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**FACULTY OF PHARMACY AND SCIENCE**

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We hereby declare that

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as

**PARTICIPANT**


at


**International Seminar**

***“Challenges of the Development of Natural Compound as Drug  
for Infectious and Degenerative Diseases”***


***January 10<sup>th</sup>, 2015***

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**Drs. H. Budi Arman, M.Kes., Apt.**  
Dean of Faculty of Pharmacy and Science  
University of Muhammadiyah Prof. DR. HAMKA



  
**Drs. H. Sediarmo, M.Farm., Apt.**  
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# PROCEEDING INTERNATIONAL SEMINAR

CHALLENGES OF THE DEVELOPMENT  
OF NATURAL COMPOUND AS DRUG FOR INFECTIOUS  
& DEGENERATIVE DISEASES



Faculty of Pharmacy & Sciences  
University Of Muhammadiyah Prof. DR. HAMKA  
(UHAMKA)  
Jakarta, January 10, 2015



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**CHALLENGES OF THE DEVELOPMENT OF NATURAL COMPOUND  
AS DRUG FOR INFECTIOUS & DEGENERATIVE DISEASES**

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Rahma Elfiyani, M.Farm., Apt.; Yudi Srifiana, M.Farm.,Apt.; Siska, M.Farm., Apt.;  
Hariyanti, M.Si., Apt.

Reviewers :

Prof.Dr. Oliver Kayser, Prof. Dr. Ibrahim Jantan, Ph.D, Prof. Dr. Krisana Kraisintu,  
Ph.D, Prof. Dr.Endang Hanani SU.,M.Si Apt., Dr. Priyanto, M.Biomed.,Apt, Dr. Hadi  
Sunaryo, M.Si., Apt., Drs. Inding Gusmayadi, M.Si,Apt., Dr. H. Priyo Wahyudi, M.Si.

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Phone : +62-8611070, 86603233

Fax : +62-8611070

website : [www.ffs.uhamka.ac.id](http://www.ffs.uhamka.ac.id)

Email : [intl.ffsuhamka@gmail.com](mailto:intl.ffsuhamka@gmail.com)

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***International Conference “Challenges Of The Development Of Natural Compound  
As Drug For Infectious & Degenerative Diseases”***

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## **Remarks of the Dean of Faculty of Pharmacy & Sciences (FFS) UHAMKA**

Assalamu'alaikumWr.Wb.

Distinguished ladies and gentlemen

First of all, on behalf of FFS UHAMKA, I would like to welcome to all of you in FFS UHAMKA Jakarta. Thank you very much for your attention to come and attend the international seminar in FFS UHAMKA. I hope we are all in health condition and in the shadow of God.

The conference is organized by FFS UHAMKA in collaboration with sponsors like PT. Triasindo Jaya , Indolab and UHAMQUA. This event is as part of the routine activities with the purpose are: discuss an update on the challenges of drug development for infectious and degenerative diseases based on natural product and provide a forum for exchange of information on the latest technologies involved in the development of natural compounds as drug.

In this seminar participants from student, lecturer, researchers have been attended and 4 speakers within field of Pharmaceutical sciences will be presented paper with theme —Natural Compound as Therapy for Infectious and Degenerative Diseases|. Besides that, this conference followed by presentation researchers in form of oral and poster presentation. Herewith we would like to express our gratitude to all participants, presenters, and special thanks to plenary speakers for joint us to day to share advance knowledge and expertise in this scientific event in FFS UHAMKA.

The FFS gratefully acknowledges the Rector of UHAMKA University, minister of Health of Indonesia, and sponsors for the nice collaboration in bringing this seminar. Furthermore, personally, I would like to express my deep appreciation to members of the Organizing Committee, for the good teamwork and their great effort to bring success to the seminar.

Finally, I wish all participants could benefit from the seminar and have an enjoyable moment in FFS UHAMKA Jakarta.

I look forward to thank you all for attending this seminar

Wassalamualaikum Warrohamatullahi Wabbarokatuh

**Drs. H. Budi Arman, M. Kes, Apt.**



## **Remarks From Rector**

*Bismillahirrahmanirrahim,*

***Your Excellency, Minister of Health Republic of Indonesia***

***Respected Resource Persons***

***Respected Participants, Ladies and Gentlemen***

On behalf of University of Muhammadiyah Prof. Dr. HAMKA (UHAMKA), I would like to warmly welcome you all to attend and participate in the International Seminar on —Challenges of the Development of Natural Compound as Drug for Infectious and Degenerative Disease, on Saturday, January 10, 2015 at Auditorium UHAMKA.

This international seminar is a very prestigious and academic event which has to be appreciated since the topics and sub-topics such as Natural Product Chemistry, Pharmacology, Molecular Biology and Biotechnology and Pharmaceutical Technology & Compound are crucial issues today, particularly in the pharmaceutical discipline.

This academic event becomes more significant as there are some respected experts and resource persons who know how in the field of pharmacology, biotechnology, pharmaceutical technology and compound. Through this seminar, they present their research findings and scientific experiences and share them to the participants. We wish that all participants will get valuable lesson learned from these resource persons and experts.

In addition to the presentation from keynote speaker and experts, there are also poster sessions which display the research findings which, hopefully, inspire other participants to make further research dealing with the current issue in the development of natural compound as Drugs for Infectious and Degenerative Diseases.

To make this international seminar successful, I do hope that all participants are very active to quest and explore the given ideas occurred during this seminar so that this will provide significant contribution to the development of pharmacy in particular and drugs or medicines in general for the sake of humanity health.

At last, I would like to express my sincerely thank all resource persons, Prof. Dr. Nila Djuwita F. Moeloek, Sp.M (K) (Minister of Health Republic of Indonesia) , Prof. Dr. Ibrahim Jantan (UKM), Prof. Dr. Endang Hanani, SU., M.Si (UHAMKA), Prof. Dr. Oliver Kayser ( The Technical Biochemistry, TU Dortmund, Germany), and Prof. Dr. Krisana Kraisintu (Faculty of Oriental Medicine, Rangsit University, Thailand).

Jakarta, January 2015

Rector,

Prof. Dr. H. Suyatno, M.Pd.

## **DRUG AND HERBAL RESEARCH CENTER**

**Ibrahim Jantan**

Faculty of Pharmacy, Universiti Kebangsaan Malaysia, Jalan Raja Muda Abdul Aziz,  
50300 Kuala Lumpur, Malaysia

### **ABSTRACT**

Drug discovery involves integration of enormous spectrum of research activities, beginning from initial target identification and validation, through assay development, high throughput screening (HTS), hit identification, lead optimization and finally the selection of a candidate molecule for clinical development. The single target or bullet - based approach has been the dominant paradigm to discover natural small organic molecules from natural resources as new leads or models for the development of synthetic molecules for the discovery of drug targets. However, the reductionist approach in finding bioactive natural products from the tropical rainforests at several major pharmaceutical companies had generally declined in the early eighties due to the many major hurdles faced by them such as difficulties in obtaining sufficient supply of high quality natural products screening libraries, ownership issues and research in this field is lengthy, expensive, highly complex and ineffective with low success rate. On the other hand, the process of drug development is often a risky and costly endeavor. Natural products drug discovery has been marginalized in favor of the rational design of synthetic compounds to target specific molecules after the advent of HTS, combinatorial chemistry and advancement in the knowledge of molecular mechanisms, cell biology and genomics. There was a revival of natural products drug development in the later part of the eighties and this was partly due to the advances in chromatographic and spectroscopic techniques which have had a tremendous impact on the isolation and structure elucidation of the constituents of medicinal plants and the development of series of bioassay methodologies which were fast, easy to perform, quantitative and could selectively detect biologically active molecules at very low levels. Recently there is a growing interest to use innovative approaches to drug discovery from natural products by network pharmacology which integrates systems biology and pharmacology. The integrated multidisciplinary concept of multiple targets, multiple effects and complex diseases in network pharmacology have enriched our understanding of complicated pathogenesis and multi-target pathologies of systemic diseases and reduced difficulty in identifying relevant interventions to target such complexities. The '-omic' technologies in system biology have now been widely used to correlate and elucidate multiple targets and network of human diseases and drug actions. The concept of network pharmacology is especially useful in accurately translating and interpreting the therapeutic effects of herbal medicines into modern biochemical and biological meanings. Herbal medicines may serve as valuable resources for network-based multi-target drug discovery. Multi-target drugs could be developed from herbal extracts by first evaluating the efficacy of the extracts, followed by identification of their major bioactive components and redevelopment of a completely new multi-component formulations composed of the major bioactive components in order to reach a synergistic and optimal combination. In this paper, the use of integrated and multi-target approach to discover new antioxidant and anti-inflammatory drug leads will be illustrated as examples.

**Keywords:** drug discovery, reductionist approach, network pharmacology, multi-target drugs, antioxidants, anti-inflammatory.



# **METABOLIC ENGINEERING STRATEGIES AND CONCEPTS IN GENE TECHNOLOGY FOR MODIFICATION AND OPTIMIZATION OF MEDICINAL AND AROMATIC PLANTS : EXPECTATION AND REALITIES**

**Oliver Kayser**

Technical University Dortmund  
Technical Biochemistry  
Emil-Figge-Strasse 66, 44227 Dortmund  
oliver.kayser@bci.tu-dortmund.de

## **ABSTRACT**

In recent years classic genetic and molecular biology strategies (Bioballistics, *Agrobacterium tumefaciens* transformation, recombinant enzymes) for production of natural compounds or even breeding of medicinal and aromatic plants have expanded and improved productivity of plant-derived fine chemicals. Among those high value natural products with medicinal and cosmetic purpose (e.g. essential oils, paclitaxel, artemisinin, Vinca-Alkaloids) play a major role. Applying genetic and biotechnological techniques like metabolic engineering, site directed mutagenesis, and pathway optimization for plant optimization to reduce costs and increase productivity are in the main focus of academia and industry. Because of some drawbacks with plant cell cultures and isolated enzymes giving no sufficient high production for commercialization, research strategies shifted more and more to metabolic engineering. From the past, engineering a microorganism is proven as a valuable tool and concepts have been transferred to plant science and opened new promising perspectives for improving plants and cell lines. First, engineering crop plants was conducted, but applying these techniques for medicinal plants is rather new and has not yet been explored so well. Today cloning and expression of multiple genes in polycistronic vectors and genomic integration is of high interest and allows the reconstitution of biosynthetic pathways in heterologous organisms either plants or microorganisms. Combining science and engineering in this research field was claimed as *Combinatorial Biosynthesis* and later as *Synthetic Biology*. *Synthetic biology* includes a large number of subareas, including enzymology, protein assembly and interactions, metabolomics, gene regulation, signal transduction and computational biology and is considered as a future approach for biotechnological plant optimization. The possibilities show exciting perspectives for the exploitation of medicinal and aromatic plants to increase the level of wanted natural products, gain insight in metabolic pathways even for new biosimilar chemicals, to improve nutritional and health promoting effects of food (nutraceuticals), and to reduce the amount of unwanted by products with potential toxic or allergic activities.

Dixon, R.A. 2005. Engineering of plant natural product pathways, *CurrOpin Plant Biol.* 8:329-336

Staniak, A., Bouwmeester, H., Fraser, P.D., Kayser O., Martens, S., Tissier, A., van der Krol, S., Wessjohann, L. & Warzecha, H. (2014) Natural products - modifying pathways in plants. *Biotechnol J.* 2013. 8: 1159-1171



Staniak, A., Bouwmeester, H., Fraser, P.D., Kayser, O., Martens, S., Tissier, A., van der Krol, S., Wessjohann, L., Warzecha, H. (2014) Natural products - learning chemistry from plants. *Biotechnol J.* 2014, 9(3): 326-336



# **HERBAL MEDICINE DEVELOPMENT : SCIENTIFIC TRANSFORMATION OF NATURAL COMPOUNDS INTO EFFECTIVE DRUGS**

**Krisana Kraisintu**

Rector of College of Oriental Medicine, Rangsit University, Thailand

## **ABSTRACT**

Indigenous flora of tropical countries are abundant of compounds with pharmacological activities which could be transformed into therapeutic agents and drugs for infectious and degenerative diseases. The normal sequence for development of pharmaceuticals by this approach usually begins with the identification of active lead molecules, detailed biological assays, and formulation of dosage forms in that order, and followed by several phases of clinical studies designed to established safety, efficacy and pharmacokinetic profile of the new drugs. Employing a multidisciplinary approach to drug development from medicinal plants, Thailand is capable of manufacture GMP certified herbal medicinal products in several dosage forms on an industrial scale. The adverse effects of chemical based drugs and the escalating costs of conventional health care, longer life expectancy and life style related problems have brought with them an increased risk of developing chronic, debilitating diseases such as cancer, neurological, infectious, cardiovascular, immunological, inflammatory and genetic diseases. The availability of modern scientific methods for the cultivation, selection, manufacture and clinical evaluation of herbal remedies has made it increasingly feasible for scientists to transform herbal medicinal plants into a modern industrial enterprise capable of making significant contribution to both health care delivery and the economic growth of developing countries.

# INDONESIA TRADITIONAL MEDICINES DEVELOPMENT EVIDENCE BASED APPROACH

**Endang Hanani**

University of Muhammadiyah Prof Dr. HAMKA, Jakarta, Indonesia

## ABSTRACT

Traditional herb (jamu) is a part of culture and national resource in Indonesia, and has been consumed for several hundreds year ago in Java. The existing documents show that the traditional herb medicine has been used by royal families from the Mataram / Surakarta and Madjapahit palace in form of herb preparation as Jamu and cosmetics. More than 7500 species are known as medicinal plants around 400 have been registered, so they are used by the community as Indonesian traditional medicines. Traditional medicine/Jamu has been past down from generation to generation to maintain body fitness, health care, cosmetic and physiological body function and even to treat specific illness. Although formally not acceptable by the medical doctor, jamu are continuously being development used by the community. Based on the medicinal basic research carried out by Ministry of health (2010) showed that the Indonesian more than 50% use Jamu. On the other side the medical doctor still not accept, the reason is have no scientific research / evidence based data. Researcher start to search evidence based of medicinal herb for supporting scientific data.

The used of *Andrographis paniculata* for diabetes mellitus patients. The *A. paniculata* capsule showed that administration of APC for 14 days fasting blood glucose levels lower compared to PC (placebo capsule) but not significantly. The APC significantly reduced blood glucose 2 hours after meal. The reducing effect of *Morinda citrifolia* capsule was investigated on total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) in hypercholesterolemia patients. Sixty subjects divided into 2 groups; for experimental (*M. citrifolia* capsule) and placebo (P capsule). Both groups received 2 capsules, 3 times daily for 14 days. The result suggested that *M. citrifolia* capsule significantly reduced TC and LDL-C levels. The mixture of essential oils of *Pogostemon cablin*, *Jasminum sambac* and *Zingiber officinale* significantly reduce the thigh circumference measurements, skin roughness and photographic data was an improvement in skin surface appearance in women cellulite. *Carica papaya* capsule (2 capsules 3 times daily) had significantly increased the platelet count, maintained stability of hematocrit in the normal level, shorten hospitalization in dengue fever patients, and accelerates the increased in platelet count compared with the control.

We suggest those evidence based research will be make the Indonesia herbal medicine more develop, and will be accepted by the health society.

Keywords : *Andrographis paniculata*, *Carica papaya*, *Morinda citrifolia*, *Jasminum sambac*, *Pogostemon cablin*, *Zingiber officinale*



## CONTENT

IMUNOMODULATORY ASSAY OF  $\beta$ -GLUCAN OF WHITE-OYSTER MUSHROOM (*Pleurotus ostreatus*(Jacq.) P. Kumm) ON THE MURINE INNATE IMMUNE SYSTEM

**Priyo Wahyudi.....17**

EFFECT OF INCREASING HPMC CONCENTRATION ON PARTICULATE DISSOLUTION OF SOLID DISPERSION SYSTEM KETOPROFEN-HPMC

**Ani Pahriyani, Inding Gusmayadi, Onny Indriyani.....29**

SYNTHESIS AND SOME PROPERTIES OF CARBOXYLMETHYL-CHITOSAN AFTER IRRADIATED

**Gatot Trimulyadi Rekso.....39**

COMPARISON OF SODIUM LAURYL SULPHATE, SODIUM BENZOATE, POLYAETHYLENE GLYCOLUM 6000 AS LUBRICANT ON DISSOLVING TIME OF EXTRACT CIPLUKAN (*Physalis angulata* L.) EFFERVESCENT TABLET

**Ari Widayanti, Hadi Sunaryo, Nurita Sari.....47**

EFFECT OF TAMARIND (*Tamarindus indica* Linn.) IN DECREASING CONTENTS OF MERCURY (Hg) AND PLUMBUM (Pb) IN WATER SPINACH (*Ipomoea aquatica* Forssk.)

**Yusnidar Yusuf, Vera Ladeska, Atiyyatul Maula.....56**

ANDROGRAPHOLIDE EFFECTS AGAINST INHIBITION OF HEME DETOXIFICATION IN VITRO

**Risdawati Djohan, Mohamad Sadikin, Sri Widia K. Jusman, Din Syafruddin.....63**

HEPATOPROTECTIVE ACTIVITY TEST OF ETHANOL FRACTION OF *Ocimum americanum* L LEAFS AGAINST CARBON TETRACHLORIDE INDUCED IN RATS

**Hayati, Sediarmo, Rangga.....73**

IDENTIFICATION DRPs IN WRONG DRUG CATEGORY AND DRUG INTERACTION TO TYPE-2 DIABETES MELLITUS INPATIENTS IN GATOT SOEBROTO ARMY CENTRAL HOSPITAL JAKARTA

**Zainul Islam, Hadi Sunaryo.....86**

POTENTIAL ROLES LEAVES EXTRACT OF BABADOTAN (*AGERATUM CONYZOIDES* L.) AND BINAHONG (*ANREDERACORDIFOLIA* (TEN) STEENIS) AND ITS COMBINATION AS ANTI HYPERGLYCEMIA IN INSULIN RESISTANCE ANIMAL MODEL

<b>Patonah, Ari Yuniarto, Zahniah Nur Putri.....</b>	<b>96</b>
CONSTRUCTION YEAST SHUTTLE VECTOR CONTAINING DENGUE VIRUS 3 NON-STRUCTURAL NS1 ENCODING GENE EXPRESSION CASSETTES FOR SUBUNIT DENGUE VACCINE CANDIDATE	
<b>Vanny Narita, Wahyu Hidayati, Tjahjani Mirawati Sudiro.....</b>	<b>102</b>
MOLECULAR DOCKING STUDIES OF FLAVONOIDS OF GUAVA LEAVES ( <i>Psidium guajava</i> L.) TO $\alpha$ -GLUKOSIDASE RECEPTOR	
<b>Supandi<sup>1</sup>, Rizky Arcintha, and Ulfa Nurhamidah.....</b>	<b>110</b>
THE EFFECT OF $\beta$ -LACTAM ADMINISTRATION ON NEW INFECTION BY ESBL PRODUCTION BACTERIA AT PERSAHABATAN HOSPITAL	
<b>Numlil Khaira Rusdi, Tri Kusumaeni, Erna Pratiwi.....</b>	<b>120</b>
DETERMINATION OF TOTAL FLAVONOID CONTENT AND ANTIOXIDANT ACTIVITY ASSAY IN SEVERALLY PART OF ETHANOL FRACTION OF CASSIAVERA ( <i>Cinnamomum burmanii</i> [Nees] Bl)	
<b>Dira, Wida Ningsih and Vinni Rahayu Ningsih.....</b>	<b>129</b>
THE CAPSULE AND TABLET FORMULATION OF ETHANOL EXTRACT OF RED GINGER ( <i>Zingiber officinale</i> , Roxb.)	
<b>Fifi Harmely, Dira, Lilis Kurniawati, Chris Deviarney.....</b>	<b>135</b>
THE COMBINATIONS ETHANOL EXTRACT OF GINGER ( <i>ZINGIBER OFFICILALE ROSCOE</i> ) AND ZINC AS ANTI ATHEROSCLEROSIS IN HYPERCHOLESTEROLEMIC NEW ZEALAND RABBITS	
<b>Priyanto, Agik Suprayogi, Nastiti K, Dewi Ratih.....</b>	<b>144</b>
SUBCHRONIC TOXICITY TEST OF COMBINATION OF GINGER ( <i>Zingiber officinale Rosc.</i> ) EXTRACT AND ZINC ON SWISS WEBSTER MICE	
<b>Hadi Sunaryo, Siska, Dwitianti, Rizky Arcintha Rachmania, Roja Fathul Mubdy.....</b>	<b>157</b>
THE LEUKOCYTE PROFILE OF INFLAMMATION RABBIT AFTER THEADMINISTRATION BRANDED KETOPROFEN AND MUCOADHESIVE GRANULE	
<b>Salman Umar, Suyanda Dwina, Yufri Aldi.....</b>	<b>165</b>
ACUTE TOXICITY STUDY OF ETHANOL EXTRACT OF COAT BUTTON ( <i>TRIDAX PROCUMBENS</i> L.) HERB IN SWISS WEBSTER MICE	

# **SUBCHRONIC TOXICITY TEST OF COMBINATION OF GINGER (*Zingiber officinale* Rosc.) EXTRACT AND ZINC ON SWISS WEBSTER MICE**

**Hadi Sunaryo. Siska. Dwitianti. Rizky Arcintha Rachmania. Roja Fathul Mubdy**

Faculty of Pharmacy and Science University of Muhammadiyah Prof. Dr. Hamka  
Corresponding author : [hadi\\_itb@yahoo.com](mailto:hadi_itb@yahoo.com)

## **ABSTRACT**

The combination of ginger (*Zingiber officinale* Rosc.) extract and zinc has the effect of lowering levels of glucose, triglycerides, cholesterol and anti-oxidants. This study aimed to determine the safety administration of combination ginger extract and zinc, through subchronic toxicity test. Parameters measured were body weight, liver and kidney histopathology, SGOT, and SGPT. The study used a sample of 20 male mice, divided into one control group and one treatment group. The extract was given orally through a sonde for 75 days. The treatment group were given a combination of ginger extract and zinc (ginger 30mg / 20g BW + zinc 0.4mg / 20g BW ) and control group was given a water. After 75 days of treatment sample blood the heart and then checked SGOT and SGPT. Collected statistical from result with the method of independent samples T test showed no significant difference between the levels of SGOT and SGPT control group to the treatment group. It can be concluded combination ginger extract and zinc did not show any toxic effects in subchronic and did not cause toxicity and damage to vital organs, such as liver and kidney.

**Keywords:** subchronic toxicity . ginger extract and zinc, SGOT, SGPT

## **INTRODUCTION**

Studies on medicinal plants need to be done so that it can be used safely and effectively. Pre-clinical trials are one of step drug testing.

Subchronic toxicity test is one of preclinical trials for test the toxicity and safety of a given compound with repeated doses in animal specific, for less than three months. This test is intended to reveal the toxic effects of test compounds as well as to show whether the toxic effects related to measure of the dose (Donatus, 2005).

Diabetes mellitus is a chronic disorder of the metabolism of carbohydrates, fats, and proteins (Robbins 2007). Lipids in diabetics caused by insulin deficiency. It occurs due to disruption of the function of insulin because of the complications of high blood

lipid levels, especially cholesterol and triglycerides (Widyastuti 2001). DM is a degenerative disease. So patients need treatment special diet, lifestyle regularly and heavily dependent on drugs hypoglycemic (Baines 1999).

Ginger (*Zingiber officinale* Rosc.) is one of medicinal plants in Indonesia which has a high economic value and has many benefits. Ginger contains essential oils. With major components zingiberen, zingiberol, and gingerol oleoresin. With the major components (POM RI 2004) useful for pain relief, anti-inflammatory, and antibacterial (Latif 2002).

Zinc (Zn) is one of micro minerals needed for each cell in the body. Adequacy of these minerals is essential in keeping optimal health. Zn deficiency in diabetics can lead to disruption of the immune system (Jacobus 2000). In addition to antioxidant properties of zinc can also reduce levels of cholesterol and triglycerides (Reiterer *et.al* 2005).

In previous study mentioned that the combination of 70% ethanol extract of ginger (*Zingiber officinale* Rosc.) and zinc at a dose of 3 mg / 20g BW + Zn 0.4 mg / 20g BW can lower blood glucose levels, triglycerides, total cholesterol, LDL, and raise levels of HDL (Sunaryo Hadi *et al.* 2013; Sunaryo Hadi *et al.* 2014). If the activity is given the combination of ethanol extract of ginger and zinc have activity as antihypercholesterol, antihyperglycemia and this can contribute to the development of drugs by utilizing the results from natural materials. But still uncertain safety of the compound. Therefore, it was conducted one of the pre-clinical trials that subchronic toxicity tests to ensure the safety and the highest dose in the repeated use of a compound. By using the highest therapeutic dose administered repeatedly for 75 days to determine the effect of the combination of ethanol extract of ginger and zinc.

## **MATERIALS AND METHODS**

### **Materials:**

Ginger was obtained from the Institute for Medicinal Plant Research, Bogor. Material after drying in a temperature of about 50°C, powdered extract was then made thicker with the maceration using ethanol 70%.

### Test Animal:

White male mice *Swiss webster* strain. aged 2-3 months weighing about 20-30 grams. As many as 20 mice were divided into one control group and one treatment group.

### Methods:

#### Extract Preparations

As much as 25 kg of dried ginger produces 2.5 kg of powder ginger. Then ginger powder was extracted using maceration method using 70% ethanol as a liquid maserat and produced 18.8 L maserat. Maserate results obtained using a vacuum rotary evaporator and the resulting extract in the oven until viscous.

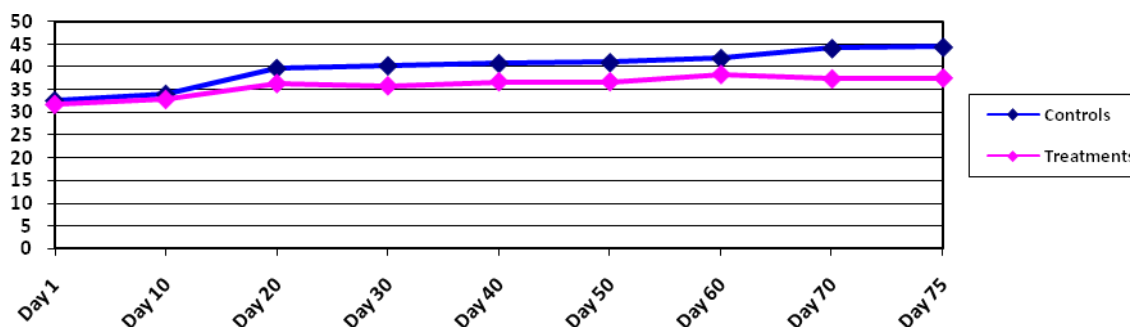
The test material was administered orally via sonde each day for 75 days. The health condition of the test animals was checked every day to know the symptoms of toxic effects and weighed every day. The control group was given food and drink and the standard treatment group received a dose (ginger 30mg / BW + zinc 0.4mg/20g BW). At the end of 75 days the animals were anesthetized with ketamine then try surgery for blood sampling through the heart to be examined SGOT and SGPT. After the blood was collected through the heart followed by taking the liver and kidneys for making preparations for histopathology as macroscopic observation in a standard way using hematokisilin eosin staining for the presence or absence of histopathologic abnormalities.

### RESULTS

The experimental results Subchronic toxicity combination ginger extract and zinc are listed in the table.

**Table 1.** The average weight observations mice for 75 days.

Groups	Days								
	1	10	20	30	40	50	60	70	75
Controls	32.7	34.1	39.8	40.4	40.9	41.1	42	44.2	44.5
Treatments	31.9	33	36.5	36	36.9	36.9	38.5	37.5	37.7



**Figure 1. The average weight observations mice for 75 days.**

**Table 2.** Results of macroscopic examination of the liver and kidneys of mice after 75 days.

Groups	Macroscopic Observation	Liver	Kidney
Control	Color	Normal	Normal
	Form	Normal	Normal
Treatment	Color	Normal	Normal
	Form	Normal	Normal

**Table 3.** The average yield SGOT and SGPT examination mice.

Groups	SGOT	SGPT
Control	13.9794 u/L	8.79 u/L
Treatment	17.6026 u/L	16.5476 u/L

## DISCUSSION

Early stages of this research is the determination. Determination aims to get the true identity of the plants that will be tested its efficacy. so it can be provide the certainty about the truth of these plants. Based on the results of determination of plants that will be used as the main substance in this study is completely ginger (*Zingiber officinale* Rosc.).

Making the ginger simplicia begins with sorting so ginger wet clean of impurities such as soil attached. then be washed using water flowing. After cleaning ginger sliced

with the aim of expanding the material surface to accelerate the drying process. The drying process was done by aerated in order not damage the active substance content of ginger.

The extraction method used in this study is maceration. This method was used because it is easy and simple and did not require heating so it is suitable to active substances which did not resistant heating. The first stage was conducted by soaking the crude drug powder with liquid extract. Extract fluid used was ethanol 70%. because ethanol is more selective against fungi and bacteria so it is difficult to grow. did not toxic and its has well absorb. The water content in 70% ethanol serves to break down the cell walls that contain the active substance resulting in swelling of the cell so that ethanol can enter the cell and the active substance attracted by the solvent. At the time of immersion occasional stirring to flatten the concentration of the solution due to the concentration difference between the solution in the cell and outside the cell solution. Maserat separation using filter paper with no pollen extracts goal that brought into maserat. Maserat obtained was concentrated using a rotary vacuum evaporator so that there was a separation between the active substance and the solvent used is based on differences in boiling point. Concentration using a low temperature process  $\pm 50^{\circ}\text{C}$  in order not to affect the quality of the active substance. Then dried in an oven to remove residual solvent in order to obtain ethanol-free viscous extract.

Viscous extract obtained was conducted phytochemical screening. to determine the compounds contained in the viscous extract. Screening results was obtained a positive result in phytochemical screening are alkaloids, flavonoids and triterpenoids.

In this research sub-chronic toxicity test combination of 70% ethanol extract of ginger with zinc using white mice strains Swiss Webster. Sub-chronic toxicity test was conducted by giving a combination of ethanol extract of ginger with zinc for 75 days and once daily dosing.

The selection of the dose was based on the highest therapeutic dose that did not result in death was obtained in acute toxicity tests. Giving time of ginger extract combination With zinc for 75 days. Selection of 75 days to fulfill the requirements of observation subchronic toxicity test which is usually between 4 weeks to 3 months (Donatu 2005). Then did the histology of liver and kidney in the control group and the treatment group and checks the value of SGOT and SGPT. It was conducted to determine the possible target organs affected by a combination of 70% ethanol extract of ginger with zinc and comparing SGOT SGPT of control group with SGOT SGPT of treatment group.

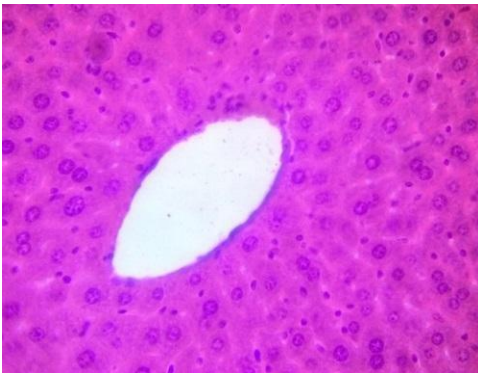


Research using animal testing young adults in a sense still in the process of growth that can be known directly and optimal effect of the test material by using parameters observation of symptoms of toxic effects and weighing during the experiment. It turns out that the results of the experiment shows that the weight of test animals during the 75-day study did not decrease, even increased and the provision of test materials for 75 days did not cause toxic effects on mice.

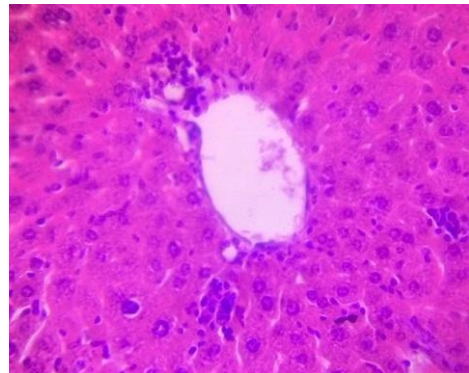
On macroscopic examination of the liver and kidneys of mice was not found specific abnormalities or within normal limits.

Histological examination was conducted on liver and kidney of white mice qualitatively by looking at the composition of the liver structure namely central venous cells and cells of hepatocytes.

While in the kidneys by looking at the structure of the glomerulus. Can be seen in Figure 1. 2. 3 and 4.

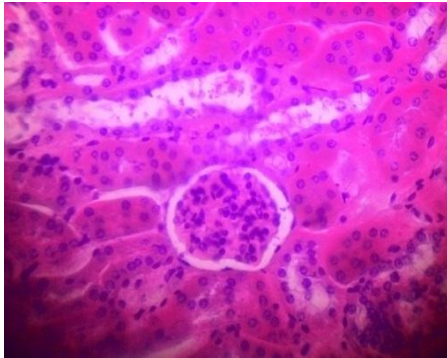


**Figure 2. Preparat of histology liver of control group.**

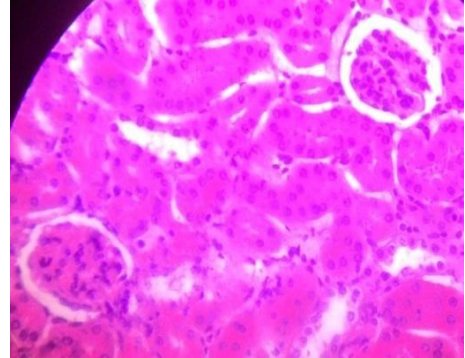


**Figure 3. Preparat of histology liver of treatment group.**

Histological examination of the liver preparations between the control group with treatment group found slightly difference in which in Figure 2 structure central venous, endothelial cells look normal. while in Figure 3 the structure of endothelium damaged by inflammation so that the structure of central venous becomes damaged.



**Figure 4. Preparat of histology kidney of control group.**



**Figure 5. Preparat of histology kidney of control group.**

Examination of histological preparations renal glomerular structure found slightly difference between the control group to the treatment group. In Figure 4 is a normal glomerular structure. In Figure 5 seen the widening gap between the glomerulus and Bowman's capsule.

Another thing to consider is the examination of SGOT and SGPT. but found no significant difference in the levels of SGOT and SGPT after statistically tested with t-Tests (Table 3).

## **CONCLUSION**

Giving a combination of extracts of ginger (*Zingiber officinale* Rosc.) with zinc at a dose (ginger extract 30mg / 20g BW mice and Zn 0.4 mg / 20gBW mice) for 75 days. based on the observation of body weight. liver and kidney histopathology. and examination of the value of SGOT and SGPT did not show any toxic effects and damage to vital organs. such as liver and kidney.

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