

PROCEEDING INTERNATIONAL SEMINAR



ISBN: 978-602-71959-2-9

METABOLIC SYNDROME Now and Future Trend



Supported by:



TRIASINDO JAYA

CV. Rizki Triputra Jaya

**FACULTY OF PHARMACY AND SCIENCE
UNIVERSITAS MUHAMMADIYAH PROF. DR. HAMKA
JAKARTA, 13TH AUGUST 2016**

National Library: in the Catalog of Publication (ICP)

Faculty of Pharmacy and Sciences Universitas Muhammadiyah Prof. DR. HAMKA

PROCEEDING: *Metabolic Syndrome: Now and Future Trend*, First edition, Jakarta, 2016

PROCEEDING

METABOLIC SYNDROME: NOW AND FUTURE TREND

copyright © Faculty of Pharmacy and Sciences, Universitas Muhammadiyah Prof. DR. HAMKA

Editors:

Drs. Inding Gusmayadi, M.Si., Apt.; Dr. Priyanto, M.Biomed, Apt.; Nora Wulandari, M.Farm., Apt.; Lusi Putri Dwita, M.Si., Apt.; Numlil Khaira Rusdi, M.Si., Apt.; Siska, M.Farm., Apt.; Supandi, M.Si., Apt.; Wahyu Hidayati, M.Biomed.

Reviewers:

Prof. Patrick Anthony Ball, Ph.D. (Australia); Thitima Doungnern, MPharm, Pharm.D., BCPS, BCP (Thailand); Dr. Baharudin Ibrahim (Malaysia); Prof. Dr. Endang Hanani SU., M.Si., Apt.; Dr. Priyanto, M.Biomed., Apt; Dr. Hadi Sunaryo, M.Si., Apt.; Dr. H. Priyo Wahyudi, M.Si.; Dr. Yusnidar Yusuf, M.Si.

Cover Design:

Firmansyah, dan Achmad Furkon

Publisher and Printing:

Faculty of Pharmacy and Sciences, Universitas Muhammadiyah Prof. DR.

HAMKA Jl. Delima II/IV, Islamic Centre, Perumnas Klender, Jakarta Timur

Phone: +62-21-8611070, +62-21-86603233

Fax: +62-21-8611070

Website: www.uhamka.ac.id or www.ffa.uhamka.ac.id

Email: intl.ffa.uhamka@gmail.com or ffa_uhamka@yahoo.com

First Edition, August 2016

Copyright reserved

All right reserved

ISBN:

978-602-71959-2-9

ISBN 978-602-71959-2-9



International Seminar Metabolic Syndrome: Now and Future Trend

Organizing Committee:

Advisory	: Prof. Dr. H. Suyatno, M.Pd. (Rector of UHAMKA)
Responsible	: Drs. Budi Arman, M.Kes., Apt. (Dean of Faculty of Pharmacy and Science, UHAMKA)
Steering Committee	: Dr. Hadi Sunaryo, M.Si., Apt. (Vice Dean) Dra. Sri Nevi Gantini, M.Si. (Vice Dean) Ari Widayanti, M.Farm., Apt. (Vice Dean) Kori Yati, M. Farm., Apt. (Head of Pharmacy Department)
Organizing Committee	
Chairman	: Nora Wulandari, M.Farm., Apt.
Secretary	: Lusi Putri Dwita. M.Si., Apt.
Treasure	: : Dwityanti M.Farm., Apt Laili Yuliasuti, SE.
Program	: Daniek Vivianhari, M.Sc., Apt Yudi Srifiana, M.Farm., Apt. Ni Putu Ermi Hikmawanti, M.Farm.
Scientific	: Drs. Inding Gusmayadi, M.Si., Apt. Dr. Priyanto, M.Biomed., Apt. Numlil Khaira Rusdi, M.Si., Apt. Siska, M.Farm., Apt. Supandi, M.Si., Apt. Wahyu Hidayati, M.Biomed.
Secretariat	: Landyyun Rahmawan S, M.Sc., Apt. Ani Pahriani, M.Sc., Apt Elly Wardani, M.Farm., Apt. Rizky Archintya R, M.Si. Firmansyah
Sponsorship& Publication	: Rini Prastiwi, M.Farm., Apt. Vera Ladeska, M.Farm., Apt. Kriana Efendi, M.Farm., Apt.
Food and Beverage	: Ema Dewanti, M.Si. Iin Nurul Mutmainah Dewi Rosmalita Anisah Bajri Rifky Doni Kurniawan
Logistic	: Zainul Islam, M.Farm., Apt. Fahjar Prisiska, M.Farm., Apt Maulani Achmad Furkon Cecep Gunawan Achmad Rizky Rizkillah, SE Jumhana Heri Hendriawan

PREFACE

The Metabolic Syndrome: Now and Future Trend is a seminar held by Faculty of Pharmacy and Science Universitas Muhammadiyah Prof. DR. HAMKA, Jakarta, Indonesia on Saturday August 13rd 2016. The subjects discussed include the current and future trend of various components, therapy, as well as prevention, and challenges of drug development for Metabolic Syndrome. We will discuss those topics with leading experts invited from several countries, including Thailand, Malaysia, Australia, as well as Indonesia. Using the latest research and studies as a basic, these experts will conduct spirited discussions for the international exchange of knowledge and ideas. We hope this seminar will contribute to your professional development and relationship.

To get complete seminar, an International Proceeding we make. We thank to all author of whole articles for this Proceeding, all reviewer both home and abroad, all organizing committee, and to all the participant for their responses to our request for abstract submissions.

Again, thank you for attending the seminar on Metabolic Syndrome: Now and Future Trend 2016, we hope this proceeding will give you an advantage for building your knowledge especially in Metabolic Syndrome, clinical pharmacy, and pharmacy in general.

Thank you.

Jakarta, August 13rd 2016

Editors

FOREWORD
DEAN OF FACULTY OF PHARMACY AND SCIENCES
UNIVERSITAS MUHAMMADIYAH PROF. DR. HAMKA

Assalamualaikum warahmatullahiwabarakatuh,

Excellency, Distinguished Guests, Ladies and Gentlemen,

As the Dean of Pharmacy Faculty of Universitas Muhammadiyah Prof. DR. HAMKA (UHAMKA), I would like to extend my warmest greetings and welcome to our distinguished speakers and participants of the International Seminar on Metabolic Syndrome: Now and Future Trend.

It is a great pleasure for UHAMKA to be host of this seminar. We believe that it will be a lot of flaw in this event. Therefore, we expect criticism and suggestion from all of you, my distinguished guest.

Through this international Seminar, I wish that all the participants get fruitful discussion and it should promote International collaborations as an integral aspect of the research. And I would like to express my gratitude to the distinguished speaker, Prof. Patrick Anthony Ball from Charles Darwin University, Australia, Dr. Thitima Dounggern from Prince of Songkla University, Thailand, Dr. Baharudin Ibrahim from Universiti Sains Malaysia, Malaysia, and Dr. Hadi Sunaryo, M.Si., Apt from UHAMKA, Indonesia, for the willingness to attend and to share their knowledge, and to the participants who came from many region, and to everyone who contributed to the success of this event.

Finally, I would like also to express my appreciation to all the committees for their support to this seminar.

Wassalamu'alaikum warahmatullahiwabarakatuh.

Sincerely yours,

Drs. Budi Arman, M.Kes., Apt.
Dean of FFS UHAMKA

CONTENT

AUTHOR (S)	TITLE	Page
Baharudin Ibrahim, Arwa Mohamed Amin Mostafa	<i>ASTHMA AND METABOLIC SYNDROME - WHERE IS THE LINK?</i>	1
Hadi Sunaryo, Siska, Dwitiyanti, Rizky Arcinthya Rachmania	<i>COMBINATION OF GINGER EXTRACT (Zingiber officinale Roscoe) AND ZINC AS METABOLIC SYNDROME IN HIGH CHOLESTEROL DIET DIABETIC MICE</i>	5
Nasila Waeteh, Rahmah Elfiyani, Pramulani Mulya Lestari	<i>THE EFFECT OF INCREASING CARRAGEENAN AND KONJAC CONCENTRATION ON PHYSICAL CHARACTERISTIC OF CHEWABLE LOZENGES GUAVA LEAVE EXTRACT (Psidium guajava L.)</i>	12
Aprilita Rina Yanti Eff, Irvani Rakhmawati and Tyas Putri Utami	<i>ETHANOL EXTRACT OF Phaleria macrocarpa (Scheff.) Boerl IMPROVEDHEARTHISTOLOGICALCHANGESIN DOXORUBICIN INDUCED RATS</i>	18
Priyo Wahyudi, Siska, Dian Ayu Anggorowati	<i>ALPHA-GLUCOSIDASEINHIBITORYACTIVITYOF ENDOPHYTIC BACTERIA METABOLITES OF DAUN SALAM</i>	25
Mamik P. Rahayu, Reslely Harjanti, Gunawan P. Widodo, Mae S. H. Wahyuningsih, Supargiyono	<i>IN VITRO CYTOTOXIC ACTIVITY OF METHANOLIC EXTRACT AND CHLOROFORM FRACTION OF KARANDAS LEAF (Carandas carissa L.) ON HELA CELL</i>	30
Irma Rachmaniar, Rahayu Gusti Kurniawan, Hadi Sunaryo, Rini Prastiwi	<i>IN VITRO CYTOTOXICITY ASSAY OF ETHYL ACETATE AND DIETHYL ETHER FRACTION OF BREADFRUIT LEAVES METHANOL EXTRACT ON HeLa CELL LINE</i>	36
Andriana Sari, Hanifa Fuadiyah	<i>OUTPATIENT ADHERENCE TO ANTIDIABETIC ORAL (ADO) TREATMENT: A CASE STUDY AT PRAMBANAN PUBLIC HOSPITAL</i>	41
Aris Widayati, Fenty, Phebe Hendra	<i>CORRELATION BETWEEN BODY MASS INDEX AND APO B / APO A1 RATIO AMONG ADULTS IN RURAL AREA OF YOGYAKARTA INDONESIA</i>	46
Taty Rusliati Rusli	<i>EFFECT OF LIME RIND ESSENTIAL OIL ON PHYSYCO-CHEMISTRY OF ANTIACNE CREAM</i>	50
Dwi Utami, Ilma Nugrahani, Slamet Ibrahim	<i>PREPARATION AND CHARACTERIZATION OF MEFENAMIC ACID-NICOTINAMIDE CO-CRYSTAL SYNTHESIZED BY MELT CRYSTALIZATION METHOD</i>	55
Yelly Oktavia Sari, Yahaya H., Omar I.	<i>BEHCET'S DISEASE: A CASE REPORT</i>	61

ALPHA-GLUCOSIDASE INHIBITORY ACTIVITY OF ENDOPHYTIC BACTERIA METABOLITES OF DAUN SALAM (*Syzygium polyanthum* (Wight) Walp.)

Priyo Wahyudi ^{1,2)}, Siska ²⁾, Dian Ayu Anggorowati ²⁾

1. Agency for the Assessment and Application of Technology (BPPT), Jakarta

2. Faculty of Pharmacy and Sciences, UHAMKA - Jakarta

Abstract: Diabetes mellitus is a metabolic disease associated with abnormally high level of the sugar glucose in the blood. One of the treatment to lower the level of blood sugar is using the drug which inhibit the activity of α -glucosidase. Daun salam (*Syzygium polyanthum* (Wight) Walp.) also known as bay leaves is a medicinal plant contains active compound which showed α -glucosidase inhibitory activity. As every vascular plant contains endophytic bacteria, the purpose of this study was to determine the alpha-glucosidase inhibitory activity of endophytic bacteria's metabolites of bay leaves. Isolation of endophytic bacteria was conducted using direct plating method of bay leaves using NA medium. The obtained bacterial isolates then cultivated in a liquid F4 medium, incubated for 5 days, and harvested by centrifugation to obtain endophyte's metabolites. Supernatant was used for enzyme inhibitory assay using p-nitrophenyl-Alpha-D-glucopiranoside (p-NPG) as a substrate. Result showed that the alpha-glucosidase inhibitory activity of the metabolites of 5 endophytic bacteria isolates were 37.67%; 37.77%; 36.21; 45.81%; and 41.90%. respectively. It can be concluded that the metabolites of endophytic bacteria of bay leaves have alpha-glucosidase inhibitory activity.

Keywords: daun salam, endophytic, alpha-glucosidase, p-NPG assay

Introduction

Diabetes mellitus is a metabolic disorder genetically and clinically manifestate of the loss of carbohydrate tolerance. Diabetes mellitus could be divided into two type i.e. diabetes type 1 and diabetes type 2 (Schteingart 2005). Department of Health of Republic of Indonesia reported that there is not less than 150 million people of over the world suffered diabetes mellitus (Depkes RI 2005). Oral antidiabetic drugs that currently available were sulfonylurea, biguanide, glitazon, meglitinid, and acarbose. Acarbose is one of antidiabetic drug derived from microbial metabolites which inhibit alpha-glucosidase activity, that caused retard polysaccharide and disaccharide absorption in intestine (Priyanto 2009).

Inhibition of alpha-glucosidase will lower blood glucose level (Suherman and Nafrialdi 2012). One of the herbs that has an inhibitory activity of alpha-glucosidase is daun salam or bay leaf (Dalimartha 2000). Zang *et al.* (2006) reported that almost all classes of vascular plants and grasses examined to date are found to host endophytic organisms. Secondary metabolites can be derived from endophytic microbes that have been isolated from the plant. Endophytic microbes are microscopic living organisms (bacteria and fungi) that live-in plant tissue, leaves, roots, fruits, and stems (Simarmata *et al.* 2007). Exploration of endophytic microbes is expected to produce secondary metabolites that have properties like metabolites produced by the host plant (Pujiyanto *et al.* 2012). Studiawan and Santosa (2005) reported that the bay leaves extract can lower blood glucose levels in mice induced by alloxan.

According to Mayur *et al.* (2010), alpha-glucosidase inhibitory activity assay can be performed using₅₀ spectrophotometric method with the substrate p-nitrophenyl- α -D-glucopiranoside (p-NPG). Handayani *et al.* (2006) reported that extracts of daun salam or bay leaves had inhibitory activity of alpha-glucosidase with IC value of 28.0975 ppm. Pujiyanto and Ferniah (2010) reported that acarbose can be used as a comparative drug trials alpha-glucosidase inhibitory activity in vitro. Alpha-glucosidase activity can be detected from the breakdown of p-NPG into p-nitrophenol which measured using a microplate absorbance reader at a wavelength of 415 nm. Inhibition of alpha-glucosidase seen from the lower p-nitrophenol formed, the higher the alpha-glucosidase inhibition that occurs. The problem of this study was whether the metabolites of bay leaves endophytic bacteria have inhibitory activity of alpha-glucosidase. The purpose of this study was to determine the alpha-glucosidase inhibitory activity of metabolites of bay leaves (*Syzygium polyanthum* (Wight) Walp.) endophytic bacteria.

Material and Method

Sample of daun salam. Daun salam or bay leaves (*Syzygium polyanthum* (Wight) Walp.) was collected from Balai Penelitian Tanaman Rempah dan Obat (Balitro) Bogor.

Isolation of endophytic bacteria of daun salam (*Syzygium polyanthum* (Wight) Walp.)

Bay leaves samples as much as 2 pieces, cleaned with running water for 10 minutes and leaf size was reduced by approximately 2-3 cm pieces. Then do the surface sterilization at bay leaf samples in a graduated manner samples were stored in 75% ethanol, and then shaken gently for 1 minute, then leaves soaked in a solution of 5.3% NaOCl for 5 minutes, and soaked again in 75% ethanol for 30 sec. The sterilization process was carried out in a laminar air flow (Khan 2007). Leaves that have dried sterile and sterile wipes allowed to stand over until the ethanol evaporates. Samples were dried and cut into pieces, one leaves diced into 4 small pieces and then grown in a Petri dish containing Nutrient Agar (Difco) media containing nystatin for the growth of endophytic bacteria. Incubation was carried out at 27-30°C (room temperature) for 5-7 days (Desriani *et al.* 2014).

Metabolite production of endophytic bacteria of daun salam

The obtained pure isolates of endophytic bacteria were further fermented in a fermentation medium. The medium was sterilized in an autoclave at 121°C for 15 minutes. Isolates of endophytic bacteria were taken and put into 10 ml medium contained test tube, and then incubated on a rotary shaker (Eyela Multi Shaker) at 120 rpm for 5 days. Microbial cells were then separated by centrifugation (Bio Lion XC-HR20) at 4000 rpm for 20 minutes. The obtained supernatant will be used as a test sample for testing the inhibition of the alpha-glucosidase enzyme (Agustina 2003).

Alpha-glucosidase inhibitory assay procedure

Alpha-glucosidase inhibitory activity assay (Table 1) was conducted by testing the blank solution, control solution, and test solution. The solutions were incubated for 30 minutes and the enzyme activity was stopped by the addition of 100 Na CO then the absorbance was read using a microplate reader 96 wells (Bio-Rad iMark) at a wavelength of 415 nm (Yuniarsih 2012; Mayur *et al.* 2010).

Table 1: Alpha-glucosidase Inhibitory Assay Preparation Scheme

Materials	Blank μl	Control μl	Assay Sample μl	Acarbose μl
Endophyte Metabolite	-	-	10	-
Acarbose	-	-	-	-
Buffer	50	50	50	50
Substrate p-NPG	25	25	25	25
DMSO	10	10	-	-
Buffer	25	-	-	-
Enzyme α- glucosidase	-	25	25	25
Na CO	100	100	100	100

The percentage of inhibition of α-glucosidase enzyme activity can be calculated by the formula:

$$\% \text{ Inhibition of metabolites of endophytic} = \frac{A_C - A_X}{A_C} \times 100\% \dots\dots\dots (1)$$

$$\% \text{ Inhibition acarbose} = \frac{A_C - A_A}{A_C} \times 100\% \dots\dots\dots (2)$$

Note:

Abs C = Absorbance of control – Absorbance of

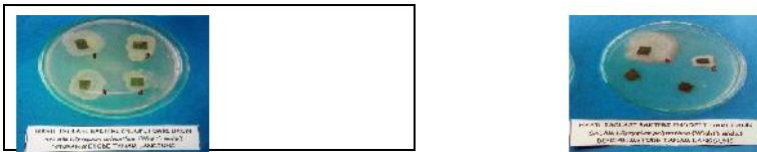
Blank Abs X = Absorbance of sample Abs A =

Absorbance of Acarbose

RESULT AND DISCUSSION

Isolation of endophytic bacteria of daun salam (*Syzygium polyanthum* (Wight) Walp.)

Figure 1: Isolation of Endophytic Bacteria of Daun Salam Which Obtained Six Bacterial Isolates



Isolation of endophytic bacteria was conducted to obtain pure cultures of endophytic bacteria, using Nutrient Agar medium. Giving nystatin into the medium as an antifungal were intended so there is no mold growing at the time of isolation (Desriani dkk. 2014). Isolation of bacteria was conducted using direct planting. Observation of the isolation was performed for 5 – 7 days. on day 5 the observation had been shown to result in isolates of endophytic bacterial. In one plate that contained 4 isolates which were successfully isolated seen from the growth of endophytic bacteria that grow on the different leaf pieces. Isolates 1 and 2 were taken from the top leaf pieces. Isolates 3 and 4 were taken from the bottom leaf pieces. On the other plate, there were 2 isolates which were successfully isolated and taken from the upper leaves (Figure 2).

Metabolite production of daun salam endophytic bacteria

Metabolite of endophytic bacteria was produced by isolates endophytic bacteria through sub-merged fermentation for 5 days. According Margino (2008) sub-merged fermentation aims to produce secondary metabolites of endophytic bacteria. Supernatant of fermentation product was used for alpha-glucosidase inhibitory activity assay represents of endophytic metabolites. The supernatants, were prepared by centrifugation at 4000 rpm for 20 minutes (Margino 2008).

Table 2: Supernatant Contained Metabolite of Endophytic Bacteria of Daun Salam After Sub-Merged Fermented for 5 Days

Isolate code	Volume of supernatant from replication (ml)			Average volume of supernatant (ml)	SD
	1	2	3		
Isolate DA1	8,2	7,9	8,6	8,23	0,35
Isolate DA2	7,6	8,5	8,2	8,10	0,46
Isolate DA3	8,1	9,2	8,0	8,73	0,57
Isolate DA4	8,3	8,2	8,0	8,17	0,15
Isolate DA5	9,0	8,3	8,8	8,7	0,36

Alpha-glucosidase inhibitory assay

Alpha-glucosidase inhibitory assay was conducted using the enzyme alpha-glucosidase (*Sigma-Aldrich USA*) with a concentration of 0.2033 units/ml and the substrate p-nitrophenyl- α -D-glucopyranoside (p-NPG) (*Sigma-Aldrich USA*) with a concentration of 5 mM. Enzyme inhibitory assay was conducted by measuring the absorbance of p-nitrophenol as the enzymatic reaction product (Pujiyanto and Ferniah 2010). Result of absorbance and inhibition percent of each isolate can be seen in the Table 3.

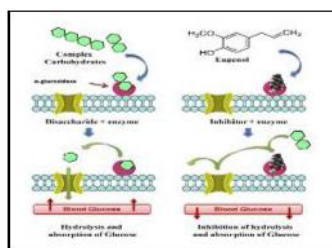
The lowest inhibition of enzyme activity caused by endophytic metabolite was 36.21% which produced by isolates DA3, and the highest was 45.81% which produced by isolates DA4 (Table 3). Difference in the percentage of inhibition at each metabolite of endophytic might cause by the content of secondary metabolites were different in each isolate. As Radji (2005) mentioned that the endophytic bacteria could produce biological compounds or secondary metabolites that are like the host plant. Result of this assay proved that endophytic bacteria of bay leaves or daun salam could produce secondary metabolites, which have alpha-glucosidase inhibitory activity that were like the host plant (leaves) extract. As has been reported Handayani *et al.* (2006) that active compound of daun salam or bay leaf extract, which inhibit alpha-glucosidase was eugenol.

Table 3: Inhibitory Activity of Alpha-Glucosidase of Endophytic Bacteria of Bay Leaves Metabolites and Acarbose Using Microplate Reader at 415 nm

Sample Test	Absorbance	Percentage of enzyme inhibition (%)
Blank	0.05	
Control	2.52	
Isolate DA1	1.56	37.67
Isolate DA2	1.54	37.77
Isolate DA3	1.58	36.21
Isolate DA4	1.34	45.81
Isolate DA5	1.44	41.90
Acarbose	0.42	82.99

Metabolite of endophytic bacteria that works as an inhibitor was suspected of having a reversible competitive mechanism. Endophytic metabolites compete with p-NPG to occupy active site of enzyme, forming an enzyme – inhibitor complex, thus causing enzyme inhibition. Eugenol was thought to be secondary metabolites produced by endophytic bacteria of bay leaf that acts as an inhibitor of alpha-glucosidase. Singh *et al.* (2016) reported that eugenol has two mechanisms work in treating diabetes that lowers blood glucose by inhibiting α -glucosidase (Figure 2) and prevents the formation of AGE by binding to ϵ -amine groups on lysine, cluster 4 'OH of compound eugenol which may potentially capable of binding to amine groups of lysine residues in the protein molecule, and competitively inhibits the binding of glucose.

Figure 2: Alpha-glucosidase Inhibitory of Eugenol (Singh *et al.* 2016)



Inhibitory percentage of acarbose greater than metabolites of bay leaves endophyte. Acarbose more effective in inhibiting the activity of alpha-glucosidase compared to metabolites of endophytic bacteria, because acarbose is a microbial oligosaccharide that have been commercialized as oral antidiabetics. In inhibiting alpha-glucosidase, acarbose works irreversible competitively by occupying the active site of enzyme, forming an enzyme – inhibitor complex (Poedjadi 1994; Tjay dan Rahadja 2007). Inhibition of alpha-glucosidase activity causes the inhibition of breakdown of polysaccharides into monosaccharides, which ultimately lowering glucose levels in the blood.

Conclusion

Based on this study, it can be concluded that it has acquired five isolates of endophytic bacteria from daun salam or bay leaves (*Syzygium polyanthum* (Wight) Walp.) and metabolites produced by the five isolates of endophytic bacteria have inhibitory activity of alpha-glucosidase.

References

Agustina EM. 2003. Isolasi dan Penapisan Kapang Endofitik Tanaman Trengguli (*Cassia fistula* L.) sebagai Penghasil Senyawa Antimikroba. *Skripsi*. Fakultas Farmasi Universitas Pancasila. Jakarta. Dalimartha S. 2000. *Atlas Tumbuhan Indonesia Jilid 2*. Niaga Swadaya. Jakarta. Hlm 162.

Departemen Kesehatan RI. 2005. *Pharmaceutical Care Untuk Penyakit Diabetes Melitus*. Departemen Kesehatan RI. Jakarta. Hlm 8,13,45.

Handayani R, Kardono LSB, Wulansari JM. 2006. Aktivitas Antihiperqlikemia pada Fungsional Drink Daun Salam (*Eugenia polyantha*) Sebagai Inhibitor Enzim α -glucosidase. *Jurnal Ilmu Dan Teknologi Pangan*. 4(2): 33-46.

- Margino S. 2008. Produksi Metabolit Sekunder (Antibiotik) oleh Isolat Jamur Endofit Indonesia. *Majalah Farmasi Indonesia*. **19**(2): 86-94.
- Mayur B, Sandesh S, Shruti S, Sung-Yum S. 2010. Antioxidan and α -glukosidase Inhibitor Properties of *Carpesium abrotanoides* L. *Journal of Medicinal Plants Research*. **4**(15): 1547-1553.
- Poedjiadi A. 1994. *Dasar-Dasar Biokimia*. UI Press. Jakarta. Hlm. 164.
- Priyanto. 2009. *Farmakoterapi & Terminologi Medis*. Leskonfi. Jakarta. Hlm 165-168.
- Pujiyanto S, Ferniah RS. 2010. Aktivitas Inhibitor alpha-glukosidase Bakteri Endofit PR-3 yang Diisolasi dari Tanaman Pare (*momordica charantia*). *BIOMA*. **12**(1): 1-5.
- Pujiyanto S, Suwanto A, Budiarti S, Darusman LK. 2012. Alpha-glukosidase Inhibitors Activity and Characterization of Endophytic Actinomycetees Isolated from Some Indonesian Diabetic Medicinal Plants. *International Journal of Pharmacy and Pharmaceutical Sciences*. **14**(1): 327-333.
- Radji M. 2005. Peranan Bioteknologi dan Mikroba Endofit Dalam Pengembangan Obat Herbal. *Majalah Ilmu Kefarmasian*. **2**(3): 113-126.
- Schteingait DE. 2005. Pankreas : Metabolisme Glukosa dan Diabetes Melitus. Dalam: Prince SA, Wilson LM (Eds.). 2002. *Patofisiologi Konsep Klinik Proses-Proses Penyakit Volume 2 Edisi 6*. Penerjemah: Pendit BU, Hartanto H, Wulansari P, Mahanani DA. EGC. Jakarta. Hlm 1260-1262.
- Simarmata R, Lekatompessy S, Sukiman H. 2007. Isolasi Mikroba Endofitik dari Tanaman Obat Sambung nyawa (*Gynura procumbens*) dan Analisis Potensinya Sebagai Antimikroba. *Berkala Penelitian Hayati*. **13**: 85-90.
- Singh P, Jayaramaiah RH, Agaware SB, Vannuruswamy G, Korwar AM, Arand A, Dhaygude VS, Shaikh ML, Joshi RS, Boppana R, Kulkarni MJ, Thulasiram HV, Giri AP. 2016. Potential Dual Role of Eugenol in Inhibiting Advanced Glycation End Products in Diabetes: Protomic and Mecanistic Insights. *Scientific Report*. **6**:18798.
- Studiawan H, Santosa MA. 2005. Uji Aktivitas Penurunan Kadar Glukosa Darah Ekstrak Daun (*Eugenia polyantha*) pada Mencit yang Diinduksi Aloksan. *Media Kedokteran Hewan*. **21**(2): 62-65.
- Suherman SK, Nafrialdi. 2012. Insulin dan Antidiabetika Oral. Dalam: Gunawan SG, Setiabudy R, Nafrialdi, Elysabeth. (Eds). *Farmakologi dan Terapi*. Departemen Farmakologi dan Teraupetik Fakultas Kedokteran UI. Jakarta. Hlm 493-494.
- Sweetman SC. (2009). *Martindale 36th Edition the Complete Drug Reference*. The Pharmaceutical Press. London. Hlm 436.
- Tjay TH, Rahadja K. 2007. *Obat-Obat Penting Edisi Enam*. Alex Media Kompetindo. Jakarta. Hlm. 747-749.
- Yuniarsih M. 2012. Uji Aktivitas Antidiabetes Ekstrak dan Fraksi dari Ekstrak n-Heksan Buah Ketapang (*Terminalia catappa* L.) Sebagai Inhibitor α -glukosidase dan Penapisan Fitokimia dari Fraksi Taraktif. *Skripsi*. Fakultas MIPA. Universitas Indonesia. Jakarta.
- Zang, W, D. Becker, Q.A. Cheng. 2006. Mini review of recent W.O, Resent patents on anti-infective drug discovery, **1,1**, 225-230