

The 1<sup>st</sup> CICM International Conference

# "Translational Research: From Bench to Bedside"

for Celebrations on the Auspicious Occasion of Her Royal Highness Princess Chulabhorn's 60<sup>th</sup> Birthday Anniversary

28<sup>th</sup> - 29<sup>th</sup> August 2017





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# **SCIENTIFIC PROGRAM**

# Monday 28<sup>th</sup> August

	20 August		
8.00-8.45	Registration		
8.45-9.45	Plenary Session 1		
9.45-10.00 10.00-11.30	"Extrinsic and Intrinsic Types of Atopic Dermatitis"  Prof. Yoshiki Tokura  Professor and Chairman, Hamamatsu University School of Medicine, Japan  Refreshment  Invited speakers		
	Room A	Room B	Room C
	Chair: Prof. Kesara Na- Bangchang, CICM, Thammasat University, Thailand Co-chair: Asst. Prof. Wanna Chaijaorenkul, CICM, Thammasat University, Thailand	Chair: Assoc. Prof. Natta Rajatanavin, Ramathibodi hospital, Mahidol University, Thailand Co-chair: Dr. Premjit Juntongjin, CICM, Thammasat University, Thailand	Chair: Prof. Shingo Takesawa, Department of Medical Engineering, Kyushu University of Health & Welfare, Japan Co-chair: Assoc. Prof. Taweeporn Sittiracha, CICM, Thammasat
	"Pharmacogenomics- Based Research for Preventing Adverse Drug Reactions" Dr. Ryosuke Nakamura, National Institute of Health Sciences, Ministry of Health, Japan	Symposium: "Psoriasis"  "Phototherapy & Future Development for Dermatology"  Prof. Morita Akimichi, Professor and Chairman, Nagoya City University,	University, Thailand  "Water Treatment for Hemodialysis: Experience & Current Standard in Thailand" Air Marshal Dr. Kolasorn Pakchotanon, Bhumibol Adulyadej Hospital, Thailand
	"Cancer Gene Mutations and Current Trend of Cancer Treatment" Prof. Thongbliew Prempree, Chularat3 Hospital and Bumrungrad Hospital, Thailand "Natural Compounds as Modulators of Epigenetic Events" Prof. Marc Diederich, College of Pharmacy, Seoul National University, Korea	"Immunological Aspects of Psoriasis & Its Therapies" Prof. Yoshiki Tokura, Professor and Chairman, Hamamatsu University, Japan	"Water Treatment for Hemodialysis: Technology & Advancement in Japan" Prof. Shingo Takesawa, Department of Medical Engineering, Kyushu University of Health & Welfare, Japan

11.30-12.30	Lunch symposium		
	Room A Lunch symposium 1 supported by Bio-Rad Laboratories., Ltd.	Room B Lunch symposium 2 supported by Dermcor Pharmaceutical Co., Ltd and Zione Corporation Co., Ltd.	Room C Lunch symposium 3 supported by Takeda (Thailand), Ltd.
	Moderator: Dr. Saranyoo Ponnikorn, CICM, Thammasat University, Thailand	Moderator: Assoc. Prof. Nopadon Noppakun, Division of Dermatology, Chulalongkorn University, Thailand	Moderator: Prof. Boonchua Dhorranintra, Faculty of Medicine, Siriraj Hospital, Mahidol University
13.00-15.00	"A Breakthrough of droplet digital PCR for liquid biopsy in precision Adam Ng, Field and Application Specialist, SEA	"Hair Loss vs. Hair Regrowth" Assoc. Prof. Nopadon Noppakun, Division of Dermatology, Chulalongkorn University, Thailand Dr. Suparuj Lueangarun, Division of Dermatology Chulabhorn International College of Medicine, Thammasat University, Thailand Assoc. Prof. Ratchathorn Panchaprateep, Division of Dermatology, Chulalongkorn University, Thailand	"Beat the Silent Killer Roles of L-T Type CCB" Group Caption Dr. Pongsathorn Gojaseni, Department of Medicine, Bhumibol Adulyadej Hospital, Thailand
13.00-15.00		Opening Ceremony Token of Appreciation Award By Center & Center of Exceller	
15.00-15.30		Refreshment	
15.30-16.30		Poster presentations	
16.30-17.30		Oral presentation	
	Room A Chair: Prof. Andrew Owen, University of Liverpool, UK	Room B Chair: Prof. Yoshiki Tokura, Hamamatsu University School of Medicine, Japan	Room C Chair: Prof. Dr. Somboon Kietinun, CICM, Thammasat University, Thailand
	"Incidence and risk factors for colonization of multidrug-resistance organisms (MDROs) among patients undergoing elective orthopedic surgery at Thammasat University Hospital"  Dr. Nuntra Suwantarat, CICM, Thammasat University	"Preparation of Gynura pseudochina DC. var. hispida Thv. leaf extract ointment and its efficacy in treating chronic plaque psoriasis"  Prof. Boonchua Dhorranintra, Faculty of Medicine, Siriraj Hospital, Mahidol University	"Current trends of balloon laryngoplasty in Thailand" Thanakrit Sathavornmanee, CICM, Thammasat University



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	"Celecoxib and p38	"Topical tofacitinib drive	"Pediatric
	MAPK inhibitor	hair growth in mouse hair	laryngotracheal
	SB203580 inhibit	follicle by stimulate	separation following a go-
	cadmium-induced PGE2	expression of Noggin and	cart injury"
	secretion from human	reduce expression of	Polpatt Jitpakdee,
	astrocytes"	BMP-4"	CICM, Thammasat
	Ruedeemars Yubolphan,	Thanet Pongcharoensuk,	University
	Faculty of Science, Mahidol	CICM, Thammasat	
	University	University	
	"Cytotoxic interaction of	"Efficacy of topical	"Contributions of
	the three major bioactive	Tofacitinib in promoting	SIDCER/FERCAP to the
	constituents isolated from	hair growth in non-	development of national
	Atractylodes lancea	scarring alopecia:	accreditation programs
	(Thunb.) DC. against	mechanism via VEGF	for ethics committees in
	human	induction"	the Philippines and
	cholangiocarcinoma cell"	Jindapa	Thailand"
	Pongsakorn Martviset,	Thummakriengkrai,	Arthur Navarro
	CICM, Thammasat	CICM, Thammasat	CICM, Thammasat
	University	University	University
	"Growth Inhibitory	"The efficacy of 1550-nm	"Disclosure of informed
	Activity of β-eudesmol on	Erbium-Glass fractional	consent and ethics
	Cholangiocarcinoma Cells	laser treatment and its	committee approval in
	is Associated With	effect on the expression of	international Thai
	Suppression of Heme	insulin-like growth factor	scientific journals"
	Oxygenase-1 Production	1 and Wnt/β-catenin in	Junjira Laothavorn,
	and STAT3	androgenetic alopecia"	CICM, Thammasat
	Phosphorylation"	Nawaporn Ungpraphakorn,	University
	Vivek Mathema,	CICM, Thammasat	
	CICM, Thammasat	University	
	University		
	"The effects of sea	"Consumer attitude	"Pediatric facial
	cucumber (Holothuria	toward health focused	lipoblastoma in the head
	scabra) on human	interior design"	and neck: case report and
	mesenchymal stromal	Seksan Leelathipkul,	review of the literature"
	cells derived from	Chularongkorn University	Withita Utainrat,
	placenta"		Ban Mo Hospital
	Jutarat Saengsuwan,		
	CICM, Thammasat		
	University		
18.00-21.00		Gala Dinner	
22.00	Oral & Poster Presentation Awards		
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# Tuesday 29<sup>th</sup> August

	August		
8.30-9.30	Plenary Session 2		
	"Nanotechnology-Enabled Drug Delivery: Progress, Challenges and Imminent Opportunities" Prof. Andrew Owen, Department of Molecular and Clinical Pharmacology, University of Liverpool, UK		
9.30-10.00	Department of Motecular	Refreshment	inversity of Errespoot, en
10.00-11.30		Invited speakers	
10.00-11.50			
	Room A	Room B	Room C
	Chair: Prof. Suradej Hongeng, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Thailand Co-chair: Dr. Saranyoo Ponnikorn, CICM, Thammasat University, Thailand	Chair: Prof. Hidemi Goto, Nagoya University, Japan Co-chair: Dr. Nuntra Suwantarat, CICM, Thammasat University, Thailand	Chair: Assoc. Prof. Sombat Muengtaweepongsa, Faculty of Medicine, Thammasat University, Thailand Co-chair: Assoc.Prof. Kanvee Viwatpanich, CICM, Thammasat University, Thailand
	"Recent Advances & Future Directions in Stem Cells Therapy" Prof. Suradej Hongeng, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Thailand	"What You Should Know About Liver Cirrhosis" Dr. Sith Siramolpiwat, CICM, Thammasat University, Thailand	"Monitoring and Management of ECMO: A Review of Current Issues" Dr. Marut Chantra, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Thailand
	"Stem Cells & Targeted Therapy in Modern Oncology" Assoc. Prof. Pithi Chanvorachote, Faculty of Pharmaceutical Science, Chulalongkorn University, Thailand	"Helicobactor pylori Infection & Clinical Consequences" Prof. Ratha-korn Vilaichone, Faculty of Medicine, Thammasat University, Thailand	"Optimal Targeted Temperature in Clinical Practice" Assoc. Prof. Sombat Muengtaweepongsa, Faculty of Medicine, Thammasat University, Thailand
	"An Update on Strategies for HIV Prevention and Treatment" Dr. Timothy Cressey, Programme for HIV Prevention & Treatment (PHPT), Chiangmai University, Thailand	"How Can Surgery Help Obese Patients?" Assoc. Prof. Suthep Udomsawaengsup Department of Surgery, Faculty of Medicine, Chulalongkorn University, Thailand	"Continuous Renal Replacement Therapy (CRRT) in Critically III Patient with ECMO" Asst. Prof. Nattachai Srisawat, Faculty of Medicine, Chulalongkorn University

11:30-12:30	Lunch symposium			
	Room A Lunch symposium 4 supported by Bang Trading 1992 Co., Ltd.	Room B Lunch symposium 5 supported by Fujifilm	Room C Lunch symposium 6 supported by Techno Medical Public Co., Ltd.	Room D Lunch symposium 7 supported by Dentium (Thailand) Co., Ltd. and Osstem Implant. Co., Ltd.
	Moderator: Asst. Prof. Junya Pattaraarcharchai, CICM, Thammasat University, Thailand	Moderator: Dr. Dhave Setabutr, CICM, Thammasat University, Thailand	Moderator: Assoc.Prof.Taweepom Sittiracha, CICM, Thammasat University, Thailand	Chair: Asst. Prof. Lertrit Sarinnaphakorn, Faculty of Dentistry, Thammasat University, Thailand  Moderator: Dr. Parinda Tasanarong, CICM, Thammasat University, Thailand
	"Delivering Scalable and Economically Viable Cell Therapies" Dr. Anthony Lim, Product Manager GE Healthcare Life Sciences ASEAN	"Advances in Gastrointestinal Endoscopy" Prof. Hidemi Goto, Nagoya University, Japan Prof. Varocha Mahachai, Bangkok Hospital, Thailand	"Medical Device Industry in Thailand Era 4.0" Preecha Bhandtivej Chief Operating Officer, Techno Medical Public Co., Ltd.	"Digital Age and Dentistry" Dr. Pojanart Poomprakobsri, Dentium (Thailand) Co., Ltd.  "Update Digital Dental Workflow" Dr. Chanchai Kingwatanakul, Osstem Implant. Co., Ltd.

# TRAINING WORKSHOPS

Workshops	Speakers	Date & Time	Venue
"Perfusion Crisis Management" Techno Medical Public Co., Ltd.	Prof. Saw Huat Seong, Nicole Teo, Nongchana Klangsuk,	Day 1 (28 August 2017)  • 09:00-11:45  • 15:00-17:00  Day 2 (29 August 2017)  • 08:45-14:00	Floor 7
<b>"Online HDF in Practice"</b> <i>Nikkiso</i>	Seksun Uppasri, Pratya Kaptaphol	Day 1 (28 August 2017)  • 15:00-17:30	Floor 6
"Spectra XT-Going Beyond QS Nd: YAG Laser" "LASEMD-Skin Perfecting & Hair Regrowth Laser" Laser Engineer Co., Ltd.	Assoc. Prof. Ratchathorn Panchaprateep	Day 1 (28 August 2017) • 14:30-15:30	Room D (3005)
"Calorie Restriction with Optimum Nutrition (CRON) – The Longevity Diet" Vitallife Wellness & Anti- Aging, Bumrungrad International Hospital	Asst. Prof. Dr. Pansak Sugkraroek, Dr. Wanwiput Sanphasitvong, Dr. Kamon Chaiyasit	Day 2 (29 August 2017) • 13:00-16:00	Room C (4019)
"Digital PCR in Precision Medicine" Bio-Rad Laboratories Ltd.	Adam Ng	Day 2 (29 August 2017)  • 13:00-16:00	Lab
"Training Meditation: วิทิสา สมาธิ" Chao Phya Abhaibhubejhr Hospital Foundation, Thailand	Nattaree Srisa-arn	Day 2 (29 August 2017) • 13:00-16:00	Room A (Main)
OneGuided (Osstem Guided Surgery System) Osstem Implant. Co., Ltd.	Dr. Chanchai Kingwatanakul	Day 2 (29 August 2017) • 13:00-16:00	Room B (2007)
"Augmentation and Ridge Spliting, Hand-On" Dentium (Thailand) Co., Ltd.	Dr. Pojanart Poomprakobsri	Day 2 (29 August 2017)  • 13:00-16:00	Room D (3005)
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# INVITED SPEAKERS' ABSTRACT

## **Extrinsic and Intrinsic Types of Atopic Dermatitis**

Professor Yoshiki Tokura

Department of Dermatology, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku, Hamamatsu 431-3126, Japan

Although several criteria for the definition of atopic dermatitis (AD) have been approved, there still exist variations in the diagnosis of AD because of its heterogeneous aspects. The clinical phenotype of AD can be classified into the extrinsic and intrinsic types. Extrinsic AD and intrinsic AD are defined according to IgE-mediated sensitization, namely the presence or absence of specific IgE for environmental allergens. Intrinsic AD can be defined as serum IgE levels \( \leq 200kU/L \) or 200<IgE\( \leq 400 \) plus class 0 or 1 of IgE specific to D. pteronyssinus or D. farinae, and extrinsic AD was defined as 400<IgE levels or 200<IgE≤400 plus class 2 or more of the specific IgE. The incidence of extrinsic AD and intrinsic AD are ~80% and 10-20%. The female predominance in intrinsic AD is well known. The skin manifestations of the two types of AD are indistinguishable. However, intrinsic AD may lack the features of filaggrin (FLG) gene mutation-associated skin lesions, including ichthyosis vulgaris and palmar hyperlinearity. Meanwhile, it was reported in Dutch patients that the Dennie-Morgan fold is significantly more often present in the intrinsic type. The skin barrier function is highly impaired in extrinsic AD and relatively preserved in intrinsic AD. The barrier impairment induces allergic responses to external protein antigens in extrinsic, but not intrinsic AD. Loss-of-function mutations in FLG represent a strong genetic predisposing factor for AD. While 5-9% intrinsic AD cases had FLG mutations, about 33-44% extrinsic AD patients possessed FLG mutations, Extrinsic AD patients show high levels of Th2 cytokines, such as IL-4, IL-5 and IL-13, and intrinsic AD is linked with lower levels of IL-4 and IL-13. Circulating IFN- $\square^+$ T cell frequency was higher in intrinsic than extrinsic AD in our study. The frequency of circulating Th17 cells is tended to be higher in intrinsic AD than in extrinsic AD. In the lesional skin, positive correlations between Th17-related molecules and SCORAD are only seen in patients with intrinsic AD. Intrinsic AD showed significantly higher percentages of positive patch test reactions than extrinsic AD to Ni, Co and Cr. Metals show a mixed Th1- and Th2-type cytokine response in peripheral T cells from sensitized patients, which is different from Th2-stimulatory protein antigens.

**Keywords:** Atopic dermatitis, Extrinsic, Intrinsic, Metal

## Nanotechnology-Enabled Drug Delivery: Progress, Challenges and Imminent Opportunities

Professor Andrew Owen<sup>1,\*</sup>

Nanomedicines are currently at various stages of development across indications, and broadly aim to either improve oral bioavailability, target drugs to infected cells, or provide long-acting parenteral options. There are two overarching strategies that have been employed for creation of nanomedicines. The first strategy involves the creation of solid drug nanoparticles (SDNs) where the particle is composed of the drug, blended with pharmaceutical excipients to stabilise its surface interactions and prevent aggregation. This approach has been successfully applied to oral drug delivery formats for improving bioavailability, facilitating dose reduction strategies to reduce costs and alleviate pressure on global manufacturing capacity. More recently, SDN formulations have also been developed as long-acting injectables (LAI) for several indications including schizophrenia, contraception and HIV. LAI medicines provide therapeutic pharmacokinetic exposure for a period measurable in months from a single intramuscular depot injection, mitigating issues of patient adherence that are of particular concern when chronic administration is required. The second overarching strategy involves the use of nanocarrier systems composed of lipid-based, polymer-based, or inorganic nanoparticles with drug either encapsulated within them or functionalised on their surface. These approaches have been developed to improve targeting to diseased cells or tissues, by either capitalising on anatomical features (passive targeting) or by functionalisation with a targeting ligand such as an antibody (active targeting). Several nanocarrier medicines have entered the clinic in diseases such as cancer and fungal infections, and early research is underway to develop analogous materials for other diseases. This presentation will provide an overview of current nanomedicine developments and successes, and postulates several areas for further development.

**Keywords:** Nanomedicine, Drug Delivery, Pharmacokinetics, Dose Optimisation

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<sup>\*</sup> Chair of the Board of Trustees, British Society for Nanomedicine

#### Pharmacogenomics-Based Research for Preventing Adverse Drug Reactions

Dr. Ryosuke Nakamura

Division of Medicinal Safety Science, National Institute of Health Sciences, Setagaya-ku, Tokyo, Japan 158-8501

Adverse drug reactions (ADRs) can be classified into two categories; (1) Type-A ADRs such as sleepiness by anti-histamine drugs and diarrhea/neutropenia by anti-cancer drugs, and (2) Type-B ADRs such as severe cutaneous adverse reactions (SCARs). While Type-A ADRs may occur in everyone and are dependent on the pharmacological mechanisms of the drug, Type-B ADRs have been known as 'idiosyncratic' reactions caused by genetic factors of the patients, and thus, are independent on the pharmacological properties of the drug. Since the prevalence of the Type-B ADRs (especially, severe ADRs) are generally low, the biggest obstacle in the implementation of pharmacogenomics-based personalized medicine to avoid Type-B ADRs would be how to collect case samples with enough statistical power. In this symposium, I would like to introduce the Japanese version of nation-wide case-collecting network (JSAR research group), especially in the case of SCARs such as Stevens-Johnson syndrome (SJS) / toxic epidermal necrolysis (TEN). Regarding carbamazepine-induced SJS/TEN, we have identified human leukocyte antigen (HLA)-B\*15:11 as a unique risk allele in Japanese population. I would also like to show some genetic factors associated with the onset of SJS/TEN discovered with our case samples.

**Keywords**: Pharmacogenomics, adverse drug reactions, SJS/TEN

#### **Cancer Gene Mutations and Current Tread of Cancer Treatment**

Professor Thongbliew Prempree, M.D., Ph.D.

Chularat3 Hospital and Bumrungrad Hospital, Thailand

It is now accepted worldwide that cancer caused by gene mutation. This mutation occurs in gene normally found in our normal cell. One normal cell has about 25,000 genes working for cell to grow and has variety of function. Gene consists of DNA and functions through replication and translation. Gene product which is protein could change according to change in DNA (mutation). At present, mutation of gene can be studied by using DNA sequencing and protein by IHC (Immunohistochemical study). Cancer can have single gene mutation such as GIST cancer or multiple genes mutation such as colon, breast and lung cancers. Interestingly, most human cancers do have multiple genes mutation. In my presentation, we will have lung cancer as an example of genes study and treatment by targeted medicine. As we now know, lung cancer has been one of the most common cancers in Thailand. It is expected to have 30-40 cases of lung cancer among 100,000 population or simply put it 25 new cases per day and expect 24 cases to die from cancer in spite of treatment. We embarked on NSCLC study and targeted medicine treatment with close FU several years ago and have been reporting our result in World Lung Cancer meeting regularly. Our gene study showed mutation of EGFR gene particularly Exon 19 classical mutation, Del E746-T751 or Exon 21 mutation L858R. Patients whose lung cancer gene showed these two classical mutation will respond very well to first generation TKI (Tyrosine Kinase Inhibitor). But when lung cancer had additional mutation of KRAS1 or KRAS2 gene, the response of those lung to TKI will be less. Our presentation will also show the resistance to first generation TKI when secondary activating mutation of EGFR did occur. The second and third generation TKI had been available now for lung cancer patients with excellent success. The overall result of our lung cancer project will be presented in this talk. In addition to extensive presentation of lung cancer as an example of cancer treated by targeted medicine, we also start our Immune Checkpoint treatment for various cancers as well.

**Keywords:** Cancer, Mutation, DNA

## **Natural Compounds as Modulators of Epigenetic Events**

Professor Marc Diederich

Department of Pharmacy, College of Pharmacy, Seoul National University, Seoul 151-742, South Korea

Natural compounds are the fundament of pharmacological treatments and more than 50% of all anticancer drugs are of natural origins or at least derived from scaffolds present in Nature. Over the last 25 years, molecular mechanisms triggered by natural anticancer compounds were investigated. Emerging research showed that molecules of natural origins are useful for both preventive and therapeutic purposes by targeting essential hallmarks and enabling characteristics described by Hanahan and Weinberg. Moreover, natural compounds could change the differentiation status of selected cell types. One of the earliest response of cells treated by pharmacologically active compounds is the change of its morphology leading to ultra-structural perturbations: changes in membrane composition, cytoskeleton integrity, alterations of the endoplasmic reticulum, mitochondria and of the nucleus lead to formation of morphological alterations that are a characteristic of both compound and cancer type preceding cell death. Apoptosis and autophagy were traditionally considered as the most prominent cell death or cell death- related mechanisms. By now multiple other cell death modalities were described and most likely involved in response to chemotherapeutic treatment. It can be hypothesized that especially necrosis-related phenotypes triggered by various treatments or evolving from apoptotic or autophagic mechanisms, provide a more efficient therapeutic outcome depending on cancer type and genetic phenotype of the patient. In fact, the recent discovery of multiple regulated forms of necrosis and the initial elucidation of the corresponding cell signaling pathways appear nowadays as important tools to clarify the immunogenic potential of non-canonical forms of cell death induction.

Keywords: Natural compounds, Epigenetic, Cancer

## **Recent Advances & Future Directions in Stem Cells Therapy**

Professor Suradej Hongeng

Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Thailand

#### **Stem Cells & Targeted Therapy in Modern Oncology**

Associate Professor Pithi Chanvorachote

Department of Pharmacology and Physiology, Faculty of Pharmaceutical Sciences, Chulalongkorn University, Bangkok, Thailand

As a key regulator of cancer aggressiveness and subsequent metastasis, the certain subpopulation of cancer cells exhibiting phenotypes of stem cells of self-renewal and differentiation into various linages of cancer cells, so called cancer stem cells (CSC), has recently attracted much attention due to the possibility for the development of novel CSC-targeted therapies. Therefore, identification of the potential factors facilitating transformation of the normal cancer cell to CSC and its regulatory mechanisms will provide new insight in cancer cell biology, which can be utilized for the development of new therapeutic strategies against aggressive cancer. Our works have focused on the regulatory roles and mechanisms of substances including nitric oxide (NO), iron and zinc ion on cancer stem cell (CSC) properties in human lung cancer cells. We found that NO as well as iron exposure could enhance CSC signals, markers, and behaviors in the lung cancer cells, while treatment of the lung cancer cell with zinc exhibited the opposite effect. Taken together, we provided important insights regarding roles and mechanisms of endogenous and exogenous substances in regulating cancer stemness. Even though clinical and in vivo data are of necessity, this knowledge based on cellular and molecular investigations offered a potential opportunity to develop a new strategy in treating lung cancer by targeting CSC potentiating factors and signals. Also, the impact of cancer microenvironment-derived mediators and exogenous compounds on cancer cell behaviors might draw an interest toward investigation those reactive species as a possible target in supporting lung cancer treatments or use with caution in high cancer-risk population.

**Keywords:** Stem cells, Targeted therapy, Cancer stem cells

## An Update on Strategies for HIV Prevention and Treatment

Dr. Timothy Cressey<sup>1,2,3</sup>

<sup>1</sup>PHPT-IRD UMI 174, Division of Medical Technology, Faculty of Associated Medical Sciences, Chiang Mai University, Thailand; <sup>2</sup>Department of Molecular & Clinical Pharmacology, University of Liverpool, UK, <sup>3</sup>Department of Immunology & Infectious Diseases, Harvard T.H. Chan School of Public Health, Boston, USA

The aim of this presentation is to provide an update on the increasing number of effective strategies for HIV prevention and the recent advances in antiretroviral therapy (ART). In 2014, the Joint United Nations Programme on HIV/AIDS (UNAIDS) announce the ambitious "90-90-90" treatment targets in the quest to end the AIDS epidemic. By 2020, it is expected that (1) "90% of all people living with HIV will know their HIV status; (2) 90% of all people with diagnosed HIV infection will receive sustained antiretroviral therapy; and (3) 90% of all people receiving antiretroviral therapy will have viral suppression. Achieving these treatment targets will also have a major impact on reducing new HIV transmissions. At the same time, there have also been major advances in strategies for HIV prevention. The global roll-out of ART for all HIV-infected pregnant women is already leading to significant reductions in the number of new HIV infections in children, with several countries officially declaring the elimination of mother-to-child transmission of HIV, including Thailand. Multiple randomized placebo-controlled clinical trials have demonstrated that daily oral tenofovirbased Pre-Exposure Prophylaxis (PrEP) is safe and reduces the incidence of HIV between 48% to 75% across a range of high risk populations. Considerable efforts are now underway to attain the global target of reaching 3 million people at high risk of HIV infection with PrEP by 2020. For ART, new fixed dose combinations are now available which have reduced long-term side effects; however, the development of formulations for children remains challenging. Sustained adherence to PrEP and ART is often difficult for many patients. An exciting research area is in the field of "Long-Acting" (LA) antiretrovirals which may reduce ART from a daily oral regimen to an injectable formulation every 4- or 8-weeks. Several prevention and treatment studies using LA-antiretrovirals are ongoing. Overall, significant scientific breakthroughs have led to a major reduction in global HIV transmission and AIDS-related mortality and with continued efforts it will be possible to active the goal of ending the HIV epidemic by 2030.

**Keywords:** HIV, Pre-Exposure Prophylaxis (PrEP), Prevention of mother-to-child-transmission (PMTCT), Antiretroviral Therapy (ART)

## Phototherapy & Future Development for Dermatology

Professor Morita Akimichi, M.D., Ph.D.

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Natural sunlight has beneficial effects for various skin conditions and immunoregulatory functions. Phototherapy utilizes the beneficial effects and immunoregulatory functions of natural sunlight. Phototherapy is used for refractory skin disease when topical steroid treatment is not effective. Ultraviolet light (UV) phototherapy using narrowband UVA (311-313 nm) is a well-established treatment for refractory skin disease, such as psoriasis. UV phototherapy has two primary modes of action: apoptosis induction and immune suppression. Narrowband UVB depletes pathogenic T cells by inducing apoptosis and induces regulatory T cells. UVB, psoralen and UVA (PUVA), and UVA-1 (340–400 nm) are useful treatments of refractory skin diseases, and can be used in conjunction with topical steroids. Selective wavelength phototherapies are used to minimize the carcinogenic risks of UV exposure. UVA-1 effectively penetrates the dermal layers, and is thus superior to UVB, which is mainly absorbed by the epidermis. Excimer light (308 nm) therapy effectively targets affected skin without undue exposure of other areas and increases the levels of T regulatory cells. Fewer treatments and a lower cumulative UVB dose are other advantages of excimer light; the greater carcinogenic risk is ameliorated by the reduced number of treatments needed. We previously evaluated the effects of bath-PUVA therapy on Th17/Treg balance in peripheral blood obtained from patients with psoriasis. Bath-PUVA therapy significantly reduces the number of Th17 cells. Treg function is significantly increased and Treg function is restored to almost normal levels. The Treg Functional Ratio is inversely correlated with the Psoriasis Area and Severity Index score. These findings confirm that Treg are dysfunctional in psoriasis patients, and that bath-PUVA therapy restores Treg function in most patients. Furthermore, activated Treg (aTreg) are significantly increased in the early sessions of bath-PUVA therapy and later diminished afterward. The psoriasis lesions improved concomitantly with the increase in aTreg. Bath-PUVA therapy resolves the Th17 and Treg imbalance in patients with psoriasis and induces aTreg. Treg are induced in exposed skin by the clerstering a certain dendritic population. Based on these mechanism analyses, phototherapy effects have led to several improvements in the design, protocols and light sources as UV-LED, providing several options to patients with skin disease.

Keywords: Bath-PUVA, Narrow-band UV, Phototherapy, Regulatory T cells, B

## **Immunological Aspects of Psoriasis & Its Therapies**

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Psoriasis is one of the most common inflammatory keratotic skin diseases. The involvement of interleukin (IL)-17-producing T cells in its pathogenesis has been clarified. Th17 cells and their cytokines, IL-17A and IL-22, play an essential role, and IL-22 may be prerequisite for acanthosis. IL-17A and IL-22 stimulate keratinocytes to produce IL-8, GM-CSF, TNF-α, CXCL10, and vascular endothelial growth factor (VEGF), thereby inducing inflammation, neutrophil accumulation, and angiogenesis. For maintaining Th17 cells, IL-23 is required and released from TNF-α-producing inflammatory dendritic cells (DCs). In addition, plasmacytoid DCs (pDCs) secreting interferon (IFN)α play an initiative role for the development of psoriatic lesions. Psoriatic patients have been treated with various modalities, such as topical ointments, photochemotherapy/ phototherapy, retinoids, methotrexate, and cyclosporine. Recently, biologics, phosphodiesterase-4 (PDE4) inhibitors, Janus kinase (JAK) inhibitors, and topical combination ointments are also used. The above cytokine network in the pathogenesis of psoriasis has been proven by the therapeutic effectiveness of cytokineblocking biologics, including antibodies against TNF-α, IL-23/IL-12p40, IL-17A, and IL-17 receptor. Trials of anti-IL-23p19 antibodies are being undertaken. After treatment with anti-TNF-α or anti-IL-23/IL-12p40 antibodies, the high-responders showed significant decreases in serum IL-22 and VEGF, whereas serum IL-22 levels in the non-responders were elevated. This alteration was not found in patients treated with anti-IL-17A antibody. Because of the technical difficulty, the majority of previous reports on skin-infiltrating Th17 cells have shown only histological findings, and alteration of pathogenic skin-infiltrating Th17 cells has not been fully investigated. We used the skin-derived T cell expanding ex vivo system. The expanded T cells reflect the original T cell population. We demonstrated that the number of skin-infiltrating T cells, particularly Th17 cells, was decreased by topical vitamin D3 (VitD3) analogue monotherapy and the combination of VitD3 and corticosteroid. In addition to its suppressive effect on Th17 cells, VitD3 also can depress IFN-α production and chemotactic migration of pDCs. A new drug, PDE4 inhibitor can normalize cAMP, and a promising drug, JAK-STAT inhibitor may suppress intracellular signaling pathway upon which many different proinflammatory signaling pathways converge.

**Keywords**: Dendritic cell, IL-17, Psoriasis, T cell

#### What You Should Know About Liver Cirrhosis

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Cirrhosis is the irreversible fibrosis of the liver, the end stage of a final shared pathway in chronic damage to a major vital organ. The major causes of cirrhosis include chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infection, alcoholism, and nonalcoholic steatohepatitis. The transition from chronic liver disease to cirrhosis involves inflammation, activation of hepatic stellate cells with ensuing fibrogenesis, angiogenesis, and parenchymal extinction lesions caused by vascular occlusion. The average life expectancy of a patient with compensated cirrhosis is 10 to 13 years, and the average life expectancy may be as low as 2 years if there is decompensation. Most chronic liver disease is notoriously asymptomatic until cirrhosis with clinical decompensation occurs. Decompensating events include ascites, sepsis, variceal bleeding, encephalopathy, and non-obstructive jaundice. Patients with cirrhosis should be treated when possible for the underlying liver disease to stop disease progression. Cirrhotic patients with viral hepatitis should be assessed for antiviral treatment. The liver has considerable regenerative potential, and reversal of cirrhosis has been described in patients with alcoholic cirrhosis who abstained from alcohol, patients with HBV infection who underwent antiviral therapy, and patients with nonalcoholic steatohepatitis who underwent bariatric surgery. Portal hypertension, rather than hepatocyte failure per se, is the underlying cause of most of the complications of cirrhosis and subsequent mortality. Current recommendations are that all patients with cirrhosis should be screened for varices. Treatment options include nonselective beta-blockers for varices, irrespective of size, or endoscopic band ligation for medium or large varices. In cirrhosis, portal hypertension and splanchnic vasodilation, resulting mainly from increased production of nitric oxide, is the main pathophysiological mechanism of ascites. In patients with a new presentation of ascites, a diagnostic tap should be used to screen for underlying infection. Initial management consists of education of the patient about limiting dietary sodium intake and oral diuretic treatment. Refractory or difficult-to-control ascites necessitates an assessment for liver transplantation. The development of encephalopathy is an ominous sign in cirrhosis, because the associated 1-year mortality rate is up to 64%. Overt encephalopathy is generally transient and linked with a precipitating event, such as use of sedatives, constipation, dehydration, infection, or gastrointestinal bleeding. Guidelines recommend 6monthly ultrasonographic screening, because it results in more effective treatment of smaller hepatocellular carcinoma. Liver transplantation is a therapeutic option in patients who develop decompensation or hepatocellular carcinoma with cirrhosis.

**Keywords:** Liver Cirrhosis, Hepatitis B virus (HBV), Hepatitis C virus (HCV)

#### Helicobactor pylori Infection & Clinical Consequences

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Helicobacter pylori has high prevalence in Asian countries and has been linked to the development of gastric inflammation, peptic ulcer disease and gastric cancer. Prevalence of H. pylori infection is high in Thailand approximately 30% with highest prevalence in North and North Eastern parts (40-50%) and lowest in Southern part (20%). However, the incidence of gastric cancer in Thailand is approximately 3.9/100,00 per year which is much lower than that reported in Japan which is approximately 60/100,000 per year. This paradox may be explained by difference in H. pylori strains, host responses and environmental factors. The prevalence of certain pathogenic bacterial genotypes may be associated with the diversities of *H. pylori* related diseases and may vary among geographical regions. Thailand is at the cultural cross roads between East and South Asia. It has been suggested that in this region, the predominant H. pylori genotype changes from East Asian to South Asian. Our study demonstrated that H. pylori East Asian strain (cagA 1a, cag right end type (non-I) and vacA (nons1b)- (m1b or m2)) was an independent determinant predictor of gastric cancer (adjusted OR 13.7; 95% CI=2.2-85.6) and peptic ulcer disease (adjusted OR 6.1; 95% CI=1.2-29.8). For the host response, we confirm that IL-1 polymorphisms (both IL-1\beta-511 and IL-1Rn genotypes) combined with cagA 1a genotype were predictive of increased gastric mucosal cytokine levels (such as IL-1 and IL-8) thus suggesting that both the host factors (IL-1 polymorphisms) and bacterial factors (cagA genotype 1a versus 2a) influence gastric mucosal cytokine levels and may determine the disease outcome. Moreover, the prevalence of *H. pylori* infection in Thailand is still high in gastric cancer, peptic ulcer disease and gastritis (93%, 92%, 58% respectively) comparable to Japan (100%, 100%, 69%) and the United States of America (80%, 100%, 72%). For the antibiotic resistance, metronidazole resistance has reached more than 40% in many areas and clarithromycin resistance found in 10%. Multi-drug resistant is a growing problem. Triple therapy regimen is now less effectiveness and need newer regimens such as sequential and concomitant therapy for initial approach for the infected patients. All of the data support the idea that Thailand is an ideal site for epidemiological studies attempting to relate *H. pylori* genotypes and host factors to outcome.

### **How Can Surgery Help Obese Patients?**

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#### Water Treatment for Hemodialysis: Experience & Current Standard in Thailand

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The quality of water treatment system used for hemodialysis is one of the most vital components in providing good hemodialysis care. In the beginning era of hemodialysis technique there was many clinical occurrence reports, some patients died, due to chemical and biological contaminants in water used for hemodialysis. Nowadays, despite there are better development of water treatment system and hemodialysis technique, which make hemodialysis procedure more easy and safety, but in the opposite way, these new technology of hemodialysis, such as ultrafiltration control machine and high flux to super high flux dialyzer, cause internal back filtration in dialyzers and increase risk of water contaminants. Many organizations have set up quality standards of water used for hemodialysis. The most widely accepted standards are AAMI (Association of Advancement of Medical Instrumentation), European Pharmacopoeia and the most recent one is ISO. Those standards defined upper limits of chemical and microbiological contaminants in dialysis water and dialysis fluid and recommended practices for preparing purified water. In Thailand, Nephrology Society of Thailand have launched guideline for preparation of water used for hemodialysis in 2007 and revised it last year (2016). To achieve water quality according to the standards, the component of water purification system should consist of reverse osmosis unit (RO) and Pre-treatment unit which must include two carbon filters in series. The other important system which are vulnerable to microbial overgrowth and biofilm formation is distribution system for feeding purified RO water to hemodialysis machine and other points of use. The key issues in minimizing the microbiological problems are the good sanitary designs of piping system and frequently disinfection. The overall water treatment system must be validated by performing regular monitoring and maintenance to ensure that whenever the water is used for hemodialysis its quality is comply with standard all the time.

Keywords: Hemodialysis, Water, Reverse osmosis

#### Water Treatment for Hemodialysis: Technology & Advancement in Japan

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Japanese hemodialysis quality is listed top in the world by DOPPS results. This is caused by the many clinical studies with a lot of kidney disease patients during over 40 years in Japan. Patient has a hemodialysis treatment of mild blood flow around 200mL/min., and is kept 4hrs single use dialyzer treatment with pure water dialysate. Water quality effects to a patient condition who has a long term hemodialysis over 3 years. All the dialysate water in dialysis units is controlled by clinical engineer by using microbial analysis and endotoxin concentration (ET). In many dialysis unit, dialysate ET of Central Dialysate fluid Delivery System (CDDS) is kept under 0.001EU/mL. CDDS is very easy for operation and effective to decrease bacteria and ET. CDDS and clinical engineer support the high quality of dialysate, and many patients enjoy their hemodialysis life over 20 years.

Keywords: hemodialysis, CDDS, bacteria, endotoxin, QOL, clinical engineer

#### Monitoring and Management of ECMO: A Review of Current Issues

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A use of extracorporeal membrane oxygenator (ECMO) to support critically ill patients has increased over the past decade due to an improvement in machine design and an increasing in ECMO training center worldwide. Report from extracorporeal life support organization (ELSO) registry in 2016 shows a large increasing in ECMO use in adults with respiratory and cardiac failure. Survival to hospital discharge rate in respiratory diseases has slightly improved. Much improvement in survival rate is observed in cardiac diseases in both pediatrics and adults, partly because of modification of management to optimize left ventricular support and recovery. Reports of extracorporeal life support cardiopulmonary resuscitation also increased each year but no significant survival is observed in the past 5 years. Indications are still unclear and not consistent between institutes. The common extracorporeal life support adverse events reports in the ELSO registry are hemorrhage, renal failure, and infection<sup>1</sup>. Unfractionated heparin is still the most anticoagulation use for ECMO. Many centers now uses multiple methods to monitor effect of heparin instead of only activated clotting time as in the past. Direct thrombin inhibitors provide an alternative to heparin with more reports on safety and efficacy were published.

**Keywords**: extracorporeal membrane oxygenator (ECMO), monitoring, critically ill patients

#### **Optimal Targeted Temperature in Clinical Practice**

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Targeted temperature management (TTM) shows the most promising Neuroprotective Therapy against hypoxic/ischemic encephalopathy (HIE). In addition, TTM is also useful for treatment of elevated intracranial pressure (ICP). HIE and elevated ICP are common catastrophic conditions in patients admitted in Neurologic intensive care unit (ICU). The most common cause of HIE is cardiac arrest. Randomized control trials demonstrate clinical benefits of TTM in patients with post-cardiac arrest. Although clinical benefit of ICP control by TTM in some specific critical condition, for an example in traumatic brain injury, is still controversial, efficacy of ICP control by TTM is confirmed by both in vivo and in vitro studies. Several methods of TTM have been reported in the literature. TTM can apply to various clinical conditions associated with hypoxic/ischemic brain injury and elevated ICP in Neurologic ICU. Two main purposes of targeted temperature management (TTM) in patients admitted in neurological intensive care unit are neuroprotective therapy and intracranial pressure (ICP) control. TTM is the most potent neuroprotective treatment due to its numerous methods of protection against ischemic/hypoxic injury. TTM provides capable ICP reductive action. Two most popular methods using in clinical practice and clinical trials are invasive endovascular technique and non-invasive surface cooling. Fast induction, smooth maintenance and slow rewarming are the important steps to achieve ideal TTM.

**Keywords:** Targeted temperature management, Neuroprotective therapy, Ischemic/hypoxic encephalopathy, Intracranial pressure, Surface cooling, Endovascular cooling

### $Continuous\ Renal\ Replacement\ The rapy\ (CRRT)\ in\ Critically\ Ill\ Patient\ with\ ECMO$

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# ORAL PRESENTATION ABSTRACT

### Cytotoxic interaction of the three major bioactive constituents isolated from *Atractylodes lancea* (Thunb.) DC. against human cholangiocarcinoma cell

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Cholangiocarcinoma (CCA) is a major type of bile duct cancer with high morbidity and mortality, particularly in patients with advanced stage. Treatment of CCA remains unsatisfactory due to the lack of sensitive and specific diagnostic tool for early detection as well as effective chemotherapeutics. Combination therapy is one of the key approaches applied in several diseases including cancers to exploit pharmacodynamic synergistic effects and to delay the emergence of drug resistance. The cytotoxic activities of the three major bioactive compounds isolated from the rhizomes of Atractylodeslancea (Thunb) DC.,i.e.,β-eudesmol (BE), atractylodin (AT), and hinesol (HS), as a single compound or combinations, were evaluated in human CCA cell CL-6 cell line using MTT assay. The cytotoxic interaction between two compounds were initially assessed at five distinct concentration ratios (10:0, 7:3, 5:5, 3:7, and 0:10) using isobologram analysis. The combination of BE and AT produced additive effect with sum FIC (fractional inhibitory concentration) of 0.967±0.02 (mean  $\pm$  SD). The combination of BE and HS as well as AT and HS produced synergistic effect with sum FICs of 0.685±0.08 and 0.767±0.09, respectively. Based on the IC<sub>50</sub> (concentration that inhibits cell growth by 50%) of each compound (21.5, 24, and 91µM for BW, AT and HS, respectively), the interaction between the three compounds was further evaluated using the concentration ratio of BE:AT:HS of 1:1.5:2.5. The combination index (CI) values at IC<sub>50</sub> and IC<sub>90</sub> (concentration that inhibits cell growth by 90%) were calculated from a series of five concentrations of each compound (triplicate analysis) using CompuSyn<sup>TM</sup>. The sum FIC of the combination between BE and AT at the IC<sub>50</sub> and IC<sub>90</sub> were 0.998±0.11 and 1.21±0.19, respectively, indicating additive interaction. The sum FIC of the combination between BE and HS at the IC<sub>50</sub> and IC<sub>90</sub> were 0.35±0.19 and 0.84±0.31, respectively, indicating synergistic interaction. The sum FIC of the combination between AT and HS at the IC<sub>50</sub> and IC<sub>90</sub> were 0.411±0.06 and 0.58±0.32, respectively, indicating synergistic interaction. The combination of the three compounds produced strong synergistic interaction based on results of the polygonogram analysis of the fraction affected (F<sub>a</sub>) at the IC<sub>50</sub> and IC<sub>90</sub> (0.519±0.10 and 0.65±0.17, respectively). Results support the use of the combination of these three bioactive compounds for treatment of CCA.

**Keywords:** Cholangiocarcinoma, β-eudesmol, atractylodin, hinesol

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### Growth inhibitory activity of $\beta$ -eudesmol on cholangiocarcinoma cells is associated with suppression of heme oxygenase-1 production and STAT3 phosphorylation

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Cholangiocarcinoma (CCA) is a progressively lethal form of cancer generally arising from malignant transformation of hepatic biliary cholangiocytes. The objective of the study was to investigate in vitrogrowth inhibitory activities of bioactive sesquiterpenoid β-eudesmol in relation to its underlying potential effect on heme oxygenase-1 (HO-1) production and STAT3 phosphorylation in cholangiocarcinoma cells. Human cholangiocarcinoma (CL-6) and normal human embryonic fibroblast (OUMS) cells were used in this study. Cell cytotoxicity was evaluated using MTT assay. Cell culture morphologywas visualized using light microscopy. Nuclear morphology was determined using DAPI staining and fluorescence imaging. Anti-proliferative effect was evaluated using colony forming assay. Cell migration was studied using wound healing assay. Relative fold of mRNA expressions were evaluated using Real-time PCR. Protein expression was determined using western blot. B-eudesmol treatment exhibited selective cytotoxicity towards CL-6 as compared to OUMS cells. The compound treatment suppressed colony forming ability of CL-6 cells. β-eudesmol induced nuclear fragmentation of CL-6 cells and significantly decreased wound healing ability of CL-6 cells in presence or absence of interlukin-6 stimulation. It also significantly suppressed mRNA expression of multiple genes associated with cell proliferation, HO-1 enzyme production, and STAT3 activation. The compound treatment resulted in decreased expression of HO-1 and significantly suppressed STAT3 phosphorylation in CL-6 cells. In summary, results suggest that β-eudesmol exerts potent growth inhibitory activityonCCA cells which might be linked to its inhibitory effect on HO-1 production and STAT3 phosphorylation.

**Keywords.** β-eudesmol, cholangio carcinoma, heme oxygenase, STAT3

### Celecoxib and p38 MAPK inhibitor SB203580 inhibit cadmium-induced PGE<sub>2</sub> secretion from human astrocytes

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Cadmium (Cd) is an environmental pollutant that can accumulate in the brain. Chronic exposure of cadmium is linked with brain cancer and neurodegenerative disorders. Our previous study revealed that non-toxic concentrations of cadmium can be taken up into human astrocytes and initiated inflammatory response by inducing the release of proinflammatory cytokine interleukin-6 (IL-6) and IL-8. Another study in murine astrocytes reported that cadmium can trigger inflammation through upregulation of cyclooxygenase-2 (COX-2). However, the alteration of prostaglandin E<sub>2</sub> (PGE<sub>2</sub>), a final metabolite of COX-2 pathway, and the effect of celecoxib, a selective COX-2 inhibitor, on cadmium-induced cytotoxic and prostaglandin synthesis have not been investigated. The present study investigated the effects of cadmium chloride (CdCl<sub>2</sub>) on the prostaglandin pathway along with the protective effect of celecoxib in U-87 MG human astrocytoma cells. Cell viability was determined by MTT assays. Expression pattern of COX-2 mRNA was analyzed by quantitative real-time PCR. Extracellular concentrations of PGE<sub>2</sub> were measured using ELISA. MAPK and NF-κB inhibitors were used to identify the mechanism underlying cadmium-induced the release of PGE<sub>2</sub>. Exposure of U-87 MG cells with 10 µM CdCl<sub>2</sub> for 6 h resulted in an increase of extracellular concentrations of PGE<sub>2</sub>. Cotreatment with 25 µM celecoxib for 6 h reversed cytotoxic effects of 20 and 30 µM CdCl<sub>2</sub> on astrocytes, while celecoxib itself did not affect the cell viability. ELISA analyses showed that celecoxib decreased cadmium-induced PGE<sub>2</sub> release at 6 h. Additionally SB203580, a p38 MAPK inhibitor, decreased COX-2 upregulation and PGE<sub>2</sub> release at 6 h after exposure to 10 µM CdCl<sub>2</sub>. In contrast to a previous study in murine astrocytes, other MAPK inhibitors and an NF-kB inhibitor did not decrease COX-2 mRNA and PGE2 levels. The results indicated that the effect of cadmium on prostaglandin synthesis in human astrocytes was mediated by p38 MAPK pathway. Taken together, our data suggested that COX-2 and p38 MAPK inhibitors could be used for prevention of cadmium induced cytotoxicity and inflammation in the brain.

**Keywords:** Cadmium, Inflammation, COX-2, PGE<sub>2</sub>, Celecoxib

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### The effects of sea cucumber extract (*Holothuria scabra*) on human mesenchymal stem cells derived from placenta

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The sea cucumber *Holothuria scabra* is an economically important aquatic species, which is found in coastal area and naturally distributed in Asian countries, including China, Japan, Malaysia, Thailand, Viet Nam, Indonesia and Philippines. Sea cucumbers have received considerable attention because of their self-regeneration ability. The knowledge of regeneration process, including the factors that regulate this process, may provide a new application to target the treatment of degenerating diseases mammals and humans, especially in cases where the endogenous pathways in mammal may have been lost. This study focused on the effects of sea cucumber extract (H. scabra) on the proliferation of mesenchymal stromal cells (MSCs) derived from human placenta. The H. scabra crude protein extracts were prepared from the body wall (BW) and viscera (VI) by using different extraction buffers, including 0.1M phosphate buffer saline (PBS) and 0.1M acetic acid buffers. The SDS-PAGE showed protein abundance, with various molecular mass, within the BW and VI extracts using 0.1M PBS buffer. Less protein abundance was observed for all organ extracts using 0.1M acetic acid buffer. However, proteins with molecular mass of ~38 kDa and ~17 kDa were highly detected in the extracts from different organs investigated. The MSCs were isolated from the human placentas and were then treated with different doses of sea cucumber extracts. The cytotoxicity and cell proliferation after treatments were evaluated using MTT assay. The results indicated that H. scabra protein extracts at low doeses did not show toxic effect to MSCs, while they could increase the cell number at the range of 0.01 µg/ml to 25 µg/ml. We found that the treatment of 0.1 and 1 µg/ml of H. scabra extracts increased the proliferative rate of MSCs when compared with the sham. This suggested an in vitro proliferative potency of the sea cucumber extracts on MSCs derived from the human placenta. While further studies are required, this finding has firstly provided the evidence that the sea cucumber extracts could be potentially used to induce in vitro MSC proliferation.

**Keywords**: *Holothurian scabra*, Mesenchymal stromal cells, Sea cucumber extract, Cell proliferation

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### Preparation of *Gynurapseudochina DC*. var. *hispidaThv*. leaf extract ointment and its efficacy in treating chronic plaque psariasis

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Gynurapseudochina DC. var. hispidaThv. leaveshave long been used effectively to treatpsoriasis plaques as a Thai traditional drug. The purpose of this study is to extractcrude active principles from Gynurapseudochina leaves, preparation of suitable topical ointment, performing the subacute toxicity test in animals, conducting a clinical trial in patients with chronicpsoriasis plaques topically and preliminary investigating its mechanism of action. Dark greensemisolid crude extract was obtained from Gynurapseudochinadried powdered leaves by 95 percent ethanol (yield: 17.8 percent wt/wt) 10 percent w/w crude extract ointment (GP ointment) was prepared. The GP ointment passed the topical subacute toxicity test done in guinea pigs (24 animals). Clinical investigation, histological andimmunohistological studies (No. of patients : 25); The GP ointment could significantly decrease psoriasis plaque erytherma, scaling and induration as assessed by the Target Area Score (TAS), Psoriasis Severity Index (PSI) and Physician Global Assessment Score (PGA). The GP ointment efficacy was comparable with those of 0.1 percent Triamcinolone acetonide cream (0.1 percent TA cream). Immunohistological study revealed the diminution of phosphorylated NF-<sub>K</sub>B-P65,Ki-67. 10 percent GP ointment was prepared by alcoholic crude extract of Gynurapseudochina DC. var. hispidaThv. Leaves. The ointment caused no subacute toxicity in guinea pigswhen applied topically. The GP ointment could improve psoriasis lesions similar to 0.1 percent TA cream. The possible mechanism of action proposed is decreasing phosphorylated NF-<sub>K</sub>B-P65,Ki-67which would be further confirmed.

**Keywords:** *Gynurapseudochina DC.* var. *hispidaThv.* Ointment, psoriasis plaque, Triamcinoloneacetonide, NF-<sub>K</sub>B-P65, Ki-67

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### Topical tofacitinibdrivehair growth in mouse hair follicle by stimulate expression of Noggin and reduce expression of BMP-4

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Recently hair loss disorders are highly concerning problem in generalized population. Many are cause by failure to entry the growth phase of hair follicle (anagen) and arrested in telogen phase including non-scaring alopecia. Tofacitinib, one of Janus kinase inhibitor, is used as an Immunomodulatory agent. Nowadays many clinical trials are focus on improvement of several hair loss disorders by tofacitinib but the efficacy and mechanism of this effect are not yet understood. This study aimed to explain the new mechanism of topical tofacitinib for promoting hair growth in mice. Topical tofacitinibwas applied on shaved C57BL/6 mice with telogen hair once daily for 21 consecutive days compare to vehicle. After day 21, we evaluated the rate of hair regrowth, ratio of anagen hair. Tissues of mice were taken for evaluate expression of Noggin and bone morphogenetic protein 4 (BMP4) mRNAby RT-PCR. Topical tofacitinib treated miceshowed increase in thickness, length of hair and higher ratio of anagen hair compare to vehicle treated mice. In topical tofacitinib treated group, RT-PCR also show significant increase expression of Noggin (P < 0.05) and reduce expression of BMP4 (P < 0.05) compare to vehicle treated group, resulted in premature entry of anagen and leading hair growth. The previous studies have shown that tofacitinib can promote hair growth in both mice and human by promoting entry of anagen, hair follicle stem cells and anti-inflammatory process. This study helps us understanding further more on the efficacy and mechanism of topical tofacitinibby stimulate expression of Noggin and reduce expression of BMP4, the important molecules that involve in onset of growth phase.

Keywords: Tofacitinib, Noggin, BMP4, Hair growth

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### Efficacy of topical tofacitinib in promoting hair growth in non-scarring alopecia: mechanism via VEGF induction

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Tofacitinib, a Janus Kinase 3 (JAK3) inhibitor, recent studies have shown that inhibition of JAK-STAT pathway promotes hair growth. However, the efficacy and mechanism of tofacitinib in promoting non-scarring hair loss still under investigated. This study aims to evaluate the efficacy and mechanisms of topical tofacitinib on hair growth in mice model. Eight-week-old male C57BL/6 mice were divided equally into four experimental groups and treated topically with tofacitinib, minoxidil, or vehicle once daily for 21 days. Weekly photographs were taken to determine area of hair growth and hair growth rate. Tissue samples were collected at experimental endpoint for histopathological evaluation. Anagen-maintaining growth factors mRNA and protein expression including vascular endothelial growth factor (VEGF) and insulin-like growth factor -1 (IGF-1) were determined by RT-PCR and ELISA technique, respectively. The results showed that tofacitinib-treated group exhibited significantly more hair regrowth than either the minoxidil-treated or control group significantly since day7 through day21 (P<0.05). Topical tofacitinib also promoted more rapid hair growth rate in comparison to topical minoxidil or control (P<0.001). Histopathology showed distinct increase in the number of hair follicles mostly in the anagen phase in tofacitinib-treated group, whereas in minoxidiltreated and DMSO-treated group were more often classified in catagen and anagen phase. VEGF mRNA and protein expression in tofacitinib-treated group showed significantly higher in value as compared to that of others (P<0.05). IGF-1 mRNA expression was not up regulated in mice treated with tofacitinib. In conclusion, topical tofacitinib is significantly efficient in promoting hair growth. The increasing of VEGF expression and its anti-inflammatory effect suggest a partial role in promoting hair growth. This study will be beneficial in developing a new therapeutic option for nonscarring alopecia.

Keywords: JAK3 inhibitor, non-scarring alopecia, hair growth, VEGF, IGF-1

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### The efficacy of 1550-nm Erbium-Glass fractional laser treatment and its effect on the expression of insulin-like growth factor 1 and Wnt/β-catenin in androgenetic

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Androgenetic alopecia (AGA) is a non-scarring hair loss problem with multiple etiologies. The standard treatment of AGA continues to be limited. A new and effective treatment for AGA is 1550nm erbium-glass (Er:Glass) fractional laser treatment. The wound healing process associated with this treatment is believed to be due to the stimulation of hair regrowth by releasing abundant cytokines and growth factors, but the mechanism of healing is still unclear. Both the Wingless-related integration site (Wnt) proteins and insulin-like growth factor 1 (IGF-1) are important molecules that promote new hair growth. The aim of this study was to evaluate the efficacy of 1550-nm Er:Glass fractional laser treatment and determine the messenger ribonucleic acid (mRNA) levels of IGF-1 and Wnt/β-catenin in patients with female pattern hair loss (FPHL) and AGA. Twenty-three male and female patients with AGA Hamilton-Norwood stages III-IV (including type III vertex) or FPHL Ludwig types I-II were enrolled. They received 12 1550-nm Er:Glass fractional laser treatments at 2week intervals. A scalp biopsy was performed on each patient at baseline and 24 hours after the 3rd laser treatment to evaluate mRNA levels of Wnt10A and IGF-1. Global and target photographs were collected monthly. Histopathological samples were collected at baseline, and during the 1st, 2nd, and 3rd months. All adverse effects were reported during the study. Significant increases in hair count and shaft diameter that occurred from month 4 until the end of the study were observed. Histological results showed increases in the follicular unit, anagen hair count, and the anagen:telogen ratio. No upregulation of Wnt10A and IGF-1 mRNA was observed. We concluded that 1550-nm Er:Glass fractional laser treatment can increase hair density and shaft diameter in patients with AGA. The mechanisms by which 1550-nm Er:Glass laser treatment induces new hair growth may not be limited to Wnt10A/β-catenin or IGF-1 expression.

Keywords: Androgenetic alopecia, Female pattern hair loss, Fractional laser, Wnt/β-catenin, IGF-1

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### Incidence and risk factors for colonization of multidrug-resistance organisms (MDROs) among patients undergoing elective orthopedic surgery at Thammasat University Hospital

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In Thailand, the high prevalence of multidrug resistant organisms (MDROs) has been a reported. There is limited data on incidence of MDROs colonization and outcome in patients undergoing elective orthopedic surgery. Thus, we performed MDROs surveillance screening (swabs from nose, throat, groins, and rectum) in patients undergoing elective orthopedic surgery at the Thammasat University Hospital between March and August 2016. MDROs were defined as Gram-negative bacteria possessing extended-spectrum β-lactamases (ESBLs), Carbapenem-resistant Enterobacteriaceae (CRE), and non-lactose fermenting Gram-negative bacteria resistant to at least 3 antibiotic classes, methicillin-resistant Staphylococcus aureus(MRSA), and vancomycin resistant enterococci (VRE). MDROs were identified by the Vitek®2 automated system. Antimicrobial susceptibility testing (disk diffusion test) was performed using the Clinical and Laboratory Standards Institute Interpretive Guidelines. Incidence of MDROs colonization upon admission was determined. Patient's clinical characteristics, risk factors for MDROs infection, procedure types and antibiotic prophylaxis were prospectively collected. Surgical sites infections (SSIs) and complications up to 6 months after surgery among the patients with and without MDROs colonization were compared. Of 384 swabs tested from 96 patients (median age, 58 years), ESBL-producing Escherichia coli (ESBL-E. coli) was identified in 31 rectal swabs (31/96, 32.3%) and 7 groin swabs (7/96, 7.3%). Seven patients (7.3%) were diagnosed with SSIs. A higher rate of SSIs was found among patients with ESBL-E. coli colonization (6/31, 19.4%) compared to patient without ESBL-E. coli colonization (1/65, 1.5%; P= 0.004, OR 15.36, 95%CI 1.7-356.3). From the multivariate logistic regression analysis, SSIs were significantly associated with ESBL-E.coli colonization (P=0.009, adjusted OR18.29, 95% CI 2.05-162.99). In conclusion, we found a high incidence of ESBL-E. coli colonization and rate of SSIs in patients who had elective orthopedic surgery. These patients did not have any other risk factors for MDROs infection. Active screening for colonization of ESBL producing pathogens and appropriate antibiotic prophylaxis guidance need further evaluation to reduce rates of SSIs.

**Keywords:** MDROs, orthopedic surgery, surgical site infections

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#### Current trends of balloon laryngoplasty in Thailand

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To describe the current trend in balloon laryngoplasty usage and experience by practicing otolaryngologists in Thailand. Anonymous 11 question online and paper survey of otolaryngologists on their current balloon laryngoplasty practices. Subjects and Methods: Current practices and experience in balloon laryngoplasty were queried with multiple choice and open-ended questions. Laser use is the most commonly utilized instrument to treat airway stenosis in Thailand. 86% of respondents do not have experience with balloon dilatation; yet, almost half (47.6%) report they perform a minimum of ve airway surgeries per year. Most respondents had been in practice for less than 6 years (41%) and reported that they did not have exposure to balloon use during residency training. The largest barrier reported for the use of balloon instrumentation in the airway is inexperience (44.4%) followed by cost (38.3%), yet most feel that treatment in airway stenosis could bene t by usage of balloons (95.5%). Most otolaryngologists in Thailand do not have experience with the use of balloon dilatation and lack of exposure remains the largest barrier to its use. Otolaryngologists in Thailand feel that increased usage of balloons in the airway could improve airway stenosis treatment in the country.

Keywords: Balloon laryngoplasty, Pediatric otolaryngology, Endoscopic airway surgery

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#### Pediatric laryngotracheal separation following a go-cart injury

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Less than one percent of trauma admission cases are categorized as pediatric neck trauma. Nevertheless, due to an increasingly mobile society, there has been an increasing frequency of pediatric neck trauma with motor vehicle accidents being the most common mechanism of injury. We present a case of laryngotracheal separation from a blunt, clothesline injury to the neck in a pediatric patient. We also review the literature and discuss the benefit of balloon airway dilation and its assistance in the management of laryngeal trauma and its resultant effects.

Keywords: pediatric neck trauma, go-cart injury

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### Contributions of SIDCER/FERCAP to the development of national accreditation programs for ethics committees in the Philippines and Thailand

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One of the aims of the recognition program of the Strategic Initiative for Developing Capacity in Ethical Review (SIDCER)/Forum for Ethical Review Committees in the Asia and Pacific Region (FERCAP) as a voluntary assessment mechanism for ethics committees (ECs) in the Asia-Pacific region is to promote capacity building and quality improvement in ethical review by supporting the establishment of national accreditation systems. The objective of this research was to evaluate the contributions of SIDCER/FERCAP to the development of accreditation programs for ECs of the Philippine Health Research Ethics Board (PHREB) and the National Ethics Committees Accreditation System of Thailand (NECAST). The methods employed for this research were primarily qualitative methods, includingdocument/textual analysis, participant observation, as well as semi-structured interviews conducted during 8 Joint PHREB-SIDCER/FERCAP accreditation/recognition surveys and 8 Joint NECAST-SIDCER/FERCAP accreditation/recognition surveys from 2014 to 2016. Results of this research show that SIDCER/FERCAP made significant contributions during the planning stage for and ongoing implementation of the PHREB and NECAST accreditation programs. SIDCER/FERCAP contributions differ though owing to variations in the terms of reference with PHREB and NECAST and the policies, requirements, and standard operating procedures (SOPs) of the national accreditation programs. Although different, SIDCER/FERCAP inputs to PHREB and NECAST contributes to the over-all success of the national accreditation programs. In line with continuous capacity building and quality improvement in ethical review to protect human participants in health research, this research recommends incessant supportfor the establishment of national accreditation systems for ECs in other areas/countries in the Asia-Pacific region.

Keywords: Ethics Committees, Accreditation, Philippines, Thailand, FERCAP, SIDCER

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### Disclosure of informed consent and ethics committee approval in international Thai scientific journals

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In addition to facilitating the open exchange of information among researchers, the publication process can also serve as an important final safeguard against the dissemination of unethically conducted research through strict submission requirements. Many internationally recognized journals and publishers such as the Journal of the American Medical Association (JAMA), SAGE, and Springerhave adopted the International Committee for Medical Journal Editors (ICMJE) Recommendations and explicitly required, as part of their submission policies, that authors disclose the obtainment of informed consent and ethics committee (EC) approval in their manuscript. Despite this increasing vigilance, many international journals still fail to raise their policies to meet this higher standard. Theobjective of this study was to observe the adoption rates of the ICMJE Recommendations that recommends the requirement of authors to disclose EC approval and obtainment of informed consent in their manuscripts and the extent to which such adoption has been implemented in Indonesia. Using the search function in the PubMed database, 4,127 articles published in Thailand between 2014 and 2016 were retrieved. Articles were then screened for editorials, reviews, case reports and non-human subject related researchwhich were excluded from the analysis. Instructions to the authors were obtained from the official websites of the journals in which the retrieved articles were published. Retrieved articles were then reviewed for disclosure statements regarding ethical approval and obtainment of informed consent. Results show that authors have acted at a higher standard than journal requirements, yet some confusion still remains. To help push authors and the scientific community to higher international standards, journals should specifically set out the disclosure statements requirement in their instructions to authors.

Keywords: publication ethics, informed consent, ethics approval

#### Pediatric facial lipoblastoma in the head and neck: case report and review of the literature

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Lipoblastomas remain a rare and clinically perplexing entity in the head and neck. We review a case that presented as a rapidly enlarging periparotid lesion in an infant and review the literature. Retrospective case review. A eight-month old male presented to the Pediatric Otolaryngology clinic with a newly evident small sub-centimeter left sided preauricular lesion initially suspected to be a first branchial cleft cyst. Magnetic resonance imaging (MRI) later revealed a large soft tissue mass with invaginations into the temporalis muscle and parotid gland. Given the large growth elicited from initial presentation to time of imaging, fine-needle aspiration (FNA) was ordered, but inconclusive. Open biopsy was performed consistent with a benign fatty tumor. Given the persistently enlarging size, the patient's family opted for surgical management. En bloc resection of the mass with preservation of the parotid gland was performed without injury to the facial nerve. Pathologic review revealed a lipoblastoma. The child has been followed for three months without recurrence. Facial lipoblastomas are a rare anomaly that can manifest with rapid enlargement in the infant population. Our case's rapid enlargement initiated concerns of malignancy prompting an open biopsy. The Otolaryngologist should be reminded of this rare anomaly when evaluating a child with a rapidly enlarging masses in the head and neck. We present a case report including that of a patient whose lesion's location prompted concerns for facial nerve injury. The treatment of choice for these patients include near complete excision of the lesion while maintaining preservation of associated structures.

**Keywords:** lipoblastom, Magnetic resonance imaging (MRI), fine-needle aspiration (FNA)

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#### Consumer attitude toward health focused interior design

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Environmental impact on health and allergy remains significant. The role of interior design and material selection for health related issues, specifically allergic rhinitis (AR) remain underreported. Moreover, there is lack of data regarding consumer interest in interior design and material selection focused on health for those living in the inner city. This is the descriptive study utilizing a questionnaire to survey inhabitants of prosperous districts in the city of Bangkok. We investigated in 150 people who live the central business district (Silom, Sukumvit, Sathorn, Pathumwan, Thonglor) about their attitude toward health and impact on their spending with regards to dwelling. The questionnaires were conducted via an external surveyor group. The demographic data, budget of interior design and attitude towards design on health concerns were collected. The International Survey of Asthma, Allergy in Childhood (ISAAC) questionnaire was used to evaluate the prevalence of nasal with eye symptoms or nasal symptoms within the past 12 months of diagnosed allergic rhinitis in the surveyed. There were 150 respondents to this questionnaire. 56% were female and 56% of those surveyed were aged < 40 years. 62% of subjects had a family history of health problems. The most common problem reported was allergic diseases. Sixty-five percent reported rhinitis symptoms within the past twelve months. The subjects with rhinitis symptoms including eye symptoms was (37%). Most rhinitis symptoms were reportedly mild. Seventy percent of subjects reported having experience with investing in interior design while willing to invest < less than 100,000 baht for health focused design. The subjects aged > 40 years were willing to pay for health focused design. This was significantly higher than those less than 40. (p < 0.05) The number of people who live in condominiums were higher in the age less than 40 years old group. The subjects aged more than 40 years of age were living in a significantly larger area compared to their younger counterparts. The health expenses were significantly higher in people aged > 40 years of age. The 3 most common attitudes toward interior design focused on health were its effect on health problems, design could prevent illness and personalized design for health issues is an important decision to make when investing in design. The 3 most common customer attitudes who had experience in previous investment in interior design and without experience were not different. The attitudes toward design and design impact on health between the AR and non-allergic rhinitis (NAR) groups were not significantly different. Allergic rhinitis remains a significant health concern. Consumer attitudes toward health focused design is varying. Most over the age of 40 reveal a trend towards interest in health focused design. This age group also have a higher number of health issues, occupy larger areas, and are willing to invest a larger sum of money than their younger counterparts. Further research needs to be done to assess the potential financial impact this attitude could have on the realty market.

**Keywords:** Interior design, decoration, health, allergy

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# POSTER PRESENTATION ABSTRACT

## Prevalence of polymorphisms in antifolate-resistant gene markers *pvdhfr* and *pvdhps* in *Plasmodium vivax* isolates collected in Palawan, Philippines

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The emergence of drug-resistant Plasmodium vivax imposes problems in malaria control and elimination in some parts of the world most especially individuals from developing countries who are routinely exposed to the infection. In this study, single nucleotide polymorphisms (SNPs) in Plasmodium vivax dihydropteroate synthase (pvdhps) and Plasmodium vivax dihydrofolate reductase (pvdhfr) genes which are believed to be involved in sulphadoxine-pyrimethamine drug resistance were determined among P. vivax isolates collected in Palawan, Philippines. Analysis at specific codons I13, P33, F57, S58, T61, S117, and I173 associated with pyrimethamine resistance in the pvdhfr gene revealed that 75.9% (n=66/87) of the samples carried double mutation at position S58R and S117N, while only 18.4% (n =16/87) of the isolates carried the wild-type haplotype. For the pvdhps gene, the codons involved in sulfadoxine resistance S382, A383, K512, A553, and V585 were investigated. Single mutation at position A383G was observed in 68.0% (n =68/100) of the samples, whereas 26 out of the 100 samples (26.0%) harbored the wild-type gene. The observed allele combinations: SAKAV-IPFSTSI (wild-type), SGKAV-IPFRTNI, and SGKAV-IPFSTSI were the most common haplotypes from the three study sites. Of these, Puerto Princesa harbored the highest number of SGKAV-IPFRTNI alleles, while Rizal carried the most number of the wild-type haplotypes detected. This study provides important views on the molecular patterns of sulfadoxine/pyrimethamine resistance and situations on *P. vivax* malaria infection in the Philippines. The observed presence of mutations in the antifolate drug-resistant associated gene markers pvdhfr and pvdhps may impose a major global health problem especially in a developing country such as the Philippines.

**Keywords:** Plasmodium vivax, pvdhfr, pvdhps, antifolate resistance, sulfadoxine-pyrimethamine

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### Impact of genetic and clinical factors on trough to dose ratio of tacrolimus in Thai kidney transplant recipients

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Tacrolimus is a highly effective immunosuppressive drug widely used in kidney transplantation. Prescribing the optimal tacrolimus dose is challenging because of its pharmacokinetic variability. Influences of various clinical factors and genetic polymorphisms of the cytochrome P450 (CYP) 3A5 and CYP oxidoreductase (POR) on tacrolimus pharmacokinetics were reported. The purpose of this study is to determine genetic and clinical factors which impact tacrolimus trough concentration to dose ratio (C<sub>0</sub>/dose) of tacrolimus in stable Thai kidney transplant recipients. Tacrolimus blood concentrations at steady state together with the associated clinical and biological data of 191 Thai adult kidney transplant recipients were collected on Day 90 after their transplantation. Tacrolimus whole blood concentrations at pre-morning dose were measured by chemiluminescent microparticle immunoassay. Age, hemoglobin level, serum albumin concentration, prednisolone dose, and CYP3A5 and POR 28 polymorphisms were tested for possible inclusion in the regression model. The median (IQR) of tacrolimus doses was 4.0 (3.0, 5.0) mg/day or 0.07 (0.05, 0.10) mg/kg/day. The corresponding mean (±SD) of trough concentrations was 6.0 (±2.1) ng/ml and the median (IOR) of dose-normalized trough concentrations was 81.06 (54.34, 122.42) ng/ml per mg/kg/day. The multiple linear regression equation derived by stepwise approach was Log C<sub>0</sub>/dose (in ng/ml per mg/kg/day) = 1.828 - 0.299 (if CYP3A5 expressers) + 0.26 (hemoglobin in g/dl) - 0.478 (prednisolone dose in mg/kg/day);  $R^2$ =0.336 (p<0.001). At 3 months post-kidney transplantation, CYP3A5 polymorphisms, hemoglobin level and prednisolone dose significantly influence dose normalized trough concentration of tacrolimus. These factors should be considered when performing the therapeutic drug monitoring of tacrolimus in stable kidney transplant recipients.

Keywords: CYP3A5, POR, genetic polymorphisms, kidney transplantation, tacrolimus

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### An alternative high performance liquid chromatography with ultraviolet detection for determination of piperaquine in plasma

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The treatment of malaria is becoming increasingly difficult due to *Plasmodium falciparum* resistance to almost all of the available antimalarial drugs including artemisinin derivatives. Piperaquine (1,3bis-[1-(-7-chloroquinolyl-4)-piperazinyl-1]-propane) is a bisquinoline antimalarial drug belonging to the 4-aminoquinoline group. Analysis of piperaquine in human biological fluids is therefore a prerequisite step for dose optimization of piperaquine combination therapy based on pharmacokinetic information in patients with malaria. A simple, sensitive, selective and reproducible method based on liquid chromatography was developed for the determination of piperaquine in plasma samples. Piperaquine was separated from the internal standard mefloquine on a reversed phase C18 column, with the mobile phase consisting of a mixture of acetonitrile, 0.1% trichloroacetic acid, and phosphoric acid (15: 85: 0.035, v:v:v) running at a flow rate of 1.0 ml/min. Retention times of piperaquine and mefloquine were 9.95 and 14.11 min, respectively. Ultraviolet detection was set at the wavelength 354 nm. Sample preparation was done by extraction with 1 M sodium hydroxide and diethyl ether (2:5, v:v). Good precision and accuracy were obtained for both within-day repeatability and day-to-day reproducibility. Limit of quantification (LOQ) for piperaquine was accepted as 10 ng/ml using 500 µl plasma sample. The mean recoveries for piperaquine and internal standard were between 88.8-91.7%.

Keywords: Piperaquine, HPLC, plasma

Efficacy of MAS063DP lotion vs 0.02% triamcinolone acetonide lotion in improving post ablative fractional carbon dioxide laser resurfacing wound healing in atrophic acne scar treatment: A split face, triple-blinded, randomized, controlled trial

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Fractional carbon dioxide (FrCO<sub>2</sub>) laser is effective for atrophic acne scar treatment but the downtime following this procedure is unavoidable. Postoperative topical steroid decreases the risk of this downtime, but in the meantime increases other side effects. The objective of this study was to evaluate the clinical efficacy and safety of the moisturizer containing anti-inflammatory ingredients including 5% panthenol, madecassoside, and copper-zinc-manganese (experimental cream) versus 0.02% Triamcinolone acetonide (TA) cream to improve wound healing and decrease adverse effects and downtime after FrCO<sub>2</sub> laser treatment in acne scar. We conducted a double-blind, split face, randomized controlled trial in 20 subjects, with FrCO<sub>2</sub> laser treatment on both sides of their faces, and randomly treated with these 2 post-treatment regimens on each side of the face for 7 days. We evaluated the result by using the questionnaires, the expert panel assessment of the photography, downtime and side effects evaluated by subjects, and facial scanning by the Antera 3D device. The result revealed that both the experimental cream and 0.02% TA cream significantly decreased postlaser downtime including swelling, redness, crusting and scaling in 5-7 days. Moreover, they produced lower of the PIH incidence when compared with petrolatum from the previous study. There was no significant different of the efficacies to decrease downtime between the experimental cream and the 0.02% TA cream. Hence, the moisturizer containing 5% panthenol, madecassoside, and copper-zinc-manganese yielded comparable efficacies to 0.02% TA cream for the improvement of wound healing, decreased adverse reactions and downtime after FrCO<sub>2</sub> laser irradiation. This moisturizer could be a novel treatment modality for the reduction of post-ablative laser downtime by using non-steroidal anti-inflammatory agents in a bid to avoid adverse effects from steroids and improve wound healing process.

**Keywords:** Panthenol, Madecassoside, Copper-Zinc-Manganese, Fractional ablative laser, Downtime

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#### The potential role of platelet-rich plasma in melasma treatment

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Melasma is an acquired hyperpigmented skin disorder commonly found in Thailand. Despite several treatments for melasma, the results are variable success with certain complications. This study aimed to assess the effectiveness of Platelet-Rich Plasma (PRP) in melasma treatment. Ten female patients with bilateral mixed-type melasma were enrolled in a split-faced, single-blinded prospective trial. PRP was randomly injected intradermally to one side of the face and normal saline to the other side every 2 weeks for 4 times. All patients were instructed to use only the specific moisturizer and cleanser with SPF50 sunscreen applying to both sides of the face in the morning. PRP was prepared by the centrifugation of 13.5 ml collected-blood in YCELLBIO Kit. Then, the injection of PRP 0.1ml/cm2 was performed to the entire melasma area on one side of the face. The subjects were afterwards examined by Mexameter, Modified MASI score, and Antera® 3D Analysis equipment. Patients' self-improvement score was assessed at baseline, 2nd, 4th, 6th week, and 1-month follow-up after the complete treatment protocol. mMASI score of PRP group was significantly changed from baseline to week 10 compared with that of control group, with the mean of  $1.03 \pm 0.44$  (P = 0.042\*). Meanwhile, the improved patients' self-assessment score from baseline was observed at week 2,4,6 and 10 with statistical significance. Though, a significant difference between both regimens did not reveal significant with regard to objective assessments, there are some trends in more reducing pigmentation from PRP than control. Overall, the side-effects were mild and resolved spontaneously within a few days. Hence, the intradermal (ID) PRP could be an adjuvant therapy for melasma. However, larger and longer randomized, double-blinded, placebo-controlled trials are recommended for long-term efficacy and safety.

**Keywords:** Melasma, Melasma Treatment, Platelet-Rich Plasma (PRP)

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#### Antimalarial activity of isolated compounds from Stephania venosa

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Malaria is a fatal infectious disease in tropical and subtropical regions especially along the Thailand-Myanmar and Thailand-Cambodia borders. Effective development of new alternative antimalarial drugs development is urgently required due to the spread of artemisinin resistant *Plasmodium falciparum* in Southeast Asia. The aim of this study was to assess the antimalarial activity of the isolated bioactive compounds from *Stephania venosa*. The phytochemical analysis of the extract was investigated by using HPLC. The *in vitro* antimalarial activities of the bioactive compounds were assessed using SYBR green-I assay. Results revealed that berberine chloride, stephanine and oxocrebanine alkaloids are major components found in *S.venosa*. The median IC<sub>50</sub> values of three bioactives against 3D7 and K1 were less than 10 μg/mL for both clones. The median IC<sub>50</sub> values of stephanine were 2.0 and 2.5 μg/mL, respectively. The median IC<sub>50</sub> values of oxocrebanine were 2.2 and 2.7 μg/mL, respectively. It could be concluded that berberine chloride has the promising antimalarial activity and *in vivo* activity should be confirmed in malaria-infected mouse model.

**Keywords:** Antimalarial activity, berberine chloride, stephanine, oxocrebanine



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#### Neuroprotective effect of Perilla frutescens in vitro

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One of the neuropathologic hallmarks of Alzheimer's disease (AD) is the excess accumulation of amyloid- $\beta$  peptide (A $\beta$ ) in brain. This incident promotes neurotoxic, reduction of synapse, increase neurodegeneration and cell death, leading to loss of cognitive process and dementia. In AD patients, the accumulation of  $A\beta$  including misfolded and unfolded proteins in the endoplasmic reticulum (ER) generate a stress condition, called ER stress, that engages the unfolded protein response (UPR). UPR eliminates the misfolded proteins via protein degradation mechanisms by inducing proteases and chaperone proteins; GRP78/Bip to maintain homeostasis. If resolution fails, pro-apoptotic events are triggered including CHOP activation. The previous study has shown omega-3 fatty acid could suppress ER stress in neurons. Therefore, this study was to investigate the mechanism of dry and fresh leaf extract and seed oil extract of *Perilla frutescens*, which compose of omega 3, to relieve ER stress induced by A\(\beta\). The results have shown that dry and fresh leaf extracts and Perilla seed oil could inhibit Aβ-induced cytotoxic in neuroblastoma cells. The nuclear morphological changes by Hoechst 33342 staining show the characteristics of apoptotic cells. Furthermore, fresh leave extract could reduce GRP78/Bip expression in Aβ-induced ER stress cells, on the other hand dry leaf extract and Perilla seed oil induced the expression of this protein. However, no expression of CHOP protein was induced by any extracts comparing to tunicamycin (Tm), the ER stress inducer. Overall, even though we could not prove clearly whether dry and fresh leaf extract and Perilla seed oil could relieve Aβinduced ER stress in neuroblastoma cells, the therapeutic strategy in ER stress suppression in neurodegenerative disease is becoming interesting. Therefore, further in vitro study on efficiency of Perilla seed oil with high omega 3 in AD treatment should be improved and developed.

**Keywords:** neuroprotective, *Perilla frutescens*, amyloid-β peptide, ER stress

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Validation of a limited sampling strategy to predict mycophenolic acid area under the concentration time curve in Thai kidney transplant recipients

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Mycophenolate mofetil (MMF), a prodrug of mycophenolic acid (MPA), is an antimetabolite immunosuppressant widely used in kidney transplantation. The efficacy of MMF has been proven in reduction of kidney allograft rejection. The target MPA area under the concentration time curve 0-12 hours after MMF dose (AUC) has been suggested at 30-60 mg\*h/L. Various limited sampling strategy (LSS) have been developed to predict measured MPA AUC. We aim to evaluate the equation which was derived from MPA concentrations at 3 different time-points within 2 hours after dose in a Caucasian population during early period post-transplantation and high correlation between predicted and measured AUC was reported by Pawinski et al. ( $r^2=0.862$ ). Seventeen kidney transplant recipients who received a triple maintenance immunosuppressive regimen of tacrolimus plus MMF twice daily and steroid were included in this study. Blood samples at pre-dose and 0.5, 1, 2, 3, 4, 6, 8, and 12 hours after the morning MMF dose were collected on day 3 post-transplantation. Plasma MPA concentrations were measured by fluorescent polarization immunoassay. Measured AUC (AUCm) was calculated by the linear trapezoidal rule. Predicted AUC (AUCp) was estimated by the LSS equation using MPA concentrations at pre-dose ( $C_0$ ), 0.5 hours ( $C_{0.5}$ ) and 2 hours ( $C_2$ ) after dose; 7.75  $+6.49C_0 + 0.76C_{0.5} + 2.43C_2$ . The correlation between AUCp and AUCm was determined. Bias and precision were used to evaluate the predictive performance of the LSS equation. The mean percentage prediction error (MPPE) and the mean absolute percentage prediction error (MAPE) of less than 15% were considered acceptable. The mean ± SD of AUCm and AUCp were 42.59 ± 13.78 mg\*h/L (range: 25.98-69.41 mg\*h/L) and  $48.69 \pm 17.04 \text{ mg*h/L}$  (range: 17.99-79.31 mg\*h/L), respectively. There was a moderate correlation between AUCm and AUCp ( $R^2 = 0.469$ , p < 0.01) with MPPE of 16.29% (95% CI, 0.55 to -32.04) and MAPE of 25.53% (95% CI, 13.73 to 37.33). In conclusion, the correlation between the predicted MPA AUC and the measured MPA AUC was moderate. The equation had high bias and imprecision. An LSS equation with a better predictive performance in predicting MPA AUC during the early period after transplantation is needed for our kidney transplant recipients.

Keywords: AUC, LSS, MMF, MPA, kidney transplantation

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### Efficacy of topical botulinum toxin type A in liposomal cream for treatment of primary axillary hyperhidrosis, a double-blind, randomized, split site, vehicle control study

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The treatment of Primary Axillary Hyperhidrosis (PAH) using traditional needle-based botulinum toxin type A (BTX-A) delivery has been proven to be effective. However, it is mainly associated with adverse events following the injections. BTX-A is water soluble drug with large molecule size and considered as highly resistant to transdermal delivery. Hence, we aimed to evaluate the efficacy of noninvasive pharmaceutical enhancing skin penetration method using multilamellar liposomal beaded capsule of topical BTX-A, which was passively loaded and delivered through epidermal papillae and ductular portion to the sweat gland, in the treatment of PAH. Hence, this research aimed to evaluate the efficacy and safety of BTX-A in multilamellar liposomal beaded capsule cream for the treatment of PAH compared to vehicle cream, a prospective, randomized, double blinded, split site study was conducted in participants, aged 18-50 years with hyperhidrosis severity scale (HDSS) of 2-4. The amount of sweat reduction was evaluated using transepidermal water loss (TEWL) measurement. Thirty units (U) of BTX-A, combined with multilamellar liposomal based cream to bind the toxin, was randomly applied to one axilla and the vehicle without BTX-A to the other axilla once daily before bedtime for seven days. Clinical improvement was evaluated using TEWL, Iodine Starch Test (IST) and HDSS for every 2-week for 8 weeks. Twenty participants, with mean (SD) age of 37.55 (9.41) years, were recruited into the study. Of these, 16 (80%) and 4 (20%) cases were female and male, respectively. The topical BTX-A treated side demonstrated the significant sweat reduction from TEWL (mean (SD.)) than vehicle treated side for 31.19 (5.88) vs 32.21 (6.48) (p=0.242),  $25.43 \pm 4.48$ vs  $33.49 \pm 4.9$  (p<0.001),  $28.39 \pm 4.46$  vs  $34.86 \pm 5.01$  (p<0.001),  $28.94 \pm 5.03$  vs  $36.09 \pm 4.58$ (p<0.001), 34.41  $\pm$  7.84 vs 38.35  $\pm$  8.71(p<0.001) g/m<sup>2</sup>/h, at the base line, 2<sup>nd</sup>, 4<sup>th</sup>, 6<sup>th</sup> and 8<sup>th</sup> week of follow-up, respectively. Moreover, the topical BTX-A treated side demonstrated the significant sweat improvement from clinical grading by panel assessment of IST photography than vehicle treated side for 2.25±0.91 vs 0.75±0.85 (p<0.001), 1.90±1.02 vs 0.40±0.50 (p<0.001), 1.40±0.88 vs 0.30±0.92 (p<0.001),  $0.55\pm0.60$  vs  $-0.20\pm0.77$  (p=0.001), at the base line,  $2^{nd}$ ,  $4^{th}$ ,  $6^{th}$  and  $8^{th}$  week of follow-up, respectively. HDSS score significantly showed a great improvement between the BTX-A treated and the vehicle treated groups (p<0.001) No side effect was observed. In conclusion, 30U of BTX-A inversion with multilamellar liposomal beaded capsule cream could provide statically significant effective treatment outcomes of PAH compared to the vehicle control side from TEWL, the improvement of IST, HDSS with no side effects. Hence, the topical BTX-A in multilamellar liposomal beaded capsule could be an innovative painless and cost effective treatment of PAH.

**Keywords:** Botulinum toxin; Topical botulinum toxin; Axillary Hyperhidrosis

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## Validation and application of a liquid chromatography/tandem mass spectrometry assay for quantification of dihydroartemisinin in plasma of healthy adults

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Dihydroartemisinin (DHA) is a crucial component in Artemisinin-based Combination Therapy (ACT) for treatment of uncomplicated Plasmodium falciparum malaria in Indonesia. Inadequate plasma DHA concentration may select resistance and would subsequently hamper malaria elimination program. The aim of the study was to establish a laboratory readiness in the National Institute of Health Research and Development, Ministry of Health of Indonesia for artemisinin resistance monitoring program through validation and application of a liquid chromatography/tandem mass spectrometry (LC-MS/MS) assay for quantification of DHA in plasma of healthy adults. Samples were prepared by micro-elution solid-phase extraction in 96-wellplate format. Dihydroartemisinin was separated in Acquity UPLC<sup>TM</sup> BEH C18 column (50 × 2.1 mm, 1.7 µm) with mobile phase containing acetonitrile-ammonium acetate 10 mM pH 3.5 (50:50, v/v) at flow rate of 0.3 mL/minute. A triple quadruple mass spectrometer coupled to positive tandem mass spectroscopy was used for detection. A stable isotope-labelled DHA was used as internal standards. Calibration curve over a concentration range of 1.00-1000 ng/mL proved to be linear with correlation coefficient greater than 0.995. Accuracy and precision were within 15% for bias and variation (20% at the lower limit of quantification). Limit of quantification was 1 ng using 5 µL sample. The mean recovery for DHA and the internal standard were greater than 90%. The method was successfully used to analyzed pharmacokinetic samples from five healthy subjects.

**Keywords:** Dihydroartemisinin, LC-MS/MS, malaria

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#### Biomarkers for the diagnosis of cholangiocarcinoma: a systematic review

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Cholangiocarcinoma (CCA) is a highly malignant tumor of the bile duct caused by the liver fluke. Opisthorchis viverrini. It is a major public health problem in many Southeast Asian countries including Thailand. Prognosis of CCA is poor due to its silent characteristics and limited therapeutic measures. Its slow progression makes it difficult for early diagnosis and most patients are detected only in advanced stages. Many studies have attempted to establish potential biomarkers that can be used to diagnose the disease at early stages. However, different biomarkers showed varying capacities in differentiating CCA from other resembling tumors and no single biomarker could be established that could be used in routine practice. This study aimed to review all relevant articles on the biomarkers for diagnosis of CCA and point out the promising candidate biomarkers that can actually be used in clinical setting. A thorough search was done in Pubmed and Science Direct for articles that investigated CCA biomarkers as the main subject and presented results in terms of sensitivity and specificity. Required data were extracted for the types of biomarkers studied and results obtained. A total of 42 articles were selected that fulfilled the inclusion criteria (14 on serum biomarkers, 22 on tissue biomarkers, 1 on bile biomarkers, 4 on both serum and tissue biomarkers and 1 on biomarkers in urine). Carbohydrate antigen 19-9 (CA 19-9) and Carcinoembryonic antigen (CEA), either alone or in combination with other biomarkers, are the most commonly studied biomarkers in the serum. Their sensitivity and specificity ranging from 47.2 to 98.2% and 89.7 to 100% respectively. While in the tissue, gene methylations and DNA related markers were the most studied. Their sensitivity and specificity ranged from 58 to 87% and 98 to 100% respectively. Some articles studied biomarkers in both serum and tissues, particularly CA 19-9 and CEA, and found out that the sensitivity and specificity ranged from 33 to 100% and 50 to 97.7% respectively. Some other biomarkers studied include microRNA, exostosin1, cathepsin, heat shock protein and serum angiopoietin in the serum and human aspartyl, HPC2, WFA, MAP kinases and tight junction proteins in the tissues. Although, many biomarkers that have some role in the early detection of CCA were established, yet it is difficult to single out any particular marker that could be used in the routine clinical setting for diagnosis of CCA. Either a combination of markers or other laboratory tests might have to be applied in order to confirm the diagnosis. Nevertheless, the use of biomarkers could be helpful as a screening tool for those people who are at risk of infection, in specific areas.

Keywords: Cholangiocarcinoma, bile duct cancer, Klatskin tumor, diagnosis, markers

#### Cytotoxic and apoptosis inducing activities of β-eudesmol against cholangiocarcinoma cell line

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Cholangiocarcinoma (CCA) is a form of bile duct cancer that has high mortality rate, particularly in Thailand.  $\beta$ -Eudesmol, a compound isolated from *Atractylodes lancea* (Thunb) DC. has been shown to exhibit promising activity against CCA both *in vitro* and *in vivo*. The aim of this study was to further evaluate the mechanisms through which the compound exerts its anti-CCA activity. The CCA cell line (CL-6) was exposed to  $\beta$ -eudesmol at various concentrations. Cytotoxicity and apoptosis inducing activity were investigated using MTT assay and flow cytometry, respectively. Western blotting was performed to assess STAT1/3 activation and heme oxygenase-1 (HO-1) production in CL-6 cells. The results demonstrated that the IC<sub>50</sub> (concentration that inhibits cell growth by 50%) of  $\beta$ -eudesmol in CL-6 was 39.33±1.15  $\mu$ g/mL (mean±SD) and cell cycle arrest was observed at the G1 phase. Moreover,  $\beta$ -eudesmol potently induced cell apoptosis at 48 h after exposure. Inhibition of protein activation of both STAT1 and STAT3 by suppressing the STAT phosphorylation was observed in a concentration-dependent manner.  $\beta$ -Eudesmol exposure also inhibited HO-1 expression in CL-6 cells in a time-dependent manner. The results suggest that  $\beta$ -eudesmol holds therapeutic potentials and demands further in-depth studies on its mechanisms of action.

**Keywords:** β-eudesmol, *Atractylodes lancea*, cholangiocarcinoma, cell cycle arrest, cell apoptosis

#### Biomarker screening from plasma of cholangiocarcinoma patients using proteomics approach

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Cholangiocarcinoma (CCA) is the cancer of bile duct arising from epithelial cells and develops along the biliary tree. Control of this type of cancer is unsatisfactory due to limitation of efficient early diagnostic tool and effective treatment. The aim of the study was to investigate the potential candidate biomarkers for diagnosis of CCA. Differential changes in the levels of protein expression in plasma samples obtained from CCA and non-CCA patients were analyzed using proteomics approach. A total of 4,173 proteins were separated from 40 samples (20 each of the CCA and non-CCA plasma samples) by gel-based and LC-MS/MS. Six and 21 proteins were found only in CCA and non-CCA plasma samples, respectively. Calmodulin-like protein (gi|4885111) which was detected only in the CCA samples was identified for its role in heterotrimeric G-protein signaling pathway-rod outer segment phototransduction (P00028) pathway. The silencing mediator of retinoic acid and thyroid hormone receptor alpha (gi|4885111) which was detected only in non-CCA samples was identified for its roles in notch signaling pathway (P00045) and huntington disease pathway (P00029). Four candidate proteins were identified as potential biomarkers for CCA, *i.e.*, calmodulin-like protein 3, coiled-coil domain-containing protein 158, ring finger protein 130, isoform CRA\_c, and the long-chain-fatty-acid--CoA ligase 5 isoform a.

**Keywords:** cholangiocarcinoma, proteomics, biomarkers, LC-MS/MS

## Elevated urinary 20-HETE levels link cadmium exposure to tubular dysfunction and hypertension among women in a high-exposure area (Mae Sot) in Thailand

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Cadmium (Cd) exposure through food contamination is a common problem worldwide. The most frequently reported adverse health effect of Cd exposure is injury to kidney proximal tubular epithelium. This nephron segment plays an indispensable role in blood pressure control. Cytochrome P450 (CYP) enzymes, such as CYP4A11 and CYP4F2, are expressed in renal tubular epithelial cells and, in turn, produce 20-hydroxyeicosatetraenoic acid (20-HETE), which is involved in salt balance in the kidney. In vascular smooth muscle cells, 20-HETE is known to be a local vasoconstrictor and thus is pro-hypertensive. Epidemiologic studies have provided evidence linking tubular Cd toxicity to development of hypertension, but pathogenic mechanisms have not yet been defined. The objective of the study was to investigate the association between cadmium exposures, urinary 20-HETE levels, blood pressure and kidney function and toxicity in non-occupationally exposed populations. A group of Thai women with hypertension (n, 110), aged 33-55 years (mean 47.2 years) and age- and localitymatched normotensive controls (n, 115) were recruited from cadmium-exposed population in Thailand's Mae Sot District, Tak Province. Urinary and blood Cd were measured for each person. Kidney toxicity was assessed by urinary excretion of albumin, N-acetyl-beta-glucosaminidase (NAG) and  $\beta_2$ -microglobulin ( $\beta_2$ -MG). Kidney function was evaluated with estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula. A stepwise, multivariate regression and logistic regression were used to evaluate the relationships between exposure indicators, urine 20-HETE levels, blood pressure, estimated kidney function, and toxicity biomarkers. Urinary 20-HETE levels showed a positive association with urinary Cd levels (β=0.414, P<0.001). Urinary 20-HETE levels ≥469 pg/ml were associated with an increased risk of kidney toxicity (prevalence odds ratio 1.89 [95% CI 1.04, 3.45], P=0.04). Association between urinary 20-HETE levels and systolic blood pressure (β=0.218, P=0.041) was apparent in the normotensive group. High blood pressure was associated with kidney injury ( $\beta$ =0.154, P=0.018) and kidney function deterioration ( $\beta$ =-0.129, P=0.041). These data suggest Cd exposure may enhance renal production of 20-HETE, which appears to especially affect systolic blood pressure. Exposure to dietary Cd could thus be a risk factor in the development of hypertension.

**Keywords**: Albuminuria; Blood Pressure;  $β_2$ -Microglobulin; Cadmium; Cytochrome P450 enzymes; 20-Hydroxyeicosatetraenoic acid; 20-HETE; Hypertension; Kidney function; *N*-acetyl-β-D-glucosaminidase

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### Phytochemistry and toxicity of crude water soluble extract of *Tradescantia fluminensis* in wistar rats

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Tradescantia fluminensis is used as an alternative treatment in Thai traditional medicine for renal failure. Information on its toxicity and phytochemical properties have been limited. The aim of the study was to investigate phytochemical constituents and toxicity (acute and subacute) of the crude water-soluble extract of *T. fluminensis* in Wistar rats. For acute toxicity, the extract was administered orally at the highest starting dose level (5,000 mg/kg body weight) and signs of toxicity were observed during the first 30 minutes, periodically during first 24 hours, and then daily for 14 days. For subacute toxicity, the extract was given at the daily oral dose of 1,000 mg/kg body weight for 28 days and signs of toxicity were observed daily. The phytochemical constituents (phenols, flavonoids, anthocyanins, triterpenes/steroids, alkaloids, anthraquinones, coumarin, saponins, quinone, tannins, sugar, proteins and amino acid, glycosides, fat and essential oil, and phloroglucinol) of the extract were determined based on color intensity or precipitate formation. Results of toxicity testing revealed good tolerability profile of the extract with no significant sign of toxicity; no animal died during the observation period. The major constituents of the extract included phenol, tannins, and saponins.

**Keywords**: *Tradescantia fluminensis*, phytochemical screening, acute toxicity, subacute toxicity, crude extract

Clinical efficacy of 0.5% topical mangosteen extract in nanoparticle loaded gel compared with 1% clindamycin gel in treatment of mild to moderate acne vulgaris: a 12-week, split face, double-blinded, randomized, controlled trial

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Propionibacterium acnes (P.acnes) are involved in all stage of pathogenesis of acne and the resistance strains of P.acnes currently becomes the concerning problem. 0.5% (w/w) mangosteen nanoparticle loaded gel (MNLG) containing alpha-mangostin, a xanthone derivatives from mangosteen fruit rind extract, with anti-inflammatory, anti-oxidant, and anti-microbial properties. Hence, this extract could be a treatment option for acne vulgaris. We aimed to evaluate the efficacy of MNLG compared with 1% clindamycin gel in treatment of acne vulgaris. Mild to moderate acne vulgaris patients, aged 18-40 years, were enrolled in this double-blinded, split-face, randomized, control study. 2.5% benzoyl peroxide was applied to both sides of the face once daily for 5 minutes and washed off, before being randomized for MNLG and 1% clindamycin application onto either the left or the right side of their faces twice daily for 12 weeks. Treatment efficacies were evaluated using both clinical and biometric measurement. Twenty-eight patients, 24 female (85.7%) and 4 male (14.2%), with Global Acne Grading system score of 15.43 + 5.96 were included with mean  $\pm$  SD age were  $25.14\pm5.8$ . In the MNLG treatment group, there was a significant improvement from baseline to the week 12 with the reduction comedone count from  $6.07 \pm 5.52$  to  $2.24 \pm 1.92$  (p = 0.001), and the significant reduction of inflammatory lesion counts from  $18.32 \pm 13.45$  to  $6.8 \pm 6.34$  (p < 0.001), with the statistical difference since 2 weeks after treatment, but no statistical difference from clindamycin treated side. The expert panel assessment of clinical improvement revealed the improvement of clinical severity score from the median (IQR) of 2.33 (2, 2.83) to 1.33 (1, 1.67), (p < 0.001). Post acne erythema (PAE) evaluated by biometric measurement significantly noted the decrease of hemoglobin index from 1.51 to 1.44, (p < 0.001) at 12 weeks. The expert panel porphyrin severity grading identified the significant reduction of porphyrin from 2.61 (0.58) to 1.27 (0.35), (p < 0.001), with no statistical difference from clindamycin. Hence, MNLG yielded significant efficacies in the treatment of acne comparable to 1% clindamycin gel for the improvement of comedone, inflammatory lesion count, clinical evaluation, porphyrin and PAE after 12 weeks. Hence, MNLG could be an option of herbal medication in treatment of acne following its anti-inflammatory, anti-oxidant, and anti-microbial properties to prevent the overuse of topical antibiotics in acne patients.

**Keywords**: *Garcinia mangostana*, Alpha-mangostin, Mangostin fruit rind, Nanoparticle, Acne vulgaris, Herbal medication

# Potential biomarkers between Burkholderia pseudomallei wild type and its rpoN2 mutant strain using MALDI-TOF mass spectrometry application

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Melioidosis is a disease infected by Burkholderia pseudomallei, which is a motile, Gram-negative bacillus. It can survive under various environmental stress conditions and invade to several kinds of host cells, including phagocytic and non-phagocytic cells. Previous studies have been reported that this bacterium can switch colony morphology under starvation, which is classified into seven types. The rpoN2 mutant strain has been constructed and shown its importance to control some virulent genes. In our experiment, B. pseudomallei wild type and rpoN2 mutant were cultured on Ashdown's agar for observing colony morphology changes and used the whole-cell matrix-assited laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS) to identify biomarkers. This technique is currently used as a rapid tool for discovering the unique biomarkers in biological samples. The results showed that colony morphology of the rpoN2 mutant was similar to the parental strain as well as the protein profiles obtained from whole-cell MALDI-TOF MS. In addition, we also demonstrated the potential seven candidate biomarkers mass ions at m/z 3,519, 3,689, 4,158, 6,323, 7,435, and 7,650 for discriminating these two strains. Therefore, our present study shows that the mutated rpoN2 gene slightly affects the changes of colony morphology compared to wild type, resulting in similar colony appearances. However, whole-cell MALDI-TOF MS still has ability to provide the efficient candidate biomarkers for differentiating these two strains.

**Keywords:** Burkholderia pseudomallei, rpoN2, colony morphology, whole-cell MALDI-TOF MS

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#### MCP-1-2518 polymorphisms in Thai population

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The monocyte chemoattractant protein-1 (MCP-1) is one of the key chemokines that regulate migration and infiltration of monocytes/macrophages. Polymorphisms of this gene at the amino acid position 2518 has been reported to be associated with malaria disease severity. This preliminary study investigated the frequency of the polymorphic MCP-1-2518 [A>G (rs1024611)] in Thai population residing in areas along the Thai-Myanmar border, Tak province of Thailand. Sixty-three blood samples were collected from patients with *Plasmodium falciparum* malaria. Genomic DNA was extracted and amplified by Polymerase Chain Reaction (PCR) followed by Restriction Fragment Length Polymorphism (*RFLP*) using PvuII enzyme. The restriction sizes of the polymorphic gene were as follows: A/A (940 bp), G/G (650, 290 bp), and G/A (940, 650, 290 bp). Of the 39 samples (61.9%) with successful gene amplification, 21(53.85%), 9(23.08%) and 9(23.08%) samples were genotypes as G/A, G/G and A/A, respectively. Analysis of the association between MCP-1 genotypes and malaria disease severity in larger number of patients is underway.

Keywords: MCP-1-2518, Polymorphisms, malaria, PCR, RFLP-PCR

Combined loading of ticagrelor and clopidogrel and platelet inhibition in patients with acute ST segment elevation and high risk non ST-segment elevation myocardial infarction undergoing percutaneous coronary intervention

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Platelet reactivity during percutaneous coronary intervention (PCI) in patient with ACS is associated with early and long term outcome. Whether combined loading of ticagrelor and clopidogrel has better platelet inhibition compared to clopidogrel alone in this clinical setting is not known. We aim to assess effect of loading of ticagrelor plus clopidogrel and clopidogrel alone-on platelet inhibition in patients with acute ST-segment elevation (STEMI) and high-risk non ST-segment elevation myocardial infarction (NSTEMI) undergoing PCI within 2 hours. Clopidogrel-naive patients with acute STEMI or high-risk NSTEMI who were undergoing PCI were enrolled to this study after giving informed consent. After randomly assigned to one of antiplatelet loading strategies before PCI; group A (ticagrelor 180 mg plus clopidogrel 600 mg) or group B (clopidogrel 600 mg), all patients received conventional dose of 325-mg aspirin and maintenance dose of 75 mg/d of clopidogrel. Clinical and laboratory data were obtained. Blood test for platelet reactivity was performed using the VerifyNow P2Y12 assay at 0, 2 hours after antiplatelet loading. There were 5 patients in group A and 4 patients in group B. Median door-to-balloon time in each group were 110 and 133 minutes, respectively. Mean platelet reactivity at 2-hour after P2Y12 inhibitors ingestion, after excluding one patient who vomited study drugs, was significantly lower in group A than in group B (97.3 vs. 282.25 PRU, p-value =0.001) No immediate vascular complication was observed during index hospitalization of each patient. Outpatient 30-day follow-up of all patients showed one case of cerebral infarction and two cases of minor GI bleeding in group B while no cardiovascular event or clinical bleeding occurred in group A. Combined loading of ticagrelor and clopidogrel had significantly better platelet inhibition than clopidogrel loading alone in patients with acute STEMI and high risk NSTEMI undergoing PCI.

**Keywords:** Ticagrelor, Clopidogrel, STEMI, High risk NSTEMI, Percutaneous coronary intervention, Platelet function test

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#### Clinical practice of using the Xpert MTB/RIF assay at Thammasat university hospital

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Thailand is classified by World Health Organization as one of the highest countries with tuberculosis (TB) burden. Early detection of patients with TB could bring a good control of a disease. Nevertheless, the existing diagnostic methods of TB remained to be insensitive (AFB smear microscopy) and long turn around time (TB cultures). The Xpert MTB/RIF Assay is a novel rapid molecular diagnostic test for the detection of M. tuberculosis (MTB) complex and Rifampin (RIF)resistance gene. It is a qualitative, automated, real-time polymerase chain reaction (PCR) in vitro diagnostic test for detection of MTB-complex DNA in sputum (in both smear positive and negative) and at the same time, detecting the RIF-resistance associated mutations of the rpoB gene with in less than 2 hours. The Xpert MTB/RIF assay intends to aid the diagnosis of pulmonary TB, using in conjunction with other clinical and laboratory findings. We performed a retrospective review on results of the Xpert MTB/RIF assay (at Pathum Thani Hospital), TB cultures and MTB/NTM test (real-time PCR at Faculty of Allied Health Science, Thammasat University) on expectorated sputum samples from patients with suspected TB at Thammasat University Hospital (TUH) during January 2016 and March 2017 (15 months). Patients' clinical characteristic and criteria for using Xpert MTB/RIF assay based on Reach-Recruit-Test-Treat-Retain: RRTTR project (Stop TB and AIDS through RRTTR: STAR, the Global fund and Ministry of Health Thailand) were determined. Positivity rate of MTB complex detection with RIF resistance gene detection using Xpert MTB/RIF assay, TB culture and MTB/NTM PCR test were compared. Of 533 sputum specimens tested, 9 patients had positive AFB smear and 524 patients had negative AFB smear. Abnormal chest X-ray (31.71%), extra-pulmonary TB (30.39%), diabetes (9.76%) and HIV infection (7.88%) were common criteria for testing. In sputum samples with positive AFB smear, positivity rate of Xpert MTB/RIF assay, TB culture and MTB/NTM PCR test were 100% (9/9), 50% (2/2) and 100% (1/1), respectively. In sample samples with negative AFB smear, positivity rate of Xpert MTB/RIF assay, TB culture and MTB/NTM PCR test were 12.97% (68/524), 6.54% (10/524) (P = 0.03) and 6.41% (5/78) (P = 0.03), respectively. RIF-resistance genes were detected in only 2 sputum samples. In summary, Xpert/RIF assay has significantly increased positivity rate in negative AFB smear samples. Our data emphasize the benefit of real-life clinical practice of using rapid molecular diagnosis for active TB detection in Thailand.

**Keywords:** Tuberculosis, Rifampin resistance, PCR, molecular diagnosis

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### Study the wisdom of folk healers in four regions of Thailand using herbs *Bauhinia strychnifolia* Craib

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Yanang Daeng (Bauhinia strychnifolia Craib.) is the medicinal plant which has popularly used in Yasothon province more than 50 years ago. Even though, Yanang Daeng was used for a treatment of poisoning, elimination of pesticides, an effect of poisonous mushrooms, alcohol poisoning, breast milk stimulation in women after delivery, promotes health, nourishment and reduce fatigue, the systematic and comprehensive data which is useful in health promotion system still lacked. Therefore, study aimed to gather the knowledge and experience from the folk healers, herbal growers or seller about the usage of Yanang Daeng. This study was conducted using in-depth interview and group discussions from folk healers (doyen), herbal growers or sellers in four sectors throughout Thailand including Yasothon, Lampang, Prachinburi and Songkhla province. The results showed that the number of folk healers (doyen), herbal growers or sellers was found to be 59 people from 3 sectors which consisted of 67.80% male and 32.20% female. Furthermore, the age of the participants was studied and the results showed that they aged ranged among 61-80, 41-60, 20-40 and more than 81 years old which respectively accounted for 49.15%, 30.51%, 13.56% and 6.78%. More than this, the research also found that the folk healer from Northern has a continuously experience in term of usage of Yanang Daeng and also invariably passed on knowledge to the student. The Northern folk healers from Thin district (Lampang province), Hang Dong district (Chiang Mai) and Saraphi district (Chiang Mai) told that the most of Yanang Daeng which transported into the market was collected from the local forest. In addition, the report from Lampang Herbal Protection Club has focused on the distribution of herbal products for medicinal use of Yanang Daeng which was not only used to cure insecticides, insect bites, poisonous mushrooms or mollusk, alcohol-drugs poisoning, dysfunction in postpartum women with fatigue, anorexia and lack of milk, but also used in pets or farming animals by using leave, stem and root as milk stimulant. For the treatment of patients who receive the toxins, some folk healers will grind the root with water or water from washing rice, then the patient will be immediately received a single dose portion of 2 tablespoons, but the others will boil the leave and stems (fresh or dry) and give the patient a single dose portion range from ½ to 1 glass. In emergency case, they will use 10 fresh leaves, then squeeze with water or water from washing rice, and immediately give to patient as a potion. Moreover, the folk healers recommended to the villager that they should use leaves rather than using vine or root to prevent the extinction of Yanang Daeng and also suggested them to plant Yanang Daeng near their household for convenient use. In conclusion, Yanang Daeng is potent in solving the urgent poisoning problem in the community before receiving further treatment.

Keywords: Bauhinia strychnifolia Craib., Yanang Daeng, wisdom

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#### Cytotoxic activity and inducing effect of plumbagin on cholangiocarcinoma cell apoptosis

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Cholangiocarcinoma (CCA) is a cancer that arises from the epithelial cell of the bile duct both inside and outside the liver. CCA is an important public health problem in several parts of Southeast Asia particularly in the northeastern region of Thailand. Plumbagin (5-hydroxy-2-methyl-1,4-naphthoquinone) is a major constituent isolated from the root of *Plumbago indica* Linn. The compound has been shown to exhibit a wide spectrum of pharmacological activities. The aim of the study was to investigate the cytotoxic and apoptosis inducing activities of plumbagin on the human CCA cell line CL-6. Based on results of the cytotoxicity testing using MTT assay, mean (+SD) IC50 (50% inhibitory concentration) of plumbagin was  $24 \pm 3.3 \, \mu M$ . The compound induced CL-6 cell apoptosis with chromatin condensation and nuclear fragmentation compared with untreated cell.

Keywords: Cholangiocarcinoma, Plumbagin, Apoptosis

### Antiviral and anti-inflammatory activities of α-mangostin from Garcinia mangostana Linn. against dengue virus

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Dengue virus (DENV) infection is a global public health problem. The severity of disease in the patients with dengue infection correlates with high viral load and excessive immune activation which creates a cascade of cytokine production called "cytokine storm". Currently, neither a preventive vaccine nor an effective therapeutic agent is available for DENV infection. Inhibition of DENV and cytokine production would be one strategy to obtain therapeutic effect for DENV infection. In this study, the antiviral and anti-inflammatory activities of α-mangostin (α-MG) from Garcinia mangostana Linn. against DENV infected HepG2 cells were investigated by determining its effect on cell infection rate, viral production, and cytokine/chemokine expression following infection of the cells with dengue virus. Results showed that  $\alpha$ -MG effectively inhibited DENV in the infected cells. Treatment of DENV infected cells with α-MG significantly reduced cell infection rate and the release of virus into the culture supernatant. Furthermore, α-MG effectively reduced cytokine (IL-6 and TNF- $\alpha$ ) and chemokine (RANTES, MIP-1 $\beta$ , and IP-10) transcription. The inhibitory activities of  $\alpha$ -MG on cytokine/chemokine gene expression was more potent than that of the antiviral drug ribavirin and the anti-inflammatory drug dexamethasone. α-MG could be a promising compound for further development as antiviral candidate against DENV infection. Its potent anti-inflammatory activity would also support the anti-DENV activity.

**Keywords:** Dengue Virus, α-Mangostin, Antiviral, Anti-Inflammatory, Cytokine, Chemokine



# Effects of active targeting nanoparticles delivering chemotherapeutic drugs and traditional medicines in cancer therapy: systematic review

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Most of cancer patients are treated with chemotherapeutic drugs and suffered from side effects of the drugs because of non-specific of chemotherapeutic drugs to the cancer cells. Moreover, poor water solubility and pharmacokinetic profiles of the drugs and chemotherapeutic drug resistance can cause treatment failure. For the past decades, nanoparticles are extensively developed as drug delivery system of various chemotherapeutic drugs to increase efficacy and safety of the drugs and to overcome chemotherapeutic drug resistance. Active targeting nanoparticles which are conjugated targeting ligands of cancer cells on the surface of nanoparticles play an important role to increase specificity of the drugs to the cancer cell and enhance cellular uptake by receptor-mediated endocytosis. Nowadays, several traditional medicines or natural active compounds have been found anticancer activities and also delivered by active targeting nanoparticles. Here, this review present the effects of active targeting nanoparticles loading chemotherapeutic drugs and traditional medicines in cancer therapy. Literature search was conducted through PUBMED database search until March 2017 with term - nanoparticle, chemotherapy, traditional medicine, herbal medicine, natural medicine, natural compound, cancer treatment, and active targeting. There are 61 articles were included to extract according to inclusion and exclusion criteria from total 695 articles. The targeting ligands conjugated on the surface of nanoparticles are carbohydrates/polysaccharides, proteins/peptides, folic acid, antibody/antibody fragment, aptamer and hyaluronic acid. All studies showed that active targeting nanoparticles of chemotherapeutic drugs or traditional medicines increase specific-cellular uptake and/or cytotoxicity in vitro compared to non-targeted nanoparticles that lead to higher drug accumulation in the cancer cells. And in vivo tumor growth inhibition activities were also found to be greater in active targeting nanoparticles with low side effects to the normal cells. Active targeting nanoparticles presented various advantages to enhance efficacy and safety of chemotherapeutic drugs and traditional medicines in vitro and in vivo. However, further study in clinical still needed to investigate the effects of active targeting nanoparticles of chemotherapeutic drugs and traditional medicines in cancer patients.

**Keywords:** Nanoparticle, Chemotherapy, Traditional medicine, Cancer treatment, Active targeting

## Genetic polymorphisms of *mdr*1 and *bcrp* (*abcg*2) genes in Burmese patients with *Plasmodium* falciparum malaria

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Polymorphisms of the two genes MDR1 (multidrug resistance-1) and BCRP (breast cancer resistant protein)/ABCG2 (ATP-binding cassette sub-family G member 2) which encode transport proteins were investigated in 134 Burmese patients with acute uncomplicated *Plasmodium falciparum* residing in malaria endemic area along the Thai-Myanmar border using PCR-RFLP. The frequencies of MDR1 C1236T genotypes were 76.7% (CC) and 23.3% (CT). For MDR1 G2677T SNP, genotype frequencies were 7.9% (GG) and 92.1% (TT), whereas for MDR1 C3435T SNP, genotype frequencies were 13.0% (CC), 80.2% (CT) and 6.8% (TT). The frequencies of BCRP G34A genotype were 40.6% (GG), 48.5% (GA) and 10.9% (AA), whereas the frequencies of BCRP C421A genotype were 8.6% (CC), 31.2% (CA) and 60.2% (AA). Information on MDR1 and BCRP gene variants is useful for further analysis of the relation with treatment response with antimalarial drugs in this group of patients.

**Keywords**: Genetic polymorphism; drug transporter genes: MDR1 and BCRP; acute uncomplicated *Plasmodium falciparum* malaria

### Digital ischemia following carbon dioxide laser and tourniquet for digital procedure in elderly patient with atherosclerosis risk factors

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Digital tourniquet with/without epinephrine is commonly used in local anesthetics when operating on digits. However, the complications such as digital ischemia could occur following tourniquet application. We reported an elderly patient with atherosclerotic risk factors underwent digital tourniquet, partial nail plate removal and carbon dioxide laser treatment for subungual wart that developed digital gangrene. The successful treatment consisting of wound-dressing, oral and topical antibiotics, aspirin, isosorbide dinitrate ointment and red low level energy laser therapy resulted in almost complete recovery of skin color and function of the digit in 3 months. It is emphasized that in the elderly patient with atherothrombosis, the digital tourniquet should be cautiously applied under minimal pressure and appropriate duration of time, to prevent the vascular complications of the digit.

Keywords: finger tourniquet, safety, phalangeal surgery, digital ischemia

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### The effect of cultivated area, extraction solvents, and each part of *Bauhinia strychnifolia* Craib on cytotoxicity

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Bauhinia strychnifolia Craib or Ya-Nang-Daeng in Thai is mainly found in North and Northeast of Thailand. It is widely used to detoxify food toxicity. It had been also reported that ethanol extract of Ya-Nang-Daeng has highest antioxidant activity. However, its cytotoxity has not been elaborately studied. Therefore, in this study we try to explore more effective and safety way of using Ya-Nang-Daeng extract. The results showed that Ya-Nang-Daeng extracts from Yasothorn and Nakornpathom Provinces had different finger print patterns, especially, Leaf extract. Moreover, the amounts of Quercetin, which is a common antioxidant in Ya-Nang-Daeng extract, were significantly different among the extracts regardless of cultivated areas. The amounts of Ouercetin in the extracts from high to low were Leaf (Ethanol) extract, Stem (Ethanol) extract, Leaf (Water) extract, and Stem (Water) extract, respectively. In addition, the antioxidant activity was proportion to Quercetin amount in the extract. The results from cytotoxicity test in SH-SY5Y cells, a neuroblastoma cell line, showed that Stem extracts were very toxic to the cell more than Leaf extracts. Cytotoxicity of the extracts from high to low were Stem (Ethanol) extract, Stem (Water) extract, Leaf (Ethanol) extract, and Leaf (Water) extract, respectively. In conclusion, Leaf (Ethanol) extract had highest antioxidant activity corresponding to Quercetin amount in the extract and this activity did not depend on cultivated area. Stem extracts had higher cytotoxicity effect than those of Leaf extract. The amount of extracts that elicited no cytotoxicity should be lower than 100 ug/ml for Leaf (Ethanol) extract; 50 ug/ml for Leaf (Water) extract; 25 ug/ml for Stem extracts.

Keywords: Bauhinia strychnifolia Craib, cytotoxicity

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### Charaterization of G6PD deficiency variants in primaquine treated- *Plasmodium vivax* population along Thai-Myanmar border

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Primaquine (PQ), an 8-aminoquinolines, has been the only generally available hypnozoitocidal and schizonticidal anti-malarial drug for the radical cure of *Plasmodium vivax* infection. The main adverse effect of primaquine is hemolytic anemia in individual glucose-6-phosphate dehydrogenase (G6PD) deficiency. G6PD deficiency mostly caused by difference single base missense mutations and the variation of G6PD deficiency effect severity of hemolytic anemia in primaquine treated malaria patients. The purpose of this study was to determined G6PD deficiency variants in *Plasmodium vivax* patients who received primaquine drug regimen and living in malaria endemic area along Thai-Myanmar border. A total of 100 P. vivax isolates collected from endemic areas along the Thai-Myanmar border were analyzed using polymerase chain reaction and restriction fragment length polymorphism (PCR/RFLP). Three specific primers of each G6PD deficiency variants mostly found in Thailand and Myanmar were investigated including Mahidol variants (487G>A), Chinese-4 variants (392G>T), and Viangchan variants (871G>A). Five percent of isolates were identified as G6PD deficiency with Mahidol variant. The coexistence might be related to high hemolytic risk in malaria patients leading to severity due to insufficient of G6PD enzyme. No Chinese-4 and Viangchan variants were found. Dosage regimen of primaquine for treatment of Plasmodium vivax malaria in Thai-Myanmar border may need to be optimized, based on G6PD variants information. With this limited G6PD variants, other variation of G6PD should be required to obtain accurate genetic mapping of G6PD variants in Burmese and Thai population residing in malaria endemic areas along Thai-Myanmar boder.

**Keywords:** Plasmodium vivax, Primaquine, Glucose-6-phosphate dehydrogenase (G6PD) deficiency

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# CYP2C9, CYP2C19, CYP2D6, CYP3A5 polymorphism in East Asians and South East Asians: systematic review

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Genetic Polymorphism is one of the factor responsible for the inter-individual and interethnic variability in drug response. Many studies in major populations like Caucasians, Asians and Africans has shown evidence of differences in the genotype frequency of major drug metabolizing Cytochrome P450 enzymes. The objective of this systematic review was to compare the genotype frequency among Asians particularly among East Asians and South Asians. We conducted a systematic review of studies published using Pubmed database. We identified 13, 15, 9 and 7 studies for CYP2C19, CYP2C9, CYP2D6 and CYP3A5 respectively in Chinese, Japanese, Koreans, Taiwanese, Malaysians, Philippines, Singaporeans, Vietnamese, Thai and Burmese populations. Interethnic differences in the genotype frequency of CYP2C19, CYP2C9, CYP2D6 and CYP3A5 are comparable among the 10 populations of East Asians and South East Asians. These populations share common ancestry and sufficient number of studies has predicted comparable result but no systematic review of these most prevalent polymorphic drug enzymes.

Keywords: Genotype frequency, CYP2C19, CYP2C9, CYP2D6, CYP3A5, Asians

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### Systematic analysis on the application of statistical tools for data analysis in cholangiocarcinoma research in Southeast Asia

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Statistics is one of the important tools for data analysis in the publication process of all types of research including health sciences research. While the number of research publications has been increasing, the number of research articles with misuse or inappropriate use of statistical methods has also been increasing. The objective of the study was to apply systematic analysis approach to summarize research articles relating to cholangiocarcinoma (CCA), the bile duct cancer, including the application of statistics for data analysis. Misuse and/or misinterpretation of statistics in the research articles were also identified. The research articles conducted in the ten Southeast Asian countries during the year 2010-2015 were retrieved from PubMed database and were classified into seven scientific disciplines based on the predefined inclusion/exclusion criteria. Results showed that of the 369 articles, Thailand was the country of which CCA-related research articles were most published (342 articles, 93%). Disease diagnosis, biology/biochemistry, and pharmacology constituted the three main research disciplines. Two hundreds and seventy-nine (75.61%) articles applied both descriptive and inferential statistics for data analysis. Misuse or inappropriate use or unclear application of statistical analysis procedure in these articles was further identified as: no information provided regarding sample size estimation procedure (87.93%), unclear statistical hypothesis (one-tailed or two-tailed) (74.61%), unclear data distribution (no normality test) (58.20%), lack of information provided regarding the statistical significance level used (a) (10.22%), and inappropriate data presentation (7.12%). Regarding statistical tests applied, three main statistical tests were t-test (20.42%), chi-square test (15.24%), and survival analysis (12.80%). Misuse (inappropriate data presentation) of each test accounted for 7.14%, 8.51% and 5.06%, respectively.

Keywords: Systematic review, Statistics, Cholangiocarcinoma, Research articles

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### K13 propeller domain mutations in *Plasmodium falciparum* isolates collected from Thai-Myanmar border area in 2006-2010

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The K13 propeller domain mutation has been proposed as a useful molecular marker for detection and monitoring of artemisinin resistant *Plasmodium falciparum*. Genomic DNA of *P. falciparum* isolates was extracted from 243 dried blood spot or whole blood samples collected from patients with uncomplicated falciparum malaria residing in areas along the Thai-Myanmar border during 2006-2010. Nested PCR and sequencing were performed to detect mutations in K13 propeller domain of *P. falciparum* at codon 427-709. Thirty-seven out of 243 (15%) *P. faciparum* isolates carried each of the 23 single nucleotide polymorphisms. Amino acid variants were detected with low prevalence (0.4-3.3%). Seventeen mutations had previously been reported elsewhere and 6 mutations were newly detected. The C580Y was found in 2 isolates (0.8%). Double mutations were found in 3 isolates (1.2%) at codons F446I + R529K, F446I + E455K, and F451I + E567D, respectively. The F446I and N458Y mutations were predominantly detected in the isolates collected in 2007 and 2009, respectively, while P574L mutation was detected in the isolates collected during 2006-2010. Common K13 mutations previously been reported in the areas along the Thai-Myanmar border were detected in this study with low prevalence. It needs to be confirmed whether the observed new and double mutations in these *P. falciparum* isolates are linked with clinical artemisinin resistance.

**Keywords:** Plasmodium falciparum, artemisinin resistance, K13 gene, PF3D7\_1343700, sequencing



#### Cellular mechanisms of action and resistance of *Plasmodium falciparum* to artemisinin

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The recent reports of high failure rates and decline in in vitro sensitivity of Plasmodium falciparum to artemisinin-based combination therapies (ACTs) suggest the possibility of clinical artemisinin resistance along the Thai-Cambodian and Thai-Myanmar borders. The study investigated cellular mechanisms of action and resistance of P. falciparum to artesunate (stage specific activity, interaction with hemozoin, and anti-oxidant levels) in the two paired P. falciparum isolates (MSF046 and MSF060) collected before treatment with a 3-day artesunate-mefloquine and at the time of recrudescence. In addition, the link of these cellular mechanisms to the polymorphisms of the candidate artemisinin resistant genes (pfatp6, pfcrt, pfmdr1, pfmrp1 and K13 propeller) was also investigated. Morphological change was observed in both pairs of the primary and recrudesced P. falciparum isolates during 12-48 hours of exposure to artesunate at IC<sub>90</sub> (concentration that inhibits parasite growth by 90%). A marked decrease in parasite viability was found in the recrudesced isolates of both MSF046 and MSD060. The extent of the reduction (% change of baseline) in total glutathione concentrations was significantly lower in recrudesced (32.1 and 1.7%) compared with primary (45.5 and 53.7%) isolates of both MSF046 and MSF060. The extent of reduction of hemozoin content in MSF046 was significantly higher in the recrudesced (76.8%) isolate compared with the primary isolate (99.5%). For MSF060 on the other hand, increase in hemozoin content was found in the recrudesced isolate and the extent of such increase was significantly higher in recrudesced (93.1%) than the primary isolate (87.5%). Polymorphism of K13 (N458Y) together with pfmdr1 copy number correlated well with sensitivity of both isolates to artesunate. Results of this preliminary study suggests possible role of glutathione-dependent detoxification system as well as heme degradation as cellular mechanisms of action and resistance of artemisinins.

**Keywords**: *Plasmodium falciparum*; artemisinin-based combination (ACT); artemisinin resistance; hemozoin; glutathione

#### Prevalence of hemoglobinopathies in Indonesian population

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Prevalence of carriers with hemoglobinopathies is relatively high in the areas where malaria is endemic. This systematic review was performed to identify types of hemoglobinopathy and summarize their common mutations in Indonesian population. Terms of use for searching of the were "α-thalassemia", "β-thalassemia", "hemoglobin literatures "hemoglobinopathy", "red cell disorder", "thalassemia", and "Indonesia". Studies in both malaria endemic and non-malaria endemic areas of Indonesia were included (South Sulawesi, Jakarta, Southwest Sumba regency, Surabaya, and Central Jaya). Data extraction was performed in 5 out of 348 publications. Three publications were reported from random volunteers while the other two were reported from β-thalassemic patients. Hemoglobin disorders found with the high frequency in surveyed random volunteers were α-thalassemia, β-thalassemia, and hemoglobin E. Hemoglobin O Indonesia [ $\alpha I$ -globin gene codon 116 (Glu116Lys or G-A)] was detected with rare frequency. For the β-thalassemic patient group, the most common alleles were codons 26 (G-A) and IVS-1 nt5 (G-C) and genotype carrying Hb E/ \(\beta\)-thalassemia [codon 26(G-A)/IVS-1 nt5 (G-C)] was the most frequent genotype.

**Keywords:** hemoglobinopathies, thalassemia, malaria, Indonesia

### Systematic review on prevalence and variant of G6PD deficiency in malaria endemic areas in Indonesia

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Primaquine is currently recommended for radical treatment in *Plasmodium vivax*, as well as a gametocytocidal agent in uncomplicated *Plasmodium falciparum* infection. The clinical uses of primaquine are however limited by its severe intravascular hemolysis in patients with glucose-6-phosphase dehydrogenase (G6PD) deficiency. The aim of this systematic review was to investigate the prevalence and variants of G6PD deficiency in Indonesian population who residing in malaria endemic areas. The published literatures were searched from two databases. The terms of searching keyword including "G6PD", "malaria", and "Indonesia" were jointly used. Ten out of 45 retrieving literatures were included for further analysis. The WST-8/1-methoxy PMS method, formazan ring method and commercial kit were selected method use for screening of G6PD deficiency. PCR-RFLP and sequencing were employed for variant detection. Results showed low prevalence (0.2-19.5%) of G6PD deficiency distributed in the surveyed areas. The class II G6PD Vanua Lava mutation was the most common variant observed in the surveyed population (40% of the deficient individuals). Routine G6PD deficiency screening is required in Indonesian malaria patient individuals before treatment with primaquine.

**Keywords:** G6PD deficiency, malaria, G6PD variant, Indonesia, systematic review

#### The allergenic UV filters exposure in different types of sunscreen product sold in Thailand

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The active ingredient of sunscreen products are UV filters. Many of available UV filters in the market can cause photocontact or contact allergy. Types of sunscreen are considered by the consumer before they decide to buy a product. From the literature review, there are no survey studies of active ingredient in sunscreen product in ASEAN. This study, aims to evaluate the allergenic UV filter exposure to the consumer in different types of sunscreen product. The sunscreen product ingredients label from the randomized store in Bangkok were collected and analyzed. Of 244 examined sunscreen products, 70(29%) products were cream, 135(55%) were liquid, 24(10%) and 15(6%) were spray. The results showed that avobenzone, octocrylene and octinoxate which are the common allergenic UV filters were found significantly (p=0.001, p=0.002, p=0.004; respectively) different between types of sunscreen product. The oxybenzone which is the most common UV filter cause photocontact allergy was found not different between types of sunscreen products. In conclusion, a type of sunscreen product is one of the factors that determine the different exposure to allergenic UV filters. This study could be benchmark information for further study in the field of contact dermatitis in ASEAN.

**Keywords:** sunscreen, UV filters, photoallergic contact dermatitis, market survey

#### Prevalence of bacterial isolates in LAO PDR from 2012 to 2015

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Pathogenic bacteria are bacteria that can cause infection. Although most bacteria are harmless or often beneficial, some are pathogenic, with the number of species are seen to cause infectious diseases in humans. Lao PDR has a limited sources, fund and information on prevalence of bacterial infection from the government sectors and as well bacteriology traditional culture was not popular in country. This study was to investigate the prevalence of bacterial isolated from clinical samples in Lao PDR during 2012 to 2015. Data reviewed of laboratory information and results to find the association between risk factor (gender, age, region, year, source and types of samples) and occurrences of bacteria infection were analyzed. Total of 6789 specimens were collected and selected for analysis, 1341, 1873, 1588 and 1987 specimens from year, 2012, 2013, 2014 and 2015 respectively. The prevalence of at least one bacterial infection from 2012 to 2015 were 45.1%, 30.8%, 30.6% and 33.8%, respectively. The decreasing infection trend was statistical significant. This might be the result from successful health policy in Lao PDR. The factors that influenced the infection rate were sex, age, region, source of collection and year.

Keywords: Lao PDR, bacterial infection, pathogenic

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### Heme oxygenase-1 gene polymorphism in *Plasmodium vivax* malaria patients from Southern Thailand

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Malaria is one of the most important public health problems in tropical and sub-tropical countries. In Thailand, the common causative parasites are *Plasmodium vivax* and *Plasmodium falciparum*. The severity of malaria affect by several factors including heme oxygenase-1 (HO-1). The HO-1 is an enzyme that play important role in heme degradation process, yielding biliverdin/bilirubin, carbonmonoxide (CO) and ferrous iron. The human HO-1 gene promoter contains the (GT)<sub>n</sub> repeat polymorphism which may contribute to the fine tuning of the transcription and severity of malaria. Long (GT)<sub>n</sub> alleles have been found associated with malaria by linked to resistance to cerebral malaria (CM). The association between HO-1 and malaria disease was described in some population. The objective of this study was to investigate the genetic polymorphism of (GT)<sub>n</sub> repeated length in malaria patients from southern part of Thailand. One hundred samples of dried blood spot from *Plasmodium vivax* malaria patients were collected from Southern Thailand. Genetic polymorphism and genotype frequencies were determined by using PCR technique. The results indicated that long (GT)<sub>n</sub> repeated length has more frequencies than short (GT)<sub>n</sub> repeated length among the patient from Southern part of Thailand. Therefore, HO-1 might indicate a protective effect to against severity in *Plasmodium vivax* infection.

Keywords: Heme oxygenase-1 (HO-1), Plasmodium vivax, malaria

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### In vitro activities of dihydroartemisinin and piperaquine against Plasmodium falciparum-infected hemoglobinopathic red blood cells

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α-Thalassemia, β-thalassemia and hemoglobin E are hemoglobinopathies which are commonly found in population living in malaria endemic area. Ineffective hemoglobin production leaves over debris or unbound hemoglobin-induced oxidative stress that influences parasite growth and antimalarial drug sensitivity. The objective of the study was to investigate in vitro sensitivity and interaction of the artemisinin-based combination therapy (ACT), i.e., dihydroartemisinin (DHA) and piperaguine (PPO) on Plasmodium falciparum-infected hemoglobinopathic red blood cells (RBCs). Fifteen samples identified as normal (n = 5), hemoglobin E (n = 9), and  $\alpha$ -thalassemia (n = 1) RBCs were used for cultivation of 3D7 (chloroquine sensitive) and K1 (chloroquine resistant) P. falciparum clones. Both parasite clones were exposed to DHA and PPQ at the maximum concentrations of 20 and 300 nM, respectively. Antimalarial activities of each drug and the combination (DHA:PPQ ratio of 0:10, 3:7, 5:5, 7:3 and 10:0) were determined using SYBR green I assay. Results were expressed as concentration that inhibits parasite growth by 50% (IC<sub>50</sub>) and sum fractional IC<sub>50</sub> of the isobologram analysis. The 3D7 P. falciparum clone was found to be more sensitive to PPQ than the K1 clone [median (95% CI) IC<sub>50</sub> of 32.8 (24.7-39.0) vs 53.9 (46.4-64.9) nM, respectively]. On the other hand, K1 P. falciparum clone was more sensitive to DHA than the 3D7 clone [median (95% CI) IC<sub>50</sub> of 4.53 (3.45-5.20) vs 2.10 (1.92-3.02) nM, respectively]. The sensitivity of both drugs to both P. falciparum clones were generally similar in all types of infected RBCs. It was noted however for the relatively higher sensitivity of DHA (IC<sub>50</sub> = 2.01 nM) in the 3D7 P. falciparum-infected  $\alpha$ -thalassemic RBCs, while the sensitivity to PPQ ( $IC_{50} = 60.2 \text{ nM}$ ) was relatively lower. No antimalarial interaction between DHA and PPQ was found in both clones of P. falciparum-infected normal RBCs. In the P. falciparum-infected hemoglobin E RBCs, the antagonistic interaction was found in the 3D7 clone, but not in the K1 clone (no interaction). In the P. falciparum-infected □-thalassemic RBCs, the interaction between DHA and PPQ was synergistic in the K1 but not in 3D7 (no interaction) clone. These results suggest that hemoglobinopathic RBCs influences antimalarial activities of DHA and PPQ and this may result in variability in antimalarial treatment outcomes.

**Keywords**: Dihydroartemisinin, Piperaquine, *Plasmodium falciparum*, hemoglobinopathic RBC

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# Cytotoxic activities of the ethanolic extract of *Kaempferia galanga* Linn. and its active component against human cholangiocarcinoma cell line and peripheral blood mononuclear cell

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Kaempferia galanga Linn. (KG) is one of the plants in the Zingiberaceae family. Its rhizome extract has been used traditionally in Southeast Asia for analgesic and anti-inflammatory activities. Cholangiocarcinoma (CCA) is a bile duct tumor and which is an important public health problem in the northeastern region of Thailand. Standard chemotherapeutics for treatment of CCA is currently unsatisfactory. The aim of the study was to investigate cytotoxicity of the ethanolic extract of KG rhizomes including its bioactive compound ethyl-*p*-methoxycinnamate (EPMC) against the human CCA cell line CL-6 and peripheral blood mononuclear cell (PMBC). The mean (±SD) IC<sub>50</sub> (concentration that inhibits cell growth by 50%) values of KG extract, EPMC, and the reference drug 5-fluorouracil (5-FU) in CL-6 cell were 82.56±24.89, 93.63±22.34 and 19.45±12.37 μg/ml, respectively. The corresponding IC<sub>50</sub> values for the PBMC cell were 227.87+16.54μg/ml, 96.14±9.82 and 502.14±11.71 μg/ml, respectively. Results provide as a first-step, screening information on potential anti-CCA and cytotoxic effects of the KG extract and EPMC. Confirmation of anti-CCA activities in animal models is required for their further development as chemotherapeutics for treatment of CCA.

Keywords: Kaempferiagalanga Linn., cholangiocarcinoma,

Efficacy of tranexamic acid intradermal microinjections in reducing risk of post-inflammatory hyperpigmentation after Q-switched Nd: YAG laser for treatment of solar lentigines: A pilot randomized controlled trial

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Postinflammatory hyperpigmentation (PIH) after solar lentigines removal using 532-nm QS Nd: YAG laser is a major concerned cosmetic side effect, especially in patients with darker skin type. Previous studies have been conducted for the efforts to prevent PIH after laser treatment, yet without highly effective results. Thus, this study aimed to evaluate the efficacy and safety of tranexamic acid (TA) intradermal microinjections in reducing risk of PIH after the 532-nm QS Nd: YAG laser for treatment of solar lentigines. Twenty-six solar lentigines of thirteen patients received 532-nm QS Nd: YAG laser treatment. Then, the 50 mg/mL of TA was intradermally injected to one random lesion and normal saline to another as control group. Pigmentation was measured by the mexameter as melanin index (MI) and erythema index (EI) at the baseline, 2<sup>nd</sup>, and 4<sup>th</sup> weeks. The results showed the improvement of each lesion at the  $2^{nd}$  and  $4^{th}$  weeks, with the mean improvement scores of 90 + 10.8in the TA group and 75.77 + 16.56 in the control group (4 weeks after treatment, p < 0.05). Whilst, mean MI decreased from  $352.9 \pm 75.13$  to  $313.05 \pm 67.69$  in the TA group (baseline vs. 4 weeks after treatment, p < 0.05) and from 354.13  $\pm$  78.85 to 326.64  $\pm$  62.97 in the control group (baseline vs. 4 weeks after treatment, p = 0.061). Hence, intradermal TA injection can efficaciously be an effective and safe therapeutic modality in reducing hyperpigmentation after solar lentigines treatment using 532-nm QS Nd: YAG laser.

**Keywords:** Tranexamic acid, Solar lentigo, Postinflammatory hyperpigmentation, Q-switched 532-nm Nd: YAG laser



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### Development of high resolution melting analysis in preimplantation genetic diagnosis of alpha thalassemia-1 Southeast Asian type (SEA)

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Alpha-thalassemia 1 Southeast Asian type (SEA) is a common monogenic blood disorder in Asian population. The 25% chance of conceiving Bart's hydrops fetalis could be concerned in carrier couples. The preimplantation genetic diagnosis is the alternative method for selecting the normal embryo before implantation. Whereas, prenatal genetic testing has been done for high risk diagnosed couples in thalassemia syndrome during pregnancy period. The real-time PCR with high resolution melting analysis (HRM) has been implemented for the high sensitivity and accuracy test for SEA mutation with limited sample as biopsied single cell from embryo. The purpose of this study was to design an assay for the detection of alpha-thalassemia SEA type which was assigned on real-time gap-PCR and high resolution melting (HRM) analysis. The biopsied single cell embryos at day 5 from the disease-carrier parents have been done in this analysis with the confirmation using informative short tandem repeated (STRs) linkage analysis. Here, the real-time gap-PCR and HRM analysis can be easily used for alpha thalassemia-1 SEA allele detection. HRM result could distinguish the wild type alpha globin gene and mutant allele. The informative STRs analysis revealed the confirmed test was distinctly identified the inherited STRs in pedigree from the family. Our developing molecular technique as the real-time gap-PCR and HRM analysis offers the rapid and accuracy method for the preimplantation genetic diagnosis (PGD) and prenatal test of alpha-thalassemia 1 Southeast Asian type (SEA).

**Keywords:** alpha-thalassemia 1 Southeast Asian type (SEA), high resolution melting analysis, preimplantation genetic diagnosis, prenatal test

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### Mutagenic and apoptotic activities of ethanolic extract and bioactive components of *Atractylodes lancea* (thunb) DC. in cholangiocarcinoma cell lines

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Cholangiocarcinoma (CCA) is the cancer of bile duct that has high incidence and high mortality rate, particularly in the Northeastern part of Thailand. *Atractylodes lancea* (Thunb) DC. (AL) has been traditionally used as crude extract for treatment of several diseases in China, Japan, and Thailand. It contains several bioactive components with pharmacological activities against CCA. The present study focused on the effects of AL ethanolic extract (ALE) including the two major bioactive constituents of AL, *i.e.*, atractylodin and  $\beta$ -eudesmol on mutagenicity and apoptotic activity using micronucleus test and JC-1 fluorescence method. CCA cell lines (CL-6 and HUCCT-1) and normal human embryonic fibroblast cell line (OUMS-36T-1F) were used in this experiment. The result showed that ALE, atractylodin and  $\beta$ -eudesmol increased the number of micronucleus in CL-6 and HUCCT-1 cells compared with untreated cells. Such effect was not observed in OUMS-36T-1F cell. Induction of cell apoptosis by ALE and atractylodin were observed in CL-6, HUCCT-1 and OUMS-36T-1F cells, whereas induction of cell apoptosis by  $\beta$ -eudesmol was found only in CL-6 cells. AL ethanolic extract, atractylodin and  $\beta$ -eudesmol could be the promising candidates for further development as anti-CCA drugs due to their potential apoptosis effects. Nevertheless, their mutagenic effects although non-sugnificant, need further confirmation in other *in vitro* as well as *in vivo* models.

**Keywords:** *Atractylodes lancea* (Thunb) DC., micronucleus, mutagenicity, JC-1 fluorescence method, apoptosis

#### Multidrug resistance tuberculosis in Bhutan

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In 2015, there were an estimated 10.4 million new tuberculosis (TB) cases worldwide, of which 1.0 million (10%) among children and there were an estimated 480 000 new cases of multidrug-resistant TB (MDR-TB). This study was aimed to understand the common mutations seen in the MDR isolates depicted by the line probe assay (LPA) performed on the MDR-TB isolates from Bhutanese patients. Retrospectively the results of LPA was collected from the National TB reference laboratory (NTRL) from February 2014 to December 2016. There were 14.4% (57/395), 16% (52/326,) 10.7% (54/506) MDR-TB cases in 2014, 2015 and 2016, respectively. Mono resistance to isoniazid was found more frequently compared to rifampicin by over 5 times. The most prevalence polymorphisms of ropB gene were nt530-533 (WT8), nt513-517 (WT3), and S531L (MUT3) and nt315 (WT1) and S315T1 (MUT1) of katG gene. More than 75% of the MDR cases were due to dual mutations in the ropB and katG genes (71.9% in 2014, 86.5% in 2015 and 88.9% in 2016). Among all the 163 MDR isolates of the three consecutive years, the most frequent combination of mutation observed (127/163, 77.9%) was the loss of ropB WT8 (530-533) with MUT3 (S531L) and the loss of katG WT1 (315) with MUT1 (S315T1). The loss of ropB WT8 (530-533) accounted for 93.9% (153/163), closely followed by WT3 (513-517) with 82.2% (134/163). WT7 (526-529) composed of 4.3% (7/163 cases) of MDR-TB. About 85% (138/163) of ropB MUT3 (S531L) was detected followed by 3 cases each of MUT2A and 2B. Ninety eight percent of MDR had WT bands missing and 93% had katG MUT1 bands depicting mutations in S315T. katG MUT2, S315T2, was the most uncommon mutations with only a single case in 2014. No mutations or loss of ropB WT1, ropB WT2 and ropB WT6 have been detected in the MDR isolates, however in the RIF-MR no mutations were found from ropBWT1 through ropBWT6. Losses of ropB WT7 and 8 were found to be the most common finding among the Bhutanese isolates. Mutations in katG commonly composed of the loss of WT with or without MUT1 and 2. Occasional involvement of inhA gene was found at -15/-16 (WT1), -8 (WT2) and C15T (MUT1) with or without MUT1 band. However, no mutations in katG and inhA were observed together at any location. Mutations in katG and inhA were however detected in MDR along with mutation in ropB gene. This is the first study where LPA depicted INH and RIF-drug-resistanceconferring mutations in MDR-TB in Bhutan. In resource limited country like Bhutan LPA has contributed immensely towards diagnosis of MDR-TB. However solid culture alongside LPA would provide a clearer picture of the mutations and help guide of accurate treatment for the TB patients.

**Keywords:** Bhutan, tuberculosis, line probe assay

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#### Mathematical modeling of apoptosis pathways of β-eudesmol in cholangiocarcinoma

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Cholangiocarcinoma (CCA) is the second cause of death in primary liver cancer worldwide and the primary cause of death among all cancers in the northeastern Thailand. Chemotherapeutics for treatment of this type of cancer remain unsatisfactory. Dysfunction of the genes involved in cell cycle arrest and cellular apoptosis including p53 transcription factor, mdm2, bax, bcl2, and Fas/FasL, leads to CCA development. The objective of this study was to investigate the change in mRNA expression levels of the genes involved in cell cycle arrest and apoptosis pathway in CCA, i.e., p21, p53, bax, bcl2, caspase 3, caspase 8, and caspase 9. The ultimate goal was to propose an alternative approach for discovery and development of cancer chemotherapeutic drugs through the application of mathematical modeling with inputs of experimental data. The expression level of mRNA was measured using real-time PCR. The computational simulation was performed using mathematical equations with inputs of experimental data. The mRNA expression levels of the CCA cell were investigated following exposure to the candidate compound  $\beta$ -eudesmol at the IC<sub>50</sub> of 35  $\mu$ g/ml. The mRNA expression of p53, caspase 3, caspase 8, caspase 9, and bax were significantly different between the cells exposed to \(\beta\)-eudesmol and control. Significant correlations between mRNA expression levels and cell death were observed with p53 (r = 0.973), caspase 3 (r = 0.975), caspase 9 (r = 0.713), bax (r = 0.841), and p21 (r = 0.381). Based on multivariate linear regression model, only p53 and caspase 8 showed significant inhibitory effect on cell growth. It was concluded that βeudesmol exerted its inhibitory effect on CCA cell growth through both intrinsic and extrinsic apoptosis pathways. Model stability was tested by increasing 10% of mRNA expression parameters. There was only one parameter with sensitivity greater than 0.2. The model was found to be highly stable with no amplified parameter errors. In addition, this mathematical modeling based on the experimental data of the mRNA expression levels of the p53 and caspase 8 involved in apopotosis pathway could be applied as a useful tool for predicting cancer cell death following exposure to the candidate compounds.

**Keywords**: Mathematical modeling, apoptosis pathway, cholangiocarcinoma, β-eudesmol

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# Physiologically based pharmacokinetic (PBPK) modeling in cancer therapy: a systematic review of model applications and verification

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Physiologically Based Pharmacokinetics (PBPK) model is one of the computational models which mimics human physiology and can be applied to simulate drug concentration profiles over time in plasma and various organs. Regulatory agencies including USFDA and EMA have recommend PBPK models as supportive information for drug regulatory submission. The number of publications as well as regulatory submissions related to PBPK modeling has been increasing dramatically in various diseases including cancers in recent years. The objectives of this review were to 1) identify and illustrate the applications of PBPK models in cancer therapy in each phase of drug development, 2) explain important factors for PBPK model development, 3) compare and identify AFEs (averagefolding errors) in PBPK modeling applied in each phase of drug development, and 4) evaluate PBPK model based on USFDA suggestions and recommendations. Articles were initially searched from PubMed database using the terms "Physiologically based pharmacokinetics or PBPK" [all fields] and "model" [all fields], and "cancer" [all fields]. This was followed by PubMed Central (PMC) and Cochrane Library searching for the abstracts and article titles related to these terms. Additional hand searching was also conducted to obtain more articles. The inclusion criteria were: articles with fully described PBPK models, articles on anticancer drug, and articles published in English between 2000 and February 2017. A total of 61 published articles met the predefined criteria, and were classified into: in vivo studies, first-in-human (FIH) studies, cancer research, studies in special population, and DDI studies. Comparison of difference in median AFE among the five was performed using Jonckheere-Terpstra test at a statistical significance level of  $\alpha = 0.05$ . Most of the PBPK application was on DDI studies (9 articles, 31%), while that on FIH was lowest (8 articles, 13%). Of these articles, 13 articles were population-based PBPK model (simulate virtual population) with covariates and matched demographic data. PBPK model can successfully be applied for dose optimization of anticancer drugs in various groups of patients. In addition, its application offers benefits to drug development as it reduces the number of participants in clinical trials or number of animal in experiments. The accuracy of model prediction depends on integration of relevant parameters.

**Keywords**: Systematic review, PBPK model, cancer, applications

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#### Pharmacokinetics of tacrolimus in early post-kidney transplantation

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Tacrolimus is the most commonly used calcineurin inhibitors for prevention of allograft rejection after kidney transplantation. Optimizing immunosuppressive management during the early period after kidney transplantation is crucial but pharmacokinetics studies of tacrolimus in Thai transplant recipients during this period are scarce. We aim to evaluate the pharmacokinetic profile of tacrolimus in Thai adult kidney transplant recipients who received oral tacrolimus twice daily on Day 7 after transplantation. Of 10 living-related kidney transplant recipients who received tacrolimus twice daily in combination with mycophenolate and prednisolone, venous blood samples were collected on Day 7 after transplantation only if there was no tacrolimus dose change for at least 4 doses prior to the blood sample collection. Whole blood tacrolimus concentrations at 0, 1, 2, 4, 6, 8, and 12 hours after the morning dose were measured by chemiluminescent microparticle immunoassay. Area under the tacrolimus concentration over 12 hour curve (AUC) were calculated by linear trapezoidal rule. The maximum concentrations (Cmax) and time to Cmax (Tmax) were obtained directly from the concentration-time profiles. Tacrolimus pharmacokinetic profiles were obtained from 10 Thai patients with the mean±SD of serum creatinine of 1.22±0.29 mg/dl on day 7 after kidney transplantation. The mean±SD of tacrolimus dose were 0.14±0.07 mg/kg/day, the corresponding mean±SD of tacrolimus AUC was 160.57±32.56 ng\*h/ml with median (IQR) of Cmax and Tmax were 25.10 (23.07, 41.90) ng/ml and 1 (1, 2) hours, respectively. And the mean±SD of tacrolimus concentration at pre-morning dose (Ctrough) was 8.18±1.62 ng/ml. There was a strong positive correlation between Ctrough and AUC (r=0.765, p<0.01). In conclusion, pharmacokinetic profile of tacrolimus on day 7 after kidney transplantation was determined in Thais. All but one participants have their AUCs within clinically acceptable range of 120-200 ng\*h/ml.

**Keywords**: AUC, immunosuppressive drug, kidney transplantation, pharmacokinetics, tacrolimus

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### Optimization of the extraction method, preparation of oral pharmaceutical formulation and toxicity testing of *Atractylodes lancea* (Thunb.) DC

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Cholangiocarcinoma (CCA) is the cancer of bile duct with high incidence and mortality rate especially in the northeastern region of Thailand. Standard treatment with conventional chemotherapeutic drugs is disappointing with low cure rates. The anti-CCA potential of the ethanolic extract of Atractylodes lancea (Thunb.) DC. (AL) has been demonstrated in the previous studies. The current study was divided into three parts: (1) optimization of the extraction method, (2) preparation of oral pharmaceutical formulation (capsules) of the standardized AL extract, and (3) investigation of acute and subchronic toxicity of AL capsules in Wistar rats. Three different extraction methods, i.e., maceration (95% ethanol, 25-30 °C, 7 days), sonication (95% ethanol, 25-30 °C, 30 minutes), and heat-reflux (95% ethanol, 95 °C, 50 minutes), were initially used to prepare AL ethanolic extract with maximum extraction efficiency (%yield) and cytotoxic activity. Quality control of the extracts was evaluated based on relative amounts of the marker compound, \u03b3-eudesmol and atractylodin, using HPLC. The maceration method, although not the most efficient method, was selected for further optimization as it is relatively simple, cost-effective, and applicable to large scale production. Considering the compromised performance of the extraction efficiency and cytotoxic activity, double maceration for 24 hours was selected as the most optimal condition for preparation of the AL extract for non-clinical and clinical studies and large scale production of the pharmaceutical formulation. The dried AL extract was formulated in one capsule (No. 00) with lactose (water-soluble filler), sodium lauryl sulfate (surfactant), and talcum (glidant) at the ratio of 1:1.25:0.005:0.095. The pharmaceutical properties of the AL capsule were evaluated using standard procedures. Results showed acceptable properties of the formulation (bulk density, solubility, tapped density, Hausner ratio, compressibility index, angle of repose, flowability, weight variation, disintegration, and dissolution). Results of toxicity tests showed the oral pharmaceutical formulation of the standardized extract to be well tolerated with virtually no toxicity up to the highest recommended dose of 5,000 mg/kg body weight (single and repeated doses).

Keywords: Atractylodes lancea (Thunb.) DC., Capsule formulation, acute and subchronic toxicity

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# Cytotoxic, apoptotic and inhibitory activities on cell migration of atractylodin in cholangiocarcinoma cell line

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Cholangiocarcinoma (CCA) is an important cancer in the Great Mekong region, particularly in Thailand. Limitation of treatment option and the lack of effective diagnostic tool for early detection of CCA are of major concerns for the control of this type of cancer. The aim of the study was to investigate cytotoxic, apoptotic and inhibitory activities on cell migration of atractylodin, the active constituent of *Atracylodes lancea* (Thunb.) DC. against CCA cell line CL-6. MTT assay was used to test cytotoxicity and Real-Time Cell Analyzer Dual purpose: RT-CA DP system was used to test cell migration. CellEvent<sup>TM</sup> Caspase-3/7 assay was specific test to inducing activity on cell apoptosis. The median IC<sub>50</sub> (concentration that inhibits cell growth by 50%) of cytotoxic activity of atractylodin was 39.5 μg/ml. Atractylodin produced inhibitory activity on cell migration including inducing activity on cell apoptosis. Results suggest the potential role of atractylodin for further development as chemotherapeutic for CCA.

Keywords: Cholangiocarcinoma, atractylodin, cytotoxicity, cell migration

# Effect of methotrexate and narrowband ultraviolet-B radiation on the transcriptional and protein levels of interleukin-33 in plaque psoriasis

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Interleukin (IL)-33 is a newly identified cytokine of the IL-1 family. The IL-33 expression is strongly upregulated in the nucleus of keratinocytes in psoriasis. However, the role of IL-33 in psoriasis is unclear, and IL-33 expression in the lesional psoriatic skin after conventional systemic treatments has not been investigated. The aim of this study was to compare IL-33 mRNA and protein expression before and after treatments with methotrexate (MTX) and narrowband ultraviolet-B (NBUVB). Patients with moderate to severe psoriasis were treated with MTX or NBUVB phototherapy until a 75% reduction in psoriasis area and severity index (PASI75) was achieved or until 12 weeks of treatment. Tissue samples from psoriatic plaques and serum were obtained from patients before and after treatment. The mRNA level of IL-33 in tissue was measured by quantitative reverse transcription polymerase chain reaction (RT-PCR), and IL-33 level in the serum was evaluated by enzyme-linked immunosorbent assay (ELISA). IL-33 mRNA and serum levels were downregulated after treatment with MTX. The results obtained from data analysis revealed a significant decrease in IL-33 protein expression (p = 0.028). IL-33 expression tended to be elevated after treatment with NBUVB. There was a strong negative correlation between IL-33 serum levels and PASI score after treatment with MTX (r = -0.69, p = 0.06), and with NBUVB (r = -0.90, p = 0.034), in psoriasis patients. These results suggest that IL-33 production appears to be associated with inflammatory skin in psoriasis, but may not be involved in the main pathogenesis of psoriasis.

**Keywords:** Interleukin-33, methotrexate, narrowband UVB, psoriasis

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# Atractylodin from *Atractylodes lancea* (Thunb) DC induces apoptosis and inhibits growth of human cholangiocarcinoma cells

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Cholangiocarcinoma (CCA) is a progressively fatal form of cancer arising from malignant transformation of hepatic biliary cholangiocytes. Countries like Thailand, Laos and Cambodia are known to have high incidences of this cancer. The objective of this study was to evaluate growth inhibitory activity of atractylodin, a bioactive sesquiterperioid present in the rhizomes of *Atractylodes lancea* (Thunb) DC. in human CCA cell line CL-6. The cytotoxicity and potential effects of atractylodin on cell cycle arrest of CL-6 cells were investigated using standard MTT assay and flow cytometry, respectively. In addition, western blotting was used to evaluate the effect of atractylodin on STAT 1/3 activation and heme oxygenase-1 production. The results showed that atractylodin exhibited cytotoxic activity with IC<sub>50</sub> (concentration that inhibits growth by 50%) of 221.25  $\pm$  11.42  $\mu$ M (mean  $\pm$  SD). It proficiently induced apoptosis at 48 h after treatment and cell cycle arrest was observed at G1 phase. Moreover, atractylodin treatment resulted in suppression of STAT1/3 activation and HO-1 production in CL-6 cells. Taken together, the results suggest therapeutic potentials of atractylodin and further in-depth studies are ongoing to investigate mechanism of cytotoxicity of this compound.

**Keywords:** Atractylodin, cholangiocarcinoma, heme oxygenase, STAT1/3

### Anti-proliferative activity of atractylodin and its potential suppressive effect on nuclear factor-KB expression in cholangiocarcinoma cells

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Cholangiocarcinoma is a progressively lethal form of cancer generally arising from malignant transformation of hepatic biliary cholangiocytes. The objective of this study was to evaluate the antiproliferative effect of atractylodin, a bioactive sesquiterperioid present in rhizomes of Atractylodes lancea (Thunb) DC., and to determine its potential effects on major NF-κB protein expression in cholangiocarcinoma-associated cell line CL-6. Standard 3-(4,5-dimethyl-2 thiazoyl)-2,5-diphenyl-2Htetrazolium bromide (MTT) assay was used for accessing viability of CL-6 cells. Normal human embryonic fibroblast (OUMS) cell was taken as control cell line. Colony formation and wound healing assay were conducted to access the effects of atractylodin treatment on cell proliferation and directional migration activity of CL-6 cells, respectively. Western blot was used for evaluating levels of nuclear factor-KB (NF-KB) protein expression. Attractylodin exhibited selective cytotoxicity towards CL-6 as compared to OUMS with mean (±SD) 50% inhibitory concentration against cell growth (IC<sub>50</sub>) of 221.25  $\pm$  11.42 and 352.45  $\pm$  6.91  $\mu$ M, respectively. Exposure to the compound dosedependently inhibited colony formation ability and decreased wound closure potential of CL-6 cells. Western blot analysis indicated that atractylodin treatment inhibited NF-κB (p50), NF-κB (p52) and NF-κB (p65) protein expression in both dose- and time-dependent manner. These results suggests that atractylodin exerts growth inhibitory and anti-proliferative activity against CL-6 cells which may be linked to suppression of key NF-κB proteins expression. Taken together, these results indicate atractylodin as a potential chemotherapeutic candidate in cholangiocarcinoma research and demands further in-depth study to explore the underlying molecular mechanisms.

Keywords: Atractylodin, Atractylodes lancea (Thunb) DC., cholangiocarcinoma, CL-6, OUMS

#### Pharmacological activities of cyclooxygenase (COX) inhibitors against malaria

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Cyclooxygenase (COX) enzyme is the key enzyme responsible for prostanoids production. The enzyme plays an important role in the inflammatory process and pathogenesis of several diseases including malaria. In this study, both selective and non-selective COX-2 inhibitors, (aspirin, ibuprofen, piroxicam, and naproxen) including the combinations were investigated for their antimalarial activities in vitro. Antimalarial activity was assessed using the SYBR Green I fluorescent-based assay. For mefloquine-aspirin combination, the test wells consisted of varying concentrations of mefloquine and aspirin at the ratios of 200:0, 140:30,000, 100:50,000, 60:70,000, and 0:100,000 nM. The concentration ratios for artesunate-aspirin were 50:0, 35: 30,000, 25: 50,000, 15: 70,000, and 0: 100,000 nM. The median (range) concentrations that inhibit parasite growth by 50% (IC<sub>50</sub>) of aspirin against K1 and 3D7 Plasmodium falciparum clones were 1889.7 (1600.8-2792.8) and 2417.2 (912.0-2630.4) nM, respectively. The corresponding values for mefloquine were 10.1 (8.1-13.9) and 23.4 (22.9-24.7) nM, respectively. The corresponding values for artesunate were 2.5 (1.6-3.4) vs. 2.2 (1.2-3.2) nM, respectively. The IC<sub>50</sub> values of ibuprofen, piroxicam and naproxen were greater than 100,000 nM for both clones. The median (range) sum fractional inhibitory concentration (FIC) of mefloquine-aspirn interaction for K1 and 3D7 P. falciparum clones were 0.82 (0.79-1.0) and 0.97 (0.83-1.1), respectively. The corresponding sum FICs of artesunate-aspirin were 0.94 (0.88-0.95) and 0.95 (0.92-0.97), respectively. Results indicate indifferent antimalarial interaction between these two drugs when used in combination.

**Keywords:** Cyclooxygenase (COX), antimalarial activity, *Plasmodium falciparum*, drug combination

#### The in vitro antimalarial activities of quinonoids from Plumbago indica Linn

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Multidrug resistance *Plasmodium falciparum* is a global health problem worldwide especially in Thailand. Discovery and development of novel antimalarial drugs are urgently needed. Plumbago indica Linn. has been shown to exhibit a wide range of pharmacological activities including antimalarial activity. The plant contains several bioactive constitutes, notably quinonoids. This study aimed to investigate in vitro antimalarial activities of the six quinonoids of P. indica, i.e., 5-hydroxy-2-methyl-1,4-naphthoquinone, 1,4-naphthoquinone, 5-hydroxy-1,4-naphthoquinone, 2-hydroxy-1,4naphthoquinone, 5-hydroxy-1-tetralone, and 2,5-dihydroxypropiophenone against chloroquine sensitive (3D7) and chloroquine resistant (K1) P. falciparum. Antimalarial activity was evaluated based on the SYBgreen fluorescent-based assay. The concentration that inhibits parasite growth by 50% (IC<sub>50</sub>) values of 5-hydroxy-2-methyl-1,4-naphthoquinone, 1,4-naphthoquinone, 5-hydroxy-1,4-2-hydroxy-1,4-naphthoquinone, 5-hydroxy-1-tetralone naphthoquinone, dihydroxypropiophenone against 3D7 were 0.09, 9.99, 1.07, 26.24, 61.14 and 43.17, respectively. The corresponding IC<sub>50</sub> values for the K1 clone were 0.07, 8.22, 1.44, 27.43, 59.76 and 62.09, respectively. The results indicated the potent antimalarial activities of quinonoids isolated from P. indica particularly naphthoquinones.

Keywords: Plasmodium falciparum, Plumbago indica Linn., quinonoids, antimalarial activity

#### The in vitro antimalarial activity of Atractylodes lancea (Thunb) DC

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Multidrug resistance *Plasmodium falciparum* is a global health problem worldwide particularly in Thailand. The development of novel antimalarial drugs are urgently needed. The aim of the present study was to investigate antimalarial activity and time dependent action of the crude ethanolic extract of *Atractylodes lancea* (Thunb) DC. rhizome against 3D7 *P. falciparum* clone. Antimalarial activity was evaluated using SYBRGreen fluorescent-based assay. The  $IC_{50}$  (concentration that inhibits malaria parasite growth by 50%) value was determined using Calcusyn software. The synchronized parasites in ring stage were exposed to the extract extract at various concentrations, *i.e.*, 0.78, 1.56, 3.13, 6.25, 12.5, 25, 50 and 100 µg/ml for 3, 6, 12, 24, and 48 hr (37°C). Dihydroartemisinin (200 µM) was used as positive control. Cultures were washed out and incubated with complete media for 48 hr. The  $IC_{50}$  of the extract was 20 µg/ml. The antimalarial action started at 12 hr after parasite exposure. There was no difference in  $IC_{50}$  values following the exposure time of 24- and 48- hr. In conclusion, the ethanolic extract of *A. lancea* exhibited moderate antimalarial activity ( $IC_{50}$  between 11 and 26 µg/ml) on the trophozoite stage (12 hr) of *P. falciparum*.

**Keywords:** *Plasmodium falciparum*, *Atractylodes lancea* (Thunb) DC., antimalarial activity, time-dependent action, trophozoite

# Preliminary study of P-glycoprotein inhibitory potential by alpha-mangostin based on hCMEC/D3 cell monolayers

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Inhibition of P-Glycoprotein (P-gp), a member of ABC transporters, is a common mechanism underlying drug-drug interactions. Alpha-mangostin, the active compound from Garcinia mangostana L., showed antioxidant and cytoprotective properties. Moreover, it also has neuroprotective effects in vitro. This study aimed to determine the inhibitory potential of alpha-mangostin on P-gp, based on immortalized human brain endothelial cell lines. Herein, hCMEC/D3 cell monolayers were used to investigate the inhibitory potential of alpha-mangostin on transport of rhodamine 123 (Rh123), a fluorescent dye model substrate, via Rh123 permeability and accumulation assays using a microplate reader. In the permeability assay, the P-gp inhibitors verapamil (100 µM) and alpha-mangostin (5 μM) did not significantly affect the basolateral-to-apical permeability of hCMEC/D3 cells to Rh123. However, they increased hCMEC/D3 cell apical-to-basolateral Rh123 permeability 5- and 2-fold, respectively, compared to control (efflux buffer) levels. In the drug accumulation assay, the hCMEC/D3 cells were incubated with Rh123 (5 µM) and inbibitors [verapamil (20, 50, 100 µM) or alpha-mangostin (1, 2.5, 5 µM)] for 4 hours. The remaining amount of Rh123 in the hCMEC/D3 cells was measured to investigate the functional expression of P-gp. The presence of the P-gp inhibitor verapamil showed no significantly increased remaining amount of Rh123, whereas alpha-mangostin (5 μM) showed a more than 5-fold increase compared to the control.

Keywords: Alpha-mangostin, hCMEC/D3 cell lines, P-Glycoprotein, Rhodamine 123

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### Mitochondrial division inhibitor 1 enhances apoptotic effect of cisplatin on cholangiocarcinoma cells

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Cisplatin is the most widely used chemotherapy drug for the treatment of several cancers. Overcoming platinum drug resistance presents significant challenge in cancer treatment. The purpose of this investigation was to examine a novel drug combination using cisplatin and mitochondrial division inhibitor 1 (mdivi-1) in cholangiocarcinoma cells (CCA). KKU-214 and KKU-156 cells were derived from normal human liver tissues. Cultured cells were exposed to drugs for 48 hours following assays of cytotoxicity and apoptotic cell death. Effects of cisplatin and mdivi-1 on cell growth were determined by a MTT assay and induction of apoptosis was determined by fluorescent dye staining using acridine orange and ethidium bromide. We found that mdivi-1 significantly enhanced apoptosis when combined with cisplatin and the drug combination caused a rapid increase of reactive oxygen species as assayed by 2,7-dichlorodihydrofluorescein diacetate staining. In conclusion, our data evidence the combination of mdivi-1 with conventional chemotherapeutic drugs may facilitate the drug discovery in chemoprevention of CCA.

**Keywords:** Mitochondrial Division Inhibitor-1 (mdivi-1); Cholangiocarcinoma; Apoptosis; Cytotoxicity

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#### DMSc proficiency testing program for α-thalassemia 1 diagnosis: 13 years experience in Thailand

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Precise and accurate molecular diagnosis of  $\alpha$ -thalassemia 1 allele is one of the key factors for successful prevention and control of Hb Bart's hydrops fetalis (homozygous  $\alpha$ -thalassemia 1) in Thailand. Since 2004, the Department of Medical Sciences (DMSc), Ministry of Health has established a DMSc proficiency testing program for molecular diagnosis of  $\alpha$ -thalassemia 1. The program evaluates clinical laboratory performance based on pre-established criteria in comparison with other member laboratories. Enrollment in the DMSc program expanded from 13 laboratories in 2004 to 44 by the end of 2016. Four blind DNA samples were tested triennially and each laboratory performance at the end of each test cycle were distributed to all participating laboratories. Overall analytical accuracy (99.5%), analytical sensitivity (99.2%) and analytical specificity (99.7%) indicated excellent performance. Only 11/44 participating laboratories in 39 test cycles failed to correctly genotype the samples. Ten of the 11 laboratories resolved the problem by the end of the following test cycle and all within 3 cycles. The DMSc proficiency testing program will be expanded to cover other molecular genetic tests, such as  $\alpha$  -thalassemia, Down syndrome and cancer biomarkers, to ensure the quality of these tests in clinical laboratories throughout Thailand.

**Keywords**: proficiency testing, thalassemia, genetic tests

# GMP-Compliant manufacturing of the "DMSc Stem Pro" mesenchymal stem cells for clinical trial in retinitis pigmentosa patients

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Mesenchymal stem cells (MSCs) have a potential to represent promising therapeutic approaches for the treatment of a wide range of condition. The Department of Medical Sciences (DMSc) has cooperated with the Department of Ophthalmology, Faculty of Medical, Siriraj Hospital in the study of feasibility and safety of autologous bone marrow MSCs (DMSc Stem Pro) after intravitreal injection in Retinitis Pigmentosa (RP) patients (ClinicalTrails.gov Identifier: NCT01531348) MSC expansion protocol was developed and translated to a clinical trial. The DMSc manufacturing facility was designed to enable clinical production of novel biotherapeutics under GMP and GTP. Specific SOPs were well-written to provide and effective control for each step of the manufacturing processes. Reagents, materials and devices were carefully evaluated and selected from those suitable for clinical applications. Critical equipments should undergo periodic calibrations. Analytical methods have been developed and validated to assay sterility, purity, identity and potency. At a minimum, quality control of MSCs products should be considered on the microbiological safety tests (sterility and mycoplasma), endotoxin, characterization of cell surface antigen, viability, and MSC tri-lineage differentiation. Finally, 4 consecutive batches of the final product were validated in order to assure the consistency and reproducible quality of stem cell product before implementation in the clinical trial. Results of phase I clinical trial demonstrated that biological characterization of the MSCs were in accordance with the ISCT criteria in morphology, adhesion to plastic surface, cell surface markers expression and tri-lineage differentiation to adipocyte, osteocyte, and chondrocyte. No clinically adverse events were detected after intravitreal injection in 9 patients. These data clearly demonstrate the safety of MSCs for intravitreal administration, which in turn could support the other clinical trials of MSCs-based therapy.

**Keywords**: Mesenchymal stem cells, pigmentosa, clinical trail

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# Predictive factors of success in the management of vocal cord nodules in the pediatric population

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To investigate the predictive factors for success in pediatric patients diagnosed with vocal cord nodules undergoing speech therapy. Retrospective chart review. A review of fifty-two patients under 18 years of age who had been referred for voice therapy to treat vocal nodules at a tertiary medical center from March 2005 to March 2015 was made. Preoperative variables were analyzed to determine predictors for the need for revision surgery and associated speech outcomes. We compare our revision rate to that of previously published literature as well as analyze speech outcomes. Tertiary care medical center. Forty-six patient charts were reviewed with an average age of 7.14. Twenty-eight percent of patients were females. On average, patients who participated in voice therapy attended 5.61 therapy sessions. Roughly half of the patients held a co-diagnosis of reflux, while 32.6% had been diagnosed with allergic rhinitis (AR). The most commonly reported vocally abusive habits included excessive speaking (78.2%), loud speaking (69.7%), and shouting/yelling (43.4%). Acoustic analysis data found the average maximum phonation time was 5.45 seconds. The group as a whole demonstrated elevated frequency ranges during sustained phonation with all results greater than 30 hertz (Hz) and the group average frequency range was 104.14 Hz. The average percentage voiced during sustained phonation was 88.67. Adolescent males make up the majority of patients diagnosed with vocal cord nodules, which is comparable to previously published studies. There were no significant predictive factors noted for successful voice therapy.

**Keywords**: vocal cord nodules, voice therapy, pediatric

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# Associations of tumor necrosis factor $\alpha$ -308 polymorphism with gastritis: a systematic review and meta-analysis

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The  $\alpha$ -308 polymorphism in tumor necrosis factor is reported to be one among the many factors that lead to gastritis. However, results reported from previous studies were inconsistent. Meta-analysis is useful for detecting associations that could otherwise remain masked in studies of limited sample sizes. PubMed and Science direct literature search yielded fourteen case-control studies. Data were extracted and pooled odds ratios (OR) were calculated. Overall OR was significant in the recessive model only (OR 2.13 P<0.00001). Subgroup analysis by ethnicity showed that Asians had highest associations (recessive: OR 2.86, P<0.00001). In conclusion, the TNF $\alpha$ -308 polymorphism plays a part in gastritis progression, particularly among Asians.

**Keywords:** TNF $\alpha$ -308, tumor necrosis factor  $\alpha$ -308, polymorphism, gastritis, meta-analysis

# Associations of DC-SIGN (*CD209*) Promoter -336G/A polymorphism (rs4804803) with dengue infection:a systematic review and meta-analysis

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Dengue virus entry into a host is associated with a cell surface protein, DC-SIGN (dendritic cell-specific intercellular adhesion molecule-3 grabbing non-integrin). A common CD209-336G/A (rs4804803) polymorphism in DC-SIGN may affect severity of dengue virus infection (DEN) and incidence of dengue fever (DF) or the more severe dengue hemorrhagic fever (DHF). However, the reported associations of these two outcomes and CD-209 have been inconsistent, which prompted a meta-analysis to obtain more precise estimates. A literature search yielded seven case-control studies. We calculated pooled odds ratios (OR) and 95% confidence intervals using standard genetic models. Outlier treatment examined sources of potential heterogeneity. Subgroup analysis was performed for ethnicity and age. All significant (P = 0.02-0.05) outcomes indicating reduced risk were observed in the overall analysis (OR 0.60-0.62), and subgroups of South/Central Americans (OR 0.58-0.61) and school-age children (OR 0.41-0.80) in the DEN analysis, and Asians for DF (OR 0.59). Most pooled effects in DF and DHF were variable. Heterogeneity ( $P \le 0.10$ ) was least in DEN and most in DHF. Robustness was least in DHF and most in DEN. Conclusions: The DC-SIGN -336G/A polymorphism significantly affects DEN and DF incidence with the effect more pronounced in certain analyzed patient subgroups.

Key words: DC-SIGN (CD209)-336G/A, polymorphism, meta-analysis, dengue virus infection

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# Ethnic specific associations between the estrogen receptor- $\alpha$ gene polymorphisms and risk of uterine leiomyoma: a systematic review and meta-analysis

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Evidence that steroid hormones have a central role in modulating growth of uterine leiomyoma stem from polymorphisms in genes involved in estrogen biosynthesis, metabolism and signal transduction. We investigate associations between the *PvuII* and *XbaI* polymorphisms in the estrogen receptor- $\alpha$ gene and uterine leiomyoma. PubMed and Science Direct databases were searched for relevant studies. We estimated risk (odds ratio [OR] with 95% confidence intervals) using allele genotype comparisons. In both *PvuII* and *XbaI*, we found no significant overall associations (OR 0.84-1.34, P = 0.43-0.98). However, the Asian PvuII subgroup showed significant increased and reduced risks for the variant (OR 1.28, P = 0.04) and wild-type (OR 0.49, P = 0.003) alleles, respectively. Strengths of these pooled ORs were enhanced by the significant P values for interaction when compared with non-Asians (P = 0.01-0.05). Meta-regression analysis showed that ethnicity contributed to heterogeneity of the overall PvuII results (P = 0.003-0.04). Heterozygous genotype XbaI pooled outcome for whites indicated susceptibility (OR 1.41), significant in terms of association (P = 0.03) and interaction with the Asian subgroup (P = 0.04). In both polymorphisms, sensitivity treatment impacted upon stability of the non-Asian/white outcomes but not Asians. Overall summary estimates imply no associations with leiomyoma but suggest susceptibility among PvuII Asian carriers. The significant heterozygous XbaI pooled effects among whites require more studies for confirmation.

**Keywords:** estrogen receptor-alpha, *PvuII*, *XbaI*, polymorphisms, leiomyoma, meta-analysis

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#### Meta-analysis in biomedicine: a methodological approach

Noel Pabalan<sup>1</sup>, Suwit Chaisri<sup>1</sup>, Anthicha Kunjantarachot<sup>1</sup>

This poster outlines the steps on how to perform a meta-analysis in biomedicine in plain and clear language. There are three main reasons to do meta-analysis in biomedicine. First, there are dozens to hundreds of primary studies for a given biomedical question. One may neither have the time or inclination to read all of them. Reading even a few of these would lead to reason number two: conclusions of these primary studies do not all agree. What is one to do with such conflicting conclusions? Third, one may not have the time or extensive resources to perform laboratory work or when they have both, meta-analysis is either or both a good substitute and/or adjunct to one's research. This is good because meta-analysis adds statistical power thus raising the credibility of the research outcomes.

**Keywords:** meta-analysis, biomedicine

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# Expression and serum levels of mucin 5AC (MUC5AC) as a biomarker for cholangiocarcinoma: a meta-analysis

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Potential of biomarkers in detecting cholangiocarcinoma (CCA) would be facilitated by examining CCA-associated proteins from primary studies. One such protein is mucin5AC (MUC5AC) but inconsistency of reported associations between its expression/serum levels and CCA prompted a meta-analysis to obtain more accurate estimates. Methods: A literature search yielded 17 included articles where multiple data in some raised the number of studies to 22. We calculated pooled odds ratios (OR) and 95% confidence intervals from negative and positive readings of MUC5AC levels. We subgrouped the data by ethnicity, sample source and detection method. Results: Significant associations (P < 0.001) point to the following subgroups: (i) Thai (OR 8.32) and (ii) serum (OR 4.52). Heterogeneity in these two outcomes ( $I^2 = 90-93\%$ ) were erased by outlier treatment ( $I^2 = 0\%$ ) which also modulated the association effects (OR 2.48-2.59). Initial low heterogeneity ( $I^2 = 2\%$ ) was observed in (iii) immunoblot (OR 2.61). Significant associations of the Thai subgroup was improved with the tests for interaction ( $P_{interaction} = 0.02$ ) and robustness of the findings. Conclusions: Our pooled effect findings target the biomarker potential of MUC5AC to the Thai population.

**Keywords**: MUC5AC, biomarker, mucin5AC, meta-analysis, cholangiocarcinoma

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# Associations of tumor necrosis factor- $\alpha$ -308 polymorphism with dengue infection:a systematic review and meta-analysis

<u>Noel Pabalan<sup>1</sup></u>, Suwit Chaisri<sup>1</sup>, Sompong Tabunhan<sup>1</sup>, Mayuri Tarasuk<sup>1</sup>, Hamdi Jarjanazi<sup>2</sup>, Theodore Steiner<sup>3</sup>

Inconsistency of reported associations between the tumor necrosis factor-alpha-308 (TNFα-308) polymorphism (rs1800629) and dengue virus infection prompted a meta-analysis, to obtain more precise estimates. A literature search yielded 14 case-control studies. We calculated pooled odds ratios (OR) and 95% confidence intervals in three groups according to severity, dengue fever (DF), dengue hemorrhagic fever (DHF) and dengue (DEN) using standard genetic models. Pooled ORs were subjected to modifier treatment where re-analysis was confined to Hardy-Weinberg compliant (HWC) studies. Heterogeneity of outcomes warranted examining their sources with outlier treatment. In subgroup analysis, we compared Asian and South/Central American (SCA)/Brazilian effects. Overall pooled outcomes yielded no significant effects (OR 0.66-1.44, P = 0.08-0.96). In the dominant-codominant model, pooled effects were heterogeneous ( $I^2 = 47\%-71\%$ ) which was lost/reduced ( $I^2 = 0\%$ -43%) when outlier treatment was applied. This also yielded significant associations (OR 0.68-0.77, P = 0.02-0.05). Our results are best seen in the Asian subgroup, which in itself already yielded significant effects in DEN (OR 0.62-0.67, P = 0.01-0.02). These reduced risk findings were significant from the tests of interaction (P = 0.001-0.02) which highlights the protective effects of TNFα-308 among Asians. TNFα-308 effects on dengue are based on significance and nonheterogeneity of the post-outlier outcomes in the dominant and codominant models. Here, pooled effects may also be ethnic specific, where Asians are protected but not SCA. Both modified and Asian effects are up to 38% protective.

**Keywords:** TNFα-308GA; tumor necrosis factor-alpha; polymorphism; dengue; meta-analysis

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# Potential of RASSF1A promoter methylation as biomarker for endometrial cancer: a systematic review and meta-analysis

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An epigenetic approach to explaining endometrial carcinogenesis necessitates good understanding of RAS association domain family 1 isoform A (*RASSF1A*) promoter methylation data from primary studies. Differential magnitude of reported associations between *RASSF1A* promoter methylation and endometrial cancer (EC) prompted a meta-analysis to obtain more precise estimates. Literature search yielded eight included articles. We calculated pooled odds ratios (OR) and 95% confidence intervals and subgrouped the data by race. Sources of heterogeneity were investigated with outlier analysis. The pooled ORs (OR = 11.46) indicated increased risk of EC, mostly significant. The greater effect, when stratified by race, was reflected in the European outcome (OR 15.07). However, both findings were heterogeneous ( $I^2 = 57$ - 70%), which when subjected to outlier treatment, erased heterogeneity ( $I^2 = 0$ %) and retained significance (OR = 9.85- 12.66) were obtained. Significance of these pre- and post-outlier outcomes were pegged at  $P \le 0.0001$ . Only the Asian pre-outlier (OR = 6.85) and heterogeneous ( $I^2 = 82$ %) outcome was not significant (P = 0.12), but when subjected to outlier treatment, erased heterogeneity ( $I^2 = 0$ %) and significance (OR 23.74,  $P \le 0.0001$ ) were generated. Consistent increased risk associations underpinned by significance and robustness render *RASSF1A* with good biomarker potential for EC.

**Keywords:** RASSF1A promoter methylation, endometrial cancer, meta-analysis

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# Comparison of short term effects between hydrotherapy and land-base mobilization in frozen shoulder: a pilot study

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Frozen shoulder is the most common type of shoulder region that can affect shoulder pain or restriction of movement including quality of life in the general adult population. Land base mobilization and hydrotherapy has been used to decrease shoulder pain, increase range of motion (ROM) and improve quality of life. However, no comparative study is available. Thus, the purpose of this study was to compare short term effects of land base mobilization and hydrotherapy in frozen shoulder. Ten subjects, aged from 40 to 70 years, participated in the study. The subjects were randomly allocated into two groups; land base mobilization and hydrotherapy. Assessor evaluated outcome measures; pain level at movements by Visual Analog Scale (VAS), active ROM by goniometer and disability by Disability Arm Shoulder and Hand questionnaire (DASH) at the baseline and at 1 week follow-up. The results showed that the subjects who received the hydrotherapy significantly greater improvement of pain, active ROM in all directions and disability at 1 week follow-up (p<0.05). Additionally, changes within the group showed significant increase active ROM in all directions and decrease in pain level at movements in all directions and disability in hydrotherapy group at 1 week follow-up (p<0.05). The land base showed significant decrease pain level and increase active ROM at movements in internal rotation and flexion at 1 week follow up (p<0.05). In conclusion, the results suggest that hydrotherapy can be an alternate choice to treat the frozen shoulder in order to improve ROM, pain during movement and disability.

**Keywords:** Frozen shoulder, Land-base mobilization, Hydrotherapy

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### How elderly's perception influences health behaviour: a case study based on the health belief model

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In this case study, how elderly's perception towards health influences their health behaviour was studied based on the Health Belief Model. We used qualitative interview to gain data to create a questionnaire to collect quantitative data from 16 elderly (60 years and older). The results demonstrated that 14 participants (87.5%) had negative health behaviour. These participants perceived the seriousness of their disease to be high but it did not promote positive health behaviour unless the disease interfered with their daily and working lives. They had low perceived susceptibility as they thought they had low risk of getting the disease. They had high perceived benefits but these were outweighed by the perceived barriers. Results also showed that these participants were highly influenced by their family members. Lastly, even after receiving advice from medical professionals, they admitted that they would not follow the advice and would not be able to go through with the medication as prescribed. This case study provides preliminary findings into elderly's perception on health and how it influences health behaviour.

**Keywords:** elderly, health belief model

#### Reduction of viable bacteria in dentinal tubules treated with a novel medicament (Z-Mix)

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Background: The 3Mix-MP formulation (a mixture of metronidazole, ciprofloxacin, and minocycline; macrogol and propylene glycol) has been used to kill residual bacteria in dentinal caries. This study aimed to investigate the dentine disinfection and cytotoxicity of a novel zinc oxide (ZnO) based medicament, denoted as Z-Mix. Materials and methods: Z-Mix was prepared as a prefilled syringe of materials containing mainly ZnO, incorporated with amoxicillin, ciprofloxacin, and metronidazole (1 g% of each antibiotic). Drug penetration was measured at 24 hours and 72 hours. Streptococcus mutans, Lactobacillus acidophilus, or Enterococcus faecalis were inoculated into dentinal tubules for 30 days and were then subjected to Z-Mix or 0.2% chlorhexidine (CHX) for 48 hours. Viable bacteria in the dentine were determined using fluorescence staining. Their cytotoxicity against human dental pulp cells was assessed using an MTT assay. Results: Z-Mix obviously diffused into dentinal tubules and the root apex, compared to the 3Mix-MP (P < 0.05). Fluorescence staining demonstrated a reduction of viable bacteria at 100 mm and 500 mm below infected cavities after treatment with Zmix or CHX for 48 hours. Live and dead bacteria ratios indicated that Z-Mix exhibited markedly antimicrobial effects on inoculated bacteria in dentine samples (P < 0.05). There was no significant difference in the antimicrobial property between Z-Mix and CHX (P > 0.05). An acceptable level of cytotoxicity was observed in Z-Mix and its ingredients.

Keywords: biocompatibility; dentine disinfection; triple antibiotics; Z-Mix

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# Evaluation of total phenolic content and ABTS radical scavenging activity of lipophilic extracts from Thai medicinal plants

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Free radical or oxidant can interact with biomolecules such as nucleic acid that lead to DNA damage and disease condition. Plants could act as safe, speedy factories for disease prevention, treatment, and optimal health in human and animals. Total equivalent antioxidant capacities (TEAC) and phenolic contents of 20 lipophilic extracts of Thai medicinal plants were investigated. The aims of this study were (1) to measure total phenolics by Folin-Ciocaltau method in the comparison with calibration curve of gallic acid; (2) to estimate antioxidant activity by ABTS radical scavenging capacity assay and (3) to determine the relationship between phenolic compounds and their antioxidant activity. The lipophilic extracts with the highest total phenolic content were found in leaf, root and stem extracts of Derris indica with  $71.459 \pm 4.300$ ,  $67.625 \pm 4.773$  and  $50.541 \pm 5.441$  mg of gallic acid equivalents g-1 of dry extract, respectively. However, stem extract of *Ancistrocladus tectorius* showed the highest total equivalent antioxidant capacities (TEAC) with an EC<sup>50</sup> (Half maximal effective concentration) of  $63.816\pm4.831$  µg/mL. A negative correlation (r = -0.9638) between total phenolic content and antioxidant activity of *D. indica* and *A. tectorius* was observed in this investigation.

Keywords: Antioxidant activity, Total phenol, Plants

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### Lupus panniculitis of the scalp as the distinctive manifestation of lupus panniculitis: a review of literatures

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Lupus panniculitis of the scalp (LPS) is a rare presentation of lupus erythematosus panniculitis (LEP) with distinctive clinical features of distribution along Blaschko's line, linear, arch or annular alopecia. Hence, we review of clinical features, investigations, and treatments of this condition. The PubMed and SCOPUS Database up to August, 2017 was reviewed using keywords, "lupus panniculitis", "lupus erythematosus panniculitis", "lupus profundus", "head" and "scalp". There were 20 cases of lupus panniculitis of the scalp (LPS). The median (range) age of disease onset was 26 (10-53) years, with equal sex ratio (female: male ratio = 1:1), and the median disease duration was 12 (2-84) weeks. The most affected scalp was frequently found in parietal (70%), frontal (45%), occipital (30%), temporal (40%), and vertex (10%) areas with 70% of Blaschko's line distribution. Meanwhile, the morphologies of lesions were linear, annular, arch-shaped, and ulcer. Additionally, ANA and anti-Ro antibody were identified in 60%. In the meantime, the most common treatments comprised hydroxychloroquine, oral prednisolone, intralesional corticosteroid, and methotrexate, with treatment results of complete response and improvement. Nonetheless, the recurrence was high in 35%, with 4 cases (20%) of SLE development during the follow-up period. The rare cases of lupus panniculitis of the scalp with linear alopecia were reported. The continuous follow-up is, however, strongly recommended due to the high possibilities of recurrence and SLE development

**Keywords:** lupus erythematosus panniculitis, lupus profundus, linear alopecia, Blaschko's line



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#### Study the wisdom of *Perilla frutescens* Linn in the Upper-North of Thailand

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Perilla frutescens Linn. is a herb which is a rich source of omega 3 (54-64%), can be found in Northern of Thailand. The people in the upper Northern region are traditionally used following traditions, cultures and wisdom, which have not been documented. This research aimed to acquire the folk knowledge and experience in term of drug and food uses of P. frutescens using In-depth interview, participant's observation and group discussion from traditional therapists in 5 provinces including Chiangmai, Chiangrai, Nan, Phayao and Maehongson. The result was found that the total number of traditional therapist 200 persons. Mostly traditional therapists were female (75.50%) and male (24.50%). Their age were ranged from 51-60 years old accounted for 27.5%, 61-70 years old accounted for 26.50%, over 81 years old accounted for 7.50% and 30-40 years old 4.5%. The knowledge and usage of P. frutescens seeds accorded to the way of life in the community. The villagers consumed *P. frutescens* seeds during the harvest (November to February). Because it is a harvesting season, the new P. frutescens seeds have a pleasant aroma. Pound the P. frutescens seeds with salt, mix with the new steamed rice glutinous called "Kaow Nuk Ngah" which can be consumed as energetic breakfast. P. frutescens seeds also mixed as an ingredient in desserts or snacks such as crisp cracker, sweet stuffed dough and rice paddies for Northern tradition festivals including ordination ceremony, Buddhist lent day and house-blessing ceremony. Folk healers used the oil for helping bone fracture patients. In addition, the oil can be medicinally used by application on hair as a hair coat for nourishment, black and glossy hair. It also used as an ingredient in medicinal herbs to treat broken bones. Nowadays, the usages of *P. frutescens* seeds were decreased because the expense, growth season and wisdom transfer to descendants who conveyed within families and communities. In conclusion, P.frutescens is a potential herb which can be developed into supplement and encouraged to farm for consumption and distribution to generate income for their families and communities

Keywords: Perilla frutescens Linn., traditions, cultures, wisdom

#### Recombinant human polymorphic cytochrome P450 3A4

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The cytochrome P450 enzymes (CYP) are heme-thiolate proteins which catalyze the transfer of an oxygen atom from  $O_2$  to a substrate molecule. Substrates include endogenous compounds such as cholesterol, as well as a vast multitude of exogenous ones like plant secondary metabolites, man-made pollutants, and drugs. CYPs constitute our first-line xenobiotic clearance system. CYP3A4 alone metabolizes over 400 drugs, more than any other human CYP isoform. We propose to establish recombinant CYP3A4 production in *E. coli* bacteria for the pharmacokinetic characterization of novel drug candidates. This requires both CYP3A4 and NADPH-cytochrome P450 reductase to be made concurrently, via a bicistronic expression vector. In addition, site-directed mutagenesis allows the comparison of CYP3A4 with its naturally occurring allelic variants, e.g. CYP3A4\*12 (Leu 373  $\rightarrow$  Phe), in which the substrate-binding site is expected to be altered. The project will serve as a stepping stone for the corresponding use of other human CYP isoforms, some of which are exceptionally polymorphic and pharmacogenetically relevant.

**Keywords:** Cytochrome P450 3A4, NADPH-cytochrome P450 reductase, single nucleotide polymorphism, *Escherichia coli* 

# Bacterial stress and osteoblast responses on graphene oxide-hydroxyapatite electrodeposited on titanium dioxide nanotube arrays

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To develop bone implant material with excellent antibacterial and biocompatible properties, nanotubular titanium surface was coated with hydroxyapatite (HA) and graphene oxide (GO). Layer-by-layer deposition was achieved by coating HA on an anodic-grown titanium dioxide nanotube array (ATi) with electrolytic deposition, followed by coating with GO using anodic electrophoretic deposition. The antibacterial activity against both Gram-negative (*Escherichia coli*) and Gram-positive (*Staphylococcus aureus*) bacteria was determined based on the percentage of surviving bacteria and the amount of ribonucleic acid (RNA) leakage, and correlated with membrane disruption. The oxidative stress induced in both strains of bacteria by GO was determined by cyclic voltammetry and is discussed. Importantly, the antibacterial GO coatings on HA-ATi were not cytotoxic to preosteoblasts and promoted osteoblast proliferation after 5 days and calcium deposition after 21 days in standard cell culture conditions.

Keywords: Orthopedic Implant; Anodic Electrophoretic Deposition; Oxidation-Reduction

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#### A study of fermented spider flower as a source of probiotic lactic acid bacteria screening

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Probiotic is "live micro-organisms which, when administered in adequate amounts, confer a health benefit on the host" which was defined by WHO. The important properties for probiotic are including two major characters, the first is ability to survive in gastrointestinal tract condition and another is safety of the strains. Lactic acid bacteria (LAB), which commonly find in various sources especially in fermented food, are the group of bacteria that normally have potential to be probiotics. In this study, the 22 isolates of lactic acid bacteria were isolated from local fermented spider flower and preliminary characterized probiotic properties. Fourteen isolates (63.63%) of LAB showed ability to survive in simulated gastric fluid and all of LAB isolates (100%) survive in medium containing bile salt after 24 h. In addition, blood hemolysis has not been observed in all isolates (100%). This study can suggest that fermented spider flower might be a good source for novel probiotic screening.

**Keywords:** Orthopedic Implant; Anodic Electrophoretic Deposition; Oxidation-Reduction

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# Induction of apoptosis in human breast cancer cells by damnacanthal isolated from *Morinda* citrifolia L.

### Thararat Nualsanit<sup>1</sup>

Damnacanthal, an anthraquinone compound, is isolated from the roots of *Morinda citrifolia* L.(noni), which has been used for traditional therapy in several chronic diseases including cancer. Although noni has been consumed for a long time in Asian and Polynesian countries, the molecular mechanisms by which it exerts several benefits are starting to emerge. In the present study, the effect of damnacanthal on MCF-7 and SKBR3 breast cancer cell lines growth regulation was investigated. Treatment of MCF-7 and SKBR3 breast cancer cells with damnacanthal for 96 h indicated an antiproliferative activity. The MTT method confirmed that damnacanthal inhibited 50% of the growth of MCF-7 and SKBR3 cells (IC<sub>50</sub>) at the concentration of 30 μM and 55 μM respectively for 96 h treatment. We also examined the effect of damnacanthal on apoptosis and found that damnacanthal induced apoptosis, determined by Annexin V-fluorescein isothiocyanate/propidium iodide (PI) dyeing. In conclusion, the present study provided significant evidence demonstrating that damnacanthal induced antiproliferative activity and apoptosis in both MCF-7 and SKBR3 breast cancer cells.

Keywords: Morinda citrifolia L., Damnacanthal, MCF-7, SKBR3, anticancer activity

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# Comparison of melatonin with growth factors in promoting proliferation of cultured neural stem cells obtained from adult mouse subventricular zone

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Melatonin, a circadian rhythm-promoting molecule secreted mainly by the pineal gland, has a variety of biological functions and neuroprotective effects including control of sleep-wake cycle, seasonal reproduction, and body temperature as well as preventing neuronal cell death induced by neurotoxic substances. Melatonin also modulates neural stem cell (NSC) function including proliferation and differentiation in embryonic brain tissue. However, the involvement of melatonin in adult neurogenesis is still not clear. We showed in previous study that the proliferation and differentiation of precursor cells from the adult mouse subventricular zone (SVZ) can be modulated by melatonin via the MT1 melatonin receptor. Since melatonin and epidermal growth factor receptor (EGFR) share some signaling pathway components, we investigated whether melatonin can promote the proliferation of precursor cells from the adult mouse SVZ via the extracellular signal-regulated protein kinase /mitogen-activated protein kinase (ERK/MAPK) pathways in comparison with epidermal growth factor (EGF). Melatonin-induced ERK/MAPK pathways compared with EGF were measured by using in vitro and vivo models. We used neurosphere proliferation assay, immunocytochemistry, and immunoblotting to analyze significant differences between melatonin and growth factor treatment. In addition, the present result suggested the synergistic effect occurred of melatonin and growth factors on the activating the ERK/MAPK pathway. This study exhibited that melatonin could act as a trophic factor, increasing proliferation in precursor cells mediated through the melatonin receptor coupled to ERK/MAPK signaling pathways. Understanding the mechanism by which melatonin regulates precursor cells may conduct to the development of novel strategies for neurodegenerative disease therapy.

**Keywords:** epidermal growth factor, extracellular signal-regulated protein kinase, melatonin, mitogen-activated protein kinase, neural stem cells, subventricular zone

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# Holistic approach to diabetes mellitus (DM): a finding from community health diagnosis fieldwork in Lat Yai 2 Mhoo 11 Community, Samut Songkhram

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The purpose of our fieldwork is to identify specific health problem(s) and population in Lat Yai 2 Mhoo 11 community, giving importance to health determinants and understanding their culture and lifestyle in a holistic way. Through various data collection methods such as survey, community meeting and in-depth interview, our findings confirmed that diabetes mellitus (DM) is a prevalent health problem in the community and suggested that the community's food behaviour is a contributing factor. Thus, interventions regarding food behaviour could become our promotion of health and prevention of disease for MD 351 Holistic Healthcare 2.

**Keywords**: Community medicine, holistic approach, survey, community meeting, in-depth interview, Diabetes Mellitus, health promotion, holistic healthcare, health determinants

### Glutathione-S-transferase gene polymorphisms and cervical cancer susceptibility: interaction between *GSTM1* and *GSTM3* allele variants

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Glutathione S-transferase (GST) is a xenobiotic metabolising enzyme involved in carcinogen detoxification and the metabolism of various bioactive compounds which studies analysing the relationship between *GSTM3* and cervical cancer are still limited. The aim of the present study was to determine *GSTM3* gene polymorphisms (rs1332018 (AC+CC vs AA)) in Northeast Thais population. A case-control study was performed to determine if *GSTM3* alone or in combination with GSTM1 influenced susceptibility to cervical cancer. A DNA from 198 cancer patients and 198 ages- and sexmatched healthy controls were genotyped by TaqMan probe real-time PCR. The prevalence of GSTM3 genotypes; *AA*, *AC* and *CC* was 74.75%, 24.24% and 1.01%; and 72.22%, 23.74% and 4.04% in controls and cases, respectively. A presence of *C* allele frequency of 0.13 and 0.16 was found in the controls and in the cases, respectively. However, the result suggests that the *GSTM3* polymorphism was not found to be an independent genetic predictor of risk of cervical cancer (p>0.05). Moreover no significant interactions between *GSTM1* polymorphism and *GSTM3* were identified. Our findings suggest that *GSTM3* alone and combination with *GSTM1* gene polymorphism are not associated with cervical susceptibility.

**Keywords:** cervical cancer, *GSTM3* genotype, Northeast Thailand, genetic susceptibility, Glutathione S-transferase

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#### Tannin acid (TA): a molecular tool for chelating and imaging labile iron

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This report presents the potential utilization of tannic acid (TA) as a natural iron chelator. TA is capable of binding with small ferric complexes without competitive binding with endogenous iron-containing molecules such as ferritin and transferrin. It was observed that the extracellular iron binding of TA resulted in the formation of self-assembled Fe<sup>3+</sup>-TA complexes, which were then taken up by HepG2 cells via phagocytosis pathway with autophagy-inducing properties. Obviously, TA was found to inhibit iron-induced HepG2 cell growth. However, cellular interactions and biological responses to the treatment were found to depend on availability of iron. Based on the results of the iron efflux experiment, it can be stated that TA has the capability to mobilize iron from cells in the form of assembled Fe<sup>3+</sup>-TA complexes. Interestingly, TA-mediated cellular iron influx and efflux were successfully monitored via MRI. The results of this study suggest that TA can be used as a molecular tool for chelating and imaging labile iron. This might be a promising approach for prevention and treatment of iron-associated cancer or other iron overload disorders.

Keywords: Natural iron chelator, Tannic acid, Iron overload disorders, NTBI imaging

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# Efficacy of calcipotriol ointment for the treatment of chronic hand eczema: a randomized, double-blinded study

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Topical potent corticosteroids is the mainstay treatment in chronic hand eczema. However, there are numerous adverse effects from chronic use of topical corticosteroids. Calcipotriol, a vitamin D3 analogue has been widely used in psoriasis and was reported to achieve beneficial effects in several inflammatory diseases. This study aims to demonstrate whether topical calcipotriol alone is as effective as standard topical corticosteroids monotherapy in the treatment of chronic hand eczema. Subjects with chronic hand eczema were recruited. Each hand of the subjects was randomly allocated to be treated with either calcipotriol or desoximetasone ointment twice daily for 8 weeks. Recurrence was assessed at 4-week after discontinuation of the treatment. HECSI scores, adverse reactions and digital photographs were performed at baseline, at the  $2^{\rm nd}$ ,  $6^{\rm th}$ ,  $8^{\rm th}$  and  $12^{\rm th}$  week. Total 13 participants completed the protocol. Mean HECSI scores were up to 75% reduction in both treatments (p < 0.001) without significant difference between groups (p > 0.05). Mild scaling and mild dryness were the most common reactions found in calcipotriol and desoximetasone, respectively. Calcipotriol ointment appears to be considered as another effective and safe treatment option in chronic hand eczema. The resolution could be noticed since the second week after starting the treatment.

Keywords: calcipotriol, eczema, vitamin D

# A 24-week, triple-blinded, randomized controlled trial of biochanin A, acetyl tetrapeptide-3 and panax ginseng root extract combinations versus 3% minoxidil solution for treatment of androgenetic alopecia

Suparuj Lueangarun<sup>1\*</sup>, Ratchathorn Panchaprateep<sup>2</sup>

The standard treatment of androgenetic alopecia (AGA) is still limited by its efficacy and side effects. Moreover, in vitro study of phytopharmaceutical ingredients including Biochanin A, Acetyl Tetrapeptide-3 and Ginseng extracts showed benefit for treating AGA. This study aimed to evaluate the safety and efficacy of herbal extracts combination lotion for the treatment of AGA. We conducted a 24-week triple-blinded randomized study to evaluate the safety and efficacy of herbal extracts lotion compared to 3% minoxidil solution in both male and female AGA. A total of 32 subjects (16 males and 16 females), aged average 41.3 years, with mild to moderate AGA (Norwood III-IV and Ludwig I-II) were randomized to receive herbal extracts lotion (n=17) or 3% topical minoxidil solution (n=15) at the dose of 1 ml twice daily. After 24 weeks of treatment, patients in both groups presented significant clinical improvement with increasing of terminal hair count in the target area for 8.9% (p=0.009) and 8.68% (P=0.002) in herbal extracts lotion group and minoxidil group, respectively. HMI also significantly increased from baseline for 13.8% in herbal extracts lotion and 31.4% in minoxidil group. In addition, expert panel photographic assessment of vertex area in herbal extracts lotion group revealed 18% of subjects showed excellent improvement (score = +3) and 76% showed moderate improvement (score = +2, 40-70% increase) versus minoxidil group, 21% of subjects showed excellent improvement (71-100% increase) and 79% showed moderate improvement (40-70% increase). However, less significant response was noted at the frontal area compared to the vertex area. There was no statistical difference between herbal extracts lotion and 3% minoxidil solution in all evaluation aspects. No local adverse reactions from herbal extracts lotion were observed. However, one female subject developed scalp eczema after using 3% minoxidil solution for 6 weeks and showed satisfactory response at the end of the study after switching to herbal extracts lotion without adverse reactions. In conclusion, herbal extracts lotion showed significantly comparable efficacy to 3% minoxidil solution for treatment of mild to moderate AGA. The treatment should be considered as an option for both male and female AGA.

**Keywords**: Androgenetic alopecia, Male pattern hair loss, Female pattern hair loss, Biochanin A, Acetyl Tetrapeptide-3 and Ginseng extracts, Minoxidil solution

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### **PROCEEDINGS**

# Combined loading of ticagrelor and clopidogrel and platelet inhibition in patients with acute ST segment elevation and high risk non ST-segment elevation myocardial infarction undergoing percutaneous coronary intervention

Kumpol Chintanavilas<sup>1</sup>, Muenpetch Muenkaew<sup>1</sup>, Pisit Hutayanon<sup>1</sup>

#### **Abstract**

Platelet reactivity during percutaneous coronary intervention (PCI) in patient with ACS is associated with early and long term outcome. Whether combined loading of ticagrelor and clopidogrel has better platelet inhibition compared to clopidogrel alone in this clinical setting is not known. We aim to assess effect of loading of ticagrelor plus clopidogrel and clopidogrel alone-on platelet inhibition in patients with acute ST-segment elevation (STEMI) and high-risk non ST-segment elevation myocardial infarction (NSTEMI) undergoing PCI within 2 hours. Clopidogrel-naive patients with acute STEMI or high-risk NSTEMI who were undergoing PCI were enrolled to this study after giving informed consent. After randomly assigned to one of antiplatelet loading strategies before PCI; group A (ticagrelor 180 mg plus clopidogrel 600 mg) or group B (clopidogrel 600 mg), all patients received conventional dose of 325-mg aspirin and maintenance dose of 75 mg/d of clopidogrel. Clinical and laboratory data were obtained. Blood test for platelet reactivity was performed using the VerifyNow P2Y12 assay at 0, 2 hours after antiplatelet loading. There were 5 patients in group A and 4 patients in group B. Median door-to-balloon time in each group were 110 and 133 minutes, respectively. Mean platelet reactivity at 2-hour after P2Y12 inhibitors ingestion, after excluding one patient who vomited study drugs, was significantly lower in group A than in group B (97.3 vs. 282.25 PRU, p-value =0.001) No immediate vascular complication was observed during index hospitalization of each patient. Outpatient 30-day follow-up of all patients showed one case of cerebral infarction and two cases of minor GI bleeding in group B while no cardiovascular event or clinical bleeding occurred in group A. Combined loading of ticagrelor and clopidogrel had significantly better platelet inhibition than clopidogrel loading alone in patients with acute STEMI and high risk NSTEMI undergoing PCI.

**Keyword:** Ticagrelor, Clopidogrel, STEMI, High risk NSTEMI, Percutaneous coronary intervention, Platelet function test

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#### **Background**

The most common cause of acute coronary syndrome (ACS) is plaque rupture that is leading to thrombus formation causing arterial occlusion. Thrombus formation process initiated by platelet activation and aggregation followed by activation of the coagulation cascade. Benefit of antiplatelet therapy such as aspirin in ST-elevation myocardial infarction (STEMI) proves this pathophysiology in ACS<sup>1</sup>.

P2 Y12 inhibitors combined with aspirin are the mainstream in ACS treatment. This strategy plays role in both STEMI and non ST-segment elevation myocardial infarction (NSTEMI) management.

Recent guideline for management of STEMI recommended minimizing delays to receive reperfusion therapy by a goal to achieve a first medical contact-to –balloon time  $\leq 90$  min (preferably  $\leq 60$  min if the patient presents directly to a PCI-capable hospital or within 2 h of the onset of symptom)<sup>2</sup>. Another factor that has an impact from the timing of treatment is antiplatelet therapy. One large study shows the benefit of early initiation of P2Y 12 inhibitor in decreasing the incidence of early stent thrombosis<sup>3</sup>.

Clopidogrel, the standard P2Y12 inhibitor for most ACS patients undergoing PCI in Thailand, has several important limitations include:

- 1. Delayed onset of platelet inhibition from intestinal absorption and require two sequential oxidative steps of hepatic metabolism to convert to its active metabolite. Although in high loading dose, this process spent time for 2-4 hours.
- 2. Clopidogrel has wide interindividual variability in response, which was associated with adverse cardiovascular outcomes.<sup>4</sup>
- 3. Low inhibition of platelet aggregation (IPA) in many patients<sup>5</sup>

Ticagrelor, which has more potent and more rapid onset of platelet inhibition, is using in the standard treatment for ACS patients undergoing PCI<sup>6</sup>. But from the pharmacoeconomic reason, this drug is not widely use in Thailand.

From the limitation of antiplatelet use in Thailand, we aim to assess the effect of loading of ticagrelor plus clopidogrel (group A) and clopidogrel alone (group B) on platelet inhibition in patients with acute STEMI and high-risk NSTEMI undergoing PCI within 2 hours.

#### **Materials and Methods**

#### Study patients and treatment

18-75 Years old clopidogrel-naive patients with acute STEMI or high-risk NSTEMI who were undergoing PCI were enrolled in this study after giving informed consent. The major exclusion criteria are 1)high bleeding risk defined by history of intracranial hemorrhage or history of bleeding in previous 6 month, history of any surgery in 4 weeks, moderate to severe hepatic impairment and patient needs for oral anticoagulant, 2)an increased risk of bradycardia 3)concomitant therapy with a strong cytochrome P-450 3A inhibitor or inducer Eligible patients randomly assigned by block technic with conceal randomization to one of antiplatelet loading strategies before primary PCI; group A (ticagrelor 180 mg plus clopidogrel 600 mg) or group B (clopidogrel 600 mg). All patients received conventional dose of 325-mg aspirin. Clinical and laboratory data were also

obtained. Blood test for platelet reactivity were performed using the VerifyNow P2Y12 assay at 2 hours after antiplatelet loading. Outpatients follow up visit schedule at 1 month for clinical and safety outcomes. The study was approved by the Institutional Review Board.

#### Outcome

Primary endpoint was Platelet function test by VerifyNow P2Y12 assay method at 0 and 2 hours after loading antiplatelets. Cut point for high platelet reactivity defined as >208 PRU. Key secondary endpoints were TIMI Frame count after PCI, Complete ST-segment elevation resolution at 60 min post-PCI, Peak CKMB, cardiovascular death, non-fatal stroke, non-fatal myocardial infarction, or urgent target vessel revascularization and Incidence of major bleeding by PLATO study definition at 30 days.

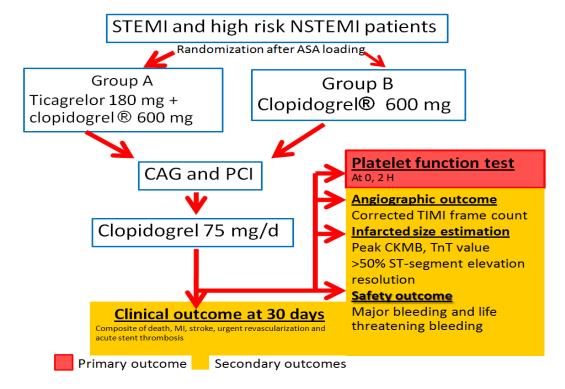


Figure 1 Study protocol

# Sample size calculation

Base on previous study from Kewin P. Bliden et al $^8$ , platelet function at 2 hours after clopidogrel 600 mg loading was  $250 \pm 100$  PRU while Benjamin Hibbert $^9$  show platelet reactivity after ticagrelor 180 mg with clopidogrel 600 mg was  $90\pm100$  PRU. These result provide sample size calculation at 80% power with alpha for 0.05 base on sample size calculation equation

N/group = 
$$\frac{2(Z_{\alpha/2} + Z_{\beta})^2 \sigma^2}{(\bar{X}_1 - \bar{X}_2)^2}$$

The calculated sample size is 7 for each group.

#### Statistical analysis

Categorical data are reported as counts and percentage and comparing using Fisher's exact test. Continuous variables are expressed as mean with standard deviation (SD). Comparison between groups was made by independent sample T test for value with normal distribution and by Mann-Whitney (Wilcoxon rank) test for continuous variables without

normal distribution. All p values were 2- tailed and P<0.05 was considered significant. All analysis performs using SPSS 18.0 for window (SPSS Inc., Chicago, IL).

#### **Results**

#### Population and patient characteristics

Nine patients presentation with acute coronary syndrome (7 STEMI and 2 high risk NSTEMI) were randomly assigned to one of antiplatelet loading strategies before PCI; group A (ticagrelor 180 mg plus clopidogrel 600 mg) N=5 or group B (clopidogrel 600 mg) N=4. Characteristics of all patients were described in Table 1 with no significant difference of age, total ischemic time or door to balloon time between both groups.

		Age			Door to balloon time	Total ischemic time	Final culprit vessel TIMI frame count	elevation	PEAK MB	PEAK TN	TClinical	
ROUP	No.	/Sex	Diagnosis	Underlying disease	(min)	(min)	(ratio to normal limit	)> 50%	(ng/ml)	(ng/ml)	outcome	Bleeding
	1	53/M	Inf STEMI	Smoking	110	170	20/1	Υ	5.03	0.084		
	2	59/F	NSTEMI	DM/HT/DLP/PreviousACS	N/A	N/A	19/0.53	N/A	9.27	1.47		
	3	62/F	<u>Inf</u> STEMI	DM/HT/DLP	80	230	22/1.1	Υ	300	3.5		
	4	49/M	AntSTEMI	HT/DLP/Smoking	120	660	24/0.67	No	137	4.57		
Α	5	73/M	Inf STEMI	DVD/old CVA	130	250	29/1.45	Υ	137.4	2.24		
	6	73/M	NSTEMI	HT/DLP	N/A	N/A	22/1.1	N/A	2.06	0.022		Minor/Clea base GU
	7	73/M	Inf STEMI	HT/DLP/Smoking	162	222	33/1.65	Υ	300	10	Lt ACA infarction	Minor/ Gastritis
	8	68/M	AntSTEMI	DLP/Old ischemic stroke	162	1062	30/0.83	Υ	191	6.14		
		5	A . (OTELN	0	75	405	44.00		000	0.0		

**Table 1** Characteristic of study patients.

One patient (No.5) in group A develop vomiting study drug at 1 H after ingestion. Mean door to balloon time in STEMI case were  $110\pm21.6$  mins in Group A and  $133\pm50$  mins in group B.

#### <u>Platelet reactivity</u>

Baseline platelet reactivity was 327±85 PRU in group A as same as 288±8.5 in group B. After loading antiplatelet for 2 hours, platelet reactivity in patients group A was 97±8.4 PRU with significant lower than platelet reactivity in patient group B 282.3 ±40 PRU (P=0.001). We excluded one patient in group A, who had higher platelet reactivity at 2 hour after loading (319 PRU) resulted from vomiting of study drugs at 1 hour after administration.

#### Angiographic outcome

In Group A, transradial approach was performed for 40% with the angiographic result showing 2 cases of RCA occlusion, 1 case of LAD occlusion and 1 case of triple vessel disease (TVD) with culprit lesion at LAD and 1 case of Minor CAD. Patients in Group B were performed via transradial approach for 75% with 2 cases of RCA occlusion, 1 case of LAD occlusion and 1 case of TVD with severe stenosis in LAD and RCA. All patients had successful PCI to culprit lesions. One patient (No.4) received bailout GP IIb/IIIa inhibitor. Mean final TIMI frame count was not different in both groups (22.8 vs. 24, p=0.808). Reliability of TIMI frame count in our study was excellent agreement (Intraobserver reliability ICC=0.826, p=0.003, Interobserver reliability ICC=0.741, p=0.018)

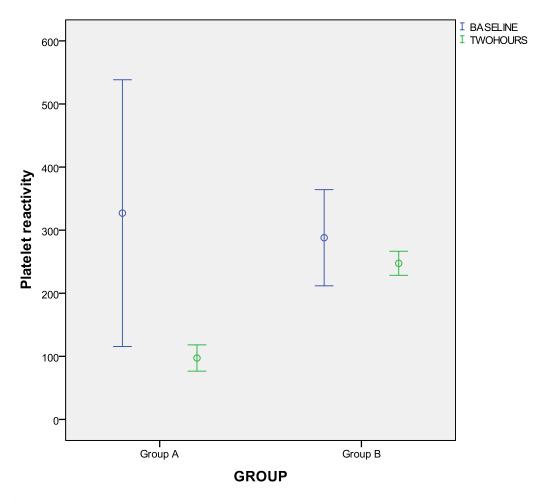


Figure 2 Platelet reactivity (PRU) following antiplatelets administration.

Comparing with normal value of TIMI frame count<sup>10</sup>, each culprit vessel showed the successfulness of percutaneous coronary intervention (TIMI frame count ratio 0.95 vs. 0.97, p=0.950)

#### Clinical outcome

ST segment elevation resolution was achieved in all patients except patient No.4 who received bailout GP IIb/IIIa inhibitor. Peak TnT and CKMB were vary between cases with non-significant lower in peak CKMB and TnT level in Group A patients (peak CKMB 118 vs. 198 ng/ml, p=0.385, peak TnT2.37 vs. 5.01 ng/ml, p=0.235). One patient in group B developed left anterior crerbral artery infarction after the procedure with complete recovery before discharge. No vascular access complication or contrast induce acute kidney injury was observed in all cases. Mean hospital stay was same in both groups (7.6 vs. 6.0 days, p= 0.593). Two patients undergoing stage PCI for non culprit lesion at the same admission. No major or fatal bleeding was observed in this study but 2 cases in group B had minor gastrointestinal bleeding. No significant different in mean Hb change between both groups was observed (1.28 vs. 2.15 gm/dl, p=0.323)

#### **Discussion**

The results of platelet reactivity test showed non-significant lower platelet reactivity in patients receiving ticagrelor plus clopidogrel (153 vs. 282 PRU, p=0.071). These results may be interfered because one patient (No. 5) vomited study drugs after ingestion for 1 hour causing abnormal platelet reactivity result (319 PRU at 2h compared with 297 PRU at

baseline). After exclusion of this patient, the result showed significant lower platelet reactivity in patients receiving ticagrelor plus clopidogrel (97 vs. 282 PRU, p=0.01). The result of our study was correlated with several previous pharmacodynamic studies<sup>8,9</sup>.

**Table 2** Laboratory result and clinical outcomes

	Group A	Group B	Р
Primary outcome			
Baseline platelet reactivity(PRU)	327±85	288±8.5	0.699
Platelet reactivity at 2 h(PRU)	97±8.4	282±40	0.001
Change in platelet reactivity(%)	68.6±10.2	14±3.25	0.006
Secondary outcomes		•	
TIMI frame count	22.8±4	24±10	0.808
TIMI frame count ratio	0.95±0.36	0.97±0.56	0.950
Peak CKMB(ng/ml)	117.7±121	198.3±141	0.385
Peak TnT(ng/ml)	2.37±1.7	5.01±4.2	0.235
Clinical outcome		One minor stroke	
Safety outcomes		2 Minor GI bleeding	
Hb change(gm/dl)	1.28±0.96	2.15±1.5	0.323

Using the standard cut point of high platelet reactivity from ADAPT-DES study, defined as high platelet reactivity >208 PRU, our study demonstrated that all patients in group B who received high dose clopidogrel alone could not achieve optimal platelet inhibition during percutaneous coronary intervention, while the patients who received the combination of ticagrelor and clopidogrel could obtain. In addition to platelet reactivity results, peak CKMB and TnT tended to be lower among the patients in group A. In our study, the difference in platelet reactivity results could not be translated into the significant difference in angiographic and clinical outcomes, this might have resulted from very low number of patient.

Our study was limited by funding problem and technical error from platelet reactivity testing which made we lost some important data that changed by time such as platelet reactivity at baseline and before GP IIb/IIIa inhibitor was given. This caused a lot of missing data and decreased the number of the patients in our study. But the result of our study strongly showed the improvement of platelet inhibition with combined loading of ticagrelor and clopidogrel. Our findings may lead to an improvement of platelet inhibition for patients with ACS undergoing percutaneous coronary intervention by increase only small cost for additional ticagrelor loading. Clinical outcome of this strategy of treatment must be assessed in a larger scale of study. Our study did not demonstrate significant bleeding in the combined P2Y12 receptor antagonists group, but in clopidogrel alone group there were 2 cases of minor gastrointestinal bleeding. Both cases were elderly, more than 70 years old. Safety for combined P2Y12 receptor antagonists should be cautious when using in the elderly person.

#### Conclusion

Combined loading of ticagrelor and clopidogrel had significantly better platelet inhibition than clopidogrel loading alone in patients with acute STEMI and high risk NSTEMI undergoing PCI.

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# Efficacy of tranexamic acid intradermal microinjections in reducing risk of postinflammatory hyperpigmentation after Q-switched Nd: YAG laser for treatment of solar lentigines: A pilot randomized controlled trial

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#### **Abstract**

Postinflammatory hyperpigmentation (PIH) after solar lentigines removal using 532-nm QS Nd: YAG laser is a major concerned cosmetic side effect, especially in patients with darker skin type. Previous studies have been conducted for the efforts to prevent PIH after laser treatment, yet without highly effective results. Thus, this study aimed to evaluate the efficacy and safety of tranexamic acid (TA) intradermal microinjections in reducing risk of PIH after the 532-nm QS Nd: YAG laser for treatment of solar lentigines. Twenty-six solar lentigines of thirteen patients received 532-nm QS Nd: YAG laser treatment. Then, the 50 mg/mL of TA was intradermally injected to one random lesion and normal saline to another as control group. Pigmentation was measured by the mexameter as melanin index (MI) and erythema index (EI) at the baseline, 2<sup>nd</sup>, and 4<sup>th</sup> weeks. The results showed the improvement of each lesion at the 2<sup>nd</sup> and 4<sup>th</sup> weeks, with the mean improvement scores of 90 + 10.8 in the TA group and 75.77 + 16.56 in the control group (4 weeks after treatment, p < 0.05). Whilst, mean MI decreased from 352.9 + 75.13 to 313.05 + 67.69 in the TA group (baseline vs. 4 weeks after treatment, p < 0.05) and from  $354.13 \pm 78.85$  to  $326.64 \pm 62.97$  in the control group (baseline vs. 4 weeks after treatment, p = 0.061). Hence, intradermal TA injection can efficaciously be an effective and safe therapeutic modality in reducing hyperpigmentation after solar lentigines treatment using 532-nm QS Nd: YAG laser.

**Keywords:** Tranexamic acid, Solar lentigo, Postinflammatory hyperpigmentation, Q-switched 532-nm Nd: YAG laser

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### **Background**

Solar lentigines are well-defined light to dark brown hyperpigmented macules appearing mostly on the exposed skin from natural sunlight or artificial sources of ultraviolet radiation (UVR). Following the faster improvement outcomes and less pain, laser treatment has become a popular therapeutic modality for those lesions. The 532-nm O-switched (OS) Nd: YAG laser is an effective laser treatment supported by high quality of evidence. Postinflammatory hyperpigmentation (PIH) is a major concerned side effect for patients with solar lentigines removal by laser treatment, especially those with darker skin type. After laser treatment, the basal cell layer is particularly destroyed. Melanin is dropped into dermis and phagocytosed by melanophage in the upper dermis, leading to dermal melanosis.<sup>2</sup> PIH is composed of excess melanin production or abnormal distribution of melanin pigment in the epidermis or dermis.<sup>3</sup> The injury of keratinocytes in epidermis from laser produces inflammatory mediators. Leukotrienes (LT) C4, LTD4, prostaglandin E<sub>2</sub> (PGE<sub>2</sub>), and thromboxane B2 can increase melanin synthesis and transfer melanin to surrounding keratinocytes.<sup>2</sup> From previous studies, the incidence of PIH after the 532-nm QS Nd: YAG laser treatment was approximately 6.67-53% in Asians and 24% in Thailand. 4-6 Many studies have been conducted to minimize risk of PIH. Postoperatively, a short-term application of topical corticosteroids can significantly reduce the risk of PIH after ablative fractional CO<sub>2</sub> laser resurfacing in Asians with atrophic acne scars. However, topical corticosteroids may interfere wound healing process with an increasing risk of acneiform eruption and infection. Tranexamic acid (TA), antifibrinolytic agent, inhibits plasminogen activator (PA) by reversibly blocking synthetic derivative of lysine binding sites on plasminogen molecules, so the plasminogen in the epidermal basal cells and keratinocytes cannot convert to the plasmin. As well, phospholipase A2 precursors for the membrane phospholipid secretion of arachidonic acid (AA), a precursor of PGE<sub>2</sub> and LT, cannot be activated. In the meantime, the keratinocyte-PA system activation by UVR induces melanogenesis process. 9 So, TA can reduce melanogenesis and inhibit inflammatory mediators. In a previous study, various forms of TA were applied on hyperpigmented lesions, including the oral and intradermal (ID) injection forms of TA which found to be effective for melasma treatment. 10, 11 Nonetheless, the oral form of TA can cause several systemic side effects, such as myocardial gastrointestinal discomfort, infarction, pulmonary embolism, thromboembolism. <sup>10</sup> Whereas, the intradermal TA injection may possibly yield efficacious outcomes in melanin reduction and anti-inflammation process for PIH treatment. Hence, this study aimed to compare the pigment alteration after solar lentigines removal using 532-nm QS Nd: YAG laser following ID injection of 50 mg/mL of TA versus normal saline.

#### **Materials and Methods**

**Patient selection:** This study was performed in patients aged 50-70 years, with at least 2 solar lentigines on the forearms, from December 2016 to January 2017 at skin and aesthetic center, Thailand Tobacco Monopoly Hospital, Thailand. Those who were pregnant, lactating, or found with abnormal wound healing, photosensitivity disorders or any skin diseases at the treatment areas were excluded. The study protocol was approved by the Human Ethics Committee of Thammasat University.

**Laser and post laser treatment:** Preoperative topical analgesic cream (2.5% lidocaine and 2.5% prilocaine; EMLA<sup>®</sup>) was applied and occluded at the lesions 45

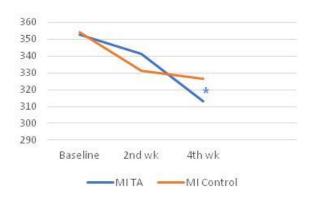
minutes before treatment. Then, all patients received a single treatment of 532-nm QS Nd: YAG laser (Spectra-XT; Lutronic, Seoul, Korea) for their solar lentigines, with spot size 1.8 mm, fluences 0.6-0.8 J/m², and energy adjusted for immediate whitening clinical endpoint. Following the laser treatment, the 50 mg/mL of TA (250 mg/ 5 mL tranexamic acid; Transamin®) was intradermally injected to one random solar lentigo as TA group at 1 cm intervals (0.1 mL/cm²), and normal saline to another as control group. After that, Vaseline was applied on all lesions twice daily until the crusts peeled off, followed by broad-spectrum sunscreen with SPF 40 for 4 weeks. Sun exposed and no topical preparations on the lesions were also suggested for all periods of the study.

Clinical evaluation: The 26 lesions of 13 cases were evaluated. As a subjective measurement, the patient's self-improvement scores in quartile scale (as: none =no improvement, minimal =1-15% improvement, mild =26-50% improvement, moderate =51-75% improvement, and remarkable =>75% improvement) were assessed at 2<sup>nd</sup> and 4<sup>th</sup> weeks after treatment. Likewise, as an objective measurement, the lesions' colour was measured by a narrow-band reflectance spectrophotometer (Mexameter MX18, Courage and Khazaka; Cologne, Germany) as melanin index (MI) and erythema index (EI) at baseline, 2<sup>nd</sup> and 4<sup>th</sup> weeks.

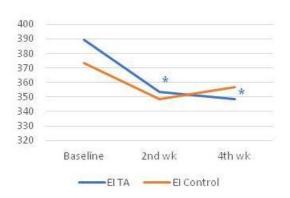
**Statistical analysis:** Data was analyzed using paired t-test by SPSS 21 software (SPSS, Chicago, IL, USA). P value <0.05 was considered statistically significant.

#### **Results**

Thirteen patients with twenty-six solar lentigines were enrolled in the study. Mean age of the patients was 62.77 years (range 50-70 years), with skin types III (23.08%), IV (46.15%), and V (30.77%). Baseline data showed no statistically significant differences between the two groups in baseline MI and EI (p > 0.05). Mean MI (Fig. 1) of the TA group decreased from  $352.9 \pm 75.13$  to  $341.21 \pm 80.71$  (2 weeks, p = 0.554) and to  $313.05 \pm 67.69$  (4 weeks, p < 0.05 vs. baseline). Meanwhile, MI for the control group decreased from  $354.13 \pm 78.85$  to  $331.05 \pm 57.37$  (2 weeks, p = 0.197) and to  $326.64 \pm 62.97$  (4 weeks, p = 0.061 vs. baseline). Significantly, the improvement of MI was observed in the TA group at the end of 4<sup>th</sup> week.

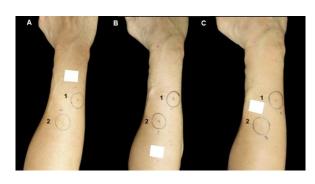


**Figure 1** Melanin index (\*P < 0.05, by paired t-test)



**Figure 2** Erythema index (\*P < 0.05, by paired t-test)

In addition, mean EI (Fig. 2) of the TA group decreased from  $389.41 \pm 56.55$  to  $353.49 \pm 47.74$  (2 weeks, p < 0.05) and to  $348.33 \pm 43.93$  (4 weeks, p < 0.05 vs. baseline). While, EI of the control group decreased from  $373.33 \pm 46.94$  to  $348.33 \pm 40.98$  (2 weeks, p = 0.133) and to  $356.87 \pm 53.02$  (4 weeks, p = 0.303 vs. baseline). The EI improvement was significantly noted in the TA group at  $2^{\text{nd}}$  and  $4^{\text{th}}$  week.



**Figure 3** Photographs of right forearm (A) Baseline (B) the 2<sup>nd</sup> week after treatment (C) the 4<sup>th</sup> week after treatment (1 = control lesion, 2 =TA injected lesion)

The patients' self-improvement scores (Table 1) in the TA group were 12/13 patients (92.31%) rated as remarkable (>75% improvement) and 1/13 patients (7.69%) rated as moderate (51-75% improvement) at the end of  $4^{th}$  week. In the control group, 7/13 patients (53.85%) rated as remarkable (>75% improvement), 5/13 patients (38.46%) rated as moderate (51-75% improvement), and 1/13 patients (7.69%) rated as mild (26-50% improvement) at the end of  $4^{th}$  week. Besides, the mean patients' self-improvement scores were  $90 \pm 10.8$  in the TA group and  $75.77 \pm 16.56$  in the control group (4 weeks after treatment, p<0.05). Moreover, two patients in the TA group have burning sensation immediately after the injection, but can resolve within one hour. As well, one patient had redness on both lesions for seven days.

**Table 1**. Patient's self-improvement scores

	TA (n =13) (%)		Control (n =13) (%)		
Self-improvement score	2 <sup>nd</sup> week	4 <sup>th</sup> week	2 <sup>nd</sup> week	4 <sup>th</sup> week	
Minimal	0 (0)	0 (0)	1 (7.69)	0 (0)	
Mild	4 (30.77)	0 (0)	5 (38.46)	1 (7.69)	
Moderate	4 (30.77)	1 (7.69)	3 (23.08)	5 (38.46)	
Remarkable	5 (38.46)	12 (92.31)	4 (30.77)	7 (53.85)	

#### **Discussion**

PIH after laser treatment is a major concerned cosmetic side effect, especially in patients with darker skin type. The Q-switched laser which is an effective treatment for epidermal lesion including solar lentigines could frequently induce PIH. Previous reports used glycolic acid, or hydroquinone preoperatively before ablative fractional CO<sub>2</sub> laser resurfacing<sup>12</sup>, and fucidic acid combined with betamethasone valerate cream post 1,064-nm QS Nd: YAG laser<sup>13</sup>, but the prevention results could not be detected. In 2015, Cheyasak et al. used postoperative topical corticosteroids (0.05% clobetasol propionate ointment) to prevent hyperpigmentation after ablative fractional CO<sub>2</sub> laser resurfacing. The result showed significant higher incidence of PIH in petrolatum alone (75%) vs. intervention (40%).<sup>7</sup> But the topical corticosteroid can make the side effects such as acneiform eruption, infection, or wound healing process interfering.

TA has a major role hyperpigmented lesions treatment especially melasma. Among various forms, ID injection and oral forms have significant result for melasma treatment. But patient will develop severe side effects especially thromboembolism events from oral TA.<sup>10</sup> In 2006, Lee et al. used 4 mg/mL of TA ID injection once a week on the melasma. The result showed significant decrease in the MASI from baseline to 8 and 12 weeks. 11 Our study used ID TA injected the lesion to reducing risk of PIH after laser treatment. We used 50 mg/mL of TA because TA was injected at the lesion for single time. Moreover, the doses of TA do not exceed 2.5 mg in each patient that is less than the antifibrinolytic dose. Side effect from TA injection in our study is the burning sensation in two patients immediate after injection and can resolve within one hour. The MI in TA group significantly decreased at the end of 4th week (p < 0.05). In the 2<sup>nd</sup> week, MI in TA group was higher than control group because some patients still had the crust at the treatment site. The patients' self-improvement score in TA group was significantly improved when compared with control group at  $2^{nd}$  and  $4^{th}$  weeks. EI in TA group decreased at the  $2^{nd}$  and  $4^{th}$  weeks (p <0.05). But the result was not significant in control group. EI did not associate with TA injection, EI was measured at two weeks after TA injection that the effect of TA may be disappeared. The patients' selfimprovement score was significantly improved in the TA group compared with the control group. In 2016, Kang et al. showed PIH from treatment of solar lentigines using 532-nm QS Nd: YAG laser presented at 4.3 weeks. 14 The further study should extend the follow-up period to observe the preventive effect of TA in the long term.

#### **Conclusion**

Intradermal TA injection can be the effective and safe therapeutic modality in reducing hyperpigmentation after solar lentigines treatment using 532-nm QS Nd: YAG laser.

#### Acknowledgements

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# Consumer attitude toward health focused interior design

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#### **Abstract**

**Introduction.** The growth of metropolitan Bangkok has been exponential within the past decade. Consumer response and interest in health related interior design and development has not been substantially investigated. Given the lack of data regarding consumer interest in interior design and material selection focused on health we attempted to query the public on the impact health makes on their residential choices.

**Methods.** This is a descriptive study utilizing a questionnaire to survey inhabitants of affluent districts in central Bangkok. The demographic data, budget of interior design, and attitude towards design on health concerns were collected. The International Survey of Asthma, Allergy in Childhood (ISAAC) questionnaire was used to evaluate the prevalence of allergic rhinitis amongst participants.

**Results.** There were 150 respondents to this questionnaire. 56% were female and 56% of those surveyed were aged < 40 years. The most common health problem reported was allergic disease Sixty-five percent reported rhinitis symptoms within the past twelve months. Seventy percent of subjects reported having experience with investing in interior design while willing to invest < less than 100,000 baht for health focused design. The health-related expenses were significantly higher in people aged > 40 years of age. The 3 most common attitudes toward interior design focused on health was its effect on health problems, the thought that design could prevent illness and personalized design for health issues is an important decision to make when investing in design.

**Conclusion.** Most Bangkokians residing in the heart of the city over the age of 40 had a trend towards interest in health focused design. This age group also had a higher number of health issues, resided in larger areas (square meters), and were willing to invest a larger sum of money than their younger counterparts.

**Keywords:** interior design, decoration, health, allergy, central business district

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#### **Background**

Allergic rhinitis remains a commonly encountered chronic condition. The prevalence of diseases associated with atopy has increased in many parts of the world over the past 20 to 30 years. [1] The incidence varies by age; increasing from infancy, peaking in childhood and adolescence, and decreasing in the elderly. [2] The allergic diseases of the airway, i.e. allergic rhinitis and asthma, are on the rise in Thailand; allergic rhinitis increased nearly 3 fold (from 17.9% to 44.2%) during the last decade alone. [3] A relatively recent study evaluating Allergic Diseases amongst University Students in Bangkok, Thailand revealed a prevalence of nasal with eye symptoms within the past 12 months to be 26.3%.[4] The most common cause of the disease is environmental implications (aeroallergens). The most common aeroallergen in Thailand are indoor allergens including house dust mite, cockroach, pets, and mold. The environmental impact on health and allergy remains significant. The design of physical environments can affect medical outcomes. The results from many studies showed that interior design and home decoration could prevent allergic exacerbations. Krieger J. et. al found that home intervention could reduce the number of asthma exacerbations and the cost of renovation is less than the cost of treatment.[5] However, the role of interior design and material selection for health related issues, specifically allergic rhinitis (AR) remains underreported. Moreover, there is lack of data regarding consumer interest in interior design and material selection focused on health for those living in the center of metropolitan cities. The main objective of this study is to survey consumer interest in interior design for health amongst people who live in the central business district (CBD) of Bangkok. The secondary outcome is to survey the prevalence of rhinitis and rhinitis with eye symptoms amongst these same people.

#### **Materials and Methods**

### Population

A cross-sectional study was performed utilizing a questionnaire. The data collection was obtained from in inhabitants who live in the CBD of Bangkok, including Silom, Sukhumvit, Sathorn, Ploenchit, Rachadamri, Phayathai, Ekamai and Pathumwan. A total of 150 subjects were interviewed by a private external surveyor group. The ethical board of the Faculty of Medicine, Thammasat University approved this study.

# Questionnaires evaluation

There were 4 parts to the questionnaire administered to volunteers. These included demographic data, and the International Study of Asthma and Allergies in Childhood questionnaire (ISAAC) which was used to evaluate the presence of nasal symptoms with eye symptoms and nasal symptoms alone within the past 12 months. This original ISAAC questionnaire was translated into Thai by a panel of Thai allergists and subsequently translated back into English to ensure the validity of the translation. This questionnaire had been previously utilized to evaluate both Thai children and adults.[6-8] The attitude and budget limits on health oriented decoration in addition to the factors associated with health interior design were also evaluated.

# Data collection and statistical analysis

The data was analyzed using SPSS software package (IBM®, Chicago, IL USA). Each patient's quality of life was then compared with students without rhinitis symptoms and those with rhinitis symptoms. A Paired t-test was utilized to compare the two groups. A p-value of less than 0.05 was considered statistically significant.

#### **Results**

A total of 150 city dwellers were interviewed. Eighty-four of those were female. The interviewed females above the age of 40 was approximately 56 percent. Over forty percent of these same females graduated with a bachelor's degree. Roughly half of the people interviewed had a salary lower than 100,000 baht / month. Forty percent of people had experience with interior design. Seventy percent of people had health problems of which 30 percent denoted asthma and/or allergic diseases. Half of those interviewed reported medical bills of over 100,000 baht/month. The subjects' characteristics and underlying medical problems are demonstrated in Table 1.

Table 1 Demographic data and underlying medical problems

		Number of people	Percentage (%)
Gender	Male	66	44
Gender	Female	84	<del>44</del> 56
Λαο	20-30	31	20.7
Age	31-40	55	20.7 36.7
	41-50	28	30.7 18.7
	51-60	28 22	
			14.7
	60+	14	9.3
Graduation Degree	Degree	37	24.7
	Bachelor's Degree	76	50.7
	Master's Degree	19	12.7
	PhD	5	3.3
	Others	13	8.7
Occupation	Employees	68	45.3
	Government firms	25	16.7
	Entrepreneur	27	18
	Retired	16	10.7
	Others	14	9.3
Income	Less than 100,000 baht	61	40.7
	100,001-150,000 baht	56	37.3
	150,001-200,000 baht	16	10.7
	200,001-250,000 baht	4	2.7
	250,001-300,000 baht	8	5.3
	300,001+ baht	5	3.3
Location of subjects (districts)	Patumwan, Ploenchit,	21	14
. , , ,	Rachadamri		
	Sathorn, Silom, Phayathai	26	17.3
	Watana, Klongtoeyi, Ekamai	53	35.3
	Petchaburi (new), Prakanong	43	28.7
	Other	7	4.7
Does the subject have interior	Has Experience	105	70
design experience?	Doesn't have experience	45	30
Does the subject have any	Yes	85	56.7
medical problem?	No	65	43.3
What type of medical problems	Asthma and Allergic diseases	28	31.5
the subjects had	Obesity Obesity	12	13.5

		Number of people	Percentage (%)
	High blood pressure	27	30.3
	Diabetes	6	6.7
	Others	16	18
Does the subject family	Yes	94	62.7
members have any medical problems?	No	56	37.3
What type of medical problem	Asthma and Allergic diseases	29	27.6
the family members have?	Obesity	10	9.5
	High blood pressure	27	25.7
	Diabetes	21	20
	Other	18	17.1
How much the subjects	Less than 10,000 baht	74	49.3
normally pay for medical	10,001-30,000 baht	46	30.7
problems?	30,001-60,000 baht	19	12.7
	60,001-100,000 baht	10	6.7
	150,000+ baht	1	0.7

Of the 150 subjects that were interviewed using the ISAAC questionnaire. A total of 98 (65%) reported rhinitis symptoms within the past twelve months, while 37.3 percent interviewed had eye symptoms. Amongst the interviewed subjects with AR, most of the patients had mild intermittent symptoms and only reported a mild effect on quality of life. Nasal symptoms occurred throughout the year amongst respondents with a peak from May-July and November-January. The type of rhinitis and eye symptoms is shown in Table 2.

Table 2 Rhinitis and eye symptoms during the past 10 months

Type of symptoms		Number of people	Percentage (%)
In the past 12 months, have you	Yes	98	65.3
ever had a Problem with sneezing or a runny or blocked nose When she/he DID NOT have a cold or flu?	No	9	6
In the past 12 months, has this	Yes	56	37.3
nose problem been accompanied by itchy-watery eyes?	No	42	28
In the past 12 months, which	January	29	29.5
month the symptom Occurs for	February	20	20.4
the subjects?	March	11	11
	April	18	18.4
	May	35	35.7
	June	43	43.9
	July	27	27.6
	August	9	9.2
	September	3	3.1
	October	7	7.1
	November	15	15.3

Type of symptoms		Number	Percentage
		of people	(%)
	December	24	24.5
In the past 12 months, how	Not at all	12	12.2
much did this noes problem	A little	63	64.3
interfere with your daily	A moderate	17	17.4
activities?	A lot	6	6.1
How many days per week has	Less than 4 days a week	133	88.7
the nose problem affected the subjects?	More than 4 days a week	17	11.3
How long of your nose	Less than 4 consecutive weeks	124	82.7
problem?	More than 4 consecutive weeks	26	17.3

**Table 3 Housing Requirements** 

· · · · · · · · · · · · · · · · · · ·		Amount	Percentage
75 01 · ·	C' 1 II	40	(%)
Type of living space owned	Single House	48	32.0
by the subject	Townhouse	31	20.7
	Condominium	40	26.7
	Apartment	27	18.0
	Others	4	2.7
Space of living area	20-40 meters squared	29	19.3
-	41-60 meters squared	37	24.7
	61-80 meters squared	15	10.0
	81-100 meters squared	19	12.7
	101-120 meters squared	24	16.0
	120+ meters squared	26	17.3
How much the subjects are	less than 500,000 baht	127	84.7
willing to invest into	500,001-1,000,000 baht	18	12.0
furniture and if there were a	1,000,001-1,500,000 baht	5	3.3
firm that offers the service of	Less than 100,000 baht	103	68.7
improving health how much	100,001- 400,000 baht	40	26.7
the subjects are willing to pay	400,001- 900,000 baht	3	2.0
for it	900,001- 1,600,000 baht	2	1.3
	1,600,001-2,500,000 baht	1	0.7
	More than 2,500,000 baht	1	0.7

The housing requirements and interior design budget is depicted in Table 3 and 4. The space of living areas was significantly bigger in people aged over than 40 years. The budget for interior decoration varies significantly between the group less than and equal to age 40 years and the group over 40 years (P < 0.05). The people aged more than 40 years old spent more money for interior decoration than their younger counterparts. Most people accepted a budget for improving health in the range of 100,000-400,000 baht. However, there was no significant difference in the budget of health interior decoration between the group less or equal to 40 years and the group over 40 years.

Table 4 The relationship between budgets and interior decoration

Fa	actors	A	P-value		
		<= 40	> 40		
What kind of living space	Single	18	30	0.00*	
the subject owns? (%)	_	(20.9)	(46.9)		
- , ,	Townhouse	18	13		
		(20.9)	(20.3)		
	Condominium	28	12		
		(32.6)	(18.8)		
	Apartment	22	5		
		(25.6)	(7.8)		
	Others	0	4		
		(0.0)	(6.5)		
How much living space	20-40 Square meters	20	9	0.04	
does the subject have?		(23.6)	(14.6)		
	41-60 Square meters	24	13		
		(27.9)	(20.3)		
	61-80 Square meters	12	3		
		(14.0)	(4.7)		
	81-100 Square meters	9	10		
		(10.5)	(15.6)		
	101-120 Square meters	9	15		
		10.5	23.4		
	120+ Square meters	12	14		
		(14.0)	21.9		
The amount of money the	less than 500,000 baht	82	45	0.00*	
subjects are willing to		(95.4)	(70.3)		
spend on furniture	500,001-1,000,000 baht	4	14		
		(4.7)	(21.9)		
	1,000,001-1,500,000 baht	0	5		
		(0.0)	(7.8)		
if there were a firm that	less than 100,000 baht	63	39	0.41	
offers the service of		73.3	61.9		
improving health how	100,001- 400,000 baht	19	21		
much the subjects are	400 001 000 0001 1	22.1	33.3		
willing to pay for it	400,001-900,000 baht	2	1		
	000 001 1 600 0001 1	2.3	1.6		
	900,001- 1,600,000 baht	1	1		
	1 (00 001 2 500 0001 1	1.2	1.6		
	1,600,001-2,500,000 baht	1	0		
	2.500.000   11.4	1.2	0.0		
	2,500,000+ baht	0	1		
		0.0	1.6		

#### **Discussion**

Very few studies have been conducted to investigate the attitude of interior design and health amongst consumers in the realty market. Allergic disease is especially lacking in the literature of its impact on consumer spending when related to interior design. Living in substandard housing can often lead to exposure to numerous triggers and higher rates of allergen sensitization. Previous studies have found that home visit programs and interventions could reduce allergic symptoms for suffering patients.[5] This is the first study in Thailand that surveys the attitudes about health interior design in residential housing near the commercial district in Bangkok. In this study, we found that the residents in this area spend more money for health when compared to the general population.[9] The prevalence of rhinitis in our study was similar with previous studies amongst Thai university student.[4, 10] This finding indicates that 30% of people were underdiagnosed with allergic rhinitis. Most rhinitis symptoms were mild and 1/3 of subjects did not recognize their symptoms. The peak of nasal symptoms in this study occurred earlier than a previous study by Uthaisangsook.[10] which mostly occurred during both the rainy and winter season. In the United States, the cost of building allergy free homes is roughly between 6,000-7,000 USD.[11] In our survey, we found that most Thai people who live in the CBD accepted the cost of health interior decoration in the range of about 3,000-12,000 USD. The attitudes toward design impact on health between the rhinitis and non-rhinitis group were not significantly different. Future research needs to be done to assess the potential financial impact this attitude could have on the realty market.

#### **Conclusion**

Consumers are becoming increasingly concerned about health promotion and prevention. Most Bankokians residing in the central business district over the age of 40 revealed a trend towards interest in health focused design. This may reflect a trend amongst the aging society and the impact they feel their health impacts their quality of life. The factors associated with health interior design may help to prevent illness, improve overall healthy environments and assure ideal materials are utilized under expert recommendation, all while benefiting the consumer.

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