faiz Mohamed Mustafar

## DEVELOPMENT AND EVALUATION OF HEALTH EDUCATION MODULE FOR THE PREVENTION OF RESPIRATORY TRACT INFECTIONS AMONG PRIVATE HAJJ AND UMRAH PILGRIMS

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**Introduction:** Hajj pilgrimage is usually associated with a regular occurrence of respiratory tract infection among pilgrims. Vaccination uptake and other preventive behaviours have generally been low among pilgrims across the globe. Despite this, there is presently no validated health theory-based health education module in Malaysia to guide the pilgrims on how to boost compliance with these preventive practices and increase their knowledge towards respiratory tract infection, preventive attitudes and practices towards prevention strategies.

**Objectives:** The general objective of this study is to develop and evaluate the effectiveness of health education modules against respiratory tract infections among Hajj pilgrims from Malaysia.

**Methods:** This study was carried out in phases comprising of development and validation of questionnaire phase, development and validation of health education module for respiratory tract infection prevention phase, baseline characterisation of pilgrims' phase, intervention phase and evaluation phase. At the first phase of the study, a cross-sectional study was conducted for the development and validation of a measurement tool using the content, construct (items response theory, exploratory factor analysis and confirmatory factor analysis) validation and reliability. This phase is followed by the development and validation of new health education module via a smartphone application. For the intervention and the evaluation phase, a quasi-experimental study was utilised, where pre-post intervention data were analysed among 52 and 50 Hajj/Umrah pilgrims in the intervention or control group, respectively. The intervention group was given health education module on the prevention of respiratory tract infections during Hajj and Umrah in the form of a smartphone application which was strictly guided by the health belief model. The control group received a smartphone application on normal Hajj and Umrah guidance from a different Hajj/Umrah travel company. Follow-up data were collected using the same questionnaire that was used during the pre-test data collection. Mixed design repeated measure ANOVA was used to analyse the effect of group, time, and group-time interaction on the dependent variables.

**Results:** There was a significant improvement in knowledge score and the main effect in the intervention group compared to the control group, based on time ( $P = 0.005$ ,  $\eta^2 = 0.075$ ). Likewise, there was significant improvement in attitude score and main effect based on time ( $P = 0.035$ ,  $\eta^2 = 0.044$ ). Similarly, there was a significant change in practice score and also main effect based on time ( $P = 0.005$ ,  $\eta^2 = 0.075$ ). The education module on the prevention of respiratory tract infections during Hajj and Umrah in the form of a smartphone application which was strictly guided by the health belief model. The control group received a smartphone application on normal Hajj and Umrah guidance from a different Hajj/Umrah travel company. Follow-up data were collected using the same questionnaire that was used during the pre-test data collection. Mixed design repeated measure ANOVA was used to analyse the effect of group, time, and group-time interaction on the dependent variables. There was a significant improvement in knowledge score and the main effect in the intervention group compared to the control group, based on time ( $P = 0.005$ ,  $\eta^2 = 0.075$ ).

Likewise, there was significant improvement in attitude score and main effect based on time ( $P = 0.035$ ,  $\eta p^2 = 0.044$ ). Similarly, there was a significant change in practice score and also main effect based on time ( $P < 0.001$ ,  $\eta p^2 = 0.155$ ) and interaction of group with time ( $P = 0.042$ ,  $\eta p^2 = 0.041$ ). Similarly, the occurrence of Respiratory tract infection (RTI) in the intervention group is lower when compared to the control group.

**Conclusion:** The new health educational intervention module developed was effective in improving the knowledge, attitude and practices toward prevention of RTI among Hajj pilgrims from Malaysia. Further studies are also needed to investigate the barriers and motivators to link the knowledge gap about the uptake of mandatory and recommended vaccine as well as the other components of the module. Therefore, Hajj agencies need to conduct health education before departure of pilgrims to prepare them against the common respiratory infections or in the event of outbreaks of infection during Hajj/Umrah.

*Supervisor:*

*Professor Dr Habsah Hassan*

*Co-supervisors:*

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*Dr Wan Arfah Nadiyah Wan Abdul Jamil*

*Professor Dr Syed Hatim Noor @ Nyi Nyi Naing*

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## EVALUATION OF POTENTIAL ANTIVIRAL PROPERTIES OF TUALANG HONEY AGAINST IN VITRO CHIKUNGUNYA VIRUS INFECTION IN VERO CELLS

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**Introduction:** Chikungunya is a mosquito-borne viral disease transmitted to human by Chikungunya virus (CHIKV) which has affected many countries around the world. CHIKV is transmitted mainly by two species of *Aedes* mosquitoes, *Aedes albopictus* and *Aedes aegypti*, and causes typically acute illness with incapacitating arthralgia, fever and rashes. Currently, there is no antiviral or licensed vaccine commercially available.

**Objectives:** In this study, we explored the in vitro antiviral activity of the Tualang honey against CHIKV in Vero cells.

**Methods:** The potential anti-CHIKV property of Tualang honey was determined in different assays including virucidal, pre-treatment, post-treatment, anti-entry and anti-adsorption, using the nontoxic concentrations of Tualang honey at different incubation hours. The viral inhibitory effect was confirmed by plaque assay after morphological changes of Vero cells were observed.

**Results:** The results showed that Tualang honey was not toxic to Vero cells at concentration between 20 mg/mL

and 5 mg/mL. This study demonstrated that Tualang honey exhibited significant antiviral activity against CHIKV. The virucidal activity of Tualang honey against different amounts of CHIKV was observed by the significant inhibition noticed in the viral titre. Remarkably, the pre-treatment of Tualang honey on Vero cells for 12 h and 24 h before infection gave the highest inhibitory effect on CHIKV especially at 48 h post-infection, with about 90% inhibition of viral titres was observed ( $P < 0.05$ ). Surprisingly, during post-treatment assay, CHIKV replication was significantly inhibited in Vero cells following post-exposure to Tualang honey for 8 h. The post-treatment of cells with Tualang honey displayed the biggest reduction of viral titre effect when compared with the other assays with percentage of inhibition 98% ( $P < 0.05$ ). However, Tualang honey did not significantly inhibit infection of Vero cells by CHIKV during the anti-adsorption and anti-entry assay with percentage of inhibition surpassed 33% to 80%.

**Conclusion:** Overall, the results from the current study suggest that Tualang honey can be explored as an alternative anti-CHIKV agent. Future study is warranted to elucidate Tualang honey mechanism of action and whether similar effects could be demonstrated in vivo.

*Supervisor:*

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*Co-supervisor:*

*Dr Rohimah Mohamud*

## DETERMINATION OF TNFR2<sup>+</sup> REGULATORY T CELLS AND CD103<sup>+</sup> DENDRITIC CELLS IN ASTHMATIC PATIENTS HOSPITAL UNIVERSITI SAINS MALAYSIA

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**Introduction:** Asthma is a common chronic inflammatory disorder of the airways. Asthma pathophysiology are resulted from an immune dysregulation of the asthmatics with insufficient of regulatory cells to induce immune tolerance and fail to maintain immune homeostasis. Dendritic cells (DC), as a professional antigen presenting cells (APC) are responsible in the allergen uptake and initiate the immune response. In addition, the tolerogenic CD103<sup>+</sup> DCs are capable to modulate the immune response by inducing immune tolerance through the interaction with regulatory T (Treg) cells. The tumour necrosis factor receptor 2 (TNFR2<sup>+</sup>) expressing Treg has been recently characterised as the most potently suppressive Tregs population.

**Objectives:** Hence, this study aimed to determine the proportion of CD103<sup>+</sup> DC and TNFR2<sup>+</sup> Treg cells in peripheral blood mononuclear cells (PBMC) of the asthmatics compared to non-asthmatic controls. In addition, the secretion levels of pro-inflammatory cytokines; IL-4 and

IFN-g and anti-inflammatory cytokines; IL-10 and TNF were measured to support the findings on CD103<sup>+</sup> DC and TNFR2<sup>+</sup> Treg cells.

**Methods:** Thirty-seven asthma patients and forty-two non-asthmatic controls were recruited in this study. Six-colour flow cytometer was used to determine the percentages of the expression of APC and Treg subset. PBMC was isolated from peripheral blood using Ficol-gradient centrifugation and stained with fluorophore-labelled antibodies. The APC subsets were identified using surface markers of HLA-DR, CD11c, CD11b, CD86 and CD103, while Treg subsets were identified using markers of CD3, CD4, CD25, TNFR2 and Foxp3, in two different antibody cocktails. The absolute counts of the cell subsets were obtained by dual platform method from flow cytometer and hematology analyzer. The cytokines from the plasma were measured using MILLIPLEX® proteomic immunoassays.

**Results:** Asthma patients showed a significantly decreased level of CD103<sup>+</sup> DC within HLADR<sup>+</sup>CD11c<sup>+</sup> ( $P = 0.008$ ) and significantly increased level of Foxp3 expressing TNFR2<sup>+</sup> Treg within CD25<sup>+</sup>TNFR2<sup>+</sup> ( $P = 0.0450$ ), CD25<sup>+</sup>TNFR2<sup>+</sup> ( $P = 0.0195$ ) and different antibody cocktails. The absolute counts of the cell subsets were obtained by dual platform method from flow cytometer and hematology analyser CD25<sup>+</sup>TNFR2<sup>+</sup> ( $P = 0.0195$ ) when compared with non-asthmatic controls. In addition, significant increased of IL-10 ( $P = 0.0198$ ) and TNF ( $P = 0.0211$ ) concentrations supported the findings on the proportion of Treg cells.

**Conclusion:** We suggested that the increased levels of Tregs in blood could continuously suppress the Th2 cells activation in the circulation which is also supported by the increased of anti inflammatory cytokines IL-10 and TNF. Overall, functional immunoregulation of the regulatory cells, particularly Tregs exhibit immune suppression and induce immune tolerance in the linked with the immune activation by the APC which corrected tolerance in the linked with the immune activation by the APC which corrected by treatments.

*Supervisor:*

*Dr Rohimah Mohamud*

*Co-supervisors:*

*Dr Tina Tan Hern Tze*

*Dr Noor Suryani Mohd Ashari*

## DETERMINATION OF COGNITIVE FLEXIBILITY BY STROOP AND ERP TEST AMONG NEUROTICISM YOUNG ADULTS

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**Introduction:** Cognitive flexibility among individuals can differed based on neuroticism level of personality.

**Objectives:** This study examined Neuroticism scores in relation to cognitive flexibility using Stroop task during

the event-related potentials (ERPs) recording for P300 components (amplitudes and latencies).

**Methods:** Overall, 20 participants took part where 10 participants in low neuroticism (LN group) and 10 participants in high neuroticism (HN) group. This study employed comparative cross-sectional design and used Mann-Whitney U test to compare the cognitive flexibility between the two groups.

**Results:** Both groups exhibited similar level in reaction times on the task. There was no significant difference in P300 amplitude between the two groups but the HN exhibited larger amplitude when performed the Stroop task which is means more attention allocation. In addition, larger P300 amplitudes elicited at the electrode Fz (frontal) and it showed activation of frontal region and parallel with past neuroimaging studies that have demonstrated role of the prefrontal cortex (PFC) when performed the Stroop task. In regard to P300 latencies, prolonged positivity of P300 latency recorded at Pz (parietal) electrode while performed the Stroop task for both groups indicated that more time is required to process the information.

**Conclusion:** Evident showed that slower processing speed for HN participants, as indicated by longer latency in responses to the Stroop task. Hence, in a nutshell, all of these findings supported previous study on the idea that individuals with high neuroticism scores have sustained attention and slower mental speed processing, therefore less able to exert cognitive flexibility than those with low neuroticism scores.

*Supervisor:*

*Dr Mohd Nasir Che Mohd Yusoff*

*Co-supervisor:*

*Associate Professor Dr Nor Azila Noh*

## KIDCOPE-CHILD IN BAHASA MALAYSIA: A STUDY ON PSYCHOMETRIC PROPERTIES AMONG THE PAEDIATRIC POPULATION

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**Introduction:** Knowledge of patients' coping process is crucial to prevent psychological distress during hospitalisation. The absence of a measure of coping for school-age paediatric patients in Malaysia poses a challenge in an objective understanding of coping among this population. The purpose of the present study was to translate KIDCOPE-child, a measure of coping for children, into Bahasa Malaysia, and report its validity and reliability.

**Methods:** In Phase 1, four translators translated KIDCOPE-child into Bahasa Malaysia. Three experts rated its content validity index (CVI). The instrument was pre-tested with 10 children aged 7 years old to 12 years old for face validity and feasibility. Phase 2 implied a correlational study design. The Bahasa Malaysia version of KIDCOPE-

child was administered to 100 participants aged 7 years old to 12 years old, who were conveniently sampled from children hospitalised at Hospital Universiti Sains Malaysia.

**Results:** A Bahasa Malaysia translation was produced. Content validity analysis found average CVI ratings of over 3.0 for all items. Face validity and feasibility were established. The most frequently endorsed coping strategies were social support (90%), emotion regulation (83%), and problem-solving (76%). Latent variable exploratory factor analysis revealed two-factor solutions: positive coping and disengagement coping. Internal reliability of the factor structure was unsatisfactory; Kuder-Richardson Formula 20 (KR20) alpha value of 0.59 for Positive Coping and 0.21 for Disengagement Coping, with an overall alpha value of 0.48.

**Conclusion:** KIDCOPE-child in Bahasa Malaysia is valid and suitable as a descriptive measure of a particular coping strategy. However, the factor structure has unsatisfactory internal reliability; hence, limiting its usefulness to provide information about different coping styles for the paediatric population in Malaysia. The finding calls for additional studies employing a more representative sampling population or development of a coping measure with more culturally relevant items that can better capture the coping strategies among the school-age paediatric population in Malaysia.

*Supervisor:*  
Associate Professor Dr Azizah Othman

*Co-supervisors:*  
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## INTERACTION OF LIPOSOMES FROM *Mycobacterium smegmatis* WITH MICE BONE MARROW

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**Introduction:** Liposomes are lipid based-nanoparticles, mainly composed of synthetic or naturally derived-phospholipid mixed lipid chains. Due to their lower cost, biocompatibility and biodegradability, much attention is devoted to them as potential carriers for targeted delivery in biomedical research for their adjuvant effects on dendritic cells (DCs), with unique capacity of stimulating primary immune responses.

**Objectives:** The aim of this study was to investigate the immune stimulating effects of liposomes derived from *Mycobacterium smegmatis* (*M. smegmatis*) on DCs.

**Methods:** Liposomes were produced from total lipids of *M. smegmatis* and characterised by scanning electron microscopy (SEM), showing spherical shape and size between 20 nm and 80 nm, which were classified as small unilamellar vesicles (SUVs). Bone marrow was obtained from Balb/c mice and cultured in the presence of growth

monocytes colony stimulating factor (GM-CSF) and interleukin 4 (IL-4) to obtain mature bone marrow derived-dendritic cells (BMDCs), and demonstrated the typical characteristics of this kind of cells after characterisation. The recognition and internalisation of *M. smegmatis* liposomes by BMDCs was demonstrated by SEM and confocal microscopy after 24 h exposure. The immune activation of BMDCs upon interaction with liposomes was studied by FACS to detect the expression of surface markers (CD86, CD11c and MHCII) and by the detection of production of cytokines (IFN- $\gamma$ )-DOG/-10 by multiplex assay.

The interaction of BMDCs with liposomes induced immune activation of these cells evidenced by the increasing of expression of these three surface markers and the secretion of IFN- $\gamma$ -WHU WKH inhibitors (chlorpromazine, filipin III and cytochalasin) of endocytosis was introduced, there was a blockage of the uptake of liposomes and immune activation of BMDCs.

**Conclusion:** Taken together these results suggest that there is an important of immune stimulatory capacity of the liposomes derived *M. smegmatis* and their uptake for the immune activation of BMDCs. Future studies will complete the evaluation of the immune stimulatory mechanisms of liposomes from *M. smegmatis* and confirm their potential for immunotherapeutic and vaccine adjuvant properties.

*Supervisor:*  
Dr Ramlah Kadir

*Co-supervisors:*  
Professor Dr Armando Acosta  
Dr Rohimah Mohamad

## ASSESSMENT OF DOPAMINE RECEPTOR DRD4 AND DRD5 MRNA EXPRESSION IN PERIPHERAL BLOOD LYMPHOCYTES OF OPIOID AND AMPHETAMINE TYPE STIMULANT DEPENDENT MALAY MEN UNDERGOING METHADONE MAINTAINENCE THERAPY

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**Introduction:** In Malaysia and throughout the Asian region the mixed opioid and amphetamine type stimulants dependence is highly prevalent which has become a major health problem. Opioids and amphetamine-type stimulants (ATS) exert their effect by altering natural dopamine neurotransmission in the brain to achieve the ultimate goal of an extracellular hyper-dopamine state hence resulting drug reward effect. Dopamine actions are mediated by specific G proteins coupled receptors of two distinct families; D1-like receptor subtypes (D1 and D5) and the D2-like receptor subtypes (D2, D3 and D4). Evidence from previous studies has suggested that peripheral dopamine systems reflect the central dopamine system's activity and pathology,

especially in neuropsychiatric diseases. Studies have been carried out widely on central dopamine systems, while investigation of dopamine systems in various peripheral organs is still limited. It has been reported that peripheral blood lymphocytes express dopamine in peripheral systems.

**Objectives:** In this study, we investigated the difference in the mRNA expression of the dopamine receptors DRD4 and DRD5 in peripheral blood lymphocytes of ATS and opioid dependent Malay male subjects undergoing methadone maintenance treatment and healthy Malay male serving as control subjects.

**Methods:** A total of 72 participants with 36 drug dependent subjects and 36 control subjects were recruited from various parts of Kuala Terengganu, Terengganu according to inclusion and exclusion criteria. Demographic data including age, height, weight, body mass index and blood pressure of all participants were recorded. A questionnaire form was given to the drug dependent subjects to assess their drug addiction status. Informed and written consent was obtained, and blood samples were collected. RNA was extracted from lymphocytes. The mRNA expression of the dopamine receptors DRD4 and DRD5 in peripheral blood lymphocytes was assessed by real-time PCR method. The demographic data of the subjects were calculated using Mann-Whitney U test. The *P*-value 0.05 was used for the statistical significance.

**Results:** There was a significant difference between drug dependent subjects and control subjects for age and systolic blood pressure parameters while other parameters were not statistically significant. The DRD4 mRNA expression level is significantly reduced in lymphocytes of drug dependent subjects compared to control subjects (*P* = 0.039). However, DRD5 mRNA expression level in lymphocytes of drug dependent subjects was not statistically significant (*P* = 0.251).

**Conclusion:** Drug dependent subjects on mixed opioid and ATS dependence undergoing methadone maintenance treatment may exhibit different patterns of dopamine receptors DRD4 and DRD5 mRNA expressions in the peripheral lymphocytes. Further studies are recommended to support the findings of the present study.

*Supervisor:*

*Dr Ruzilawati Abu Bakar*

*Co-supervisors:*

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*Associate Professor Dr Nurul Asma Abdullah*

## APPLICATION OF HIGH RESOLUTION MELTING (HRM) ANALYSIS IN DETECTION OF PDGFRA GENE MUTATIONS AMONG CHRONIC MYELOID LEUKEMIA PATIENTS TREATED WITH IMATINIB MESYLATE

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**Introduction:** A molecular detection of PDGFRA variants is highly relevant for prognosis and therapy prediction in chronic myeloid leukemia (CML) patients treated with imatinib mesylate (IM). Even though IM has shown an excellent efficacy as a frontline treatment in CML, emerging of resistance towards IM in some CML patients has become a major concern. The development of resistance can be either due to BCR-ABL dependent mechanism or BCR-ABL independent mechanism. The BCR-ABL independent mechanisms include factor in pharmacokinetics of IM such as absorption and distribution of metabolism. However, resistance to IM can also due to the involvement of others IM targeted tyrosine kinases that may play a role in the IM resistance.

**Objectives:** In response to growing demand for reliable, faster and more sensitive methods, the present study used a high resolution melting (HRM) analysis to elucidate the BCR-ABL independent mechanism involving PDGFRA tyrosine kinase, in Malaysian CML patients undergoing IM therapy using.

**Methods:** A total of 86 CML patients on IM therapy (43 IM resistances and 43 IM responses) were included in this study. Using HRM analysis, 86 CML patients were screened for PDGFRA variants of exon 10 (c.1432 T > C), exon 12 (c.1701 A > G), exon 14 (c.1977 C > A) and exon 18 (c.2525 A > T). The selected samples with showing different melting curve profile from the reference genotype was subjected to DNA sequencing analysis to validate the genotype.

**Results:** From the data analysed, two PDGFRA variants were detected in exon 10 and 12. The established HRM profile has demonstrated 100% sensitivity and specificity when compared to DNA sequencing. PDGFRA exon 10 (c.1432 T > C) showed a significant risk factor (OR 3.797; 95% CI: 1.502, 9.591; *P* = 0.005) for the development of IM resistance. PDGFRA exon 12 (c.1701 A > G) was not significant risk factor (OR 1.597; 95% CI: 0.681, 3.745; *P* = 0.281) for IM resistance. However there is no PDGFRA heterogeneity detected for both exon 14 c.1977 C > G and exon 18 c.2525 A > T.

**Conclusion:** The results suggested that PDGFRA influenced IM resistance in CML patients and further analysis are warranted to confirm the role of PDGFRA in IM resistance mechanism in CML patient.

*Supervisor:*

*Dr Nazihah Mohd Yunus*

*Co-supervisors:*

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## CHANGES OF CENTRAL MACULAR THICKNESS POST INTRAVITREAL RANIBIZUMAB AND ITS ASSOCIATED FACTORS AMONG DIABETIC MACULAR OEDEMA PATIENTS

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**Background:** Intravitreal ranibizumab (IVR) which is an anti-vascular endothelial growth factor (anti-VEGF) has become the preferred treatment option to improve the vision of diabetic macular oedema (DMO) patients. IVR acts by inhibits VEGF-A from binding to its receptors, leading to decreased in vascular permeability and thereby causing changes of central macular thickness (CMT). The response to IVR treatment is considered optimal if the changes of CMT after three months is less or equal to 280  $\mu\text{m}$ .

**Objectives:** The objectives of this study were to estimate the mean of changes of CMT and the proportion of optimal treatment response after three injections of IVR and to identify associated factors of changes of the CMT among DMO patients.

**Methods:** This was a cross-sectional study using secondary record review of the DMO patients who received three-month treatment of IVR in Hospital Universiti Sains Malaysia from 2016 to 2019. The CMT was measured by using optical coherence tomography (OCT) machines. Changes of CMT was calculated based on the differences of thickness of central macula in  $\mu\text{m}$  between baseline and at month 3. General linear regression was then applied to analyse the association of changes of CMT using STATA SE 14 software.

**Results:** A total of 153 DMO patients were included. There were 69 (45.1%) male and 84 (54.9%) female patients with a mean (standard deviation [SD]) age of 57.5 (7.70) years old and median (interquartile range [IQR]) of diabetes duration of 11 (9) years. The mean (SD) of changes of CMT was 155.5 (137.8)  $\mu\text{m}$ . After three injection of IVR, only 30.7% had optimal treatment response. Factors significantly associated with changes of CMT were baseline CMT ( $b = 0.73$ ; 95% CI: 0.63, 0.84;  $P = < 0.001$ ) and presence of subretinal fluid (SRF) ( $b = 35.43$ ; 95% CI: 3.70, 67.16;  $P = 0.029$ ). These factors explained 58.3% of the variation in changes of CMT.

**Conclusion:** There was less changes of CMT and less patients achieved optimal treatment response after three months of IVR treatment. Patients who presented with SRF and high baseline CMT had greater changes of CMT after receiving three injections of IVR treatments.

Supervisor:  
Dr Siti Azrin Ab Hamid

Co-supervisors:  
Professor Datin Dr Zunaina Embong  
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## IN VIVO EFFECTS OF SIROLIMUS AND SUNITINIB ON BREAST CANCER PROGNOSTIC MARKERS

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**Introduction:** Breast cancer is a heterogeneous disease with a wide variety of clinical, pathological, and molecular characteristics, the most commonly diagnosed cancer among females and the leading cause of women cancer death. Hormone receptor studies such as estrogen receptor (ER), progesterone receptor (PgR) and human epidermal growth factor receptor-2 (HER2/neu) are routinely done in prognosis of breast carcinoma and helps in deciding the best treatment. Sirolimus is a natural macrocyclic lactone drug from bacteria with immunosuppressive and antiproliferative properties by inhibiting mechanistic target of rapamycin (mTOR). Sunitinib is a tyrosine kinase inhibitor (TKI) with antiangiogenic properties.

**Objective:** Therefore, it will be interesting to analyse the effect of sirolimus and sunitinib in blocking the growth of breast cancer from responding to hormone stimulation.

**Methods:** In this study, invasive mammary carcinoma was induced by using 70 mg/kg body weight NNitroso-N-Methylurea (NMU) in 32 young female Sprague Dawley rats. The gene and protein expressions of ER, PgR and HER2/neu markers were evaluated by using semi-quantitative immunohistochemistry analysis and quantitative real-time PCR assay.

**Results:** Findings from the untreated-control group demonstrated that all mammary lesions are 100% malignant, histopathological characterised with invasive breast carcinoma (IBC) of three major patterns; cribriform, papillary and no special type (NST). Sirolimus treatment showed significant inhibition of mammary tumour progression and downregulate the protein expressions of ER and PgR. However, high expressions of ER and PgR genes expressed on mRNA level might due to sirolimus cause post-transcriptional regulation in gene. Meanwhile, tumour treated with sunitinib reduced in diameter after first treatment, but the diameter increased after second treatment, and consequently showed no significant downregulation of ER and PgR.

**Conclusion:** Histologically, sunitinib treated tumour did not show any aggressive ductal NST histological subtypes. All NMU-induced tumours were HER2/neu-negative scoring. Tumour regression in combination treatment shown was predicted due to sirolimus predominantly showed anticancer effect rather than sunitinib. Thus, present findings suggested that sirolimus is neither synergistic nor additive with sunitinib.

Supervisor:  
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## SURVIVAL AND PROGNOSTIC FACTORS OF MORTALITY IN PATIENTS WITH PERITONEAL DIALYSIS-RELATED PERITONITIS

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**Introduction:** Peritonitis is one of the major complications of peritoneal dialysis (PD). The median survival time and survival rate in PD patient has been studied extensively globally and varies from one country to another. However, the median survival time and survival rate of PD related peritonitis data is scarcely studied both locally and globally.

**Objective:** This study aimed to determine the survival time and prognostic factors of PD related peritonitis.

**Methods:** This study was a retrospective cohort study that used secondary data from the National Renal Registry from 2010 until 2015 located in Hospital Kuala Lumpur. Five main group variables were studied comprising of socio-demographic, clinical parameters, biochemical parameters, PD regime and medications. The outcome studied was the survival time which was calculated from the first peritonitis episode until the outcome of death. The primary event was all-cause mortality and censored outcome included patient still alive at end of study, changed to hemodialysis and loss to follow-up. Kaplan Meier estimate and life table analysis were used for univariable and Cox proportional hazard regression was used for multivariable analysis.

**Results:** Overall the study included a total of 2,002 patients. This study observed 40% of the patient had death as outcome. Overall, the mean age of the patients were 59 (standard deviation) 17.4 and 50.2% of the patients were woman. The median survival time for PD related peritonitis was 46.3 months (95% confidence interval (CI): 42.2, 56.7). The one-, two- and three year survival rates of PD related peritonitis were 75.6 (95% CI: 73.7, 77.5), 64.6% (95% CI: 62.5, 66.7) and 55.6% (95% CI: 53.3, 57.8), respectively. Five prognostic factors were identified in this study affecting survival of PD related peritonitis patients which were age (adjusted hazard ratio (aHR): 1.04; 95% CI: 1.03, 1.04), serum albumin (aHR: 1.37; 95% CI: 1.20, 1.57), onset of peritonitis (aHR: 1.24; 95% CI: 1.08, 1.43), angiotensin receptor blocker medication (aHR: 1.37; 95% CI: 1.11, 1.60) and peritonitis episode (aHR: 0.36; 95% CI: 0.27, 0.46).

**Conclusion:** Multiple Cox proportional hazard regression revealed older age, hypoalbuminemia, not on angiotensin receptor blocker, increase peritonitis episode and late onset peritonitis were significant prognostic factors of mortality. These findings provide evidence based information for clinicians and policy makers in planning preventive

measures and interventional programs for peritonitis in PD patients.

Supervisor:  
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## PUTATIVE INHIBITORY ACTIONS OF SELECTED MEDICINAL PLANTS AGAINST EXONIC SPLICING ENHANCERS

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**Introduction:** A previous study had demonstrated the successful use of isodiospyrin as an inhibitor of splicing factor and the use of a small-molecule compound as exon skipping inducer. Inhibition of serine and arginine-rich (SR) protein using isodiospyrin and their homolog results in exon skipping and indirectly restore the reading frame and protein product. Creating a novel minigene model can be used for studying the complexity of the splicing mechanism, potentially translatable into the identification of therapeutic targets in various related other conditions, such as Duchenne muscular dystrophy where the dystrophin gene is affected.

**Objective:** To determine the inhibitory actions of isodiospyrin and isodiospyrin homolog of selected medicinal plant extracts for inducing skipping in the designed minigene against exonic splicing enhancers.

**Methods:** Exonic splicing enhancers of dystrophin minigene was identified using ESEfinder 3.0 software. There are two subtypes of minigene which are genuine minigene and artificial minigene. Genuine minigene includes Gen-Ex45, Gen-Ex 51 and Gen-Ex53 while artificial minigenes with specific exonic splicing enhancers (ESE) are Art-SF2/ASF, Art-Sc35, Art-SRp40, Art-SRp55 and Art-NO ESE. All minigenes were constructed before being subjected to the cloning process and targeted minigenes were validated using sequencing before to transfection into the HEK-293 cell line for splicing assay. The assay was again validated using two methods which are luciferase assay by the fluorescent signal and another method by the presence of targeted size band after reverse transcriptase-polymerase chain reaction (RT-PCR) and were then confirmed by sequencing analysis. Six extracts from five plants similar to isodiospyrin homolog were screened using NADI software.

**Results:** Direct sequencing further validated the absence of exon after compounds exposure to all minigene, results showed no skipping in all genuine minigene, different with artificial minigene which showed all skipplings based on the RT-PCR results. After luciferase analyses, their skipping values were still far from mock minigene (standard skipping) which showed a higher threshold indicating that no skipping occurred and that luciferase assay was more sensitive than RT-PCR. Based on the result obtained, it was



proven that fewer ESE sequences in the exon are unable to retain exon. Also, there was a higher potential of skipping to occur if there are few ESE in the sequence, the presence of a silencer motif as well as when that sequence consists of positive splicing potential value. Five of the compounds were shown significantly to induce skipping after exposure to the Art-SRp55 and one of each Art-SC35 and Art-SRp40, while no compounds showed significant skipping after exposure to the Art-SF2/ASF. However, it was shown that the skipping level was not as much as that which occurred in the mock minigene that acted as a skipping standard. Interestingly, isodiospyrin showed to have a high tendency to become ESE skipper when exposed to the Art-SRp40 minigene, because it showed a significant skipping value ( $P = 0.049$ ) although with the presence of silencer motif 1 and higher SP value.

**Conclusion:** Isodiospyrin and its homologs might have shown the capacity to induce skipping, although in an ESE-specific manner, even with or without the presence of silencer motif and hnRNP A1. This approach may provide a view to further study ESE on the disease-related conditions.

*Supervisor:*

*Associate Professor Dr Aida Tegoh Haryo Sasongko*

*Co-supervisors:*

*Associate Professor Dr Muzaimi Mustapha*

*Professor Dr Zabidi Azhar Mohd Hussin*

*Professor Dr Habibah Abdul Wahab*

## FEASIBILITY OF LAUGHTER YOGA AS AN ALTERNATIVE INTERVENTION FOR ELDERLY: EFFECT ON WELL-BEING DEPRESSION AND ANXIETY

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**Introduction:** Laughter yoga based on the concept that fake laughter will provide the same benefit as genuine laughter. It is the hybrid of unconditional laughter with yoga respiratory exercise. Most of the past study about laughter involve genuine laughter, there is very limited research concerning laughter yoga in the psychological field.

**Objective:** Thus, this pilot study had aimed to examine the outcome of laughter yoga on elderly by using a two-group two-step quasi-experiment. This study had explored the effect of laughter yoga so that the feasibility of laughter yoga as alternative intervention for late life rehabilitation can be evaluated. The psychological dimensions were explored. The dimensions include well-being, depression, and anxiety.

**Methods:** The research was conducted in Kuala Terengganu. Participants were recruited among the members of Terengganu Buddhist Association and there a total of thirty-six participants had volunteered to participate in this study. The participants recruited were between sixty to eighty-five years old. Global happiness scale (GHS) and hospital anxiety and depression scale (HADS) were used

as instruments to obtain the data for this research and the relationship between these dimensions were analysed using the Statistical Package for the Social Sciences (SPSS) version 26.

**Results:** The result had indicated that there was no significant difference in outcome of the laughter yoga on well-being, depression, and anxiety.

**Conclusion:** It is suggested that laughter yoga might be feasible as an alternative intervention for elderly but only effective for a certain group of individual and suitable to be implement as a long term therapy. This research provide an empirical data for clinician and therapist that might consider to implement the intervention. Researcher also provided suggestions for future researchers in order to overcome challenges in handling future research.

*Supervisors:*

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*Dr Asma Perveen*

## EARLY AND LATE CHANGES IN ENDOTHELIAL DEPENDENT VASCULAR RELAXATION AND CONTRACTION RESPONSES IN THE MICROCIRCULATION OF DIABETIC RATS

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**PhD**

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**Introduction:** Diabetes is associated with micro and macrovascular complications which contributes to endothelial dysfunction (ED) and leads to cardiovascular diseases. ED is characterised by impairment of endothelium-dependent relaxation and increases in endothelium-dependent contraction. The endothelial cells release factors that cause endothelial relaxation and contraction. The role of these factors in the microvasculature of diabetes is not well characterised.

**Objectives:** There were three main objectives of this study; firstly, to determine the contribution of nitric oxide (NO), prostacyclin, endothelium-dependent hyperpolarisation (EDH) and thromboxane (TXA<sub>2</sub>) receptor in endothelium-dependent relaxation and contraction in the microcirculation of diabetic rats; secondly, to determine the expression of enzymes and receptors involved in mediating endothelial responses and finally to determine the early (2 weeks) and late changes (10 weeks) in the functional and molecular responses in the microcirculation of diabetes rats.

**Methods:** This study consisted of four experimental groups; normal 2-week rats, diabetic 2-week rats, normal 10-week rats and diabetic 10-week rats ( $n = 15$  rats per group). Vascular function studies were performed using wire myography. The contributions of individual EDRF (NO, prostacyclin and EDH) and TXA<sub>2</sub> receptor in mediating endothelium-dependent relaxations and contractions were evaluated in tail arteries of all the experimental

groups. The expressions and distributions of endothelial nitric oxide synthase (eNOS), cyclooxygenase-1 (COX-1), cyclooxygenase-2 (COX-2), prostacyclin synthase (PGIS), prostacyclin (IP) receptor, TXA<sub>2</sub> receptor and TXA<sub>2</sub> synthase proteins were determined by Western blotting and immunohistochemistry.

**Results:** Endothelium-dependent relaxations were significantly decreased in diabetic 2-week [Rmax; 73.49 (11.04)% versus 89.32 (10.03)%,  $P = 0.002$ ] and diabetic 10-week rats [Rmax; 58.84 (18.79)% versus 89.32 (10.03)%,  $P$ , respectively compared with normal 2-week rats. NO-mediated relaxations were attenuated in diabetic 10-week rats compared with normal 2-week ( $P < 0.001$ ) and normal 10-week rats ( $P < 0.001$ ). EDH-mediated relaxations were lower in diabetic 10-week rats compared to normal 2-week rats ( $P = 0.012$ ) and normal 10-week rats ( $P = 0.017$ ). Diminished relaxations to prostacyclin were seen in diabetic 10-week rats compared to normal 2-week (pEDH-mediated relaxations were lower in diabetic 10-week rats compared to normal 2-week rats ( $P = 0.012$ ) and normal 10-week rats ( $P = 0.017$ ). Diminished relaxations to prostacyclin were seen in diabetic 10-week rats compared to normal 2-week rats ( $P = 0.033$ ). Western blotting and immunostaining showed that diabetes reduced expression of eNOS, IP receptor and PGIS proteins in rat tail arteries. For endothelium-mediated contractions, significant increase in endothelium-dependent contractions were seen in diabetic 10-week rats supporting the findings of functional studies.

**Conclusion:** The impairment in microvascular endothelium-dependent relaxations and increased endothelium-dependent contractions were observed in diabetic rats, and this worsened by prolonged diabetes. Therefore, early prevention is necessary to manage ED which may be reversible at an early stage of diabetes.

*Supervisor:*

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*Co-supervisors:*

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*Dr Siti Safiah Mokhtar*

## APPLYING THE PROJECTIVE DRAWING TOOL – THE CHILD DRAWING HOSPITAL ON LOCALISED CHILDREN

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**Introduction:** Projective drawing has many benefits and advantages in applying in research and clinical practice, which includes assessment of emotional status and anxiety levels in children as it aids communication of thoughts and perspectives for children. However, projective tests may be limited in form of objectivity as the scoring can be fairly subjective.

**Objectives:** This research project aims to examine the validity and reliability of a projective test manual – the Child Drawing: Hospital (CD: H) administered on school – aged children with cancer in Hospital Universiti Sains Malaysia (HUSM).

**Methods:** The CD: H instruction was translated into Bahasa Malaysia according to the World Health Organisation (WHO) guidelines in order to administer the tool. The sample population was pooled from Kubang Kerian, Kelantan, whereby two groups of children were targeted one being children with cancer whom receiving treatment in the hospital and the other was their age-matched, healthy peers. Following a standardised protocol, the children drew a picture of a person in a hospital on a drawing block. Inter-rater reliability was established using expert and novice examiners' scores. Internal consistency and discriminant validity were also computed.

**Results:** A total of 42 children (children with cancer,  $n = 10$ ; healthy peers,  $n = 32$ ) were involved in this study thus 42 drawings that were collected needed to be scored. The children were ages 7 years old to 13 years old, where there were 16 boys and 26 girls. Five scorers (expert scorers,  $n = 2$ ; novice scorers,  $n = 3$ ) rated all drawings independently based on an accompanied test manual. A total of twenty drawings ( $n = 20$ ) were subjected to validity analyses where 10 children were those who had cancer and received treatment from HUSM and 10 children were the age-matched peers from Sekolah Kebangsaan Kubang Kerian 2. Inter-rater reliability between five independent scorers was good and internal consistency reliability was deemed satisfactory. Findings indicated that there was inadequate discriminant validity as only two items, which were quality of strokes from Part A and de-emphasis of body part from Part B, that significantly discriminated anxiety levels between the children with cancer group and the school children group.

**Conclusion:** In conclusion, the CD: H test and manual demonstrated good inter-rater reliability, satisfactory internal consistency reliability yet inadequate discriminant validity, at least in this study. The study's main limitation is the limited amount of sample size as it may affect the statistical analyses and results. Additional studies utilising adequate number of participants and further research regarding the psychometric properties of the CD: H projective drawing tool must be done in the Malaysian population before it could be utilised in the clinical setting to assess levels of anxiety in hospitalised children.

*Supervisor:*

*Associate Professor Dr Azizah Othman*

*Co-supervisor:*

*Dr Md Azman Shahadan*

## THE PSYCHOMETRIC PROPERTIES OF WORLD HEALTH ORGANIZATION QUALITY OF LIFE BRIEF ASSESSMENT IN MALAY (WHOQOL-BREF)

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**Introduction:** The World Health Organization Quality of Life Brief (WHOQOL-BREF) (WHOQOL Group, 1998) has been translated into the Malay language in 2003 by Hasanah, Naing and Rahman and has been widely used in Malaysia. However, lack of generalisability of sample population and type of validity used in the previous study has called for an update in psychometric properties of the instrument.

**Methods:** The study sample comprised of 301 Malaysian adults who completed the original WHOQOL-BREF, the Malay WHOQOL-BREF and DASS-21 through SurveyMonkey. To establish the model fit of the translated instrument, Confirmatory Factor Analysis (CFA) using maximum likelihood estimation were run in SPSS version 26 and AMOS version 24 were used.

**Results:** Through CFA, the original four-factor model showed a good model fit in the current study sample population,  $X^2/df = 2.08$ , comparative fit index (CFI) = 0.93 and root mean square of error approximation (RMSEA) = 0.06. Construct reliability was established through composite reliability and average variance extracted (AVE) values. All four domains had composite reliability more than 0.60, ranging from 0.79 (social relationship factor) to 0.88 (psychological health factor). All AVE values were above 0.50, except for environmental factor. Convergent validity was established with significant positive relationships between all four domains and two items from the instrument that evaluates overall QoL and general health facet ( $P < 0.01$ ). Divergent validity was established with significant negative correlations between all four factors and depression anxiety and stress-21 (DASS21) ( $P < 0.01$ ). However, only social relationships domain of the instrument showed good discriminant ability between healthy and non-healthy participants.

**Conclusion:** The Malay WHOQOL-BREF showed appropriate model fit, reliable construct and convergent validity and good construct reliability. However, the instrument was unable to discriminate between healthy and non-healthy participants. Future research should discuss the findings in clinical samples with cautions.

Supervisor:  
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Co-supervisor:  
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## PHYTOCHEMICAL SCREENING AND NATURAL KILLER CELLS IMMUNOMODULATION EFFECTS OF *Pereskia bleo* LEAVES EXTRACT ON CERVICAL CANCER CELLS

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**Introduction:** *Pereskia bleo* (*P. bleo*) is a leafy and edible plant, locally known as Pokok Jarum Tujuh Bilah which has anti-cancer properties.

**Objectives:** This study purposed to elucidate the underlying mechanism of this plant as anti-cancer in inducing cell death as well as to evaluate its immunostimulatory effects on natural killer cells (NK cells) as a potential additional anti-cancer effect.

**Methods:** In this study, the leaves of *P. bleo* were extracted using different techniques and solvent polarities, and subsequently subjected to GC-MS analysis. The extracts were tested for its cytotoxic effects on HeLa, MDA-MB-231, SW480 and NIH/3T3 cell lines using MTT assay. The most cytotoxic extract and its corresponding cancer cell lines were investigated for their cell death induction through cell cycle arrest, annexin V/PI assay and measurement of apoptotic proteins using flow cytometry. NK cells were exposed to different concentrations of ethyl acetate extract of *P. bleo* (PBEA) leaves and its proliferation rate was determined via MTT assay. NK cells from healthy individuals and cervical cancer patients were treated with 14.4 µg/mL of PBEA and co-cultured with target cells for 24 h to evaluate its cytotoxic activity. Target cells death was identified by flow cytometry while ELISA assay was performed to determine the production of perforin, granzyme B, IFN- $\gamma$  and IL-2.

**Results:** Results showed the presence of terpenoids, sterols, alkaloids, flavonoids, phenols, fatty acids and vitamin E in the extracts of *P. bleo* leaves together with new compounds namely (-)-loliolide, neophytadiene,  $\alpha$ -tocopherol,  $\gamma$ -tocopherol, squalene, 4H-pyran-4-one,2,3-dihydro-3,5-dihydroxy-6-methyl, 4-vinyl-syringol, phenol,2-methoxy-4-(1 propenyl) and hexadecanoic acid. PBEA exhibited the lowest IC<sub>50</sub> value (14.37 ± 8.40 µg/mL) indicated the strongest cytotoxic effect selectively on cervical cancer cells (HeLa). The cell cycle analysis showed inhibition of cell proliferation at G<sub>0</sub>/G<sub>1</sub> phase in PBEA treated HeLa cells as evidenced by a significant accumulation of the cells at this phase ( $P < 0.05$ ). Morphological examination on PBEA treated HeLa cell showed the presence of fragmented nuclei and condensation of chromatin while apoptosis was detected in the annexin V/PI assay. Analysis of apoptotic proteins revealed a significant upregulation of pro-apoptotic proteins (Bax, p53 and caspase-3) while downregulation of anti-apoptotic protein Bcl-2 ( $P < 0.05$ ) in PBEA treated HeLa cells. Meanwhile, NK cells proliferation at 24 h was found significantly increased compared to 48 h and 72 h of PBEA treatment ( $P < 0.05$ ) Apoptosis of HeLa cells was markedly

increased in PBEA treated NK cells from cancer patients. This extract also enhanced granzyme B and IFN- $\gamma$  expression in NK cells from cancer patients.

**Conclusion:** Thus our findings demonstrated that PBEA induced cell death in the cervical cancer cells (HeLa) and stimulate activation of NK cells from cervical cancer patients which enhanced cytotoxic effect against HeLa cells. These results provide some insight into the effectiveness of *P. bleo* as a potential chemopreventive agent which open up for further studies.

Supervisor:

Dr Norzila Ismail

Co-supervisors:

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## MITOCHONDRIAL MICROSATELLITE GENOMIC INSTABILITY AND BRAFV600E MUTATION IN CENTRAL NERVOUS SYSTEM TUMOR MITOCHONDRIAL MICROSATELLITE GENOMIC INSTABILITY AND BRAFV600E MUTATION IN CENTRAL NERVOUS SYSTEM TUMOURS

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**Introduction:** The central nervous system tumour is known as one of the fatal cancers worldwide. The accumulation of multiple genetic alterations of the nuclear and mitochondrial genome is believed to be engaged in brain tumorigenesis. Mitochondrial microsatellite instability (mtMSI) is a change in repetitive sequences of the mitochondrial genome, has been described as a high occurrence in several human cancers. Meanwhile, the BRAFV600E is the most prevalent mutated nuclear oncogene that has been identified in multiple malignancies. Nevertheless, mtMSI and BRAFV600E mutation in brain tumour cases have not been reported in Malaysia, so far.

**Objectives:** Therefore, this study aims to determine the mtMSI status and BRAFV600E mutation in a series of Malay patients with brain tumours and to evaluate their association with clinicopathological features.

**Methods:** The mtMSI alterations and BRAFV600E mutations were examined in a total of 50 paired brain tumour tissues and blood samples. The mtMSI status was analysed using mtMSI specific primers and the results were compared with the revised Cambridge references sequences (rCRS). For the analysis of the BRAFV600E mutation, the PCR-RLFP assay was used for sequence variation, followed by direct sequencing and aligned using BLAST from the NCBI site.

**Results:** The results revealed eight mtMSI alterations were detected in D310 and D16184 of the displacement loop (D-loop) region (16%). Of these, one alteration

C5TC4 > C8TC in the D16184 region has not been previously reported in the MITOMAP database identified in this study. No association was found between mtMSI status and clinicopathological data. Additionally, BRAFV600E mutation has been detected in 11 out of 50 patients (22%). Similarly, no significant association between clinical features with BRAFV600E mutation observed in this study. The correlation between mtMSI status and BRAFV600E mutation also was analysed, however, no association identified between both alterations in all screened patients.

**Conclusion:** This study provides insights into mitochondrial genome instability and BRAF mutation of brain tumor patients. A more detailed analysis involving a large number of patients is needed to establish the exact role of these genetic alterations in brain tumor cases in the Malay population.

Supervisor:

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Co-supervisors:

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Dr Farizan Ahmad

## THE EFFECT OF ABDOMINAL EXERCISE ON DIASTASIS RECTI ABDOMINAL AMONG POSTPARTUM PRIMIGRAVIDA MOTHER IN KUALA LUMPUR

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**Introduction:** Abdominal exercise for diastasis recti abdominal (DRA) during postpartum has yet to be explored in research. Despite general exercise programs in current rehabilitation, strength and conditioning programs, few studies have examined the implementation of gradual and progressions abdominal training, and the benefits therein.

**Objectives:** The objective of this study was to investigate the effects of a progressive abdominal exercise known as split tummy exercise programme (STEP) on the DRA size, pelvic floor muscle (PFM) strength, endurance and perceived urinary distress symptoms and determine the correlation between these variables. STEP module was developed based on literature review and validated by the experts.

**Methods:** A randomised control trial study design was carried out at Obstetric and Gynaecology clinic, Universiti Kebangsaan Malaysia Medical Centre (UKMMC) Kuala Lumpur and 41 pregnant women were selected. Later the participants were randomly assigned to the intervention (21 subjects) and control group (20 subjects). The participants were selected among primigravida diagnosed with DRA at 34-week gestations onward if the gap between the abdominal muscle is more than two-finger width measured with finger palpation at the umbilicus. Those with multiple pregnancies, previous abdominal and urogenital

surgery, lower caesarian section delivery, and disease that could interfere with PFM strength such as Ehlan Danlos Syndrome were excluded. The intervention group received STEP module consist of three phases of nine abdominal exercises. The progression from phase one to phase two was administered every three weeks and completed phase three at eight weeks postpartum. DRA size (using 2D ultrasound) and urinary functions (using urogenital distress inventory questionnaire [UDI-6] and incontinence impact questionnaire [IIQ-7]) were assessed at baseline and 8-weeks postpartum, whereas the PFM strength and endurance (using perineometer) was evaluated at 8-weeks postpartum for both groups.

**Results:** Out of 41 participants, 87.8% were Malays with the mean age of 28 years old (SD = 0.56) and most of them (78%) were working. After 8 weeks, both groups had a reduction of DRA size, but result between the group was not significant whereas within-group analysis, DRA size was reduced up to 27% (mean difference: 6.2; 95% CI: 3.7, 8.7) as compared to 8.2% (mean difference: 1.66; 95% CI: -1.3, 4.6) in the control group with significant intervention effect at  $P < 0.001$ . There is a significant difference in PFM strength with a mean difference of 5.89 mmHg (95% CI: 2.10, 9.68;  $P = 0.003$ ) and PFM endurance with the mean difference of 1.11 second (95% CI: 0.01, 2.22;  $P = 0.049$ ) between groups. On the other hand, for urinary function, there is no significant difference in urinary distress symptoms between-group however, within-group analysis, both groups show significant different ( $P < 0.001$ ).

**Conclusion:** The abdominal exercise using 8 weeks STEP module effectively reduce the DRA size and could be implemented for mothers with DRA. The strength and endurance of PFM are higher in the STEP group at 8 weeks postpartum and no significant difference in perceived urinary incontinence symptom between the group. Finally, no relationship was found between DRA size and PFM function and perceived urinary distress symptoms. Further research is warranted to ascertain the efficacy of abdominal exercise among a larger population.

*Supervisor:*  
Associate Professor Dr Nik Rosmawati Nik Husain

*Co-supervisor:*  
Dr Ixora Kamisan Atan

## EFFECT OF ETANERCEPT AND GOLD NANOPARTICLES ON THE EXPRESSION OF TNFR2<sup>+</sup> REGULATORY T CELLS AND CD103<sup>+</sup> DENDRITIC CELLS IN PERIPHERAL BLOOD MONONUCLEAR CELLS OF ASTHMA PATIENTS

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**Introduction:** Immune tolerance by regulatory T cells (Tregs) is one of the various mechanisms, which is employ to maintain homeostasis and protect the host against various environmental stimuli. Recently, a subset of Tregs expressing tumor necrosis factor receptor 2 (TNFR2<sup>+</sup> Tregs) is identified as a more suppressive and proliferative cell population and its regulation is reported to be impaired in respiratory dysfunction condition such as asthma. Gold nanoparticles (AuNPs), a highly potential tool in immunotherapies, are shown to be protective against key features of asthma.

**Objectives:** Hence, the current study would like to elucidate the effects of AuNPs on the expression of TNFR2<sup>+</sup> Tregs, as well as on CD103<sup>+</sup> dendritic cells (DCs), which have been shown to induce Tregs in asthmatic individuals and whether a TNFR2 agonist, etanercept, can modulate the effects of AuNPs.

**Methods:** A five-color flow cytometry assay was used to determine the expression of cell population of interest in asthmatic and non-asthmatic controls ( $n = 6$ ) and traditional ELISA assay to determine the level of TNF- $\alpha$  and IL-10.

**Results:** Stimulation of peripheral blood mononuclear cells (PBMCs) of asthmatic individuals with AuNPs for 24 h does not induce significant effects on the cell population of interest. Meanwhile, etanercept as anti-TNF is shown to significantly decrease TNFR2<sup>+</sup> Tregs ( $P = 0.0210$ ) and T effector cells TNFR2<sup>+</sup> (Teff) ( $P = < 0.0001$ ) with an increased pattern of Foxp3<sup>+</sup> Tregs only. Surprisingly, etanercept is shown to significantly increased the level of TNF- $\alpha$ , question the principal mechanism of etanercept as TNF antagonist. Correlation analysis in the current study demonstrated inverse association of CD103<sup>+</sup> DCs with Tregs including TNFR2<sup>+</sup> Tregs ( $r = -0.6853$ ,  $P = 0.0170$ ), indicates to the independency of this subset of DCs in the regulation of immune homeostasis, particularly in asthma.

**Conclusion:** Results indicated to the potential of AuNPs as potential formulation carrier for immunotherapies due to its capability to be effectively uptake by antigen-presenting cells such as DCs without inducing immune response.

*Supervisor:*  
Dr Rohimah Mohamad

*Co-supervisors:*  
Professor Dr Lim Jit Kang  
Dr Ramlah Kadir

## THE EFFECTS OF 2-METHOXY-1,4-NAPHTHOQUINONE (MNQ) ON GLUCOSE METABOLISM OF MDA-MB-231 CELLS

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**Introduction:** Quinone and its derivatives are shown to have biological activities and medicinal properties including antibacterial, antifungal as well as anticancer

activities. To date, the researchers have been focusing on targeting the chemotherapeutic drugs at the specific genes or proteins/enzymes of cancer metabolism. In this study, 2-methoxy-1,4-naphthoquinone (MNQ) was selected based on the increasing reports of its medicinal effects in promoting cancer cells death.

**Objectives:** The aim of this study is to evaluate the effects of MNQ on glucose metabolism in triple-negative breast cancer, MDA-MB-231 cells.

**Methods:** Initially, the MDA-MB-231 cells were treated with various doses of MNQ to determine the growth inhibitory effects and the  $IC_{50}$  dose. The effect of MNQ on cell growth was also tested in non-malignant breast epithelial cells, MCF10A. For further analyses, the cells were treated with  $IC_{50}$  dose of MNQ for measurement of glucose uptake, lactate production as well as the expression of glycolysis-related molecules (GLUT1, Akt, HKII and HIF1 $\alpha$ ). The effect of MNQ was also tested on the autophagy activities and the expression of autophagy-related genes (Beclin 1 and LC3).

**Results:** The results showed that MNQ inhibited the proliferation of MDA-MB-231 cells with  $IC_{50}$  values of 43, 29 and 22  $\mu$ M (24 h, 48 h and 72 h of treatment) but not in MCF10A cells. MNQ also inhibited the glycolytic activities in MDA-MB-231 cells by inhibiting the glucose uptake and reducing the lactate production. The down-regulation of GLUT1 and Akt in both gene and protein expression of MDA-MB-231 cells suggested that inhibition of glycolysis by MNQ was mediated by GLUT1/Akt signaling pathways. Increased HKII, Beclin 1 and LC3 gene expression as well as the formation of autophagosomes in MDA-MB-231 cells showed that MNQ induced the autophagy activity. The inhibition of glucose uptake into the cells may cause the nutrient deprivation and lead to the activation of autophagy in MDA-MB-231 cells.

**Conclusion:** In conclusion, the ability of MNQ to inhibit glycolysis by targeting the glycolysis-related molecules in triple-negative breast cancer cells (MDAMB-231), indicated the potential of MNQ as anticancer agent/adjuvant in breast cancer treatment.

Supervisor:

Dr Agustine Nengsih Said @ Fauzi

Co-supervisors:

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Dr Mohd Zulkifli Mustafa

## IMPACT OF DE-ESCALATION OF EXTENDED AND RESTRICTED ANTIBIOTIC ON MORTALITY

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**Background:** More data is needed about the safety of antibiotic de-escalation in specific clinical situations as a strategy to reduce exposure to broad-spectrum antibiotics.

**Objectives:** To compare the survival probabilities of patient de-escalated (early or late) against those not de-escalated on extended or restricted antibiotic, to determine the association of patient related, clinical related and pressure sore/device related characteristics on all-cause 30-day mortality and determine the impact of early and late de-escalation antibiotic de-escalation on 30-day all-cause mortality.

**Methods:** This retrospective cohort study was conducted by reviewing medical records of patients eligible for antibiotic (extended or restricted) de-escalation in medical ward Hospital Kuala Lumpur, between January 2016 and June 2019. The primary outcome of interest is 30-day all-cause mortality. Kaplan Meier survival curve and Fleming-Harrington test were used to compare the overall survival rates between early, late and those not de-escalated on antibiotic. Multivariable Cox regression was used to determine prognostic factors associated with mortality, and impact of de-escalation (early and late) on 30-day all-cause mortality. All statistical tests were carried out using STATA version 14.

**Results:** A total of 180 patients were included, with 62 deaths (34.4%) and 118 censored events (65.6%). Out of the 62 deaths, 18 deaths (29%) occurred in non-de-escalated group, 28 deaths (45.2%) and 16 deaths (25.8%) in early and late de-escalation group, respectively. Fleming-Harrington test showed the overall mortality rates were not significantly different when patient was not de-escalated on extended or restricted antibiotics, compared to those de-escalated early or later xv ( $P = 0.760$ ). Variables associated with 30-day all-cause mortality were sequential organ function assessment (SOFA) score on the day of antimicrobial stewardship (AMS) intervention (AHR 6.74, 95% CI: 3.98, 11.42;  $P < 0.001$ ), Charlson's comorbidity score (AHR 2.00, 95% CI: 1.56, 3.35;  $P = 0.009$ ), and the unavailability of C-reactive protein (CRP) trend values were found to be significant factors associated with mortality of patients with infection who were on extended and restricted antibiotic (AHR 3.10, 95% CI: 1.56, 6.10;  $P = 0.001$ ). After controlling for abovementioned confounders, early and late antibiotic de-escalation were not associated with increased risk of mortality; AHR were 0.58 (95% CI: 0.32, 1.07;  $P = 0.085$ ) and 0.77 (95% CI: 0.38, 1.54;  $P = 0.456$ ), respectively.

**Conclusion:** The results of this study reinforces that restricted or extended antibiotic de-escalation in patients does not significantly affect 30-day all-cause mortality compared to continuation with extended and restricted antibiotics. Patient Charlson's scoring index, SOFA score and unavailability of CRP trend are significant factors found to be associated with 30-day all-cause mortality.

## SURVIVAL OF END-STAGE RENAL DISEASE PATIENTS STARTING DIALYSIS IN SABAH DURING 2007 TO 2017 PERIOD AND ITS PROGNOSTIC FACTORS

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**Background:** The survival of end-stage renal disease (ESRD) patients starting dialysis and the factors associated with it is a major public health interest. The study's general objective was to investigate the survival probabilities of ESRD patients starting dialysis in Sabah and its prognostic factors.

**Methods:** This was a registry-based retrospective cohort study. All adult ESRD patients receiving dialysis treatment in Sabah between 1 January 2007 and 31 December 2017 as identified from the Malaysian Dialysis and Transplant Registry were studied. The endpoint of interest was death due to any causes. The observation time was defined as the time from the date started dialysis after onset of end-stage renal disease to one of the following, whichever came first: date of death, date of transplantation, date of last follow-up, date of recovered kidney function or end of study date on 31 December 2018. The prognostic factor of interest was dialysis modality. The other prognostic factors studied were age, gender, body mass index, diabetes mellitus comorbidity, cardiovascular disease comorbidity and several laboratory values. Survival probabilities were estimated using Kaplan-Meier method. Weighted Cox regression was used to estimate the effects of prognostic factors.

**Results:** A total of 3,628 treated ESRD patients were included in this study, yielding 12,574.5 (median, 5.1 years) person-years of observation. A total of 1,824 (50.3%) patients had died, 106 (2.9%) had lost to follow-up, 26 (0.7%) had received transplant and 18 (0.5%) had recovered. The median survival time was 4.7 years (95% confidence interval [CI]: 4.5, 5.1) and the 2, 5 and 10-year survival were 72.0% (95% CI: 71.0, 74.0), 48.0% (95% CI: 46.0, 50.0) and 28.0% (95% CI: 25.0, 30.0), respectively. Based on complete cases analysis of 1,993 patients, it was found that dialysis modality was not significantly associated with mortality after controlling for all confounders. The average hazard ratio (AHR) was 0.80 (95% CI: 0.61, 1.05) with haemodialysis as reference. The most parsimonious regression model included dialysis modality (AHR: 0.79; 95% CI: 0.60, 1.04), age (AHR: 1.63; 95% CI: 1.50, 1.77), gender (AHR: 1.23; 95% CI: 1.06, 1.43), diabetes mellitus comorbidity (AHR: 1.27; 95% CI: 1.10, 1.47), cardiovascular disease comorbidity (AHR: 1.27; 95% CI: 1.00, 1.61), body mass index (AHR: 0.90; 95% CI: 0.83, 0.98), serum creatinine (AHR: 0.85; 95% CI: 0.78, 0.93), albumin (AHR: 0.79; 95% CI: 0.74, 0.84), phosphate (AHR: 1.12; 95% CI: 1.04, 1.20), alkaline phosphatase (AHR: 1.08; 95% CI: 1.01, 1.15), potassium (AHR: 0.92; 95% CI: 0.84, 0.99), and haemoglobin (AHR: 0.78; 95% CI: 0.72, 0.84) as the potentially important prognostic factors of survival.

**Conclusion:** It was estimated that the survival probabilities of ESRD patients starting dialysis in Sabah were comparatively similar to that of the whole Malaysia. Dialysis modality was not significantly related to all-cause mortality after controlling for confounders. The most parsimonious regression model has identified twelve potentially important prognostic factors of survival.

Supervisor:  
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Co-supervisors:  
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Dr Wong Koh Wei

## DIFFERENTIAL EYE MOVEMENT BETWEEN PATIENTS WITH MILD TRAUMATIC BRAIN INJURY AND HEALTHY SUBJECTS

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**Introduction:** The detection of oculomotor abnormality among mild traumatic brain injury (mTBI) patients is crucial to observe for possible brain impairment following the head impact. Production of a saccade is associated with complex neural processes in the brain structures that are also important for cognitive functioning such as attention, memory and mental flexibility.

**Objectives:** Advancement of oculomotor technology has driven this study which is designed to differentiate between healthy subjects and mTBI patients based on oculomotor performance. This study also analysed the adverse effects using three key measures. The measures are the rate of accuracy (%), dwell time duration (msec) and first fixation duration (msec).

**Methods:** Using an experimental design, 11 healthy subjects ( $n = 11$ ) and three mTBI patients ( $n = 3$ ) who fulfilled the inclusive criteria were included. Both groups were introduced to two oculomotor tasks which are saccade and antisaccade.

**Results:** The results showed that both groups can be differentiated based on average rate of accuracy and mean of dwell time. mTBI patients reported to have a significantly lower rate of accuracy and substantially shorter average dwell time at each stimulus location for both tasks.

**Conclusion:** The adverse effects may reflect the impairment in brain structures involved in saccade generation and inhibition. Therefore, the application of eye movement assessment is believed to be practical to differentiate mTBI patients from healthy subjects and to observe adverse effects of brain injury.

Supervisor:  
Dr Mohamed Faiz Mohamed Mustafar

## PHYTOCHEMICAL CHARACTERISATION, INDUCTION OF APOPTOSIS AND ACTIVATION OF NATURAL KILLER (NK) CELL BY *Abrus precatorius* LEAVES EXTRACT ON HUMAN BREAST CANCER CELL

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**Introduction:** Cancer is still one of the global menace and poses a threat to the general world population. The search for cancer cure is also still on the race. Although conventional medicine remains the number one choice in cancer treatment, traditional approach is also still one of the favourable choices made by cancer patients to deal with this horrible disease. Traditional approaches, mainly by utilising medicinal plants are widely sought after in many countries since centuries ago. The ability of medicinal plants to exhibit their anti-proliferative activity, together with the ability to activate immune responses would be the ideal strategy to beat the disease.

**Objectives:** Therefore, understanding the mechanisms of medicinal plants displaying their anticancer properties scientifically would fill the gap of unknown knowledge about them.

**Methods:** A medicinal plant known as *Abrus precatorius* (A. precatorius) or 'saga' were used in this study. This plant has been utilised traditionally to cure various ailments including cancer. The leaves of A. precatorius were selected to be extracted by different extraction techniques which employed different types of solvent. GC-MS was employed to provide the phytochemical analysis of the extracts. The ability of those extract to inhibit proliferation in cancer cells were measured using MTT assay. The best extract exhibiting the lowest inhibitory concentration (IC<sub>50</sub>) on the selected cancer cell, was selected to determine the mechanisms of action in inducing the cell death. Cell cycle arrest analysis, apoptosis staining with annexinV/PI and quantification of the expression of p53, Bax, Bcl-2 and Caspase-3 proteins were used to determine the mechanism of cell deaths. Finally, the ability of the extract to induce immune response by activating NK cells was determined in a co-culture experiment of the NK cells with the target cell, MDA-MB-231 cells. This was observed by the analysis of target cell deaths and quantification of the secretion of cytokines, interleukin-2 (IL-2) and interferon gamma (IFN- $\gamma$ ); and the degranulation of the cytotoxic granules by quantifying the perforin (PRF-1) and granzyme B (GzmB).

**Results:** The results showed that the ethyl acetate and methanol extracts prepared using Soxhlet contained the highest phenolic and terpenoid compounds comparing to the other extracts. The methanol extract obtained by Soxhlet, APME (*A. precatorius* methanol extract), exhibited the lowest IC<sub>50</sub> value on MDA-MB-231 cells. Further analysis by flow cytometry revealed APME induced cell death on MDA-MB-231 cells via apoptosis, through DNA arrest at G<sub>0</sub>/G<sub>1</sub> cycle, coupled with an increase of p53, Bax and Caspase-3

expression and decrease of Bcl-2 expression. APME was also found to activate NK cells (from healthy donor) by causing NK cell cytotoxic activity via apoptosis in the target cells. Increased levels of INF- $\gamma$  and PRF-1 were also observed in this co-culture experiment.

**Conclusion:** These findings reflect the ability of *A. precatorius* leaves extract to exhibit the antiproliferative effect on cancer cells and stimulatory effect on NK cells from the healthy donors. This might be due to the presence of various phytochemical compounds in the extract that might act synergistically.

Supervisor:

Dr Norzila Ismail

Co-supervisors:

Dr Rohimah Mohamad

Dr Tuan Nadrah Naim T Ismail @ T Manah

## INFLUENCE OF TERT GENE EXPRESSION, TELOMERASE ACTIVITY AND TELOMERE LENGTH IN RELATION TO IMATINIB MESYLATE RESISTANCE IN MALAYSIAN CHRONIC MYELOID LEUKAEMIA PATIENTS

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**Introduction:** Chronic myeloid leukaemia (CML) is a myeloproliferative neoplasm diagnosed by the presence of the BCR-ABL fusion gene which produces a tyrosine kinase to signal a proliferation of white blood cells. The introduction of imatinib mesylate in early 2000, has dramatically increased the survival of affected patients and changed the disease management. However, failure to completely eradicate leukaemic cells and the escape of these cells from previous control has led to an intensive search for the mechanisms of resistance and subsequent treatments by which to overcome the resistance. Meanwhile, telomerase regulation and telomere maintenance are the critical factors in cell proliferation and survival which plays important roles in development of cancers. Considering telomerase as an important component in cell regulations, it is postulated that telomerase might be one of the oncogenesis mechanism in CML development and might contribute in the resistance mechanism of imatinib mesylate.

**Methods:** A total of 98 CML patients were recruited from four collaborated hospitals over the country which are Hospital Pulau Pinang, Hospital Sultanah Aminah, Hospital Raja Permaisuri Bainun and Pusat Perubatan Universiti Kebangsaan Malaysia. Samples were also collected from Hospital USM which is the research centre for this study. CML patients treated with imatinib were enrolled into this study and grouped as good response and resistance according to response of the imatinib mesylate treatment. Sixty-six of patients with good response at the beginning of samples



collection and 32 patients with resistance response were managed to recruited. However, only 90 samples were able to proceed with DNA and RNA extraction while 79 samples were successfully applied for protein extraction due to poor quality of samples obtained. Range of age was between 71 to 77 years old and represented of main ethnicity in Malaysia which were Malay, Chinese and Indian. The analysis of hTERT expression level, telomerase activity and length of telomere were performed.

**Results:** The up-regulated of hTERT expression and the presence of telomerase activity were found up to 90% in CML patients recruited in this study regardless of response group. This indicated that telomerase regulations as the indicator of cancer events in CML. However the telomerase regulations might not directly influenced the response and resistance group of treated patients. Comparison between good response and resistance group showed no significant difference ( $P = 0.463$  in hTERT expression and  $P = 0.961$  in telomerase activity). Comparison of telomere length in both groups were also showed no significant difference ( $P = 0.228$ ). The findings indicated that hTERT expression, telomerase activity and telomere length may not directly influenced the resistance to imatinib mesylate treatment.

**Conclusion:** To the best of our knowledge, there is no study comparing the expression and activity of telomerase in group of difference response to imatinib treatment in CML patients. This could consider that hTERT and the activity of telomerase together with telomere length in CML might have different contributions in resistance development compared to other solid tumours. Further more, investigations with a larger number of samples is warranted to confirm the potential influence of the telomerase and telomere components in the leukaemogenesis and imatinib resistance in Malaysian CML patients.

*Supervisor:*

*Associate Professor Dr Sarina Sulong*

*Co-supervisors:*

*Associate Professor Dr Azlan Husin*

*Professor Dr Rosline Hassan*

*Professor Dr Ravindran Ankathil*

## EFFECTS OF VITAMIN D ON VASCULAR FUNCTION AND OXIDATIVE STRESS IN THE MICROCIRCULATION OF DIABETIC

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**Introduction:** Diabetes mellitus contributes to macro- and microvascular complications, leading to adverse cardiovascular events. Vitamin D deficiency is associated with the development of diabetes-related cardiovascular complications. This study was divided into two parts: i) animal study and ii) human study.

**Objectives:** This animal study aims to determine the effects of vitamin D deficiency on i) microvascular endothelial and smooth muscle functions in normal and diabetic rats; ii) the changes to endothelial nitric oxide synthase (eNOS) protein expression and oxidative stress parameters in mesenteric arterial tissue of normal and diabetic rats and iii) to study whether oral calcitriol supplementation is able to ameliorate microvascular dysfunction in vitamin D-deficient rats. This human study aims to evaluate the effects of vitamin D deficiency on oxidative stress status in subcutaneous arteries of diabetic patients.

**Methods:** Animal study: (a) male Sprague-Dawley (SD) rats were subdivided into three equal groups of 10 rats each: (i) rats receiving 10-weeks of normal diet (Group NC), (ii) rats receiving 10-weeks of vitamin D-deficient diet (Group ND) and (iii) rats receiving 10-weeks of vitamin D-deficient diet with 4-weeks of oral calcitriol supplementation, starting from week 7 (Groups NDS). (b) Streptozotocin-induced diabetic male SD rats were subdivided into three equal groups of 10 rats each: (i) diabetic rats receiving 10-weeks of normal diet (Group DC), (ii) diabetic rats receiving 10-weeks of vitamin D-deficient diet (Group DD) and (iii) diabetic rats receiving 10-weeks of vitamin D-deficient diet with 4-weeks of oral calcitriol supplementation, starting from week 7 of diabetes induction (Groups DDS). At the end of 10-weeks, all rats were sacrificed. Rats' mesenteric arteries were isolated and dissected to undergo vascular function studies using wire myograph. Protein expression of eNOS in mesenteric arterial tissue was determined using Western blot. Immunohistochemistry was used to detect the presence and localisation of eNOS in mesenteric arteries. Superoxide dismutase (SOD) and malondialdehyde (MDA) levels in mesenteric arterial tissue; fasting blood glucose (FBG), serum 25(OH)D and calcium levels in blood were also measured. Human study: Diabetic patients were categorised into two groups based on serum 25(OH)D levels: (i) vitamin D non-deficient diabetic patients (Group DNP,  $n = 10$ ) and (ii) vitamin D-deficient diabetic patients (Group DDP,  $n = 13$ ). The levels of SOD and MDA in subcutaneous arterial tissue were measured.

**Results:** Results of animal study: (a) Normal rats. Endothelium-dependent relaxation to acetylcholine (ACh) was significantly attenuated in mesenteric arteries of vitamin D-deficient rats. Reduced SOD levels and protein expression of eNOS were observed in vitamin D-deficient rats. However, calcitriol supplementation showed no significant improvement in these parameters. Endothelium-dependent contraction to calcium ionophore (CaI) was augmented in vitamin D-deficient rats receiving calcitriol supplementation. Increased calcium levels were also found in calcitriol-supplemented vitamin D-deficient rats. (b) Diabetic rats. ACh-induced endothelium-dependent relaxation was significantly impaired in mesenteric arteries of vitamin D-deficient diabetic rats. Reduced SOD levels and protein expression of eNOS and enhanced MDA levels were found in vitamin D-deficient diabetic rats. These impairments were successfully ameliorated by calcitriol supplementation. Augmented CaI-induced endothelium-dependent contraction and impaired sodium nitroprusside (SNP)-induced endothelium-independent relaxation occurred in vitamin

D-deficient diabetic rats. However, calcitriol supplementation failed to show improvement in these vascular responses. There were no significant differences in endothelium-independent relaxation to salbutamol (SB) and contraction to phenylephrine (PE) as well as in general parameters such as body weight changes and FBG levels between study groups in both normal and diabetic rats. Results of human study: Markedly augmented MDA levels were found in subcutaneous arterial tissues of vitamin D-deficient diabetic patients. However, SOD levels in vitamin D-deficient diabetic patients showed the reduced trend ( $P = 0.072$ ) compared to vitamin D non-deficient diabetic patients.

**Conclusion:** This study demonstrated that vitamin D deficiency attenuates microvascular endothelial function in both normal and diabetic rats. The impairment for endothelial function was likely due to the diminished nitric oxide contribution, associated with reduced eNOS protein expression and augmented oxidative stress. Vitamin D deficiency in diabetic rats also impairs vascular smooth muscle function. The study also showed that calcitriol supplementation to diabetic rats with vitamin D deficiency improves endothelium-mediated vasodilation, by upregulating eNOS expression and improving oxidative stress status. However, calcitriol supplementation to normal rats with vitamin D deficiency induces hypercalcaemia, leading to augmented endothelium-dependent contraction. Besides that, vitamin D deficiency in diabetic patients as well showed augmented oxidative stress.

*Supervisor:*

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## HOUSEHOLD FOOD INSECURITY AND ITS ASSOCIATED FACTORS, DIETARY DIVERSITY AND NUTRITIONAL STATUS OF CHILDREN 6 TO 59 MONTHS OLD IN CENTRAL RIVER REGION SOUTH, GAMBIA

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**Introduction:** Food insecurity is a global public health challenge. Household food insecurity is the leading risk factor of malnutrition, claiming approximately 300,000 deaths each year. Whether directly or indirectly, due to inadequate food consumption and poor diet quality, it is also accountable for over half of all deaths among children in Sub-Saharan Africa, including The Gambia. Food insecurity is a major challenge in The Gambia, especially in the

Central River Region South. However, little is known about its determinant factors.

**Objectives:** The objective of this study was to assess the household food insecurity (food access) and its associated factors, household dietary diversity, and nutritional status of children aged 6 months old to 59 months old in Central River Region South, the Gambia.

**Methods:** A cross-sectional study was conducted among the households ( $n = 334$ ) consisted of children aged 6 months old to 59 months old. Women, as a proxy to the selected households, were interviewed as they were responsible for food acquisition and preparation of meals for their family members. The households were selected through a random sampling technique. Household food insecurity access scale (HFIAS) and Household dietary diversity score (HDDS) questionnaire were used to measure household food security and dietary diversity status, respectively. The children's nutritional status was assessed through anthropometric measurements. Weight, height/length, and mid-upper arm circumference were recorded. Weight and height/length were calculated using the WHO Anthro calculator and nutritional status was determined based on WHO (2006) reference. Multiple logistic regression analysis was conducted to identify factors associated with household food insecurity (food access).

**Results:** The findings showed that the prevalence of household food insecurity was 80.5% in the study area. Whereas 65.0% of children were stunted, 32.7% underweight and 17.1% were wasting. Moderate and severe acute malnutrition was 1.8% and 6.3%, respectively. In terms of dietary diversity status, 60.2% were at low diversified, 25.4% of them were medium diversified, and 14.4% were highly diversified. Wasting was associated with household food insecurity ( $X^2$ ,  $P = 0.030$ ), but not for stunting and underweight. Household dietary diversity was also significantly associated with household food insecurity ( $X^2$ ,  $P = 0.003$ ). Based on multiple logistic regression analysis, women employment status (adjusted odds ratio [aOR] = 4.23; 95% CI: 1.21, 14.86,  $P = 0.024$ ), husband's employment status (aOR = 4.60; 95% CI: 2.00, 10.57,  $P = 0.001$ ) and lack of market access (aOR = 2.09; 95% CI: 1.09, 3.99,  $P = 0.025$ ) were the factors associated with household food insecurity (food access) in the study area.

**Conclusion:** Household food insecurity was prevalent, and employment status regardless of either the women or their husbands and market access were the predictors of household food insecurity. Household food insecurity was associated with poor dietary diversity and malnutrition, in particular, wasting among children aged below five. Therefore, programmes to improve job opportunities should be strengthened, in particular among women to improve household food insecurity, therefore, would reduce child malnutrition in this region.

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## MODULATION OF CYTOCHROME P450S BY STROBILANTHES CRISPUS ANTICANCER SUB-FRACTION AND ITS POTENTIAL INTERACTION WITH TAMOXIFEN METABOLISM

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**Introduction:** The anticancer property of *Strobilanthes crispus* (*S. crispus*) suggests its potential benefit as an adjuvant in breast cancer treatment. Potential herb-drug interaction (HDI) has always been a safety concern in pharmacotherapy as alteration in cytochrome P450 (CYP) mediated metabolism may lead to treatment failure and toxicity.

**Objectives:** In this study, the in vitro modulatory effect of a standardised sub-fraction of *S. crispus* (F3) on five human CYPs (CYP2B6, CYP2C9, CYP2C19, CYP2D6 and CYP3A4) was first investigated.

**Methods:** Negligible inhibitory effects of F3 on all the five CYPs were observed, with IC<sub>50</sub> values more than 100-fold higher in comparison to known CYP inhibitors. The use of F3 in conjunction with conventional breast cancer therapy using tamoxifen (TAM) could be a strategy to maximise the therapeutic efficacy. Thus, the investigation of the interaction between F3 and TAM is crucial. The potential HDI was first investigated through evaluating the influence of F3 on CYP mediated TAM metabolism in vitro.

**Results:** F3 demonstrated weak mixed-type inhibition towards CYP2D6 catalysed TAM 4-hydroxylation and CYP3A4 catalyzed TAM N-desmethylation. The combined effect of TAM and F3 on the viability of MCF7 cell line was then investigated. A buffering antagonistic effect was observed from the combined treatment.

**Conclusion:** The outcome of this study suggests the low possible interactions between F3 and TAM as well as the five CYPs catalysed drug metabolism. Nevertheless, further studies are warranted to evaluate the efficiency and safety of the drug combination treatment in vivo.

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## VALIDITY AND RELIABILITY OF THE MALAY TRANSLATED VERSION OF THE CYBERBULLYING SCALE AMONG SECONDARY SCHOOL ADOLESCENTS IN MUAR, JOHOR

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**Introduction:** Cyberbullying gives negative impacts on adolescent and still under-reported in Malaysia. Cyberbullying scale (CBS) is used to measure cyberbullying; nonetheless, due to the cultural, language and environmental differences between western and eastern population, the validity and reliability need to be established before it can be used.

**Objectives:** To evaluate the validity and reliability of cyberbullying scale in Malay version (CBS-M) among secondary school students in Johor, as well as to determine the correlation with DASS-21 and online protection behaviour.

**Methods:** This is a cross-sectional study which involved self-administered questionnaire was conducted in two phases, exploratory factor analysis (EFA) phase and confirmatory factor analysis (CFA) phase. Participants were recruited using a multistage cluster sampling method. Descriptive statistics, EFA and CFA and correlation analysis were applied by using RStudio version 1.2.5033.

**Results:** A total of 401 respondents participated in this study, EFA phase consisted 138 respondents and CFA phase consisted 263 respondents. For EFA phase, the majority of the respondents were female (65.9%) and Malay (89.9%). Results for EFA showed factor loading of all the items ranged from 0.3 to 0.7, and communalities ranged from 0.08 to 0.56. All items of CBS-M were remaining in the model during the EFA phase and the measuring reliability by Cronbach's alpha was 0.87. CFA assessment reported the final model of CBS-M with a one factor model with all 14 items remaining, with the value of fit indices CFI = 0.946, TLI = 0.932, SRMR = 0.055 and RMSEA = 0.049. The fit indices were within the acceptable range. The composite reliability was 0.832. There was a significant positive correlation between CBS-M with stress, anxiety and depression.

**Conclusion:** CBS-M consisted of one factor with 14 items and has good correlation with DASS-21. The questionnaire is a valid and reliable tool to be used among young adolescents in Malaysia.

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