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PREFACE

Alhamdulillah, All praise be to god Allah the almighty, who has bestowed us his mercy and his blessing. Salvation and salutation be upon to our beloved prophet Muhammad *Shallallhualaihiwasallam*, who has brought us from the bad way to the good way and all his companions who strives in religion

This proceeding contains the papers of the talk presented in International Conference and Workshop on Pharmacy and Statistics (ICWPS) 2016. Theconference was jointly organized by Department of Pharmacy and Statistics Study Program, Faculty of Mathematics and Natural Sciences, Tadulako University. I express my big thanks to all committees and sponsors who have supported this scientific event

ICWPS 2016 was held in IT center building, Tadulako University on 26-27 November 2016. The theme of the conference is *Current Development of Medicinal Plants and Biostatistics*. The conference aims to promote interdisciplinary research in pharmacy and statistics and to disseminate research in various field of pharmacy and statistics. There are five main areas of research covered in this conference. They are*Natural Product Chemistry and Biodiversity, Pharmaceutics and Pharmaceutical Chemistry, Pharmacology, Bioactivities and Biotechnology, Clinical Pharmacy and Health Sciences, and Biostatistics*.

On behalf of ICWPS 2016 organizing committee, i am delighted to thank the invited speakers and participants who have submitted papers to this conference. Thank also to Faculty of Mathematics and Natural Sciences for its support towards the organization of the conference.

Palu, February 8th, 2017
Chair of ICWPS 2016

M. Sulaiman Zubair, PhD, Apt

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Analysis of Drugs Management on Procurement Phase In The Pharmacy of Dr. M.M. Dunda Hospital - Limboto in 2015

Teti Sutriyati Tuloli*, Madania, Anggun D.S. Bokings

Departement of Pharmacy, Gorontalo State Univercity

ABSTRACT

Drugs Management is the part of hospital management that have several phase, one of them is the procurement of drugs. The results of preliminary observations indicate the existence of some problems in the drugs procurement in the pharmacy of Dr. M.M Dunda Hospital of Limboto. The purpose of this study is to analyze the efficiency of drug management in procurement phase. This research using descriptive method with cross sectional approach retrospectively. The obtained data were analyzed quantitatively and the efficiency was measured using indicators Ministry of Health (2002), Pudjaningsih (1996) and WHO (1993). The results showed that the percentage of available capital funds with total funds needed is 100% efficient, the percentage of the allocation of funds for procurement of drugs are inefficient at Dr. M. M Dunda Hospitals (13.82%), the percentage of the number of drug items that held as planned are inefficient (67%), the frequency of drugs procurement for each item of drug are low (2.78 times), frequency of invoice error in hospital pharmacy already efficient (1.72%) and the frequency of delayed payment by the hospital to the agreed time are inefficient (10.45 days). Conclusions from the study that there are 3 (Three) Drug Procurement Indicator not efficient in Dr. M.M. Dunda Hospital.

Keywords: efficiency, drugs, management, procurement, hospital pharmacy

ABSTRAK

Pengelolaan obat merupakan salah satu segi manajemen rumah sakit yang meliputi beberapa tahapan salah satunya tahap pengadaan. Hasil observasi awal menunjukkan adanya beberapa permasalahan dalam pengadaan obat di instalasi farmasi RSUD Dr. M.M Dunda Limboto. Tujuan penelitian ini adalah menganalisis efisiensi pengelolaan obat pada tahap pengadaan. Metode penelitian ini menggunakan rancangan deskriptif dengan pendekatan *cross sectional* yang bersifat *retrospectif*. Data yang diperoleh diolah secara kuantitatif dan diukur efisiensinya menggunakan indicator Depkes (2002), Pudjaningsih (1996) dan WHO (1993). Hasil penelitian menunjukkan bahwa persentase modal dana yang tersedia dengan keseluruhan dana yang dibutuhkan sudah 100% efisien, persentase alokasi dana pengadaan obat di RSUD Dunda belum efisien yaitu (13,82%), persentase jumlah *item* obat yang diadakan dengan yang direncanakan belum efisien yaitu (67%), frekuensi pengadaan obat tiap *item* obat termasuk dalam kategori rendah yaitu (2,78 kali), Frekuensi kesalahan faktur di instalasi farmasi RSUD Dr. M.M Dunda Limboto sudah efisien yaitu (1,72%) dan frekuensi tertundanya pembayaran oleh rumah sakit terhadap waktu yang disepakati belum efisien yakni (10,45 hari). Kesimpulan dari penelitian ini ada 3 (tiga) indikator yang belum efisien pada tahap pengadaan obat di RSUD Dr. M.M. Dunda.

Kata Kunci: Efisiensi, Obat, Pengelolaan, Pengadaan, IFRS Dunda

Corresponding author : Teti Sutriyati Tuloli, email : tetisutriyati@gmail.com

1. Introduction

Hospital pharmacy services is one of the activities in hospitals that support the quality of health services. The rule of Ministry of Health number 58 in 2014 about the standard of pharmacy services said that the hospital services is a direct and responsible services for patient associated with the drug with the aim of reaching a definitive result to improve the quality of life of patient. The installation of pharmacy is one unit in the hospital that have responsible to manage all aspects relating to drug supply and usage in hospitals (Siregar and Amalia, 2004).

Drugs management is one aspect of hospital management which is very important in the provision of whole health services, due to inefficiency and disfluencies drugs management will give a negative impact on the hospital medically, socially and economically (Siregar and Amalia, 2004). Quick *et al* (1997) mentions that the drug management cycle includes four basic functions, namely selection, procurement, distribution, and use that requires the support of the organization, financing sustainability, information management and human resources management in it.

One of the very important phase of drugs management is a drugs procurement. Procurement is one of the phase being taken to meet the needs of the drugs at the installation of pharmacy in hospital after passing through a planning and selection phase.

Drugs Procurement at Dr. M. M Dunda Hospital in Limboto already use e-catalog system where the purchase of drugs is done through the Internet regulated by the Department of Health. E-catalog system already contains information about the list of the names of the drugs, types of drugs, the smallest units price of drugs and the factory name of the drugs provider. Hospital as users still meet some obstacles such as the ordering drugs access system that sometimes can not be accessed because it use by so many users from all over Indonesia at the same time. The unavailability of medication is another obstacle that is found at the hospital because when the hospital book a drug, it is unavailable in all of drug companies that trigger inefficient on health services of the hospital.

The purpose of this study was to measure the efficiency of drugs management in procurement phase in Pharmacy Installation of Dr. M.M Dunda Hospital in Limboto during 2015.

2. Experimental

This sections have 2 subsections are:

2.1 Research Design

The design of this research is quantitative descriptive by cross sectional approach method where data was obtained retrospectively to analyze the efficiency of the drugs management in

procurement phase in Pharmacy Installation Dr. M. M Dunda Hospital in Limboto during 2015.

The data that obtained in this research were primary data and secondary data. Primary data were obtained from the observation while secondary data obtained from the data the provided in the Installation of Pharmacy Department, General and Administration Department, Drugs Procurement Department and Financial Department in Dr. M. M Dunda Hospital in Limboto

2.2. Data Analysis

Data were collected and analyzed quantitatively to determine the efficiency of the drugs management in procurement phase in the Pharmacy Installation of Dr. M. M Dunda Hospital in Limboto 2015 and compared with indicators of the drug management in procurement phase according to the Department of Health (2002), Pudjaningsih (1996) and WHO (1993).

3. Results and Discussion

3.1. The Percentage of Available Capital Funds Compared with Total Funds Needed

The percentage was obtained for this indicator was 100%. Based on the standards set by Pudjaningsih (1996) in Madania (2009) for the percentage of available capital funds compared with total funds needed, the default value was set at 100%. If the percentage was adjusted with the standards was set then the the results of research was the percentage of available capital funds compared with the total fund was suitable. The results was obtained indicated the amount of available funds was able to provide the funds needed so that it was able to concluded that this indicator had been efficient. The results that was obtained also showed that there was a budget surplus that could be used for the next order period of the drugs procurement.

This is in line with the research of Maimum (2007) at the Pharmacy Installation of Saras Husada Hospital in Purworejo stated that from the funds that was provided, only 99.55% of the funds are used to fulfill the needs and still have a budget surplus that could be used in the next period.

3.2. The Percentage of the fund allocation of the drug procurement

The results of the percentage of the funds allocation of the drugs procurement in Dr. M.M. Dunda Hospital amounted to 13.82%. According Departamen of Health (2002), the default value for the percentage of funds allocation of drugs procurement is 30-40%. It showed that the percentage of funds allocation of the drugs procurement was inefficient. This inefficiency caused by the whole funds for procurement that available was in low level because the funds that allocated for the procurement of drugs are determined in accordance with hospital's revenue. The available budget was also adopted to the needs of the funds that was planned.

This is in line with the research of Wati et al (2013) in Karel Hospital that the funds allocation of the drugs procurement was only 6.51% (inefficient). This is caused by the value of the budget for the drugs procurement has been set in the budget of the Budget Revenue and Expenditure.

3.3. Percentage of the number of the drug items compared with the percentage of the drug items number held as planned

Percentage of the number of the drug items compared with the percentage of the drug items number held as plannedwas 67%. According Pudjaningsih (1996), the default value specified in the indicator of the percentage of the drug items that was held as planned was amounted to 100-120%. This meant that the drugs procurement in this indicator was inefficient. This inefficiency might becaused by the pharmaceutical wholesaler that was not able to provide drugs that as planned by the hospital and it also might be caused by the planned order of the drugs was not realized at all so that the percentage was higher than the standard.

This contrasts with the results of research Fakhriadi et al (2011) in Pharmacy Installation of PKU Muhammadiyah Hospital in Temanggung in 2006-2008 where the percentage of indicator of drug items number was held as the planned results more than 100% due to an excession of drugs procurement.

Sasongko and Octadevi (2016) argued that the inefficient of this indicator was caused by unability of all distributor to provide planned drugs by the hospital so that they must make planning selectively referring to the principle of effectiveness, safety, economical, rational and held correctly using the VEN method and ABC analysis (Quick *et al*, 1997), and appointment of a reliable supplier or appointment of good distributor that be able to service them satisfactorily.

3.4. The frequency of the drugs procurement for each drug items

The frequency of the drugs procurement for each item of the drug was 2.78 times. According to Pudjaningsih (1996), the standard values for this indicator were classified into three categories: low frequence <12x / year, medium frequence 12-24x / year, high frequence > 24x / year. The results showed that the frequence of 2.78 times was in low frequency (<12x / year). This was due to the booking of drugs by the pharmaceutical installations that was in large volume or the incompatibility of ordered drugs by the drugs procurement compared with the plan of Planning Depatrment.

According to Sasongko and Octadevi (2016), this low frequence of the drugs procurement indicated that the drugs were available in the pharmacy were drugs that have slow-moving or the booking was too high. Therefore, the improvement efforts that can be made on this indicator was to apply the Economic Order Quantity method.

3.5. The frequency of occurrence of errors invoice

The frequency of occurrence of errors invoice in Dr. M. M. Dunda Hospital in Limboto was 1.72%. According to Pudjaningsih (1996), the standard values of error invoice frequence is 1-9 times. The research showed that the error invoice frequence in the pharmacy installation of Dr. M. M Dunda Hospital in Limboto still was efficient.

According Maimum (2007), the error invoice occur because the delivered drug items is not suitable with the order. This is in line with the results of interviews with the worker of pharmaceutical intallation Hospital Dr. M. M. Dunda which revealed that the error invoice usually occured because of a communication error between the sales and the Wholesalers Pharmacy about the number of orders placed by drugs procurement department, and also because of errors price tag, and the drugs that had sent had close Expire date.

3.6. The frequency of delayed payment by the hospital to the agreed time

In this indicator, the frequency of delayed payment by the hospital was for 10.45 days. According to Pudjaningsih (1996), the standard set values for this indicator is 0-25 days. Judging from the results obtained and adjusted to the standard, it indicated that the indicators were efficient.

According to Saso and Octadevi (2016), the delayed payment of invoices is not caused by the time in the process of filing at the hospital that had long process but (in accordance with the results of interviews with chief financial officer of Dr. M. M Dunda Hospital) the delays due to late of files of invoices payment billing to insert in the Finance Department. The efforts should be made to minimize the delay events was to create a MoU (Memorandum of Understanding) on both sides.

Tabel 1. The Calculation Results of The Drugs Procurement

The percentage of available capital funds to the total needed funds		
1	Total of available funds (Rp)	8.062.279.602,00
2	Total of needed funds (Rp)	8.025.987.881,79
	The Percentage of available funds (Rp)	100%
The Percentage of funds allocation for Drugs Procurement		
1	Total of available funds (Rp)	8.062.279.602,00
2	Total of Hospital Budgets	58.309.977.848,67

	The Persentage of funds allocation of drugs procurement	13,82%
Percentage of the number of the drug procurement items compared with the planned		
1	Total of drug items were held	462
2	Total of drug items were planned	689
	The percentage of the total of drug items were held to the total of drug items were planned	67%
The Frequence of drugs procurement for each drug item		
1	Total of drug items were held	462
2	Total of Frequency of Purchases of items of drugs held	1287
	Average frequency of the drugs procurement for each drug item	2,78 times
The Frequence of Error Invoice		
1	Total of error invoices	10
2	Total of recieved invoice	580
	The avarage of error Invoice	1,72%
The frequency of delayed payment by the hospital to the agreed time		
1	The Avarage of late frequence	10,45 days

4. Conclusions

Based on the results of the study, we concluded that:

1. The percentage of available capital funds to the total needed funds was efficient, that was 100%.
2. The Persentage of funds allocation of drugs procurement in Dr. M. M Dunda Hospital was inefficient, that was 13.82%
3. The percentage of the total of drug items were held to the total of drug items were planned was efficient, that was 67%
4. The frequency of the drugs procurement for each drug items was in low level (<12x/year), that was 2,78 times
5. The frequency of Error Invoice in Pharmacy Installation of Dr. M. M Dunda Hospital in Limboto was efficient, that was 1,72%
6. The frequency of delayed payment by the hospital to the agreed time was efficient, that was 10.45 days.

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Assessment of the Usage of the Drugs in Gastritis Patients in Dr. M. M Dunda Hospital - Limboto in 2016

Madania*, Teti Sutriyati Tuloli, Yulin Agi

Departement of Pharmacy, Gorontalo State Univercity

ABSTRACT

Gastritis is an inflammation of the gastric mucosa caused by irritation and infection and it is one of the gastrointestinal health problems most often occur. The purpose of this study is to assess the usage of the drugs in patients of gastritis in Dr. M.M Dunda Hospital in Limboto during January to March 2016. The results showed that the patients of gastritis in Dr. M.M Dunda Hospital in Limboto from January-March in 2016 got a single therapy (omeprazole, sucralfate, ranitidine and antacids) and combination therapy (omeprazole-sucralfate, ranitidine-antacids, ranitidine-omeprazole-omeprazole and antacids). The usage of the drugs according to Standard of Medical Services (SMS) in Dr. M. M Dunda Hospital in Limboto was 81.82% and the usage of the drugs was not suitable with the standard was 18.18%.

Key words: Drugs Using, Dunda Hospital of Limboto, Gastritis.

ABSTRAK

Gastritis adalah peradangan (inflamasi) dari mukosa lambung yang disebabkan oleh faktor iritasi dan infeksi dan merupakan salah satu masalah kesehatan saluran pencernaan yang paling sering terjadi. Tujuan penelitian ini yaitu untuk mengkaji penggunaan obat pada pasien gastritis di RSUD Dr. M.M Dunda Limboto tahun 2016. Penelitian ini merupakan jenis penelitian deskriptif dengan pengambilan data secara retrospektif bersifat cross sectional. Data sekunder yang di peroleh dari rekam medik RSUD Dr. M.M Dunda Limboto dicatat pada lembar pengambilan data, dianalisis univariat dan diolah secara deskriptif. Hasil penelitian menunjukkan bahwa penggunaan obat pada pasien gastritis di RSUD Dr. M.M Dunda Limboto dari bulan Januari-Maret 2016 pasien gastritis mendapatkan terapi tunggal (omeprazol, sukralfat, ranitidin dan antasida) dan terapi kombinasi (omeprazol-sukralfat, ranitidin-antasida, ranitidin-omeprazol dan antasida-omeprazol). Penggunaan obat sesuai Standar Pelayanan Medis yaitu sebesar 81.82% dan 18.18% belum sesuai dengan SPM RSUD. Dr. M.M Dunda Limboto untuk penyakit gastritis.

Kata Kunci: Gastritis, Penggunaan Obat, RSUD Dunda Limboto

***Corresponding author:** Madania : E-mail: madania.tulsyahra@gmail.com

1. Introduction

Gastritis is an inflammation of the gastric mucosa caused by irritation and infection (Berardy and Lynda, 2005). Gastritis is a disease that often occurs with the characteristics of anorexia, satiety, discomfort in epigastrium, nausea, and vomiting. Gastritis are divided clinically into two types: acute gastritis and chronic gastritis. Acute gastritis is an abnormality clinical acute which have a clear causes with the typical signs and symptoms, usually occur some acute inflammatory cells. Chronic Gastritis is gastritis with no apparent cause, often is multifactorial with varying clinical phases. Chronic gastritis is closely related to Helicobacter pylori infection (Gustin, 2011).

Gastritis is one of gastrointestinal health problems most often occur. Gastritis is usually caused by irregular eating patterns, bad dietary habit, and consuming foods that is unhygienic (Hartati et al, 2014). The risk that causing of gastritis is the usage of aspirin or anti-inflammatory non-steroidal, infection of the bacteria Helicobacter pylori, the habit of drinking alcohol, smoking habits, stress, bad dietary habit and eating too much spicy food and acidic (Angkow et al, 2014).

According to the data from the World Health Organization (WHO), Indonesia ranks fourth with the number of patients of gastritis is the largest after American countries, England and Bangladesh which amounted to 430 million people with gastritis. The incidence of gastritis in Southeast Asia around 583.635 of the population each year. The percentage of incidence of gastritis in Indonesia, according to WHO is 40.8%. The incidence of gastritis in several regions in Indonesia is quite high with prevalence are 274.396 cases of 238,452,952 inhabitants. According Saydam in Randonuwu that if gastritis allowed to continue, it would damage the function of the stomach and can increase the risk for gastric cancer that cause a death. Dr. M. M Dunda Hospital in Limboto is one of the hospital with the highest cases of gastritis. Based on the results of preliminary observations made in Dr. Dunda in Limboto in 2015, one of the most prevalent diseases was gastritis. Gastritis ranked 6 out of 10 major diseases in the hospital. If seen from the number of patients with gastritis that hospitalized in Dr. M. M Dunda Hospital in Limboto, every month gastritis kept remaining to the top 10 most prevalent diseases in 2015. The number of patients hospitalized with symptoms of gastritis in January to October 2015 as many as 308 patients (10 of the Annual Report Diseases, 2015).

The main goal in the treatment of gastritis is to relieve pain, relieve inflammation and prevent peptic ulcers and complications. In addition, the therapy with drugs is intended to improve or maintain the quality of life of patients, but this kind of therapy often delivers unexpected things that can make the condition of the patient get worse. Inaccuracy of diagnosis makes the patient does not get proper treatment so that his condition get worse. (Hidayah, 2014).

Research conducted by Randonuwu et al (2013) showed that the treatment of drugs in patients of gastritis (of 15 patients) in Prof. Dr. R. D. Kandou Manado Hospital in 2013 was suitable with the Standard of Operating Procedures (SOPs), unless the usage of antibiotics was unsuitable because the patients do not reveal any bacterial infection.

The usage of the drug in patients of gastritis carried out by checking the suitability of the

usage of the drugs in patients of gastritis based on the Standards of Medical Service in Dr. M.M Dunda Hospital in Limboto. The usage of drugs in a disease can affect the quality of treatment, service and the cost of treatment received by patients. The efforts to improve the quality of medical services can not be separated from the efforts to standardize the medical service, therefore the medical services in hospitals required to have a standard of medical services which needs to be followed up by organizing some standards of operation. The entire government and private hospitals of all levels should be able to apply this standard so that the hospital can maintain the quality and produce effective and efficient services (Ministry of Health 595 / Ministry of Health / Decree / VII / 1993).

Based on the description above, the problem that arises is how to use the drugs in patients of gastritis in Dr. M. M Dunda Hospital in Limboto and whether the usage of the drugs in patients of gastritis in Dr. M. M Dunda Hospital in Limboto was suitable with the Standards of Medical Services?

The purpose of this study is to examine the usage of the drugs in patients with gastritis in Dr. M. M Dunda Hospital in Limboto and determine the suitability of the drugs using in patients of gastritis based on the Standards of Medical Services in Dr. M. M Dunda Hospital in Limboto.

2. Experimental

This study was conducted in May-July 2016 in Dr. M M Dunda Hospital in Limboto. This study was cross sectional observational research. This type of data was conducted retrospectively by performing searching of record of the treatment of patients of gastritis were hospitalized in Dr. M.M Dunda Hospital's medical records in January to March 2016.

The population that use in this study is all the data on the medical record of patients of gastritis were hospitalized in the hospital Dr. M.M Dunda Limboto in January to March 2016 with the number of patients were as many as 45 patients. The samples studies met the inclusion criteria that had the complete medical record and readable by the researcher clearly and the samples that obtained using these criteria were as many as 33 patients.

The collecting data was conducted using instruments of data collector sheet of patients of gastritis that hospitalized, include the medical record number, patient's age, sex, clinical data, name of medicine/preparations, and the dose given. The data were then grouped according to the gender, age, and treatment.

Data were analyzed using univariate (percentages) and assessed based on the reference and the selection of drugs information was customized with the Standards of Medical Services of Dr. M.M Dunda Hospital in Limboto.

3. Results and Discussion

This research results showed that the patients of gastritis populations who have hospitalized in Dr. M. M Dunda Hospital in Limboto during January to March 2016 were 33 patients that had met the inclusion criteria, and the results were presented in tabular form as follows:

Table 1. The Characteristic of the Patients of Gastritis Based on the Age during January-March 2016

Age(years)	Frequency	Percentage (%)
7 – 15	5	15.15
16 – 24	5	15.15
25 – 33	2	6.07
34 – 42	4	12.12
> 43	17	51.51
Total	33	100

According to the table 1 we can see that patients in age >43 were the most with the percentage are 51.51%. This is in line with research conducted by Salamanya (2014) concerning the study of the usage of the drugs to the patients of gastritis hospitalized in Toto Kabila Hospital in Bone Bolango District where the age group most experienced gastritis was the group of 41-64 years. This was because the more old the people, the more the gastric mucosa tends to become thinner making it more prone to gastritis disease than younger people, Fawcett and Bloom (2002).

Table 2. Characteristics of patients of gastritis categorized by gender during January-March 2016

Gender	Frequency	Percentage (%)
Male	12	36.4
Female	21	63.6
Total	33	100

Table 2 shows that of the 33 patients treated in hospitals. Dr. M. M Dunda in Limboto, the highest number of patients with gastritis were female compared to male patients with the percentage of the female were 63.6%. This is in line with research conducted by Salamanya (2014) concerning the assessment of the usage of the drugs in patients of gastritis that hospitalized in Toto Hospital in Kabila, Bone Bolango District which showed that more patients of gastritis were female. Most patients with gastritis were treated in hospitals. Dr. M. M Dunda Hospital in Limboto during January-March 2016 were women.

Gastritis disease common in women because of the level of stress in women is higher than in men, and women is more difficult to control and manage their emotions that triggers stress so it causes gastritis (Syahputra, 2012). Stress is experienced will have an effect on the digestive tract, including the stomach. Stress conditions stimulate increased production of gastric HCl. (Berardy and Lynda, 2005).

Table 3. Frequency of the usage of the drugs of gastritis disease during January-March 2016

No	The Name of the Drug	Frequency	Percentage (%)
1	Omeprazole	22	51.2
2	Sukralfate	5	11.6
3	Ranitidine	10	23.3
4	Antacida	6	14.0
Total		43	100.0

Table 3 shows that there were four types of medication prescribed by a doctor in patients with gastritis, they were omeprazole, antacids, ranitidine and sucralfate. For gastritis patients who experienced an increase in gastric acid secretion, the drug that can inhibit gastric acid secretion were given. The drug that widely most used to inhibit gastric acid secretion was omeprazole with a percentage of 51.2%.

Omeprazole was the drug widely most used because omeprazole is a gastric acid secretion inhibitors because it is better than H2 antagonists (such as ranitidine). Omeprazole shows no anticholinergic effects (such as anxiety, dry mouth, and urinary retention). This is in line with research conducted by Syahputra (2012) about the comparison of omeprazole and ranitidine in the treatment of functional dyspepsia in adolescents that omeprazole was more effective than ranitidine because it can reduce the frequency, duration and recurrence of the disease. Omeprazole inhibits the secretion of acid by inhibiting practically the enzyme H+K+-ATPase selectively in the parietal cells and suppress the secretion of hydrogen ions into the lumen of the stomach (Tjay and Rahardja, 2007).

The drugs usage that is the second largest of using after omeprazole was ranitidine. This is in line with research conducted by Salamanya (2014) concerning the study of gastritis drug use among patients that hospitalized in Toto Hospital in Kabila, Bone Bolango district where gastritis drug that was widely used was ranitidine. According Tjay & Rahardja (2007), the inhibitory effects on the secretion of acid ranitidine is more powerful than the drug cimetidine that does not hinder oxidative reshuffle of the other drugs that does not result in undesirable interactions. Ranitidine is a class of H2 receptor antagonists, which occupies the drug selectively H2 histamine receptors on the surface of the parietal cells so that gastric acid and pepsin secretion be able to reduced greatly. Ranitidine given before meals with the goal to maximise the inhibition of gastric acid secretion before stimulating the gastric acid secretion of the food, (Lacy et al, 2008).

Furthermore, the type of drugs that is widely used as an antacid ranitidine. This is in line with research conducted by Randonuwu (2013) about the study of therapy management on patients of gastritis that hospitalized Hospital Prof. Dr. Kandou in Manado which gastritis drug that was widely used as an antacid ranitidine. Antacids are the most common drugs used to treat the symptoms of mild gastritis. All drugs antacids have a function to reduce the symptoms associated with excess stomach acid, peptic ulcers, gastritis, duodenal ulcers, and symptoms such as nausea, stomach pain, heartburn and a feeling of fullness in the stomach. Antacids included into the category of weak basic compounds that react with stomach acid to form water and salt (Mycek, 2001).

According to Guyton and Hall (2016), antacids can give negative effects, especially on the use of large doses in the long term. Negative effects include kidney stones, osteoporosis, neurotoxicity, gastrointestinal disturbances and sodium intake. To protect the gastric mucosa from stomach acid attacks are also given cytoprotective agent (sucralfate) that can protect the gastric mucosa (Sukandar et al, 2009). According Dipiro et al (2005), the main goal in the treatment of gastritis is to relieve pain, relieve inflammation and prevent the occurrence of gastric ulcers and complications.

Table 4. The frequency of the usage of the drugs combination of gastritis disease during January-March 2016

No	The Name of The Drugs Combination	Frequency	Percentage (%)
1	Omeprazole-Sukralfate	4	40.0
2	Ranitidine-Antacida	3	30.0
3	Ranitidine-Omeprazole	1	10.0
4	Antacid-Omeprazole	2	20.0
Total		10	100.0

In the treatment of gastritis, single therapy is used, but some patients using combination therapy that have two types of medications. The drugs in combination therapy are usually given based on the degree of gastritis. The table above shows that the highest use of drug combinations was omeprazole-sucralfate combination (40.0%) used by 4 of the 33 patients of gastritis. Omeprazole is a low alkali which are lipophilic (soluble in fats and after absorbed in the small intestine, it can be readily pass through the membrane of fat to the compartment acidic (eg parietal cells). After that, it protonated and being an active molecule and forming covalent disulfide and disabling this enzyme (McQuaid 2007). The side effects of this drug are increasing the levels of gastrin to >500 mg/L for patients (with a percentage of 5-10%) who consume this medicine. The increasing levels of gastrin lead to the onset of pain. The pain occurs when the pH of the stomach is under 2 so that the drug must not be used in a long time (Anonymous, 2007).

Sucralfate is a drug that does not have a direct effect on the gastric acid. This is according to Salamanya's research (2014) that this class of drugs was safe enough to consume because it works on the surface (cytoprotection). Sucralfate requires an acidic pH for activation, while PPI is not stable in acidic pH (1-2) and decomposes at acidic pH (Kadzung, 2004).

The combination of ranitidine and antacids used by 3 out of 33 patients of gastritis. This is in line with Wardanaiati's research (2011) in Ahmad Mochtar Hospital, Bukit Tinggi, West Sumatera, stating that the combination of ranitidine and antacids been able to eliminate 80% of complaints within 1-2 days. The side effects of the combination of antacids and ranitidine were antacids can lead to decreased absorption of ranitidine up to 33%, so that ranitidine given interval of 1-2 hours after consuming antacids and combination of ranitidine and antacids might raise the pH intragastric. The combination of ranitidine and omeprazole used by 1 patient with gastritis, ranitidine inhibits the H2 receptor selectively and reversibly. H2 receptor excitation will stimulate gastric acid secretion thus giving ranitidine inhibits the secretion of gastric acid. Omeprazole works to control of gastric acid secretion by inhibiting the proton pump which brings H+ ions out of the gastric parietal cells (Dipiro et al, 2005). The combination of these two drugs can be used because ranitidine rarely interact with other drugs such as omeprazole.

Last combination is the combination of an antacid with omeprazole. This combination was used by 2 patients of gastritis (percentage of 20%). Omeprazole works by binding to the enzyme H+/K+-Atpase to inhibit gastric acid secretion, whereas antacids working as a low alkali that will bind to the stomach acid so that it can neutralize stomach acid (McQuaid, 2007). Based on research that has been conducted against 4 types of gastritis medication prescribed by doctors at the Hospital Dr. M. M Dunda Hospital in Limboto

from January to March 2016, all drugs were given appropriate doses of omeprazole, antacids, ranitidine and sucralfate. Of the 33 patients with gastritis, there were 22 patients given omeprazole 40 mg / day. Ranitidine was used by 10 patients with gastritis with a dose of 2 x 50 mg. Furthermore, an antacid was used by 6 patients at a dose of 3 x 5 ml and sucralfate was used by 5 patients were given 4 x 2 cth/day.

Table 5. Frequency of the suitability of the usage of the drags on patients of gastritis based on the severity of the disease

The Type of Gastritis	Gender	The Name of The Drug	Suitability with the Standard of Medicine Service			
			Suitable	(%)	Not Suitable	(%)
Acute Gastritis	Female	Omeprazole	16	57.15	-	-
		Sukralfate	3	10.71	-	-
		Ranitidine	4	14.29	-	-
		Antacid	2	7.14	-	-
		Cefotaxim	-	-	1	3.57
		Ceftriaxon	-	-	2	7.14
	Male	Omeprazol	6	30	-	-
		Sukralfat	2	10	-	-
		Ranitidin	6	30	-	-
		Antasida	3	15	-	-
		Cefotaxim	-	-	1	5
		Ceftriaxon	-	-	2	10
Chronic Gastritis	Female	Ranitidine	1	33.33	-	-
		Antacid	1	33.33	-	-
		Ceftriaxon	1	33.33	-	-
	Male	-	-	-	-	-

Table 5 shows that omeprazole was more used widely in patients of gastritis. Judging from the appropriateness of the drugs using with the Standards of Medical Services in Dr. M. M Dunda Hospital in Limboto, the usage of the drugs in patients of acute gastritis are female that met to the Standard is amounted to 89.29% and 10.71% did not meet standards. The usage of the drugs in patients of acute gastritis are male that met the Standard was 85% and 15% did not meet the Standard. The usage of the drugs in patients of acute gastritis that met the Standard was 100%. Patients of gastritis received additional therapy electrolytic solution, antiemetic, analgesic, antipyretic and anti diarrheal that was used to eliminate the clinical symptoms experienced by the patient. In addition, the patients also received antibiotic therapy. This is in line with Salamanya's research (2014) that the patients of gastritis by bacterial infection were given antibiotic therapy. Antibiotic is used to treat chronic gastritis caused by infection Helicobacter pylori. Based on the research, there are only 1 patient infected with the bacteria was given antibiotics ceftriaxone. However, from the results of other diagnoses, only 1 patients of gastritis which was caused by virus, and 5 patients did not reveal any bacterial infection were given antibiotics. According to the Ministry of Health of the Republic of Indonesia (2011) antibiotic is not given to an infection caused by a virus or illness that can heal by

themselves (self-limited). Giving antibiotics to patients who do not have a bacterial infection can lead to resistance.

4. Conclusions

The results showed that the patients of gastritis in Dr. M.M Dunda Hospital in Limboto from January-March in 2016 got a single therapy (omeprazole, sucralfate, ranitidine and antacids) and combination therapy (omeprazole - sucralfate, ranitidine - antacids, ranitidine – omeprazole - omeprazole and antacids). The usage of the drugs according to Standard of Medical Services (SMS) in Dr. M. M Dunda Hospital in Limboto was 81.82% and the usage of the drugs was not suitable with the standard was 18.18%.

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Evaluation of Drug Related Problems in Patients with Coronary Artery Disease at One Hospital North Jakarta

Nelly Suryani, Yardi bin Saibi and Annissa Fadilla*

Pharmacy Departement, Faculty of Medicine and Health Science,
Islamic State University, Syarif Hidayatullah, Jakarta, Indonesia

ABSTRACT

Nowadays, coronary artery disease or cardiovascular disease causing the highest mortality in the world, it is reported that there are 30 percent cases from global mortality. In 2010, cardiovascular disease was recorded to kill 18 million people, and 80 percent of it happened in developing countries like Indonesia. Some studies reported that Drug Related Problems (DRPs) occurs in patients who suffer cardiovascular diseases due to the overusing of drugs. Drug Related Problems (DRPs) are events or unwanted problems related to the patient's drug therapy which affects the desired outcome. The purpose of this research is to investigate the total incidence number of DRPs categories, wich the under dose, high dose, drug without indication, indication without drug, potential drug interaction and inaccuracy of drugs selecting in medical therapy of patients with coronary artery disease in installation inpatient at one hospital north Jakarta. This study is a retrospective where the data was obtained through secondary data from medical records of patients in the periodic from January to May 2016 with a cross-sectional study design. Data collection techniques using total sampling, obtained 45 samples of corresponding study inclusion criteria. The result shows that there are 81,02% of potential drug interactions, 14,42% underdose, 3,98% overdose, 0,56% of drug without an indication, but indication without drugs and inaccuracy of drugs selecting are not found. Therefore, the role of the pharmacist is important for monitoring patient drug therapy to minimize the occurrence of DRPs.

Key words: Coronary Artery Disease, Drug Related Problems, Drug Interactions

ABSTRAK

Penyakit jantung koroner (PJK) atau penyakit kardiovaskular saat ini adalah penyebab mortalitas tertinggi di dunia, dimana dilaporkan sebanyak 30% dari mortalitas global. Pada tahun 2010, penyakit kardiovaskular tercatat telah membunuh 18 juta orang, 80% terdapat di negara berkembang seperti Indonesia. Beberapa penelitian melaporkan bahwa *Drug Related Problems* (DRPs) yang terjadi pada pasien dengan penyakit kardiovaskular disebabkan karena pemakaian obat yang cukup banyak atau yang disebut polifarmasi. *Drug Related Problem*s (DRPs) merupakan suatu kejadian atau masalah yang tidak diinginkan terkait terapi obat pasien yang berpengaruh pada outcome yang diharapkan. Penelitian ini bertujuan untuk mengetahui jumlah kejadian DRPs yang meliputi ketidaktepatan dosis yaitu dosis kurang dan dosis lebih, indikasi tanpa obat, obat tanpa indikasi, potensial interaksi serta ketidaktepatan pemilihan obat pada terapi pengobatan pasien dengan diagnosa penyakit jantung koroner di instalasi rawat inap salah satu Rumah Sakit Jakarta Utara. Penelitian ini bersifat *retrospektif* dimana data diperoleh melalui data sekunder berupa rekam medis pasien periode Januari-Mei 2016 dengan desain penelitian *cross-sectional*. Teknik pengambilan data berupa *total*

sampling, didapatkan 45 sampel yang sesuai kriteria inklusi. Hasil penelitian *Drug Related problems* (DRPs) yang terjadi adalah potensial interaksi obat sebesar 81,02%, dosis obat kurang dari dosis terapi (*underdose*) sebesar 14,42%, dosis obat melebihi dosis terapi (*overdose*) sebesar 3,98%, obat tanpa indikasi sebesar 0,56% dan tidak ditemukannya kategori indikasi tanpa obat dan ketidaktepatan pemilihan obat. Hal ini menunjukkan bahwa pentingnya peran apoteker dalam melakukan pemantauan terapi obat pada pasien untuk meminimalisir terjadinya DRPs.

Kata kunci : Drug Related Problems, Interaksi obat, Penyakit Jantung Koroner

***Corresponding author:** nelly.suryani@uinjkt.ac ; icham203@gmail.com

1. Introduction

Coronary heart disease is a disorder of cardiac function of heart muscle due to lack of blood because of the narrowing of the coronary arteries. Coronary Heart Disease (CHD) or cardiovascular disease is the highest cause of mortality in the world currently, which was reported by 30% of global mortality. In 2010, cardiovascular disease has killed 18 million people. As many as 80% are in developing countries like Indonesia (Raharjoe, 2011).

The prevalence of coronary heart disease by interviewing doctors diagnosed without symptoms who ranks highest, Central Sulawesi province (0.8%), followed by North Sulawesi, Jakarta and Aceh 0.7% respectively. While the prevalence of coronary heart disease by diagnosis with symptoms of the highest in East Nusa Tenggara (4.4%), followed by Central Sulawesi (3.8%), South Sulawesi (2.9%) and West Sulawesi (2.6%) (Riskesdas, 2013). Results of research Al-Amin et al (2012) with the title of polypharmacy in patients with cardiovascular studies found that dominates experiencing polypharmacy treatment is the treatment of heart (48.04%), the treatment of gastrointestinal (24.03%), and treatment of nervous system (18, 1%).

Christin (2013) also found that the drug-related problems in hospitalized patients who received the drug in large quantities (polypharmacy) by category DRPs were found are indication not treated (47.16%), problems related to excessive drug administration with no clear indication (20,21%), administration of excessive drug for the same indication (10.28%). DRPs (Drug-Related Problem) is defined as an undesirable event or risk experienced by the patient, involving or suspected to involve drug therapy (Strand et al., 1990). DRPs can reduce the occurrence of achieving the expected therapeutic occur in patients. DRPs is actually the events that have occurred in patients, while potential DRPs is an event that is likely to happen if the pharmacist does not undertake appropriate interventions to reduce the DRPs (Nurhalimah, 2012).

According to Rani's research (2013) found that, occurrance of DRPs in cardiovascular medicine with drug interaction categories (46.19%), overdose (17.26%), underdose (10.41%), drug duplication (11.17%) and the higher DRPs have been found in drugs such as antihypertensive, antiplatelet, anticoagulant, antihiperlipidemia and antiulcers.

The other research by Hadiatussalamah (2013) in patients with a diagnosis of congestive heart failure (CHF) obtained Drug Related problems with indication without theraphy (13.56%), therapy without indication (45.76%), overdose (1.70%), and drug interactions (38.98%).

According to Health Minister Regulation No. 58 in 2014 about the standard of pharmacy services at the hospital mentioned that the pharmacy service is an activity that aims to prevent, identify and resolve drug-related problems. Besides that pharmacy demanded to realize the expansion of pharmacy services paradigm from drug oriented to patient-oriented with the philosophy of pharmaceutical services (pharmaceutical care) Pharmaceutical care is intended to improve the quality of patients life and to minimize an error in the delivery of medication or drug related problems.

Based on the above bacground that it is very important to evaluate Drug Related Problem (DPRS) in patients with coronary heart disease to achieve a therapeutic efficacy, so it can help improve the quality of services at the hospital.

2. Experimental

2.1 Materials Metode

Patients with coronary artery disease were enrolled in the period from January to May 2016 in inpatient department at one hospital north Jakarta. We collected data of the patient who were admitted to institute medical record from the hospital.

Data were collected in retrospective by taking data from medical patient records january tO may 2016 to all cases of coronary heart disease .Data taken covering characteristic patients and administration treatment received by patients for treatment

The basic demographi information of each patient: age and gender; hospital admission and discharge date, drug prescribed and disease indentified were also fixated.

Analysis frekuensi DRP by six categories, that is indication without medication, drug without an indication, overdose, underdose, potential drug interactioan and inaccuracy medicine.

Drug interaction was determined by Drug interaction Facts. Categorization of drug was determined by using Indonesia drug information (MIMS), overdose and underdose analysis based on literature from Food and Drug Adminitration.

3. Results and Discussion

A total of 45 samples were met the inclusion criteria showed that the most patients who suffer CHD is the male were 29 patients (64.45%) while female were 16 patients (35.55%).

Based on the age of the patient, the most patients who coronary heart disease is the elderly (> 65 years) were 14 patients (31.11%) and adult (46-55 years) were 14 patients (31.11%), while elderly (56-65 years) were 12 patients (26.67%), and adult (35-45 years) were 5 patients (11.11%). Based on the most of comorbidities, hypertension were 17 patients (37.77%), diabetes mellitus total of 14 patients (31.11%), CHF as many as 12 patients (26.66%), GERD as many as five patients (11.11%), patients with heart rhythm disorder and history of heart disease were 3 patients (6.66%), stroke hemmoragic were 2 patients (4.44%), dyspepsia were 2 patients (4.44%), cephalgia in 1 patient (2.22%) and without comorbidities in 1 patient (2.22%).

Tabel 1. Distribution based on characteristic patients

No.	Characteristic Patients	N=45	Percentage (%)
1.	**Sex :**		
	Female	16	35,55
	Male	29	64,45
2.	**Age (Depkes RI 2009) :**		
	Young Adult (35-45)	5	11,11
	Adult (46-55)	14	31,11
	Older (56-65)	12	26,67
	Elderly (>65)	14	31,11

Tabel 2. Distribution of comorbidities such in patients coronary disease

No.	Comorbidities	N=45	Percentage (%)
1.	Hypertension	17	37,77
2.	CHF	12	26,66
3.	Diabetes Mellitus	14	31,11
4.	Heart rhythm disorder and history of heart disease	3	6,66
5.	Stroke hemmoragic	2	4,44
6.	Dyspepsia	2	4,44
7.	Cephalgia	1	2,22
8.	GERD	5	11,11
9.	Without comorbidities	1	2,22

Tabel 3. Distribution of Patient Data by DRPs Categories in Patients With Coronary Heart Disease period from January to May 2016

DRPs Category	**Patients (N=45)**	**Percentage (%)**	**Frequency (N=527)**	**Percentage (%)**
Drug without indication	2	4,44	3	0,57
Indication without drug	0	0,00	0	0
Inaccuracy of drugs selecting	0	0,00	0	0
Inaccuracy dose:				
a. Overdose	16	35,55	19	3,61
b. Underdose	37	82,22	76	14,47
Potential drug interaction	44	97,77	427	81,33
Total			525	100

In this study, there are 6 types of DRPs observed were indications without drugs, drugs without indications, potential interactions, over dose, under dose and inaccuracy of drugs selecting.

The results showed that DRPs was occurred, there are potential drug interactions 81.02%, underdose 14.47%, overdose 3.61%, drug without indication 0.57% and there was not found DRPs category inaccuracy of drugs selecting and indication without drugs.

3.1 Drug Related Problems

According to the Pharmaceutical Care Network Europe (PCNE) drug related problems (DRPs) is a condition associated with drug therapies that disturbing or potential disturbing the desired clinical outcomes (PCNE, 2010). In therapy for patients with CHD tended to occur DRPs, because In CHD patients also had of comorbidities, so many of drugs are used to treat the patients.

For this issue, the role of pharmacy is required to minimize the occurrence of DRPs and evaluation of DRPs is necessary to avoid the occurrence of DRPs. This evaluation aims to ensure that the treatment given to the patient reach the desired therapeutic effect, safe, efficacious and qualified (Sari Novita, 2015).

Based on data from DRPs in CHD patients with or without comorbidities inpatient at the "X" hospital in North Jakarta known that the most common of DRPs is potential drug interactions 427 events (81.33%), and then under dose 76 events (14,47%), over dose 19 events (3.61%), drugs without indication 3 events (0.57%), indication without drug 0 events (0.00%) and inaccuracy of drugs selecting 0 events (0.00%). This is consistent with the results of christin research in 2013 found the presence of drug-related problems in hospitalized patients who received the drug in large

quantities (polypharmacy) and the category DRPs were found is drug without indication (1.49%), indication without drug (7 , 46%), inaccuracy of drugs selecting (1.49%), under dose (10.45%), over dose (2.99%), drug interaction (40.30%), and non-compliance (35.82 %).

3.1.1 DRPs Category Indication Without Drugs

Indications without drugs or known as DRPs need additional category of drugs is a condition where the patient has other indications but did not get the drug to treat indications. Analysis of DRPs category indicated without drugs in patients with the diagnosis of coronary heart disease with or without comorbidities was based on incoming diagnosis, laboratory test results, and the conditions during treated in hospital. Patients need additional medications if the patient received the drug which appropriate with the patient's condition, laboratory test results and diagnosis of the patient when admitted to hospital.

In this study, there was not found DRPs category indication without drugs. This result describes that the "X" Hospital North Jakarta has been giving the drug in accordance with the diagnosis, laboratory test results and the patient's condition.

3.1.2 DRPs Category Inaccuracy Of Drugs Selecting

Inaccuracy of drugs selecting is a situation where patients receive inappropriate of drug therapy, inappropriate of drug therapy means that patients didn’t receive the most effective drugs or inappropriate with the patients condition (physiological functions).

In this study, there was not found DRPs category inaccuracy of drugs selecting, because the treatment given by doctors at the "X" Hospital is adjusted to the patient's physiological condition such as kidney function and history of drug allergy.

3.1.3 DRPs Category Drug Without Indication

Drugs without indication is a situation where patients receive inappropriate drug therapy with the indication of their disease.

Based on the research, there are 3 drugs given without a clear indication that the patient numbers 4 and 5. Patients numbers 4 are given an antibiotic drug class of quinolones with trademark Farlev which usually given to patients with a diagnosis of pneumonia, the patient was hospitalized with a diagnosis of febrile (fever) and the final diagnosis was CAD, diabetes mellitus type II. At the beginning patients had a fever suspected infection, but laboratory results showed that diagnosis can not be enforced because the results of leukocytes, t platelets, MCV, MCH, MCHC, and RDW-SD was normal and results of thorax pulmonary/cor also normal which means no abnormalities or enlargement in the lungs of patients. It is also found in patients number 5, where patients given the macrolide class antibiotic for lower respiratory tract infections with trademark Mezatrin (Azithromycin) and given other antibiotics penicillin with group trademark Cinam which is usually used for skin and intra-abdominal infections. Patients admitted to hospital with the diagnosis of hypokalemia, CAD and diagnosis out: CHF, hypertension. And thers is no diagnosis saying that the patient has an infection and laboratory results showed normal leukocytes.

3.1.4 DRPs Category Over Dose

Over dose is when patients receiving drug therapy which appropriate, but the administered dose exceeds the usual dose. Administration of drugs with doses exceeding therapeutic doses can lead to increased risk of toxicity. Literature to define a category exceed the therapeutic dose DRPs

are MIMS 2016, ISO 2016, Drug Information Handbook and evidance based journal of medicine..

The results of this study found that the most widely drug with DRPs categories of over dose exceeding the therapeutic dose is citicolin that has a pharmacological effect reducing of brain tissue damage by increasing the chemical compounds the brain called phosphatidylcholine which very important for the functioning of the brain and these drugs also can expedite the flow of blood and deliver oxygen to the brain. The maximum dose of citicolin is 1 x 1000 mg per day (MIMS, 2016 and DOI, 2008), this study found 5 patients were given 2 x 1000 mg. According to the Food and Drug Administration (FDA), the FDA has set the criteria of drug bioequivalence is 80-125% bioequivalence of drugs, at 90% intervals of Area Under Curve (AUC) and the drug concentration in the blood reaches a maximum (Cmax) and the criteria used in the drug either low or high variability (Food Drug Administration, 2004). Whereas citicolin given more than 125% of the maximum dose, so it's included DRPs category over dose.

3.1.5 DRPs Category Under Dose

Administration of drugs with low doses resulting ineffective to reach the desired therapeutic effect. The dose given should be in accordance with the patients condition and the dose set at the literature such as MIMS, ISO, Drug Information Handbook, and journals of evidence based medicine. Evaluation of DRPs category under dose in a patient based on the dosage regimen given (Novita Sari, 2015). According to the Food and Drug Administration (FDA), the FDA has set the criteria of drug bioequivalence is 80-125% bioequivalence of drugs, at 90% intervals of Area Under Curve (AUC) and the drug concentration in the blood reaches a maximum (Cmax) and the criteria used in the drug either low or high variability (Food Drug Administration, 2004).

Based on the results of the study, there were 37 patients with drug doses less than the therapeutic dose and frequency of occurrence is 76. On this study DRPs category drug dose less than the therapeutic dose showed that the most of drugs types is Ranitidine 21 events, Mecobalamin 11 events, and Bisoprolol 7 events.

3.1.6 DRPs Category Drug Interaction

Drug interaction is a very avoidable from the administration of drugs which given to patients. In patients who received over 5 drugs or more will potentially get a drug interactions, because with many drug administered the possibility of drug interactions is also getting bigger. (Kurniajaturiatama, 2013). The results of drug interaction categories DRPs was obtained by the study of literature and do not observe directly, the literature used is the application of Medscape, drugs.com, Drug Interaction Fact In 2009, Stockley's Drug Interaction 8th edition, Drug Information Handbook, 2009.

The results of this research obtained there were 44 patients with potentially drug interactions of total total sample (45 patients) and 427 events. This is consistent with the results of the andi kurnia research in 2013 that the drug interaction in the ICCU hospitalization in CHD patients was found 78.43% occuring drug interactions and 192 cases of drug interaction with drugs.

The results obtained by the most potential severity of CHD patients is moderate with 285 events (66.74%), followed by the minor potential severity were 98 events (22.95%), and then the mayor potential severity as much 10.30%.

The most drugs of moderate potential severity is the ISDN combination with Ramipril (13 events). The mechanism of ramipril (ACE inhobitor) may increase the hypotensive effects of

nitroglycerin, other data showed that ramipril may prevent nitrate tolerance, in addition to ACE inhibitors also may decrease systemic vascular resistance, decreasing heart activity and further improve the effectiveness of nitroglycerin. Management of this interaction: should stop nitrate before starting an ACE inhibitor or continued with reduced dose and monitoring of blood pressure.

The second potential severity of interaction is minor severity, the most drug of minor severity is combination ISDN with omeprazole (13 events). The mechanism of omeprazole is to inhibit drug delivery of oral nitric. Antianginal effects may be reduced, and myocardial ischemia can be excacerbated. And the management of this interaction is change to the other treatment of gastric acid.

The most drug of major severity is combination of omeprazole (rhindopump) with clopidogrel (15 events). The use of PPIs with clopidogrel can reduce the cardioprotective effect of clopidogrel, the mechanism of interaction is inhibition PPI on metabolic bioactivation of clopidogrel which mediated by cytochrome P450 2C19. This mechanism would be worse if it occurs in patients who have a genetic polymorphism of cytochrome P450 2C19, which is not found the activity of this enzyme in their bodies. PPI use was associated with an increase of 70% risk of heart attack or unstable angina, an increase of 48% risk of stroke symptoms or stroke, and its management should avoid the use of both, should be considered in high-risk patients such as patients receiving dual antiplatelet therapy, patients with a history of gastrointestinal bleeding and patients receiving anticoagulant therapy simultaneously. And after a comprehensive evaluation has been done on the risks and benefits, if the PPI group was needed then use safer alternatives of PPI such as pantoprazole, dexlansoprazole or lansoprazole, or may be prescribed antacids or H2 receptor antagonists such as ranitidine.

4. Conclusions

The result of Drug Related Problems (DRPs), there are 81,02% of potential drug interactions, 14,42% underdose, 3,98% overdose, 0,56% of drug without an indication and there is not finding category indication without drugs and inaccuracy of drugs selecting. Therefore, the role of the pharmacist is important for monitoring patient drug therapy to minimize the occurrence of DRPs.

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Cost Effectiveness Analysis of Antihypertensive Drugs Usage by Combination of ACEI – CCB And ACEI – Diuretic in Outpatient Hypertension Therapy at Mintohardjo Navy Hospital Jakarta Period July-November 2015

Delina Hasan[1*], Hefni Warnetty[2]

[1]Pharmacy Departement, Faculty of Medicine and Health Science, Islamic State University, Syarif Hidayatullah, Jakarta, Indonesia
[2]Pharmacy Departement, Mintohardjo Navy Hospital, Jakarta, Indonesia

ABSTRACT

Hypertension is one of the silent killer diseases influenced by many factors. The prevalence of hypertension in Indonesia is 7.6 % in 2013 and then increased to 9.5%. This study aimed to determine the drug effectiveness and cost-efficiency in the treatment of hypertension patients who use antihypertensive drugs combinations (ACEI-CCB and ACEI-Diuretic) at outpatient unit Mintohardjo Navy Hospital Jakarta during period from June to November 2015. This study was a cohort design to measure the cost effectiveness of antihypertensive drugs combination ACEI-CCB and ACEI-Diuretic. The data were collected prospectively from medical record of outpatient hypertension visiting Mintohardjo Navy Hospital, Jakarta. The samples size was 200 patients with hypertension who meet the inclusion and exclusion criteria and divided into 2 groups. Group 1 was 100 hypertension patients using antihypertensive drugs combination ACEI-CCB and group 2 with the combination of ACEI-Diuretic. Both groups of patients who get antihypertensive drugs combination followed and observed for 3 months for each patient. The drug's effectiveness is measured by counting the number of patients having blood pressure in under control (<140/90 mmHg) and 130/80 mmHg for patients with diabetes mellitus. Cost efficiency is measured on the basis of the unit cost of each group and the value of the ratio of cost effectiveness. The results showed that the greatest effective therapetic of drug found in the combination of ACEI-CCB marked by the patient's controlled blood pressure was 98%, whereas the controlled blood pressure in the group of ACEI-Diuretic patients was only 91%. Efficiency found in the Group ACEI-Diuretic marked by the lowest unit cost of IDR 1.073.848, whereas in the Group of ACEI-CCB of IDR 1.096.790. The antihypertensive drugs combination ACEI-CCB is more effective than ACEI-Diuretic combination. The antihypertensive drug combination ACEI- Diuretik is more efficient than ACEI-CCB combination

Keywords: Antihypertensive drugs combination, Cost Effectivenes Analysis, Hypertension.

ABSTRAK

Hipertensi merupakan salah satu penyakit *silent killer* yang dipengaruhi oleh banyak faktor. Prevalensi hipertensi di Indonesia adalah 7,6% pada 2013 dan kemudian meningkat menjadi 9,5%. Penelitian ini bertujuan untuk menentukan efektivitas obat dan efisiensi biaya dalam pengobatan pasien hipertensi yang menggunakan kombinasi obat antihipertensi (ACEI-CCB dan ACEI-diuretik) pada unit rawat jalan Mintohardjo Navy Hospital Jakarta selama periode Juni hingga November 2015. Penelitian ini adalah desain kohort dengan mengukur efektivitas biaya kombinasi obat antihipertensi ACEI-CCB dan ACEI-diuretik. Data dikumpulkan secara prospektif dari rekam medis hipertensi pasien rawat jalan yang mengunjungi Rumah Sakit Angkatan Laut Mintohardjo, Jakarta. Ukuran sampel adalah 200 pasien dengan hipertensi yang memenuhi kriteria inklusi dan eksklusi dan dibagi menjadi 2 kelompok. Kelompok 1 adalah 100 pasien hipertensi menggunakan kombinasi obat antihipertensi ACEI-CCB dan kelompok 2 dengan kombinasi ACEI-diuretik. Kedua kelompok pasien yang mendapatkan kombinasi obat antihipertensi diikuti dan diamati selama 3 bulan untuk setiap pasien. Efektivitas obat diukur dengan menghitung jumlah pasien yang memiliki tekanan darah pada

kontrol bawah (<140/90 mmHg) dan 130/80 mmHg untuk pasien dengan diabetes mellitus. efisiensi biaya diukur atas dasar biaya unit masing-masing kelompok dan nilai rasio efektivitas biaya. Hasil penelitian menunjukkan bahwa efek terapi terbesar efektif pada obat yang ditemukan dalam kombinasi ACEI-CCB ditandai dengan tekanan darah terkontrol pada pasien adalah 98%, sedangkan tekanan darah terkontrol pada kelompok pasien ACEI-diuretik hanya 91%. Efisiensi ditemukan di Grup ACEI-diuretik ditandai dengan unit biaya terendah Rp 1.073.848, sedangkan di Kelompok ACEI-CCB Rp 1.096.790. Kombinasi obat antihipertensi ACEI-CCB lebih efektif daripada kombinasi ACEI-diuretik. Kombinasi obat antihipertensi ACEI- diuretik lebih efisien daripada kombinasi ACEI-CCB

Kata kunci: Kombinasi obat antihipertensi, Analisis *Cost Effectiveness*, Hipertensi.

***Corresponding author :** Delina Hasan, email : delina_hasan @yahoo.com

1. Introduction

Hypertension is a non-communicable diseases that need to be controlled because the disease is a silent killer. Hypertension is characterized by increased systolic blood pressure greater than 140 mmHg and diastolic blood pressure greater than 90 mmHg. The measurement on two occasions with an interval of five minutes with enough rest and quiet.[1]

In Indonesia the problem of hypertension is likely to increase from year to year, someone who is likely to develop hypertension or at risk for cardiovascular disease. This disease in Indonesia is a number one cause of death.

Health Research (RISKESDAS) Balitbangkes 2007 showed the prevalence of hypertension nationwide reached 7.6 %, the prevalence of hypertension varies according to age, race, education and many other variables. So the prevalence of hypertension in Indonesia according to Riskesdas 2013 amounting to 9.5 %. [2]

Prolonged hypertension can damage blood vessels in the kidneys, heart and brain, and be able increase the incidence of renal failure, coronary disease, heart failure and stroke. 3.

Handling of hypertension begins with the modification of patterns of life, if not the way it can controlled blood pressure, subsequent handling based on The Seventh of the Joint National Committee On Prevention, Detection, Evaluation, and Treatment Of High Blood Presserure (JNC7) with drug therapy antihipertensi single or combination of both. The combination of an oral antihypertensive drug treatment given if the single antihypertensive has not been able to achieve a controlled therapeutic target. The combination is often used to controlled hypertension ACEI-CC And ACEI-Diuretic. Combination therapy is very effective in decreasing systolic blood pressure for elderly people and patients with a variety of risks. The primary advantage of this therapy is the treatment cost is lower. Effective treatment with minimal cost is the hope of the therapeutic treatment of hypertension. To meet these expectations, the necessary research on the effectiveness of the drug and the cost of usage a combination of oral antihypertensi drugs on outpatient hypertension patients. The problem in the treatment of hypertension are;

- Hypertension needs treatment continuously so that it becomes a burden to the family, the Government and State. During treatment of hypertension with the drug has yet to be a single anti hypertensive delivers optimal therapy, most patients need two or more antihipertensive drugs to achieve blood pressure controlled.
- Unknown effectiveness of each combination of antihipertensive drugs (ACEI-CCB and ACEI-Diuretic) used in the treatment of patients of hypertension sufferers in Mintoharjo Navy Hospital, and yet he knew the combination where a

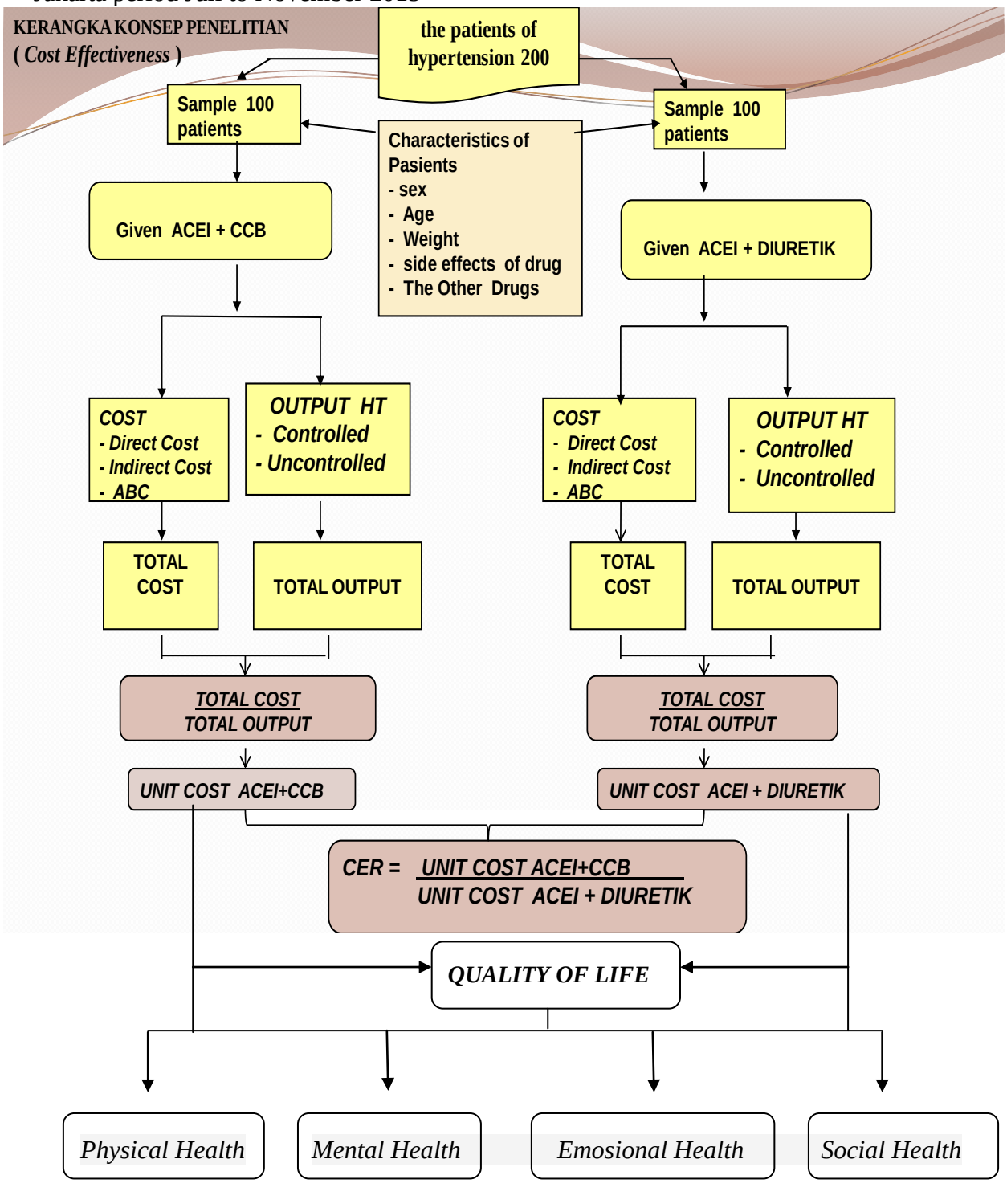
more efficient combination between the two groups (ACEI-CCB and ACEI-Diuretic) used in the treatment of patients of hypertension sufferers in Mintoharjo Navy Hospital.

- Yet he knew the unit cost (unit cost) each antihypertensive combination drugs (ACEI-CCB and ACEI- Diuretic) used in the treatment of patients of hypertension sufferers at Mintohardjo Navy Hospital Jakarta period Juli to November 2015

This study was to determine the drugs effectiveness and cost-efficiency in the treatment of hypertension patients in outpatient who use antihypertensive drugs combinations (ACEI-CCB and ACEI-Diuretic) at Mintohardjo Navy Hospital Jakarta period July to November 2015

2. Methods

1). The Framework Of Research Concept



Note: ACEI =Angiotensin Converting Enzyme Inhibitor
CCB =*Calcium Channel Blokers,*
CER = Cost Effectiveness Ratio
ABC =*Activity Based Costing*

Location of research and Research Time, Mintohardjo Navy Hospital, Jakarta, period July to November 2015. This study uses two design i.e., 1). To review the effectiveness of the drug using a cohort design by doing observation and measurement against a prospective outpatient hypertension patients from July-November 2015. The sample in this research as much as 200 outpatient hypertension patients who meet the criteria for inclusion and exclusion. Every outpatient observed during 3 months. 2.) with the design or the method of economic evaluation i.e. Cost Effectiveness Analysis to examine the cost and efficiency in the treatment of hypertension.

The population in this research is all patients suffering from hypertension treated roads in Mintoharjo Navy Hospital period July to November 2015. The sample in this study using the formula calculation results retrieved as many as 200 outpatient hypertension patients who meet the criteria for inclusion and exclusion. Next the sample is divided into 2 groups, Group A 100 patients of hypertension and hypertensive patients 100 B.

Inclusion Criteria

- Patients suffering from hypertension and treated roads in Mintoharjo Naval Hospital
- Patients examined first time never did control for a period longer than 2 weeks (associated with drug bioavailability)
- Age 35-65 years (productive age)
- Willing to be the subject of research
- The patient followed the treatment for 3 months

Exclusion Criteria

- Hypertensive patients who are hospitalized
- Drugs used instead of Antihypertensive drugs combination of ACEI-CCB& ACEI-Diuretics
- Patients who consumed more salt than 1500 mg/day and coffee consumption of 300 mg/ day
- Pregnant and lactating women

Materials

Antihypertensive-drug combination (combination of two groups)

1). Antihipertensive drug combination of ACEI-Diuretic, there are two drugs in one of combinations (Lisinopril + Furosemid)
2). Antihipertensive drug combination of ACEI-Calcium Cannel Blocker, there are two drugs in one of combinations (Lisinopril + Amlodipin)

Tools and materials for the laboratory Examination for diseases Comorbid

Data collection

1. Data treatment (drug effectiveness) of hypertension sufferers who admitted

Tools used include:

- Stethoscope-Littmann Classic II SE inchi71 28 cm,
- Tensimeter Riester Reg. No. KL 0502190139, data and results of the anamnesis
- Other physical examination tools

2. Data for the study of Economics (medical expenses) the results of the interviews with the patient through the questionnaire. The instrument used a questionnaire

Data Analysis

a. To find out the effectiveness of medications by conducting an analysis below;

1). Analysis of Univariate data, to see the distribution of each variable

2.) Chi Square Analysis to look at the relationship between the independent variable and dependent variable.

b. To perform cost analysis (Efficiency) using the Farmakoekonomi method that is Cost Effectiveness Analysis

c. Measuring the quality of life of hypertensive patients conducted using questionnaires DHRQOL (Delina Health Related Quality of Life). DHRQOL adaptation of several measuring devices, among others SF36, &EQ5D. DHRQOL in this study only measures the health (physical health, mental health, emotional health, and social health).

3. Result

The Characteristics of hypertension patientsoutpatients based on sex, age, education, work, blood pressure, comorbidities, the use antihypertensive drugscombination ACEI-CCB and ACEI-Diuretics at Mintohardjo Navy Hospital, jakarta, during the period from July to November, 2016 is as follows the sex of the majority of women, ages ranging from 35-65 years, education at most colleges and universities, the work of civil servants and private employees, systolic blood pressure ranged from 160 -200mmHg, diastolic blood pressure ranged between 90-100 mmHg, comorbidities most with type 2 diabetes mellitus, hyperlipidemia, osteoarthritis, followed by vertigo, dyspepsia and heart failure.

Table 1.The Relationship Between The Sex of Hypertension Patients With Drug Use Antihypertensive Drugs Combinations (ACEI-CCB & ACEI-DIURETIC) on the treatment of Hypertension outpatients Hypertension at Mintohardjo Navy Hospital Jakarta, Period July-November 2015

Sex	AntihypertensiveDrug Combinations				Total	
	ACEI-CCB		ACEI-DIURETIK			
	N	%	N	%		
1. Male	45	47.4	50	52.6	95	100
2. Female	55	52.4	50	47.6	105	100
Total	100	50	100	50	200	100

In the above table shows the relationship of sex with the use of antihypertensive drug combinations. Female gender more use of antihypertensive drugs combination ACEI-CCB (52.4%), while in males more likely to use a antihypertensive drugscombination ACEI-Diuretics (52.6%).

Table. 2. The relationship between the Antihypertensive Drug Combinations (ACEI-CCB and ACEI-DIURETICS) with Controlled of blood pressure on treatment of Hypertension outpatients at Mintohardjo Navy Hospital Jakarta period July-November 2015The

Antihypertensive Drug Combinations	, Controlled of Blood Pressure				Total	
	Controlled		Uncontrolled			
	N	%	N	%		
ACEI-CCB	98	98.0	2	2	100	100
ACEI-DIURETIK	91	91.0	9	9	100	100
Total	100	50	100	50	200	100

The above table shows that the treatment of patients with hypertension outpatient use of antihypertensive drug ACEI-CCB combination controlled blood pressure by up to 98%, while the outpatient hypertension using antihypertensive drugs combination of ACEI-Diuretics controlled blood pressure 91%.

Table 3. The relationship between Comorbid with Effectiveness of therapy Antihypertensive drugs Combination ACEI-CCB and ACEI-Diuretic On Treatment of Hypertension outpatients at Mintohardjo Navy Hospital Jakarta, period July-November 2015

Comorbid	Combination Drugs ACEI-CCB						Combination Drugs ACEI-Diuretik					
	Controlled		Uncontrolled		Total		Controlled		Uncotrolled		Total	
	N	%	N	%	N	%	N	%	N	%	N	%
Hiperlipidemia	33	97.1	1	2.9	35	100	19	100	0	0	19	100
Osteoartritis	14	93.3	1	6.7	15	100	16	84.2	3	15.8	19	100
DM Tipe2	36	100	0	0	36	100	26	86.7	4	13.3	30	100
Vertigo	6	100	0	0	6	100	10	90.9	1	9.1	11	100
Dispepsia	8	100	0	0	8	100	12	92.3	1	7.73	13	100
CHF	1	100	0	0	1	100	8	100	0	0	8	100
Total	98	98	2	2	100	100	91	91	9	9	100	100

In the above table shows that hypertension patientswith comorbidities who received antihypertensive drugs combination ACEI-CCB , that most of the DM tipe2, Hyperlipidemia and Osteoarthritis, following Dyspepsia, and Vertigo, however, treatment with ACEI-CCB hypertension disease controlled 98%. While hypertension patients with comorbidities who received the antihypertensive drugs combination ACEI-Diuretics, that most of the DM type 2, hyperlipidemia and Osteoarthritis, following Dyspepsia, and Vertigo, and CHF. Treatment with ACEI-Diuretics hypertension disease controlled 91%.

Table 4. The Distribution Of Direct Costs on Outpatients Of Hypertension Patients Using Antihypertensiv drugs Combination at Mintohardjo Navy Hospital Jakarta Period July-November 2015

The Components OfDirect Cost	Group Of Antihypertensive Drugs Combination ACEI-CCB	Group Of antihypertensive Drugs Combination ACEI-DIURETIK
Cost Of Antihypertesive Drug Of Combination	Rp 22.356.000	Rp 10,566,000
Cost Of Comorbid	Rp 14.111.415	Rp 13.116.210
Cost of Laboratory	Rp 9.300.000	Rp 9.640.000
Cost Of The Examinemination	Rp 15.150.000	Rp 16.750.000
Total Of Direct Cost	**Rp 60.917.415**	**Rp 50.072.210**

In the above table shows that the patients who received treatment with antihypertensive drugs combination of ACEI-CCB, which costs the most in the components of direct costs is the cost of drugs, inspection fees and drug costs of comorbids, on patients treated with antihypertensive drugs combination ACEI-Diuretics, which costs the most the direct cost component is the cost of the examination and the comorbids drug costs and drug costs.

Table 5 The Distribution Of Indirect Costs on Outpatients Of Hypertension Patients Using Antihypertensiv drugs Combination at Mintohardjo Navy Hospital Jakarta Period July-November 2015

The Components Of Indirect	Group Of Antihypertensive Drugs Combination ACEI-CCB	Group Of Antihypertensive Drugs Combination ACEI-Diuretic
Cost Of Transportation	Rp 4.943.000	Rp 5.648.000
Cost Of Acomodation	Rp 4.500.000	Rp 4.500.000
Cost of the loss of productive time	Rp 37.125.000	Rp 37.500.000
Total Of Indirect Cost	**Rp 46.568.000**	**Rp 47.648.000**

In the above table shows that the patients who received treatment with antihypertensive drugs combination of ACEI-CCB, which costs the most in the components of indirect costs is the cost of loss of productive time, on patients treated with antihypertensive drugs combination ACEI-Diuretics, which costs the most the indirect cost component is the cost of loss of Productive time.

Table 6. The Distribution Costs on Outpatient of Hypertension Patient Using the Antihypertensive Drugs Combination ACEI-CCB and ACEI-Diuretic at Mintohardjo Navy Hospital Jakarta, Period July-November 2015

Antihipertensive Drugs of Combination	Direct Cost (Rp)	Indirect Cost (Rp)	Total *Cost* (a) (Rp)	Patientswith BPControlled(b)	*Unit Cost*(a/b) (RP)
ACEI-CCB	60.917.415	46.568.000	107.485..415	98	1.096.790
ACEI-Diuretik	50.072.210	47.648.000	97.720.210	91	1.073.848

Note: BP = Blood Pressure

The table above shows that patients who received treatment with the antihypertensive drugs combinations ACEI- CCB controlled their blood pressure as much as 98 people compared to patients who received treatment with the antihypertensive drugs combinations ACEI-Diuretic controlled blood pressure just 91 people. The drugs antihypertensive combination ACEI-CCB is more effective in controlled blood pressure compare ACEI-Diuretic.

Tabel 7. The Realationship between the Quality of life (Physical Health) Controlled Blood Pressure in patients Who Received the Antihypertensive drugs Combination ACEI-CCB and ACEI-DIURETIK at Mintohardjo Navy Hospital Period July-November 2016

Physical Health	Controlled Blood Pressure				Total	
	Controlled		Uncontrolled			
	N	%	N	%	N	%
1. Not Complains	134	67	6	3	140	70
2. Chest pain, Joints pain, Low pain	28	14	4	2	32	16
3. Nausea	14	7	0	0	14	7
4. Dizzines	13	6.5	1	0.5	14	7
Total	189	94.5	11	5.5	200	100

The above table shows that patients with controlled hypertension in terms of physical health had no complaints as much as about 67%.

Tabel 8. The Realationship between the Quality of life (Mental Health) Controlled Blood Pressure in patients Who Received the Antihypertensive drugs Combination ACEI-CCB and ACEI-DIURETIK at Mintohardjo Navy Hospital Period July-November 2016

Mental Health	Controlled Blood Pressure				Total	
	Controlled		Uncontrolled			
	N	%	N	%	N	%
1. Strong	187	93.5	1	0.5	188	94
2. Weak	2	1	10	5	12	6
Total	189	94.5	11	5.5	200	100

P : 0.000

The above table shows controlled hypertension patients who have a strong mentality as much as 93.5 %.

Tabel 9. The Realationship between the Quality of life (Emotional Health) Controlled Blood Pressure in patients Who Received the Antihypertensive drugs Combination ACEI-CCB and ACEI-DIURETIK at Mintohardjo Navy Hospital Period July-November 2016

Emotional Health	Controlled Blood Pressure				Total	
	Controlled		Uncontrolled			
	N	%	N	%	N	%
1. Stable	187	93.5	1	0.5	188	94
2. Unstable	2	1	10	5	12	6
Total	189	94.5	11	5.5	200	100

P : 0.000

The above table shows controlled hypertension patients who have a stabil emotional as much as 93.5 %.

Tabel 10. The Realationship between the Quality of life (Social Health) Controlled Blood Pressure in patients Who Received the Antihypertensive drugs Combination ACEI-CCB and ACEI-DIURETIK at Mintohardjo Navy Hospital Period July-November 2016

Social Health	Controlled Blood Pressure				Total	
	Controlled		Uncontrolled			
	N	%	N	%	N	%
1. Unable to attend social activities	2	1	9	4.5	11	5.5
2. Sometimes to attends social activities	14	7	2	1	16	8
3. Able to attend social activities	173	86.5	0		173	86.5
Total	189	94.5	11	5.5	200	100

P : 0.000

The above table shows uncontrolled hypertension patients were able to carry out the social activities as much as 86.5 %

4. Discussion

In this study patients with hypertension more female, the same as the results of the study the Department of Health (2007) and research Pratama (2011).[8] This is due to hormonal changes in women, one experienced by women is the menopause phase, where the average age of women undergoing menopause ie> 50 years.

In women who have not experienced menopause hypertension is rare because it is protected hormone estrogen plays a role in increasing HDL levels. High levels of HDL are protective factors in preventing atherosclerosis which in turn will be the narrowing of blood vessels resulting in hipertensi.[9]

Hypertension patients in RSAL Mintohardjo dominated by the age group 46-55 years and> 55 years. One of the risk factors for hypertension were age, because of the increasing age of a person then decreased arterial elasticity.In this state the aorta becomes stiffer and eventually increased systolic blood pressure and volume of the aorta decrease, which will cause hypertension.[10]

Another characteristics of the subjects (patients) is comorbidities, the results of research there are 6 types of comorbidities that most are type 2 diabetes mellitus and hyperlipidemia, then followed osteoarthritis, vertigo, dyspepsia and Chronic Heart Failure.

The results of analysis of Chi Square hypertensive patients with comorbidities given antihypertensive drugs therapy combination of ACEI - CCB and ACEI-diuretics, blood pressure remains controlled means of comorbidities did not affect treatment with the combination of ACEI Antihypertensive Drugs - CCB and ACEI-Diuretik.[11]

The Chi Square analysis results indicate that the ACEI – CCB is more effective than ACEI-Diuretic is characterized by his higher learning outcomes.

This study, the aim alternative medicines that effectively and efficiently by comparing the cost analysis between antihypertensive drugs combination of ACEI-CCB with ACEI-Diuretic. A cost analysis was done by the total cost of the merger of direct costs and indirect costs of each combination. [12]

Then performed a cost analysis by the method of Pharmacoeconomics is Cost Effectiveness Analysis (CEA) in both groups combined antihypertensive drugs by comparing the total cost to the effectiveness of the therapy is achieved.

The research results obtained from the total direct costs for the combination of ACEI – CCB Rp 60,917,415.0-as for the combination of ACEI-Diuretic Rp-50,072,210.0 This is due to the price of the drug combination antihypertensive ACEI-CCB is more expensive compared to the other combinations of antihypertensive drugs ACEI-Diuretik. While the indirect costs Of this research include the cost of patients transportation, accommodation costs and the cost of the loss of productive time.

The results of research were obtained in total direct costs for patients receiving antihypertensive drugs Cobination therapy of ACEI-CCB Rp 60,917,415, and who received combination therapy of ACEI-Diuretics Rp 50,072,210, -. While the indirect costs in the study include patient transoprtasi costs, accommodation costs and the cost of the loss of productive time. Total indirect costs for the combination of ACEI - CCB Rp 46.568,000 - and for the combination of ACEI-Diuretics Rp 47.648.000, - the indirect costs of the combination drug ACEI-Diuretik greater because patients treated with the combination, group productive age works more as compared to patients receiving combination drug therapy ACEI-CCB, thus providing the difference in the value of the loss of productive time.

The Value Cost Effectiveness Ratio (CER) arelowest among the unit cost of two groups of combination drugs (ACEI-CCB and ACEI-Diuretic). The unit cost was obtained from the total cost divided by output therapy ie the number of patients who controlled blood pressure.[14, 15]

The effectiveness ofpatients with hypertension outpatient Mintohardjo Navy Hospital who received drug combination therapy of ACEI-CCB is more effective than the combination of ACEI-Diuretic. This is evidenced by the number of patients whose blood pressure controlled. In Table 6.3.2.2 can also be seen the value

of the combination drug unit Cost of ACEI - Diuretics Rp 1,073,848, -more low compared with the value of Unit Cost of drug combinations ACEI - CCB. Thus, antihypertensive treatment with the combination of ACEI -CCB is more effective than combination ACEI-Diuretik and Treatment with a combination drug ACEI - Diuretics are more efficient than the combination of ACEI-CCB.

It is supported by the results of research Avoiding Cardiovascular Events Through Combination Therapy in Patients Living with Systolic Hypertension (Accomplish) in the United States in 2003. In that study, showed that the combination of ACEI - CCB was more effective than the combination of ACEI - Diuretics which is a combination of drugs recommended by JNC VII 2003.[12]

The result of analysis showed no relationship between uncontrolled hypertension and quality of life of patients in terms of four health indicators, namely mental health, emotional health, social health and physical health. After controlled blood pressure, hypertension patients quality of life in terms of health, namely physical health, emotional, mental and social, is increasing, this is indicated by the improved health indicators to the four mentioned above. increasingly uncontrolled blood pressure patient, then further improve the quality of life of these patients.

5. Conclusion

The conclusions from the results of this research are :

- Outpatients receiving treatment with a combination drugs of ACEI - CCB is more effective compared with patients who received the combination drugs of ACEI – Diuretic at Mintohardjo Navy HospitalPeriod July-November, 2015.
- The unit cost of outpatients who received treatment with theantihypertensive drugs combination of ACEI - Diuretic lowers compared with patients who received treatment with antihypertensive drugs combined ACEI - CCB at Mintohardjo Navy Hospitalperiod July-November 2015
- Outpatients receiving treatment with antihypertensive drugs combination of ACEI -Diuretic more efficient compared with patients who received treatment with antihypertensive drugs combination of ACEI- CCB at. Mintohardjo Navy HospitalPeriod July-November, 2015.
- After controlled blood pressure increased quality of life of patients in terms of the four indicators, namely health (mental, emotional, physical and social)

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Antidiabetic Activity of Gedi Leaf Extract and Pancreas Histopathology of White Male Mice Induced by High Fat Diet and Streptozotocin

Joni Tandi[1*], Niluh Devi Yulianti[1] Yuliet[2], Yunlis S. Kenta[1]

[1]High School of Pharmaceutical Sciences - Pelita Mas Palu
[2]Department of Pharmacy, Faculty of Sciences, Tadulako University, Palu

ABSTRACT

Red gedi leaf (*Abelmoschus manihot* L. Medik forma platidactylus Bakh) is a plant that is believed to have the efficacy of medicinal plants containing chemical compounds that are believed to have potential as an antidiabetic effect and an antioxidant. This study is a continuation of our research that aims to determine the effects and histopathological feature of the pancreas in decreasing the blood glucose levels (KGD) of male rats hypercholestrolemic models of diabetes. Test animals used were male rats as many as 40 were divided into six groups consisting of normal group, negative control group, positive control group and three test groups were given EDGM with each dose of 150 mg /kg BW, 300 mg/kg BW and 450 mg / kg BW. Animal models of hiperkolestrolemic diabetes created using high fat diet (HFD) for 3 weeks and streptozotocin dose of 30 mg/kg BW given treatment for 2 weeks. The reduction in blood glucose levels were analvzed using statistical test of one way ANOVA and further post hoc Duncan test. The results showed that EDGM at a dose of 300 mg/ kg BW is effective in lowering the dose of KGD in hiperkolestrolemic diabetic rat models, comparable to the positive control of metformin.

Keywords : *Abelmoschus manihot L. Medik forma platidactylus Bakh.* high fat diet , streptozotocin

ABSTRAK

Daun gedi merah (*Abelmoschus manihot* L. Medik forma platidactylus Bakh) adalah tanaman yang diyakini memiliki khasiat tanaman obat yang mengandung senyawa kimia yang diyakini memiliki potensi sebagai efek antidiabetes dan antioksidan. Penelitian ini merupakan kelanjutan dari penelitian kami yang bertujuan untuk menentukan efek dan fitur histopatologi pankreas dalam menurunkan kadar glukosa darah (KGD) dari tikus jantan model hypercholestrolemic diabetes. hewan uji yang digunakan adalah tikus jantan sebanyak 40 dibagi menjadi enam kelompok yang terdiri dari kelompok normal, kelompok kontrol negatif, kelompok kontrol positif dan tiga kelompok uji diberi EDGM dengan dosis masing-masing 150 mg / kg BB, 300 mg / kg BB dan 450 mg / kg BW. model hewan diabetes hiperkolestrolemic dibuat menggunakan diet tinggi lemak (HFD) selama 3 minggu dan dosis streptozotocin dari 30 mg / kg BB pengobatan yang diberikan selama 2 minggu. Penurunan kadar glukosa darah analvzed menggunakan uji statistik one way ANOVA dan post hoc uji Duncan lanjut. Hasil penelitian menunjukkan bahwa EDGM pada dosis 300 mg / kg BB adalah efektif dalam menurunkan dosis KGD dalam model tikus diabetes hiperkolestrolemic, sebanding dengan kontrol positif metformin

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***Corresponding author :** Joni Tandi, Email : jonitandi757@yahoo.com

1. Introduction

Lifestyle and eating habits of modern society at this time trigger the appearance of various diseases. Consumption of fatty foods, fast food, and lack of body exercise is a bad habit that can cause other diseases such as obesity and hyperlipidemia(1). Hyperlipidemia is a disease that occurs because of excessive fatty deposits. The food that enters the body is supposed to be

metabolized by the body into energy[(2)]. However since the food intake or excessive fat and not offset by the activity of corresponding body, causing these foods to accumulate and become excessive fat in the body. This resulted in chronic hyperglycemia and complications which are serious matter[(3).]

Diabetes mellitus (DM) is defined as a disease or a metabolic disorder with chronic multi etiology that is characterized by high blood sugar levels accompanied by impaired metabolism of carbohydrates, lipids and proteins as a result of insufficiency insulin function[(4).] Insufficient insulin function may be caused by impaired or deficient the production of insulin by the beta cells of Langerhans of the pancreas gland, or due to the lack of responsiveness of cells toards insulin (WHO, 1999). In 2000 an estimated 150 million people worldwide suffer from diabetes mellitus. Criteria for the diagnosis of diabetes is that the fasting glucose levels is higher than 126 mg/dL or at 2 hours after eating is higher than 200 mg/dL[(5)].

2. Material and Methods

Distilled water, aqua pro injection, ammonia, hydrochloric acid P, hydrochloric acid 2N, citric acid, sulfuric acid, gedi red leaves, 96% ethanol, filter paper, egg yolk of duck, chloroform, pig oil, $FeCl_3$ solution, 10% NaCl solution, 0.9% NaCl solution, sodium citrate, standard feed, Dragendorff reagents, Lieberman-Burchard reagent, Meyer Wagner reagent, P Magnesium powder, sodium CMC, streptozotocin (*Bioworld USA*), wheat flour, 500 mg Metformin tablets.

Preparation of gedi red leaf extract

Leaves of red gedi (*Abelmoscus manihot* L. Medical forma platidactylus Bakh) extract was prepared by maceration method, in which 400 gram leaves of gedi red powder simplicia was extracted with 5 liters of 96% ethanol for 5 days. The extract is then filtered using filter paper to obtain filtrate. The filtrate was the undergone further evaporation using vacuum *rotary evaporator* and using a water bath until it becomes a thick extract.

Histopathology of pancreatic β cells

Pancreatic β cell histopathology testing was conducted after treatment on day 42. The test animals were sacrificed by means of cervical dislocation. Furthermore the pancreas of mice was taken, and then stored in special containers that contain 10% formalin. Pancreatic histopathology test is then performed to observe the histopathological changes made preparations pancreas after histopathology with hematoxylin eosin staining(6). Histopathology preparations was observed and scored according the category: score 0 (no necrosis of pancreatic beta cells), a score of 1 (1/4 total cell necrosis pancreatic beta / 1-25%), a score of 2 (1/2 total necrosis of pancreatic beta cells / 25-50%), a score of 3 (3/4 total necrosis of pancreatic beta cells / 50-75%) and a score of 4 (necrosis whole pancreatic cells /> 75%).

Animal test

Test animals used were male rats (*Rattus norvegicus*), which has a healthy body condition and physical condition is perfect without any flaw and weighing between 150-250 grams.

Measurement of blood glucose

Each rat blood samples from the tail vein and blood glucose levels were measured using a glucometer. Normal fasting blood glucose levels in mice in the range of 50-135 mg / dl.

Data analysis

Research data were analyzed using One Way ANOVA statistical test with a level of 95%. Data processing was performed using SPSS 16 software program.

3. Result

Phytochemical Test

Tabel 1 Phytochemical Test Result of Gedi Merah Leaf Extract

Test	Reagen	Result	
Alkaloid	Drangendrof	Deposition orange	+
Flavonoid	Concentrated HCl and metals Mg	Orange	+
Saponin	Shake + HCl 2 N	Foam	+
Tanin	$FeCl_3$ 1%	Blue black	+

Information : + Positive

The Mean Difference Decreased Levels Gkukosa After Treatment

The mean difference in decreased glucose levels after treatment is shown in table

Table 2 The average difference in glucose levels after treatment

Treatment group	Blood glucose levels **(mg/dL) ± SD**	
	Day 35	**Day 42**
Negative control	76,2±45,09 [a]	2,4±38,54 [a]
Positivecontrol	385,6±12,26 [c]	306,2±36,64 [bc]
Dose150 mg/kgBW	213,6±85,78 [b]	318,8±105,03 [bc]
Dose 300 mg/kgBW	284,8±97,94 [bc]	370±102,06 [c]
Dose 450 mg/kgBW	201,6±65,[31 b]	237,6±42,46 [b]

Information : The same alphabetical showed no significant difference.

Different alphabets showed a significant difference

Profile of blood glucose levels after treatment

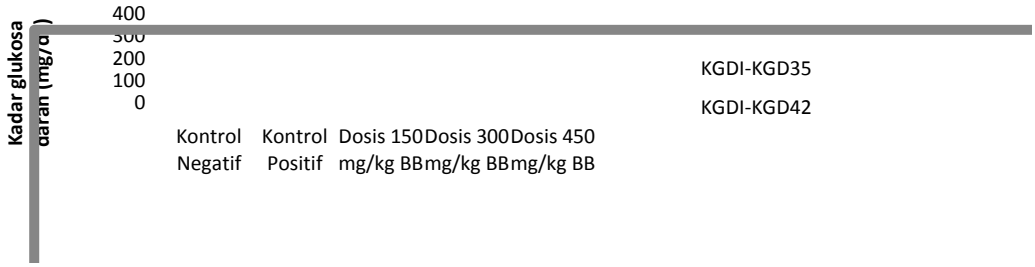

Figure 1. Profile of a decrease in blood glucose levels day-35 and day-42

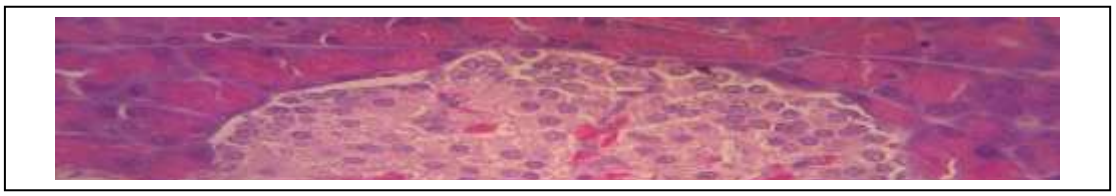

Figure 2. No necrosis of pancreatic beta cells (score of 0) (Magnification 400x)

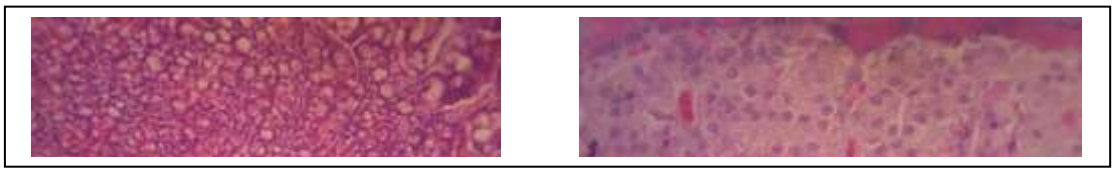

Figure 3. 1-25% necrosis of pancreatic beta cells (score 1) (HE staining, magnification 400x)

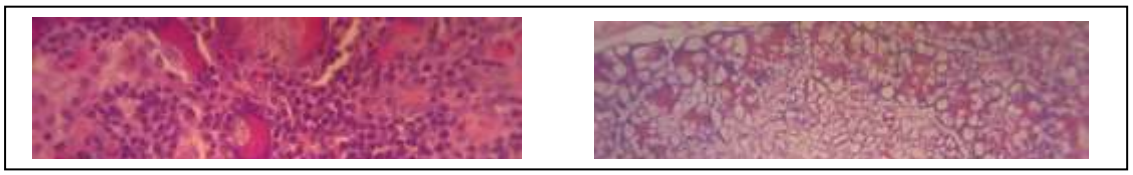

Figure 4. 1-25% necrosis of pancreatic beta cells (score 1) (HE staining, magnification 400x)

Figure 5. 50-75% necrosis of pancreatic beta cells (score 3) (HE staining, magnification 400x)

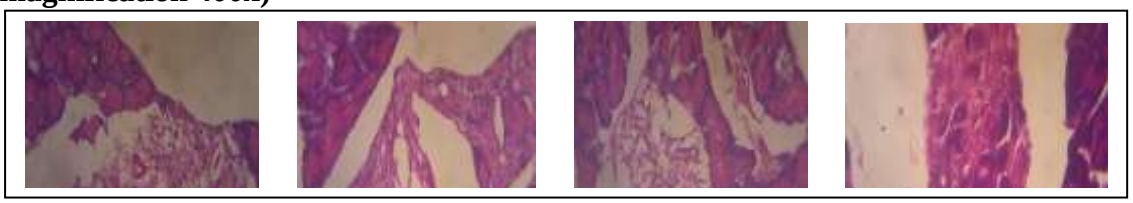

Figure 6. 75% necrosis of pancreatic beta cells (score 4) (HE staining, magnification 400x)

The result of the calculation of the number of pancreatic beta cell necrosis and a score of histological observations can be seen in Table 3

Table 3 Acquisition score of each treatment

Treatment	Value				
	Score 0	Score 1	Score 2	Score 3	Score 4
Normal control	3	0	0	0	0
Negative control	0	0	0	2	1
Positive control	2	1	0	0	0
DGM 150 mg/kg BB	2	1	0	0	0
DGM 300 mg/kg BB	2	1	0	0	0
DGM 450 mg/kg BB	2	1	0	0	0

Information : a score of 0, ie no cell necrosis of the pancreas, a score of 1 is ¼ total necrosis of pancreatic cells (1-25%), a score of 2 is ½ total necrosis of pancreatic cells (25-50%), a score of 3 is ¾ total necrosis of pancreatic cells (50- 75%) and a score of 4, namely necrosis entire pancreas cells (> 75%).

4. Discussion

This study using ethanol extract of leaves of red gedi. The extract obtained from the extraction process which is the withdrawal of the chemical constituents found in botanicals. The extraction process includes pulverizing, wetting, filtering and concentration. Wetting and screening are ways of extraction which is called maceration. Maceration method used for the test material such as leaves that have a soft texture and unknown stability of bioactive substances to heat. Advantages of maceration method is simple equipment and easy to perform as well as easily cultivated, while the disadvantage is longer time and uncompleted screening. Solvents used are ethanol 96%, which is semipolar so as to dissolve the active ingredients contained in the plant, which could be found polar, non-polar and semi-polar. Ethanol is also known to be more secure (not toxic). Viscous extract obtained from the maceration of red gedi simplisia leaves starting with 400 grams is 9.57% yield.

Testing hypoglycemic effect leaf extract of red gedi test carried out in animal models of white mice and streptozotocin induced hypercholesterolemia. Diabetes mellitus is a heterogeneous disease with many factors that influence it. The disease is characterized by metabolic disorders which are β1 cell function disorders and insulin resistance in peripheral tissues such as skeletal muscle and fat tissue and insulin resistance in the liver. This resulted in hyperglycemia. Making animal models hypercholesterolemia-diabetes is done by feeding high-cholesterol feed composition (80%), pig oil (15%), and egg yolk duck (5%) for 3 weeks and induction of streptozotocin dose of 30 mg/kg were injected intraperitoneally, Strepozotocin can induce the occurrence of diabetes in which the streptozotocin work on pancreatic ß cells through cytotoxic effects induced by reactive oxygen species (ROS) which could increase cytosolic calcium concentration simultaneously causing damage to the pancreatic ß cells quickly. STZ into the pancreatic ß cells via the GLUT-2 and cause alkylation deoxyribonucleic acid (DNA). DNA damage triggers the activation of poly-adenosine diphospat (ADP) -ribosilasi, a process that is more important than diabetogenisitas STZ than the damage to the DNA itself. Poly-ADP-ribosilasi This causes depletion of nicotinamide adenine dinucleotide (NAD +) and adenosine triphospat (ATP) cells.

According to the literature, fat can lead to diabetes because insulin stimulates lipogenesis in fat tissue and provide acetyl-Koa and NADPH needed for fatty acid synthesis, maintaining levels of the enzyme acetyl-Koa, carboxylase, which catalyzes the conversion of acetyl-Koa, be malonil-Koa and provide glycerol involved in triacylglycerol synthesis. Insulin action on glucose transport, glycolysis and glikogenesis occur within seconds or minutes, because these events mainly include the activation and inactivation of the enzyme by phosphorylation or dephosphorylation. A longer effect on plasma glucose include inhibition of gluconeogenesis by insulin. Insulin is also a potent inhibitor of lipolysis in the liver and fat tissue so that the anabolic effect does not last. Therefore, insulin reduces circulating free fatty acids. This helps the action of insulin on carbohydrate metabolism, because the fatty acids on insulin inhibits glycolysis, increased lipase activity resulting in increased lipolysis and free fatty acid concentrations in plasma and liver increased. Levels of glucagon also increase and add to the release of free fatty acids (glucagon against most of the action of insulin, and the metabolic state of diabetes is a reflection of the level of relative glucagon and insulin), most of the free fatty acids are metabolized to acetyl-CoA and further into CO_2 and H_2O through

citric acid cycle. Insulin affects the formation of VLDL and LDL, since the levels of these particles and subsequent cholesterol levels are often elevated in patients with uncontrolled.

The ethanol extract of leaves of red gedi made in three variations dose of 150 mg / kg, 350 mg / kg and 450 mg / kg. The negative control solution containing only coloidal Na CMC 0.5%. The suspension containing the active substance metformin used as a positive control for metformin are widely used among people in the treatment of insulin resistance in patients with type 2 diabetes.

Test animals used were male rats Wistar, this is because the rats have more stable hormonal cycles than female rats, and also easily bred, as well as can be used as a model of diabetic spontaneously or by induction agent diabetogenic, other than that of white mice have the ability metabolic relatively quickly so that more sensitive when used in studies of metabolic-related body. White male rats at the age of 2-3 months is a young adult mice that have optimum physiological state. Prior to use, rats adapted for 2 weeks, in order to adjust to the new of environmental and reduce stress that may interfere with the study.

Male rats were treated for 14 days on treatment 1 mice given coloidal solution of Na CMC 0.5% as a negative control, treatment 2 rats were given suspension of metformin as a positive control, treatment given leaf extract gedi 3,4,5 red with dose variation respectively 150 mg/kg, 300 mg/kg and 450 mg/kg and 6 treatment as a normal control group. Then measuring blood glucose levels in the 35th and 42nd.
At the beginning of the measurement of blood glucose levels to all the treatment group of mice which have average ranged from 85.2 to 98 mg/dL. It shows the whole of mice had normal blood glucose levels. Based on the literature of normal blood glucose levels Wistar rats ranged from 50-135 mg / dL. Blood glucose levels after three weeks of feeding high cholesterol and 1 week streptozotocin induced significantly increased between 329.4 to 533.6 mg / dL showing all the rats experienced a diabetic condition (diabetic mice that expressed when blood glucose levels higher than 200 mg dL). After being treated for 7 days (the 35^{th} day) to 14 (day 42) decreased blood glucose levels in the group given metformin and three groups of test extract (leaf extract gedi red dose of 150 mg/kg, 300 mg/kg, 450 mg/kg). Decrease difference in rats' blood glucose levels is then analyzed statistically. Based on the results of One Way Anova statistics it obtained that on day 35 and 42 showed a significant difference with p is $p = 0.000$ ($p < 0.5$) and so the test followed by post hoc Duncan to know in detail the group that has a significant difference. The test results of further post hoc Duncan on the measurement of glucose levels are described as follows:

The mean decrease in blood glucose levels male rats given 0.5% CMC Na suspension day 35 and at day 42 showed a significant difference compared to the other treatments where the difference is smaller and the decline in blood glucose levels remain high until the day- 42. This indicates that the Na CMC 0.5% had no effect on blood glucose levels so that a decrease in blood glucose levels on metformin positive control and test groups were given extracts of leaves of red gedi not affected by Na CMC as carrier.

The treatments were given the leaf extract gedi red dose of 150 mg/kg at day 35 showed the difference was not significant to the treatment leaf extract gedi red dose of 450 mg/kg, in contrast is not significant to the treatment leaf extract gedi red dose of 300 mg/kg and differ significantly from metformin treatment. On day 42 of treatment were given the leaf extract of red gedi dose of 150 mg/kg showed a decrease in blood glucose levels

are not significantly different with red gedi leaf extract treatment dose of 300 mg/kg, 450 mg/kg and metformin. A decrease in blood glucose levels gedi red leaf extract dose of 150 mg/kg on days 35 and 42 is still lower than the extract dose of 300 mg/kg. This is due to the content of bioactive substances (alkaloids, flavonoids, saponins and tannins) contained in a dose of 150 mg/kg low that an active substance that penetrates and is absorbed only small and not enough concentration to bind to the receptor.

The treatments of the leaf extract of red gedi dose of 300 mg/kg at day 35 showed no significant difference between the treatment gedi red leaf extract dose of 150 mg/kg body weight, which differ significantly from the extract dose of 300 mg/kg and metformin. On day 42 of treatment of the leaf extract of red gedi dose of 300 mg/kg showed a decrease in blood glucose levels are not significantly different with red gedi leaf extract treatment dose of 150 mg/kg and metformin. A decrease in blood glucose levels red gedi leaf extract dose of 300 mg/kg on days 35 and 42 is greater than the extract dose of 150 mg/kg and 450 mg/kg. This is due to the content of bioactive substances (alkaloids, flavonoids, saponins and tannins) contained in a dose of 300 mg/kg had a maximum concentration so that the bioactive substances that penetrate and absorbed more and is able to bind to the receptor more. As a result, the intensity of the effect of a decrease in maximal glucose levels and is comparable to the treatment given metformin. The results obtained in research is in accordance with the results of the study by Jack stated that the leaf extract red gedi has potential as an antidiabetic because it contains chemical compounds that are capable of absorbing blood glucose levels in adipocytes cells, lowers plasma glucose concentration, and reduced the increased glucose induced by STZ. The results obtained are also better as the reduction in blood glucose levels red gedi leaf extract at a dose of 300 mg/kg body weight can lower blood glucose levels.

The treatments of the leaf extract of red gedi dose of 450 mg/kg at day 35 showed no significant difference with the red gedi leaf extract treatment dose of 150 mg/kg body weight, differ significantly from the extract dose of 300 mg/kg and metformin. On day 42 of treatment of the leaf extract of red gedi dose of 450 mg/kg showed a decrease in blood glucose levels are not significantly different with red gedi leaf extract treatment dose of 150 mg/kg, the extract dose of 300 mg and metformin. A decrease in blood glucose levels red gedi leaf extract dose of 450 mg/kg on days 35 and 42 lower than the extract dose of 150 mg/kg and 300 mg/kg. This is due to the content of bioactive substances (alkaloids, flavonoids, saponins and tannins) contained at a dose of 450 mg/kg body weight too much, causing saturation of the reaction between the bioactive compounds with the receptor so that an increased dose would cause an increase in the effect of a decrease in blood glucose levels caused.

Based on the statistical results of paired samples t-test to the normal control on day 35 and 42 showed no significant difference on blood glucose levels. This happens because the normal control mice given only the standard feed and suspension CMC Na 0.5% during the study, so it does not affect blood glucose of white male rats.

Decreased levels of blood glucose male rats that had induced high cholesterol feed and streptozotocin, due to red gedi leaf extract is apparently due to the content of some classes of secondary metabolites contained in it, giving rise to a synergistic effect of hypoglycemic effect. Classes of compounds that are thought to contribute are alkaloids, flavonoids, saponins and tannins appropriate phytochemical

screening test results that showed a positive result against the group of these compounds.

Histopathologic features of the pancreas was observed that the histopathological changes in the islets of Langerhans contained in each preparation. In HE staining, the cells that exist in the islets of Langerhans indistinguishable. Therefore, the parameters of observation in this study is the change in the general morphology of the islets of Langerhans are: a change in the shape and structure as well as changes in the islets of Langerhans cells (shape, size and distribution) therein. The pathological findings in the pancreas are varied and are not always obvious and can be found in one or more changes. The observations in this study was done descriptively by observing the changes contained in each preparation.

Pancreatic ß cell mass loss can be caused by cell death due to toxic effects of excessive blood glucose, so the reduction in size of the islands of Langerhans (atrophy) that shows the level of cell damage that occurs as a result of induction strptozotocin. Clear comparisons can be observed in the area of the islets of Langerhans, Langerhans cells and acinar cells of the exocrine glands surrounding the pancreas. Normal control mice had pancreatic histology were normal (Figure 2) in which the morphology and structure of the islets of Langerhans still looks normal, Langerhans cells in it distributed homogeneously throughout the islands. There is no cell damage and changes in the structure of the islets of Langerhans. Exocrine gland acinar cells form also arranged homogeneously formed lobular-acinar lobules, so it still has a normal structure. Langerhans island rat control is still visible at least a cavity or intercellular space and lots of pancreatic beta cells producing insulin. Distribution of cells was uneven, uniform cell size and shape, the shape of the islets of Langerhans normal. On the negative control (Figures 5 and 6) seemed to change the distribution of endocrine cells is uneven, the shape and size of the cells are not uniform, some of the cell nucleus piknotis and cytoplasm dark, form islets of Langerhans irregular, it appears the widening of the spaces between cells in the islets of Langerhans , Histopathology of the pancreas in Figures 5 and 6 also showed a widening of spaces around the lobules acinar cells, because of changes in the structure and degeneration of acinar cells. Their degeneration of acinar cells, form atrophy leads to changes in cell structure, so that the cells are not able to return to its original state and cause spaces between the lobules acinar (interstitial space) or lobular acinar lumen seemed to widen.

According to Susan et al., (2011), the damaged acinar cells occurring able to reduce the function of the cells acinar as an exocrine gland of the pancreas, a decrease secretagogues stimulated by the exocrine pancreas and decrease the enzymes in the pancreas, which can cause dysfunction in the exocrine pancreas or exocrine pancreatic insufficiency (EPI) on diabetic condition, which is the inability to properly digest digest properly due to lack of pancreatic digestive enzymes. Histopathologic features of mice with ethanol extract of leaves gedi red seen in Figure 2 and 3 have the islets of Langerhans which still look normal where Langerhans cells are still distributed homogeneously, there is order arrangement of endocrine cells with a shape and a uniform size, nucleus and cytoplasm of cells normally, the islets of Langerhans appear normal with regular form is clear and easy to distinguish from pancreatic exocrine part, does not seem any widening of the space between cells. Histopathologic features of mice by administering the drug metformin are shown in Figures 2 and 3 have the islets of Langerhans which still looks normal to the level of necrosis of the

lightest in which Langerhans cells are still distributed homogeneously, there is order arrangement of endocrine cells with the shape and size of uniform, core and cytoplasm of normal cells, islets of Langerhans appear normal with regular form is clear and easy to distinguish from pancreatic exocrine part, does not seem any widening of the space between cells. However, there is a picture in the form of cell degeneration in the area of the cells stages of the process of cell death. The existence of this cariolysis may result from oxidative stress caused by free radicals or ROS. Oxidative stress produced by the high activity of the endoplasmic reticulum (ER) in acinar cells as a marker of insulin resistance. Oxidative stress in the endoplasmic reticulum causes changes in gene expression and cell survival. RE increased activity capable of generating ROS thereby affecting cell death in pancreatic tissue.

Disturbances in the plasma membrane and organelles of cells and reduced enzymatic activity of a cell can trigger cell function decline. The decline in the function of a cell is one of the causes atrophy of the cell where the cell size becomes smaller (shrinkage). Atrophy may result from a decrease in protein synthesis and increased degradation of proteins in the cell.

5. Conclusion

1. The ethanol extract of leaves of red gedi (A*belmoschus manihot L.*) with dose of 150 mg/kg, 300 mg/kg and 450 mg/kg, all have the effect of lowering blood glucose levels of male white rats (*Rattus norvegicus*) with type 2 diabetes.
2. The ethanol extract of leaves of red gedi (*abelmoschus manihot L.*) at a dose of 300 mg/kg body weight effectively lower blood glucose levels which are comparable to metformin positive control.
3. The ethanol extract of leaves of red gedi (*abelmoschus manihot L.*) has the potential to improve morphology display (shape and structure changes) histopathological island Langerhans beta cells of the pancreas gland of diabetic rats.

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Characterization of Secondary Metabolites Compound and LC_{50} Cytotoxic Test Using Brine Shrimp Lethality Test (BSLT) on Sea Cucumber *Holothuria Scabra* of Gorontalo

Widysusanti Abdulkadir and Megawati

Department of Pharmacy, Gorontalo State University

ABSTRACT

Sea cucumber (*Holothuria Scabra)* is a marine product having bioactive compounds potentially. In addition, it can also become a food and other benefit as a drug. The purpose of this research was to examine and identify of secondary metabolite compounds and cytotoxic effects of sea cucumber (*Holothuria Scabra)* extract which tested by *Brine shrimp Lethality Test* (BSLT). Research design utilized pure experimental. The data analysis of LC test utilized probit analysis. The characterization secondary metabolite and LC_{50} test of sea cucumber extract using methanol in maseration method to gain extract. The test of secondary metabolites of sea cucumber containing saponin group which marked stable foam, yellow form of flavonoid test after adding methanol-chloride acid and magnesium powder, purple form of steroid adding Lieberman-Burhard reagent and the test of alkaloid generated positive result such as white precipitate after adding ammonia and chloride acid. The test of LC_{50} was done by shrimp larvae using concentrations of 5, 10, 50, 100, 500, and 1000 ppm with three replications for each concentration. LC_{50} can be calculated from shrimp larvae death and the results were analyzed by probit design. The result of this research showed that sea cucumber (*Holothuria Scabra*) form Gorontalo contained saponin, flavonoid, steroid, alkaloid possessing LC_{50} of 11.51. It can be categorized as extremely toxic.

Keywords: $LC_{50,}$ sea cucumber *(Holothuria scabra),* secondary metabolites,

ABSTRAK

Teripang pasir (*Holothuria Scabra*) merupakan biota laut yang memiliki kandungan senyawa bioaktif yang potensial, selain sebagai bahan makanan, teripang laut juga mempunyai manfaat obat. Tujuan Penelitian ini untuk mengidentifikasi senyawa metabolit sekunder dan pengujian sitotoksik teripang laut (*Holothuria Scabra)* dengan menggunakan metode *Brine shrimp Lethality Test* (BSLT). Desain penelitian yang digunakan adalah eksperiment murni. Analisis data untuk uji LC_{50} menggunakan analisis probit. Pengujian karakteristik metabolit sekunder dan LC_{50} dilakukan pada ekstrak teripang laut (*Holothuria Scabra)* dari hasil ekstraksi maserasi menggunakan metanol. Pengujian metabolit sekunder pada sampel teripang *Holothuria Scabra* mengandung senyawa golongan saponin yang ditandai dengan busa stabil, terbentuknya warna kuning pada uji flavonoid setelah penambahan pereaksi methanol-HCl serta ditambahkan serbuk Mg, terbentuknya warna ungu dengan penambahan pereaksi Liebermen-Burhard pada uji steroid, pengujian

alkaloid menghasilkan hasil positif berupa endapan putih setelah ditambahkan ammonia dan HCl. Pengujian LC_{50} dilakukan menggunakan larva udang yang dilakukan pada konsenrasi 5, 10 ,50, 100, 500 dan 1000 ppm dengan replikasi tiga kali untuk setiap konsentrasi, LC_{50} dihitung berdasarkan kematian larva udang dan selanjutnya dianalisis probit. Hasil penelitian menunjukkan bahwa teripang laut (*Holothuria Scabra*) asal Gorontalo mengandung saponin, flavonoid, steroid, alkaloid serta mempunyai nilai LC_{50}= 11,51 ppm dengan kategori sangat toksik.

Keyword : $LC_{50,}$ metabolit sekunder, teripang laut (*Holothuria Scabra*)

***Corresponding author :** Widysusanti, Email: widisusanti553@yahoo.co.id

1. Introduction

Marine life is organism that life in the sea with a variety of features and characteristics. Currently, many marine lives are developed in order to identify compounds in marine life that can be used as medicine. One of marine life which has now been widely researched to find active compounds is sea cucumber *Holothuria Scabra.* Sea cucumber is found almost throughout the coastal waters, from shallow tidal areas to deeper waters. With diffusion rate at 38.86%, *HolothuriaScabra*is sthe most commonly found sea cucumber in Indonesia (Sudarmadji, 2003). Dried sea cucumber contains 82% protein, 1.7% fat, 8.9% water, 8.6% ash and 4.8% carbohydrate (Martoyo et al, 2000). Active compoundsin sea cucumber are triterpene glycosides (saponins), chondroitin sulfate, glycosaminoglycans, sterols, sulfate triterpen, glucose, sulfate polysaccharides, peptides, proteins (gelatin and collagen), hidrosalisilat, glycoproteins, lectins, phenols and flavonoids (Bordbar et al, 2011).

2. Experimental

True Experimental, Material used in this study was sea cucumbers *(Holothuria Scabra)* taken from Wajo,Tilamuta Sub-District, Boalemo District, Gorontalo.

2.1 Materials and Methods

Extraction

Samples were cut open and gutted and then washed to remove dirt. After that, the samples were cut into small pieces and put into a maceration container to be soaked with methanol until all surfaces were submerged perfectly. The immersion was stirred every day for 3 times and the solvent was replaced every 3 days with the same treatment. Soaking was done until the solvent of resulted immersion did not give more color or solution of resulted immersion was clear. The solutions extracted from the first day to the last day (day 15) were mixed to be evaporated to generate thick sea cucumber extract.

Phytochemical Screening Test of Secondary Metabolites

Phytochemical screening testwas conducted on dry sea cucumber extract for secondary metabolites namely saponins, flavonoids, tannins and polyphenyl, steroid/terpenoids and alkaloids.

Preparing *Artemia Salina* Larvae

Container for hatching waspartitioned into two parts, irradiated part and dark part. 20 mg of *Artemia salina* Leach larvae was put in the container which had previously been given synthetic sea water. The container was equipped with aeration and larvae were put in the dark part andleft to hatch. After 48 hours, test animals were ready for use.

Preparing Test Solution

Mother liquor was prepared bydissolving 30 mg of samples in 3 ml of ethanol, in order to obtain 10,000 ppm mother liquor. 1000 ppm test solution was generated by pipette of 1000µl of mother liquor. 500 ppm, 100 ppm, 50 ppm, 10 ppm and 5 ppm test solutionswere respectively generated by pipette 500 µl, 100 µl, 50 µl, 10 µl and 5 µlof mother liquor. The vial of test solution was then evaporated

Cytotoxic Test with BSLT Method

Each concentration of test solution was replicated as many as three times repetition.3 ml of salt water and 10 shrimp larvae were then put into each test vial and added with sea water until it reached 10 ml. In order to generate control, shrimp larvae were put in vial containing 10ml of sea water without the addition of extract. The larvae were then observed for 24 hours and the value of LC_{50} was calculated based on the mortality by comparing the number of dead larvae to the total number of larvae using probit analysis.

3. Results and Discussion

Table 1. Results of the screening of secondary metabolites of sea cucumber *Holothuria scabra*

screening	Reagent	indication	result
saponin	Hot water	stable foam	(+) Saponins
flavonoids	Methanol + HCl + Mg powder	Orange / yellow / red	(+) Flavonoids
Tannins and polyphenols	Distilled water + NaCl + FeCl3	Green / livid	(-) Tannins and polyphenols
Steroids / terpenoids	Liebermen-Burhard	Purple	(+) Steroids
alkaloids	Ammonia + HCl	white precipitate	(+) Alkaloids

Table 1 shows that the results of phytochemical screening of sea cucumber dry extract contains saponin (indicated by stable foam), flavonoids (indicated by the yellow color on flavonoid test after the addition of methanol, HCl and Mg powder), steroids (indicated by the purple color after the addition of Liebermen-Burhard on steroids test, and alkaloids (indicated by the white precipitate after the addition of ammonia and HCl on alkaloids test).

Table 2. Results of Cytotoxic Test on the extract of *Holothuria scabra* using Brine Shrimp Lethality Test (BSLT) Method

C (ppm)	The number of dead larvae			Total number of larvae uji	% of dead larvae	Log C	Probit	24 hours LC_{50} (ppm)
5	6	4	4	30	46,67%	0,69	4,90	
10	6	6	6	30	60%	1	5,25	
50	8	1	10	30	63,33%	1,69	5,33	
100	10	0	10	30	66,67%	2	5,41	**11,51**
500	10	10	3	30	76,67%	2,69	5,71	
1000	10	10	10	30	100%	3	8,09	
Control	0	0	0	30	0	0	-	

Cytotoxic test on methanol extract of sea cucumber *(Holothuria scabra)* using BSLT method involving the larvae of *Artemia salina* L as test animals performed at 5 ppm, 10 ppm, 50 ppm, 100 ppm, 500 ppm and 1000 ppm with three replications for each concentration. According to the table 2, it can be concluded that extract concentration variations generate different effect. The number of shrimp larvae used for each vial for one replication was 10, making the total number of shrimp larvae for each concentration was 30. The death of shrimp larvae is expressed in percentage. The data were then analyzed using probit table. From the calculation, the value of LC50 was 11.51 ppm .

4. Conclusions

The extract of sea cucumber (*Holothuria scabra*) contains saponins, flavonoids, steroids and alkaloids. The extract of sea cucumber *(Holothuria scabra)* is highly toxic with the value of LC_{50} at 11.51 ppm.

Acknowledgment

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The Knowledge and Behaviour of People in Rembang Disctrict in Self Medication for their Analgesic Drug

Ikhda Khullatil Mardliyah[1*], Yardi bin Saibi[1], Karyadi[2]

[1]Pharmacy Department, Faculty of Medicine and Health Science, UIN Syarif Hidayatullah, Jakarta,
[2] Nursing Department, Faculty of Medicine and Health Science, UIN Syarif Hidayatullah, Jakarta.

ABSTRACT

The use of analgesic drug in community is quite high, both drug gain from prescripstion and self medication. For self medication, the analgesic drug that used by community not just limited to over the counter drug, but also drug that actually should be gained by presription. The good understanding/knowledge in taking medication is important factor in determining the therapy outcome and minimalizing the adverse drug reaction. This research aimed to investigate the knowledge and behaviour of Rembang people in taking their analgesic medication. The desain of the research was cross sectional in order to explore the knowledge and behaviour. Data were collected using structured quesionaire. Respondent were patients come to three selected community pharmacies in Rembang district who buy their analgesic medication. The result showed that the most drug used by Rembang people in self medication for their pain problems were prescription label drug (69,1%), followed by over the counter one. Mefenamic acid was the most common pain killer drug used among them. More than a half (54,6%) patients classified into good behaviour in taking the analgesic medication. Mass media both printed and electronic was the most information source of where patient know the medication (42,1%). The most commonly reason for patients in taking the analgesic was the previous experience (36,8%). The role of community pharmcist is much needed in order to increase the patients knowledge and behaviour in taking their analgesic drug for self medication.

Keywords : analgesic, behaviour, community pharmacy, drug, pharmacist, self medication.

ABSTRAK

Tingkat penggunaan antinyeri di masyarakat cukup tinggi baik penggunaan melalui resep dokter, maupun penggunaan secara mandiri atau swamedikasi. Swamedikasi yang dilakukan terhadap obat antinyeri tidak hanya terbatas pada obat bebas atau bebas terbatas melainkan juga obat keras. Pengetahuan dan perilaku yang baik dalam penggunaan obat nyeri akan sangat menentukan keberhasilan terapi dan meminimalkan efek merugikan dari obat. Penelitian ini bertujuan untuk menetahui pengetahuan serta prilaku masyarakat dalam penggunaan obat antinyeri. Penelitian ini menggunakan disain cross-sectional guna mengeksplorasi pengetahuan dan prilaku masyarakat. Pengumpulan data menggunakaan kuesioner terstruktur . Responden adalah pasien yang datang ke tiga apotek terpilih di Kabupaten Rembang yang sedang membeli dan akan menggunakan obat antinyeri. Hasil penelitian menunjukkan bahwa obat yang digunakan oleh responden untuk tujuan swamedikasi yang tertinggi adalah golongan obat keras sebesar 69,1%, obat bebas 26,8% serta sisanya obat bebas terbatas. Asam mefenamat merupkan obat yang paling banyak penggunaannya.

Responden sebagian besar memiliki perilaku yang benar dalam menggunakan obat antinyeri (54.6%). Sumber yang digunakan untuk memperoleh informasi obat yang tertinggi adalah media massa bai cetak/elektroni sebesar 42,1%. Alasan utama dalam penggunaan obat adalah pengalaman sebelumnya yakni sebesar 36,8%. Masih diperlukannya peran tenaga kesehatan khususnya apoteker guna meningkatkan pengetahuan dan perilaku masyarakat dalam menggunakan obat antinyeri.

Kata kunci : analgesik, apoteker, apotek, obat, prilaku, swamedikasi.

***Corresponding author :** yardi@uinjkt.ac.id

1. Introduction

Analgesic drug is widely taken by people, it is estimated to cause chronic kidney desease in 1990"s(WHO, 2000). This drug was mostly taken by women each mounth for pain reliever of menstrual period and one of the cause of chronic kidney desease (Sohar E.Ali, 2010). The prevalence of self medication for analgesic drug was reported 39,4% (Pilar Carasso, et.al, 2014). Based on basic health research published by ministry of health Indonesia, the number of self medication in Indonesia is quite high.

One of the character of Indonesian family in self medication is the behavior of housewife in keeping medicine for self medication action in home. Data shows this number reach 35,2%. In practice, drug that they keep not just oer the counter dru bat also drugs that belong to prescription label drug include antibiotics, traditional medicine and unidentified drug. Theh presence of antibiotics and other prescription label drug indicated that there is irrational drug use in community setting for self medication(Riskesdas, 2013).

Self medication should concider the principle of safety and rational drug use. Pharmacist as one of the health proffesion has a role in assuring that people use their drug with safe and rational through education and advice to them. In fact this role is still not run well where their role undertaken by their assistant or others. One publication in Jakarta in 2003 reported that one hundred percent self medication was done by the pharmacy technician. The lack of knowledge in self medication could lead to irrational drug use. This work aimed investigate the knowledge and behaviour of patient in self medication action.

2. Experimental

This is the kuantitative analytical research with cross sectinal design. Sample was patient came to three selected community pharmacy in Rembang district of East Java. The research was unpair categoric analysis and sample size was determined by the following formula (Cochran, 1977) :

$$\mathrm{n} = \frac{(Z.\frac{1}{2} - \alpha)^2 . P\,(1-P)}{d^2}$$

Where :

n : sample amount

p : estimation proportion, in this case 35,2% (Riskesdas, 2013)

d : deviation degree to population wanted

Z1-α/2 : Z value at confidence level,(95% in this case)

By using the above formula, sample amount was 88 patients. Inclusion criterias were patient come to pharmacy for the purpose of self medication for pain; willing to be respondet by filling the quesionaire and exclusion criterias was people that bought analgesic drug that did not responsible to the patient directly. Respondent need to fill the informed consent.

3. Result

The most commonly information source for self medication was information media followed by family/neighbour/friend as indicated in table 1 below. The result was not correspond to two previous researches that first found that information from health profession such as docter pharmacist, nurse and others was the most one i.e 25,3% (U. Sushita 2012). The other one found that te most commonly information source for self medication was from family (Puji Pratiwi 2014). The advance development in information technology such as internet make everyone can access easly to that kind of source. This trend is good in the context of access but consideration for the appropriate source should be done. The involve of health profession is highly needed to help people to select the good source or to answer their question if any.

Table 1. Frequency dstribution of self medication based on source of information

Reason	frequency	Percentage (%)
Information media	32	42,1
Family/neighbour/friend	27	35,5
Health profession	13	17,4
ancient	4	5,3
total	76	100

Most respondent did self medication based on their previous experience as shown in table 2, followed by advice from a friend/family member. The result was not correspond to research conducted in Uni Emirat Arab (UEA) which found that mostly people did self medication because of the desease they suffer was minor ailment. The letter result seem to be better reason because that is the ood reason for self medication. Self medication is exactly intended for curing the unserious desease where people can determine their condition by themselves and that is minor ailment. By understanding their own condition they can decide by themselves which medicine to take. If they still need more information, pharmacist should be ready to help.

Advice from a friend or family member is also an important reason for respondent to do self medication. Consideration has to be remembered that the different respond to drug among one person to another could exist beside the difference in desease stage.

Table 2. Frequency dstribution of self medication based on reason

Reason	frequency	Percentage (%)
Previous experience	28	38,8
Advice from a friend/family member	26	34,2
There in not time to consult to physician	16	21,1
Expensive fee for physician	6	7,9
Total	76	100

Table 3. Frequency dstribution of self medication based on behaviour

behavior	frequency	Percentage (%)
Good	53	54,6
Less good	44	45,4
Total	97	100

Table 3 above shows that respondent behaviour in doing self medication fall into good cathegory although the gap with less good cathegory is not significant. There is still a space for helath profession especially pharmacist to take role in increasing the behavior.

Rationality in drug use is the most inportant thing. Taking drug rationally will assure the best therapy outcome.

Table 4. Frequency dstribution of self medication based on rationality of drug use

description	Percentage (%)
Right indication	24,7
Right drug	45,5
Right rute	100
Right dose	56,7
Right frequency	24,7
Right side effect	12,4
Right contraindication	97,9

Table 4 above indicated that rationality is still a problem. Right route is the highest percentage. All respondent are right in taking their medication by route. Right contraindication also place high percentage, ,means that most respondent have been eager to read which one to consider when taking the medicine. They have realized some drogs may be dangerous for pregnant women or for lactating mother for example.

Other rationality aspect in taking medicine are still low. This become the challenge for pharmacist to assure that every one right in taking the medicine. Pharmacist has important role in making people know their medication well and they also responsible so that patient take their medication in a right way.

It can be seen in table 5 the individual drugs commonly used by respondet in curing their pain. Paracetamol is the highest frequency, followed by mefenamic acid, piroxicam and etc. Paracetamol is well known analgesic trough the world include Indonesia. The cheap price of the drug may also become a reason why it is widely used. It is good analgesic for mild to moderate pain with minor side effect.

Table 5. Frequency dstribution of self medication based on the most commonly use

obat	frequency	Percentage (%)
Paracetamol	27	27,8
Mefenamic acid	21	21,7
Piroxicam	18	18,6
Diclofenac natrium	12	12,4
Methampiron	8	8,2
Ibuprofen	7	7,1
Diclofenac kalium	2	2,1
Meloxicam	2	2,1
total	97	100

The use of some prescription labeled drug as mefenamic acid, piroxicam and diclofenac natrium seem to be a serious problem. This

kind of drug should not be used for self medication in the view of legality. These drugs should be used under supervion of physician because they have more serious side effect that paracetamol for instance.

4. Conclusions

The most drug used by Rembang people in self medication for ther pain problems were prescription label drug, followed by over the counter one. Mefenamic acid was the most common pain killer drug used among them. More than a half patients classified into good behaviour in taking the analgesic medication. Mass media both printed and electronic was the most information source of where patient know the medication. The most commonly reason for patients in taking the analgesic was the previous experience . The role of community pharmcist is much needed in order to increase the patients knowledge and behavior in taking their analgesic drug for self medication.

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Inventorization and Ethnopharmacology Plant for Treatment of Infectious Diseases in Gowa and Maros District of South Sulawesi Province

Sesilia Rante Pakandang* and Djiniasti Karim

Department of Pharmacy Health Polytechnic Makassar

ABSTRACT

The research aims to inventorization indigenous natural ingredients determine. The factors affects people of South Sulawesi in selecting types of herbal medicins or herbs that are used for the treatment of infectious diseases. Contributions to health in the community is supporting the use of herbal medicines as an alternative in the treatment of infectious diseases in the community. The study was conducted in Maros representing the Bugis ethnics and Gowa representing Makassar ethnics. Samples were selected based on cluster locations: the lowlands, highlands and coastal areas in each district. Criteria of the sample; adult, once and know the uses of herbs the population remains at selected locations and could communicate verbally. Conclusion of the study is the community has been using 23 kinds of plants to treat infectious diseases. Types of plants that become local wisdom used for infectious diseases are guava, miyana, kopasanda, papaya, lime, sirih and binahong. How to use the herbs is to boil or squeeze the water from parts of the herbs, then drink the water or placed on the sore spot. The factors that determine people prefer herbs is trustable, safe, without side effects, more efficacious, easy to obtain, recover quickly and cheap. The source of the herbs usement came from generations, parents family, neighbours, friends, and health workers.

Keywords: ethnopharmacology, local wisdom, infectious diseases

ABSTRAK

Penelitian ini bertujuan untuk inventarisasi bahan-bahan alami asli menentukan. Faktor mempengaruhi orang-orang dari Sulawesi Selatan dalam memilih jenis medicins herbal atau herbal yang digunakan untuk pengobatan penyakit infeksi. Kontribusi untuk kesehatan di masyarakat mendukung penggunaan obat-obatan herbal sebagai alternatif dalam pengobatan penyakit menular di masyarakat. Penelitian dilakukan di Maros mewakili etnis Bugis dan Gowa yang mewakili suku Makassar. Sampel dipilih berdasarkan lokasi klaster: dataran rendah, dataran tinggi dan daerah pesisir di setiap kabupaten. Kriteria sampel; dewasa, sekali dan mengetahui penggunaan herbal penduduk tetap di lokasi yang dipilih dan bisa berkomunikasi secara verbal. Kesimpulan dari penelitian ini adalah masyarakat telah menggunakan 23 jenis tanaman untuk mengobati penyakit infeksi. Jenis tanaman yang menjadi kearifan lokal yang digunakan untuk penyakit menular yang jambu, miyana, kopasanda, pepaya, jeruk nipis, sirih dan binahong. Cara menggunakan herbal adalah dengan merebus atau memeras air dari bagian tumbuh-tumbuhan, lalu minum air atau ditempatkan pada tempat sakit. Faktor-faktor yang menentukan orang lebih memilih herbal yang dipercaya, aman, tanpa efek samping, lebih mujarab, mudah didapat, cepat sembuh dan murah. Sumber herbal usement berasal dari generasi, keluarga orang tua, tetangga, teman, dan petugas kesehatan.

***Corresponding author** : Sesilia Rante Pakandang, email : mamajassy@gmail.com

1. Introduction

Local knowledge society is the culture of the local community to the particular habit. Including the habit of using herbal medicine as daily necessities. Ethnopharmacology is the scientific study of traditional medicines, which continue to provide new drugs and lead molecules for the pharmaceutical industry (Houghton, 2007) .

Prospects of herbal medicines plants in Indonesia is very potential. World's plant species that have been identified are 40,000 species of plants and an estimated 30,000 species grow in the Indonesian archipelago. Besides in Indonesia is estimated there are 9,600 species of plants that have been used by 400 ethnic diversity for health maintenance and treatment of various diseases. Inheritance of traditional knowledge about herbal medicines plants which are mostly made orally, so the 300 new species of plants used as herbal medicines by traditional medicine industry, 38 products of medicinal plants listed as standardized herbal medicine and 6 products as fitofarmaka. The Indonesian government established the importance of efforts to increase the use of natural resources in the field of traditional medicine, including through the provision of a data base that is current and complete

Infectious disease is an infectious disease caused by a microorganism contamination of good bacteria, fungi, or viruses arasi Prospects of medicinal plants in Indonesia is very potential. World's plant species that have been identified are 40,000 species of plants and an estimated 30,000 species grow in the Indonesian archipelago. Besides in Indonesia is estimated there are 9,600 species of plants that have been used by 400 ethnic diversity for health maintenance and treatment of various diseases. Inheritance of traditional knowledge about medicinal plants which are mostly made orally, so the 300 new species of plants used as medicine by traditional medicine industry, 38 products of medicinal plants listed as standardized herbal medicine and 6 products as fitofarmaka. The Indonesian government established the importance of efforts to increase the use of natural resources in the field of traditional medicine, including through the provision of a data base that is current and complete (Mukti, 2011).

The therapy is administered in patients with drug-drug to treat symptomatic but often with antibiotics (Tan and Rahardja, 2010). Infectious diseases are very common in the community. Many causes conscious or not a person is often infected with microorganisms from the surrounding environment.

Community treat infectious diseases by various means including the use of herbal medicine, alone or potions. The use of herbal medicine by the public is strongly influenced by the local knowledge of local communities.

South Sulawesi is a province with 23 districts and cities consists of three major parts, namely Bugis, Makassar and Toraja. Area location and culture, greatly influence the type of local herbal remedy used, including for the treatment of infections. The location is coastal, lowland and highland each have different plant species, thus affecting the choice of plants that are used for treatment. In addition to the type of plant every region has a different way to treat the disease.

The study aims Determining local wisdom and determiner factor-factor that affects people of South Sulawesi in selecting varieties of herbal medications or herbs that are used for the treatment of infectious diseases.

The study was conducted in Maros and Gowa in South Sulawesi Province in 2016. The choice of location is Maros representing the Bugis and Gowa ethno

Makassar and has one of the scattered settlements in the coastal areas, highland and lowland.

2. Experimental

The study was conducted in Maros and Gowa in South Sulawesi Province in 2016. The choice of location is represented Bugis Maros and Gowa Makassar represent tribes and has one of the scattered settlements in the coastal areas, highland and lowland.

2.1 Population and sample

Population Gowa and Maros district.

Determining the proportion of the sample based on the cluster area and random subjects. Samples in which the public Maros District of Camba for upland areas, the District Lau for coastal regions and the District Bantimurung for low-lying areas. Sample in Gowa the District Parangloe for upland areas, District Barombong for coastal areas, District Pattalassang for low-lying areas.

Criteria sample; adult, once and know the uses of medicinal plants, the population remains at selected locations, can communicate verbally, willing to be interviewed.

The sample size for the assessment of the proportion of the population (Kuntoro, 2010)

$$n = \frac{N\,pq}{(N-1)\,D + pq}$$

N = total population of 1,072,656 inhabitants Gowa and Maros
n = number of sample
p = error limit valuation (0.5)
q = 1 - p = 0.5
D = B2 / 4
B = 10% of probability (10% x 0.5) = 0.05
Then n = 399.851 = 400. (total sample)
The calculation of the proportion of the samples selected according to the number of 3 districts selected population of Maros = 64 548 inhabitants (Lau = 24 208; Camba = 12 523; Bantimurung = 27 817), then large samples taken are 19.8% of the total sample
19.8% x 400 = 79.2 = 80 samples
District. Lau = 30 samples; District Camba = 16 samples; District Bantimurung = 34 samples
Calculation of the sample selected according to the number of 3 districts selected population of Gowa = 72 506 inhabitants (Barombong = 34 245; Parangloe = 16 411; Pattalassang = 21,850), the large sample taken is 9.7% of the total sample
9.7% x 400 = 38.8 = 39 samples
District. Barombong = 19 samples; District Parangloe = 9 samples; District Pattalassang = 11 samples

2.2 Method

Data were collected based on the observation using an interview guide then tabulated and analyzed.

3. Result and Discussion

Table 1. Types of Infectious Diseases and Herbal Medicines Used

No	Diseases	Herbal Medicines	Part of herb is used	The number of respondents who use					
				Plateau		Coastal		Lowlands	
				Camba	Paranglo e	Bantimurung	Pattalassang	Lau	Barombong
1	COUGH	Miyana	Leaf	4		8	1	7	6
		Sambiloto	Leaf	1		3		1	
		Jeruk nipis	Fruit	5	1	2	4		3
		Pepaya	Leaf			3	1		1
		Jahe	rhizome			1		1	
		Butik butik	Leaf				1		
		Jambu biji	Leaf	1					
		Kunyit putih	rhizome	1					
		Sirsak	Leaf	1					
		Pare	Leaf						1
2	FEVER	Rimpang	rhizome			2			
		Papaya	Leaf		1		3		6
		Kolas	Leaf				1		
		Jarak	sap	1					
		Sirsak	Leaf	2	1				
		Kumis kucing	Leaf	1				1	
3	FLU	Srikaya	Leaf			1			1
		Miyana	Leaf			1			
		Merica	Fruit					1	
4	SARIAWAN/ PANAS DALAM	Jahe merah	rhizome			2			
		Jarak	sap			1			
5	WOUND	Kopasanda	Leaf	1		6		2	14
		Lamun	Leaf			1			
		Jarak	Leaf	2		1		1	
		Rumput gondrong	Leaf		1				
		Buti buti	Leaf		1				
6	BOIL (BISUL)	Ubi jalar	Leaf			1			
		Kapuk	shoots			1			
		Cocor bebek	Leaf					1	
		Binahong	Leaf					2	

		Singrolo	Leaf					1	
7	ACNES	Jeruk nipis	Fruit	1	1		1		
		Binahong	Leaf	5				3	
		Balle	rhizome					1	
8	DANDRUFF	Jeruk	fruit	1			1		
9	WATER FLEAS	Kondo-kondo	Leaf				1		
10	MOLDY SKIN (PANU)	Kiti-kiti	Leaf			1	2		
		Pelutus	Leaf						1
		Gading gajah	Leaf					1	
11	ITCHY SKIN	Kunyit	rhizome	1					
12	WORMY	Delima	Root			1			
		Biring Jene	Leaf			1			
13	ABSCESSED TOOTH	Jarak	sap	1		1			1
		Bawang putih	bulbs			1		1	1
		Rumput beumba	rhizome		1				
		Sirsak	Leaf	1					
		Papaya	Leaf					1	
		Nangka	Leaf						1
14	SORE EYES	Sirih	Leaf		1	1			
		Kayu cina	Leaf				1		
15	EARACHE	Miyana	Leaf			1			
		Parappa	fruit					1	
		Anggrek	Leaf						1
		Jarak pagar	Leaf / sap						3
16	LUNG	Jahe merah	Rhizome			2			
		Kiti-kiti	Leaf			1			
		Lengkuas	Leaf			1			
17	DIARRHEA	Jambu biji	Leaf	10	10	14	7	12	10
18	CANDIDIASIS	Sirih	Leaf	8				2	
19	BODY ODOR	Beluntas	Leaf			1			2
		Kunyit	rhizome						2

Tabel 2 Types of herbs are often used for infectious diseases

No	Herbal medicines	Part of herb	Indication of herb	How to wear	The number of respondents
1	Jambu biji	Leaf	Diarrhea, cough	Boiled, squeezed the water	64
2	Miyana	Leaf	cough, flu, earache	Boiled, squeezed the water	28
3	Kopasanda	Leaf	Wound	Squeezed the water, attached	23
4	Jeruk nipis	buah	cough, acnes, dandruff	squeezed the water	20
5	Papaya	Leaf	Cough, fever, abscessed tooth	Boiled, squeezed the water	16
6	Sirih	Leaf	Sore eyes, candidiasis	Boiled, squeezed the water	12
7	Binahong	Leaf	Itchy skin, acnes	Squeezed the water, attached	10

Research carried out by door to door in the community or gathering of citizens at certain times. This is to obtain information from the general public from all walks of life, work, education, both of which can and can not speak Indonesian. Thus obtained accurate information from each community who have used medicinal plants. Community respondents are 36 men and 83 women. Uneven distribution of respondents aged 17-30 years for the age group of 28 people, 39 people 31-40 years, 41-50 years 27 people,> 50 years 25 people. Education is the most respondents varied and SD as many as 53 people, 19 people SMP, SMA 29, Diploma 11 people and no school 7 people. Jobs respondents the most was the IRT (housewife) 64 (the wives of farmers and fishermen), farmers 27 people, fisher 2 persons, self-employed 5, teachers / PNS 5, others 15 people (not working or not working and casual laborers).

Based on the analysis of data collected found 23 species of plants that have been used by people to treat infectious diseases. The number of respondents who use varies for each plant as well as to the type of disease being treated. Type of plants used are plants that exist in the surrounding environment of respondents, so the name of the plant still vary from the official name, Indonesian and regional names. Nonetheless each different plant species continue to have a different name anyway.

Local wisdom in selecting medicinal plants are the largest selection of people to choose certain types of medicinal plants based on knowledge and experience. Types of plants that become local knowledge society that is used for infectious diseases are guava, miyana, kopasanda, papaya, lime, betel, binahong. It is based on the frequency of selection of respondents for each type of plant. Seven types of plants above is selected plants by more than 10 respondents. In this study, respondents' preferences vary widely. This is caused by the level of

knowledge of the plants are still empirical only.

Based on the empirical way of using medicinal plants is part of the plant boiled or squeezed the water for drinking or placed on the sore spot. This is a general way in the community to use medicinal plants and supported by habits and existing facilities, as respondents selected were people living in the countryside.

Community use as an alternative treatment plant caused by the ability of natural plants (herbs) to reduce and cure the disease. This is because the active substances of plants may serve to increase the immune response and to disease. Alternative medicine hereinafter called CAM (complementary and alternative medicine) can improve the immune system with various stages, affecting the formation of antibodies and immune complexes, altering the balance of inflammatory and anti-inflammatory properties, as well as regulate the response of pathogens (Venkatesha et al., 2011).

Public trust in traditional medicine is still very large because most respondents could provide answers vary for types of diseases and plants used. It is caused by a variety of sources of information as well. The factors that determine people prefer medicinal plants is trust safe, without side effects, more efficacious, easy to obtain, recover quickly, cheaply. While the use of medicinal plants resources from generation to generation, parents, family, neighbors, friends, health workers.

The use of medicinal plants in the community strongly support self-reliance of rural communities in treating the disease. This is because traditional medicine is the primary choice and as an alternative treatment. As we know that health care facilities and sometimes distant and hard to reach by certain circles of society, especially those living in the highlands. So the use of traditional medicine is an extremely credible and necessary.

This research has been conducted a study ethnobotany up etnofarmakologi. Where this research has found the types of herbs used by the community based on culture or customs hereditary or local knowledge. Based on observations of plants used contain various active substances, which can then be tested as advanced research laboratories. In accordance with the theory Ethnobotany is the study of plants used by indigenous societies for food, medicine, building materials, economic application or ceremony (Farnsworth, N.R., 1994). An ethnobotanical study is carried out by gathering data of traditionally used plants by interviewing people with specific knowledge. In the Australian context, this usually includes Aboriginal women, since they often possess the most detailed knowledge (Lassak, E.V.; McCarthy, T, 2001).

Ethnopharmacology involves the observation, description, and experimental investigation of indigenous medicines and their biological activities as an approach to drug discovery (Fabricant, D.S.; Farnsworth, N.R., 2001). In our study, plants used by the Maros and Gowa communities that show significant medicinal potential are being investigated for their biologically active compounds.

4. Conclusions

Society has used 23 kinds of plants to treat infectious diseases. Types of plants that become local wisdom used for infectious diseases are guava, miyana, kopasanda, papaya, lime, betel, binahong. How to use medicinal plants are part of the plant boiled or squeezed the water for drinking or placed on the sore spot. The factors that determine

people prefer medicinal plants is trust safe, without side effects, more efficacious, easy to obtain, recover quickly, cheaply. Use of medicinal plants resources from generation to generation, parents, family, neighbors, friends, health workers.

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Isolation and Evaluation of Antimicrobial Activity of Kecombrang (*Etlingera elatior*) Leaves Extract from Masamba, North Luwu

Ismail Ibrahim, St. Ratnah, Alfrida Monica Salasa

Department of Pharmacy, Health Polytechnic, Makassar, Indonesia

ABSTRACT

Kecombrang is rich of bioactive components such as alkaloid, flavonoid, polyphenols, steroid, saponin and volatile oil. The phytochemical contents of this plant have benefit for health especially in the prevention of disease. This study aims to isolate the active compounds of Kecombrang leaves, and to evaluate the antibacterial activity of the isolated compounds using bioautography thin layer chromatography. Kecombrang leaves was extracted using ethanol 96% until obtained viscous extract. Then it was extracted by liquid-liquid extraction to get diethylether and n-buthanol extract. Each extract was isolated using TLC method. The result showed that there are 7 active compounds (spot) in ethanol extract, 5 active compound (spot) in diethyl eter extract, and 3 active compounds (spot) in buthanol extract. While the bioautography evaluation shows that the ethanol, diethyleter and buthanol extract inhibited the growth of *Escherichia coli* and *Candida albicans*

Keywords : Kecombrang , isolated compounds, bioautography, TLC, *Escherichia coli*, *Candida albicans*

ABSTRAK

Kecombrang kaya komponen bioaktif seperti alkaloid, flavonoid, polifenol, steroid, saponin dan minyak atsiri. Isi fitokimia tanaman ini memiliki manfaat bagi kesehatan terutama dalam pencegahan penyakit. Penelitian ini bertujuan untuk mengisolasi senyawa aktif daun kecombrang, dan untuk mengevaluasi aktivitas antibakteri senyawa terisolasi menggunakan bioautografi kromatografi lapis tipis. daun kecombrang diekstraksi menggunakan etanol 96% sampai ekstrak kental yang diperoleh. Kemudian diekstraksi oleh ekstraksi cair-cair untuk mendapatkan dietileter dan n-butanol ekstrak. Setiap ekstrak diisolasi menggunakan metode TLC. Hasil penelitian menunjukkan bahwa ada 7 senyawa aktif (spot) dalam ekstrak etanol, 5 senyawa aktif (spot) dalam ekstrak dietil eter, dan 3 senyawa aktif (spot) dalam ekstrak butanol. Sementara evaluasi bioautografi menunjukkan bahwa etanol, diethyleter dan butanol ekstrak menghambat pertumbuhan Escherichia coli dan Candida albicans

Kata kunci: kecombrang , senyawa bioaktif, bioautografi, TLC, *Escherichia coli, Candida albicans*

***Corresponding author** : Alfrida Monica, email : alfrida.monica@yahoo.com

1. Introduction

Currently infectious disease remains a serious problem in Indonesia, coupled with the increasingly widespread bacterial resistance to existing drugs. It encourages the importance of resource extraction antibacterial drugs are derived from natural materials such plant. A study of plants as a source of traditional medicine is necessary to provide scientific evidence that these

plants properties and is a precursor or forerunner to the synthesis of new drug compounds.

One of the plants that can be used as a traditional medicine that is kecombrang (Etlingera elatior). Kecombrang is one type of herb plants - spice native to Indonesia that belongs to the family of Zingiberaceae, local communities Luwu using Fruit kecombrang as seasoning, is also traditionally used as a medicine.

These last few years, the plant kecombrang got a very big concern for their empirical facts and evidence of scientific research, Flowers kecombrang contain chemicals such as alkaloids, flavonoids, polyphenols, steroids, saponins and essential oils. The content of phytochemical compounds in plants are known to have a very important role for health, including its function in disease prevention (Tampubolon et al., 1983; Winarti and Nurdjanah, 2005). Research on Fruit and Flower kecombrang been done by Habsah et al. (2005) that kecombrang can be used to treat some infectious diseases and degenerative diseases such as cancer and tumors. According Hudaya, (2010) and Akbar (2008) kecombrang has antibacterial and antioxidant activity (Muawanah, A., et al, 2012). In addition kecombrang as body odor remover (Sirait.N., 2008). According to Jafar et al., (2007) kecombrang contain essential oils that are bioactive (leaf 0.0735%, 0.0334% interest; stem and rhizome 0.0029% 0.0021%). According Naufalin et al., (2005) antibacterial substances from ethanol and ethyl acetate extracts of flowers kecombrang can inhibit a variety of bacteria such as *Bacillus cereus, Pseudomonas aeroginosa, Salmonella typhimurium* and *Escherichia coli.*

Research on the efficacy of other parts of the plant such as antibacterials has not been studied, so it is necessary to study the antibacterial activity test on other sites such as leaves kecombrang method bioautografi against bacteria.

Bioautografi method is a simple method used to indicate the presence of antibacterial activity or antikapang. This method combines the use of thin-layer chromatography techniques with the response of the microorganisms tested according to biological activity of an analyte that can be antibacterial, antikapang, and antiprotozoal. (Choma, I., 2005).

Based on the description above, the isolation of the active compounds kecombrang leaf extract and test the antibacterial activity against *Escherichia coli* and *Candida albicans.*

2. Experimental

2.1 Materials

Tools ; The autoclave, incubator, LAF (Laminar Air Flow), Oven, Lamp UV 254 nm, Rotavapor, water bath, cup Porcelain, Petri dish, Erlenmeyer flask, glass cup, measuring cup, capillary tube, Ose, filter paper, Chamber 20 x 20 cm , Scales electrically.

Materials; Aluminum foil, Ethanol 96% Ethyl acetate pa, hexane pa, Chloroform pa, Methanol pa, Media NA (Nutrient Agar), Mueller Hinton Agar, Sabaraud Dextrose Agar, Plate TLC, Swab sterile, *Escherichia coli, Candida albicans*, Leaf kecombrang (*Etlingeraelatior*).

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2.2 Methods

1) Extraction with ethanol

Samples in the form of dried leaves cut into small pieces and powdered, weighed 500 g, is inserted into a vessel maceration 96% ethanol was added to the submerged perfect. Then closed vessel, allowed to stand in the dark for 5 days while stirring, stirring frequently. After 5 days, strain the pulp macerated filtrate is collected and returned. Repeated up to 3 times or until simplisia perfectly filtered. The ethanol extract obtained is collected is then evaporated with a rotary evaporator and dried over a water bath, to obtain the extract 4kering. Furthermore, in the dried extract separated using a solvent ether and N-Butanol thus obtained ether extract and extract of n-Butanol.

2) Separation and Purification of Chemical Components in Thin Layer Chromatography (TLC)

The ethanol extract, ether extract and extract n-Butanol later identified as thin layer using a UV lamp 254 nm.

3) Test Bioautografi Active Compounds

15 mL of MHA liquid media that are sterilized put in a petri dish and allowed to solidify. Furthermore, on the surface of solid media reviews MHA bacterial suspension was then left for 15 minutes. Paper discs soaked into pure fractions for 5 minutes, removed and dried-aired. Subsequently placed on the media and incubated at 37o C for 24 hours. Observed inhibition zone is formed.

3. Results and Discussion

1) Results

The results of Isolationby TLC and antibacterial activity test at kecombrang leaf extract (*Etlingera elatior*) on the growth of *Escherichia coli* and *Candida albicans* can be seen in the table below:

Table 1.The results of Isolation by TLC method and Test Activities kecombrang With Leaf Ethanol Extract Liquid elution Hexane: Ethyl Acetate (8: 2)

No	Color of Spot	Rf	Inhibition of Zone Diameter (mm)							
			Escherichia coli				*Candida Albicans*			
			1	2	3	Average	1	2	3	Average
1	Yellow	0,91	-	-	-	-	-	-	-	-
2	Purple	0,63	-	-	-	-	-	-	-	-
3	Dark Green	0,58	-	-	-	-	-	-	-	-
4	Dark Green	0,41	7	6	5	6	7	7	7	7
5	Light Green	0,35	6	5	5	5,33	8	8	7	7,67
6	Yellow	0,25	6	6	6	6	-	-	-	-
7	Light green	0,18	7	7	6	6,67	5	6	5	5,33

Table 2.The Results OfIsolation by TLC method and Test Activities Diethyl Ether Leaf Extract Liquid elution kecombrang With Hexane: Ethyl Acetate (8: 2)

No	Color of Spot	Rf	Inhibition of Zone Diameter (mm)							
			Escherichia coli				*Candida Albicans*			
			1	2	3	Average	1	2	3	Average
1	Yellow	0,88	-	-	-	-	11	11	11	11
2	Purple	0,52	-	-	-	-	-	-	-	-
3	Green	0,38	10	10	10	10	7	7	7	7
4	Brown	0,25	-	-	-	-	-	-	-	-
5	Brown	0,13	8	8	8	8	-	-	-	-

Table 3.The Results of Isolation by TLC method and Activity Test Leaf Extract n-Butanol kecombrang The elution liquid Chloroform: Methanol: Water (15: 5: 1)

No	Color of Spot	Rf	Inhibition of Zone Diameter (mm)							
			Escherichia coli				*Candida Albicans*			
			1	2	3	Average	1	2	3	Average
1	Green	0,88	9	8	9	8,67	6	6	6	6
2	Purple	0,61	-	-	-	-	-	-	-	-
3	Brown	0,25	-	-	-	-	-	-	-	-

2) Discussion

In this research used the kecombrang leaves (*Etlingera elatior*) obtained from Masamba, washed, cut into small pieces and then dried with aerated to obtained simplisia. Dried Simplicia was extracted by maceration method using ethanol 96%. Liquid extracts were then evaporated using a rotary evaporator and water bath to obtain a stiff extract. Stiff extract obtained is extracted again using diethyl ether and n-Butanol thus obtained ether extract and extract of n-butanol. Furthermore, the separation of chemical compounds in extracts of ethanol, diethyl ether extract, and n-butanol extract obtained using the method of thin layer chromatography (TLC).

Separation of chemical compounds by TLC method performed using several compositions elution liquid (eluent). Determination of the elution liquid carried by the orientation using some liquid elution with different compositions thus obtained elution fluid can separate fine chemical compounds contained in each extract. Based on the results orientation, to extract the ethanol and extract diethyl ether used liquid elution Hexane - Ethyl Acetate (8: 2), while the extract of n-butanol is used fluid elution of chloroform - methanol - water (15: 5: 1) with using a UV lamp 254 nm.

Chemical compounds contained in extracts of ethanol, diethyl ether extract, and n-butanol extract after being

separated by TLC methods appear as colored spots on the surface of the TLC plate with a value Rf (rate of flow) are different. Based on the results obtained KLT known that Extract ethanol of kecombrang Leaf 7 showed 7 spot with Rf value: 0.91; 0.63; 0.58; 0.41; 0.35; 0.25; and 0.18 with UV lamp 254 nm (Table 1). In Diethyl ether extract of kecombrang Leaf showed 5 spot with Rf value: 0.88; 0.52; 0.38; 0.25; and 0.13 in UV lamp 254 nm (Table 2). In the n-Butanol Extract of kecombrang leaf showed 3 spot with Rf value: 0.88; 0.61; and 0.25 in UV lamp 254 nm (Table 3). This shows that the extract Ethanol Leaves kecombrang there are seven component compounds, extracts Diethyl ether Leaf kecombrang there are five components of the compound and the extract n-butaol Leaf kecombrang there are three components of the compound.

Results obtained from the separation of compounds by TLC followed by testing the antibacterial activity by using methods Bioautografi to see the smudges that can inhibit the growth of *Escherichia coli* and *Candida albicans*. Chemical compounds that can inhibit the growth of *Escherichia coli* and *Candida albicans* showed clear zone around the stain. Formed clear zone diameter measured its resistance. Clear zone on testing Bioautografi compared with the results of thin layer chromatography separation to see and determine how many spots with Rf values which can inhibit the growth of *Escherichia coli* and *Candida albicans*. Based on the value Rf, it can be known components in the ethanol extract, diethyl etherextract, and n-butanolextract from kecombrang leaf whose activity has antibacterials in inhibiting the growth of *Ecsherichia coli* and *Candida albicans.*

Bioautografi antibacterial activity test results are as follows, there are four chemicals compounds in the ethanol extract of leaf kecombrang which can inhibit the growth of *Ecsherichia coli*which is dark green stain (Rf 0.41) with an average diameter barrier 6 mm; light green stain (Rf 0.35) with an average diameter of obstacles 5,33 mm; yellow stain (Rf 0.25) with an average diameter barrier 6 mm; and light green stain (Rf 0.18) with an average diameter of obstacles 6,67 mm. And there are three chemical compounds can inhibit the growth of *Candida albicans*which is dark green stain (Rf 0.41) with an average diameter barrier 7 mm; light green stain (Rf 0.35) with an average diameter barrier 7.67 mm; ; and light green stain (Rf 0.18) with an average diameter barrier 5,33 mm (table 1).

In diethyl ether extract of kecombrang leaves, there are two chemical compounds can inhibit the growth of *Escherichia coli* (stain) which isgreen stain (Rf 0.38) with an average diameter barrier 10 mm; and brown stain (Rf 0.13) with an average diameter of barriers 8 mm. And there are two chemical compounds can inhibit the growth of *Candida albicans*, which is yellow stain (Rf 0.88) with an average diameter barrier 11 mm; and green

stain(Rf 0.38) with an average diameter barrier 7 mm (Table 2).

In n-ButanolExtract ofkecombrangleaf, there is one chemichal compound can inhibit the growth of *Escherichia coli*ie a stain green (Rf 0.88) with an average diameter barrier 8.67 mm. And there is one chemichal compound can inhibit the growth of *Candida albicans*ie green stain (Rf 0.88) with an average diameter barrier 6 mm (Table 3).

From the research results obtained, kecombrang leaf (*Etlingera elatior*) potential as an alternative to traditional medicine.

4. Conclusions

Based on the results, we can conclude that:

1. The result of the isolation of the active compound of kecombrang leaf showed ethanol extract obtained 7 (seven) chemical compounds (stains), diethyl ether extract obtained 5 (five) chemical compounds, and n-butanol extract obtained 3 (three) chemical compounds.
2. The ethanol extract, diethyl ether extract, and n-butanol extract of kecombrang leaf can inhibit the growth of *Escherichia coli* and *Candida albicans*

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Wound Healing Activity of *Persea Americana Mill.* Leaves Extract in Mice

Eka Siswanto Syamsul, Rizki Permatasari, Triswanto Sentat, Supomo

Pharmacy Academy of Samarinda

Jl. A.Wahab Sjahranie No.226 Samarinda, East Kalimantan

ABSTRACT

Wound healing is a complex and dynamic process of replacing devitalized and missing cellular structures and tissue layers. Persea americana Mill (Avocado) has active compounds such as persin, peptone, b-galactoside, glycosylated abscisic acid, alkaloids, cellulose, polygalacto urease, polyuronoids. The plant is used in traditional medicine for the treatment of various ailments, such as monorrhagia, hypertension, stomach ache, bronchitis, diarrhea, healing, and diabetes.The aim of present work was to evaluate the wound healing property in topical administration of ethanolic extract of leavesin mice. Avocado leaves extracts obtained using maceration method by ethanol 70%. Burns made with solder that ends are stainless plate measuring 1 cm^2 and placed on the backs of mice whose hair has shaved over 2 seconds until it forms a skin redness. The results showed that all extract concentration of 20%, 35% and 50% had good activity in the treatment of burns from the observation day 1 until 14 shows the percentage of healing of burns, respectively for 86%, 88 % and 90%. The present study demonstrates that **Avocado** leaves extract applied topically promotes healing of wounds more significantly as compared negative control.

Keywords: Persea americana leaves, wound healing, mice

ABSTRAK

Penyembuhan luka adalah proses yang kompleks dan dinamis mengganti devitalized dan hilang struktur selular dan lapisan jaringan. Persea americana Mill (Avocado) memiliki senyawa aktif seperti Persin, pepton, b-galaktosida, asam absisik glikosilasi, alkaloid, selulosa, polygalacto urease, polyuronoids. Tanaman ini digunakan dalam pengobatan tradisional untuk pengobatan berbagai penyakit, seperti monorrhagia, hipertensi, sakit perut, bronkitis, diare, penyembuhan, dan diabetes.The tujuan penelitian ini adalah untuk mengevaluasi penyembuhan luka properti dalam administrasi topikal ekstrak etanol tikus leavesin. Daun alpukat ekstrak yang diperoleh dengan menggunakan metode maserasi dengan etanol 70%. Luka bakar yang dibuat dengan solder yang ujungnya plat stainless berukuran 1 cm2 dan ditempatkan pada punggung tikus yang rambutnya telah dicukur lebih dari 2 detik sampai membentuk kulit kemerahan. Hasil penelitian menunjukkan bahwa semua konsentrasi ekstrak 20%, 35% dan 50% memiliki aktivitas yang baik dalam pengobatan luka bakar dari hari pengamatan 1 sampai 14 menunjukkan persentase penyembuhan luka bakar, masing-masing untuk 86%, 88% dan 90%. Penelitian ini menunjukkan bahwa alpukat ekstrak daun dioleskan mempromosikan penyembuhan luka lebih signifikan dibandingkan kontrol negatif.

Kata kunci: Persea americana daun, penyembuhan luka, tikus

*Corresponding author, Eka Siswanto Syamsul, email: eka8382@gmail.com

1. Introduction

The speed of wound healing can be influenced from the substances contained in drugs given, if they have the ability to promote healing by stimulating faster growth of new cells in the skin, the healing process of the wound will quickly (Adeyemi et All, 2002) , Some studies show that the potential of traditional crops as wound healing agents in addition to medical treatment for mild to moderate burns. Most people preferred traditional medicine because of the availability of a broad and there are no side effects. One of the plants that allegedly efficacious in the treatment of burns of leaves of avocado (Persea Americana Mill).

Phytochemical screening results from previous studies stated that the avocado leaves contain chemical compounds such as saponins, tannins, and flavonoids such as quercetin glycosides which can be used as a natural source of antioxidants activity (Edewor and Ibibia, 2013). Avocado leaf extract also has anti-ulcer activity is to neutralize or bind to gastric acid or reduce the production of stomach acid that can cause stomach ulcers that can be caused by severe illness or injury (Owoyele et al, 2010).

Such information encourages researchers to conduct research by using avocado leaves to determine the activity in accelerating the healing of skin burns backs of mice induced metal. The results of the study expected to provide scientific information to make the avocado leaves as one of the alternative treatment of burns.

2. Experimental

2.1 Materials and Methods

Materials used in the research are avocado leaves, 70% ethanol, amyl alcohol, Mg powder, concentrated HCl, 2N HCl, FeCl3 1%, aluminum foil, filter paper, and petroleum jelly.

he tools used are glass bottles, glass beaker, erlenmeyer, mice cages, porcelain bowls, measuring cups, stirring rod, test tubes, test tube rack, stainless plate soldering with tip diameter of 1 x 1 cm2, calipers, an analytical balance.

2.2 Crude extraction of avocado leaves

Simplicia extraction of avocado leaves done by maceration method

a. Weighed simplisia dried avocado leaves that have been through a 40 mesh sieve, 400 g simplisia powder with ethanol 70% 2 L were put into a glass container and soaked.

b. Crude soaked for three days and stirring as often as possible and extract the liquid is collected in a glass container. Then the rest of the waste is carried remaseration times.

c. After all the liquid extract obtained is then evaporated on a water bath and viscous extract obtained.

2.3 Phytochemical screening

a. Alkaloid

Simplicia powder weighed 0.5 grams was then added 1 ml of 2N hydrochloric acid and 9 ml of distilled water, heated to above tangas water for 2 minutes, cooled and filtered. Use Reagent Mayer, Bouchardat, and Dragendrof.

b. Flavonoid

The ethanol extract of avocado leaves inserted into a test tube and added 100 mL of hot water. Bring to the boil and filtered hot. Taken 5 mL filtrate and supplemented with 0.1 g of magnesium powder, 1 ml of HCl and 2 mL amyl alcohol, shaken and let it separate. 10 drops of ethanol extract of avocado leaves put in a test tube add 2 drops of concentrated HCl, Mg powder, and amyl alcohol. When formed in yellow, orange, or red on a coating amyl alcohol gave an indication of flavonoids.

c. Saponins

The ethanol extract of avocado leaves inserted into a test tube. Added enough hot water, shaken for 15 minute. If after ditetes 2N HCl permanent froth formed for approximately 10 minutes then gave an indication of saponin.

d. Tannins

The ethanol extract of avocado leaves supplemented with 10 ml of distilled water, filtered. The filtrate was diluted with distilled water until colorless. Taken 2 mL of the filtrate and add 1 to 2 drops of reagent FeCl3. When formed dark blue or dark green gives an indication of the presence of tannins.

2.4 Animal care and handling

Swiss male albino mice weighing 25–30 g of either sex were used in the study. Animals were procured from Laboratory Pharmacology Pharmacy Academy of Samarinda. The animals were kept in polyacrylic cages and maintained under standard housing conditions of temperature (24–27°C) and humidity (60–65%) with 12:12 light: Dark cycles. They were acclimatized for 7 days. The food was provided in the form of dry pellets and water ad libitum.

2.5 Study design for wound healing activity

15 test animals into 5 groups, each group consisting of three mice.

P1 = negative control (yellow vaselin)

P2 = positive control (Sibro® cream)

P3 = concentration 20% (ethanol extract of avocado leaves 20% + yellow vaseline)

P4 = Concentration 35%(ethanol extract of avocado leaves 35% + yellow vaseline)

P5 = concentration 50% (ethanol extract of avocado leaves 50% + yellow vaseline)

In this study in mice burns made by placing solder heat ends are stainless plate diameter of 1 x 1 cm2 which has been heated. On the backs of mice whose fur had been shaved affixed with solder for 2 seconds to form blisters or burns, then as a negative control smeared vaseline, ointments branded X as a positive control and three variations of the concentration of the ethanol extract of avocado leaves, written vaseline in order to extract easily applied to a burn. Basting all treatment groups performed equally 1 time every morning as much as 0.1 g for all topical.

2.6 Evaluation of wound healing activity

Wound healing activity was assessed by incision wound healing models. All woundings were carried under ether anesthesia. Wounds were treated immediately after wound creation.

$$\%WoundHealing = \frac{L1 - Ln}{L1} x100\%$$

L1 = The first day of the wound area

Ln = The day-n of the wound area

2.7. Statistical analysis

The data were analyzed using one-way analysis of variance followed by Tukey's post hoc test using SPSS-21. The data were expressed as a mean ± standard error of mean. P< 0.05 was considered statistically significant.

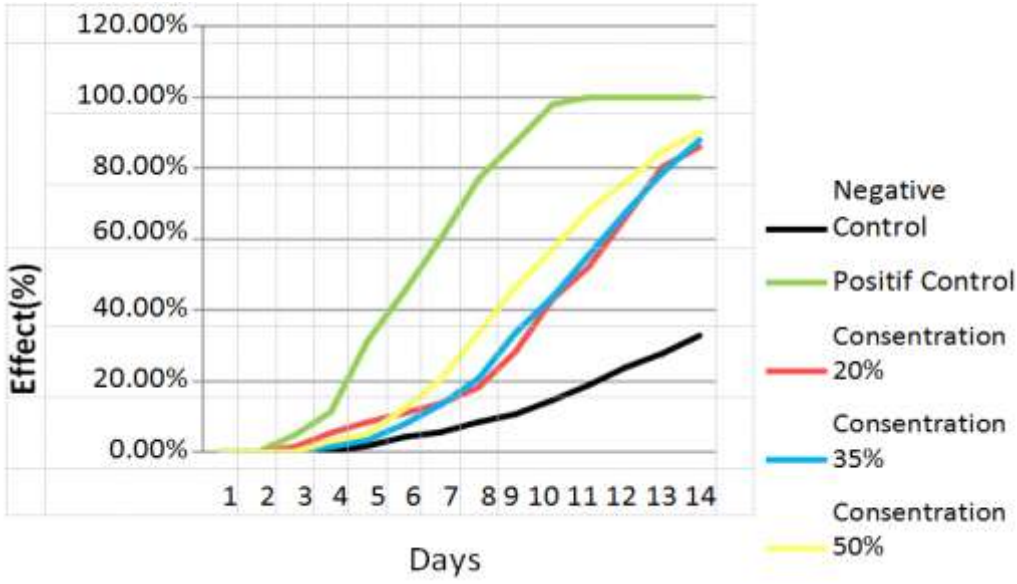
3. Results and Discussion

Maserat obtained in the form of liquid extract was filtered to separate from the pulp. Maserat have been obtained and then evaporated on a water bath to obtain a crude extract. Viscous extract obtained from 400 g simplisia with 2 L of fluid is 93.27 g so that the yield obtained 24.58%. Condensed extract is then stored in a container in which by silica gel to prevent the growth of mold or mildew on the condensed extract.

Identification was conducted to determine the active compound in the form of secondary metabolites contained in the ethanol extract of avocado leaves. Compounds identified secondary metabolites include alkaloids, flavonoids, saponins and tannins because the metabolites are suspected of a healing effect on burns. Identifying secondary metabolites in this research method is to use reagent drops. The results of the identification of metabolites can be seen in table 1.

Table 1. Phytochemical Screening

No	Compound	Result
1	Alkaloid	+
2	Flavonoid	+
3	Tannin	+
4	Saponins	+

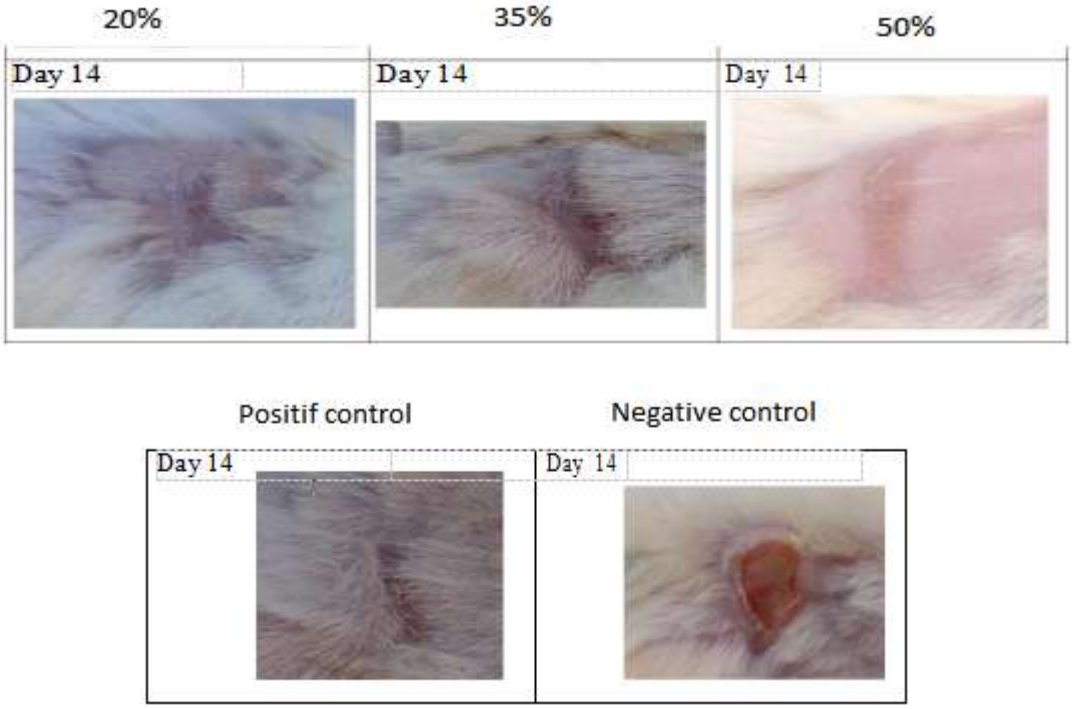


Pic 1. Wound Healing Effect (%)

The graph shows that the negative control which simply smeared with vaseline yellow depicts slow wound healing, on the 5th day only seen their healing process and on day 14 only have a percentage of 32.67% cure for yellow vaselin as a base for preparations ointment acts as a wound dressing which inhibits evaporation of water in the skin layer. Positive controls were smeared with Sibro® cream experiencing rapid wound healing where on the 3rd day have seen the healing process and on the 11th day burns healing have had a percentage of 100%. This is because the composition of the positive control in the form of an Sibro® cream not only has one active substance in the preparation salepnya that can help the healing process of burns quickly. Active ingredient Sibro® cream is radix scutellariae, Phellodendri cortex and rhizomes coptidis that have active compounds such as alkaloids are berberine (Uchiyama, 1989) which is useful as

an agent anti-inflammatory as well as having antibacterial activity which does not cause irritation to the skin (Widagdo, 2004). This ointment also has gone through many trials like preclinical trials and clinical tests before they can be marketed.

The data for the extract concentration of 20% indicates that on the 3rd day there is a change in the wound but was small and on day 14 had a recovery percentage of 86.00%. The extract 35% begin to see the changes on the 4th day and the recovery percentage of 88.00% on the day 13th. The extract 50% of visible changes in the 4th day with a recovery percentage of 90.00% on the 14th day. This shows that the ethanol extract of avocado leaves have activity in the wound healing.



Pic 2. Observation of wound healing in male mice at days 0-14

LSD test results showed each group has significant difference except for the concentration of 20% and 35% no significant difference, which means the healing effect of the same concentration. The test results also show that the concentration of 50% has a significant difference from positive control which means the ability of a concentration of 50% the same as the positive control in the activities of the healing of burns on the backs of white mice.

The initial stage of the proliferative phase is assisted by fibroblasts are cells that produce collagen. In this phase, the collagen will work connecting tissues in burns to help restore skin tissue strength and speed healing of burns. On the 7th day scab begins to be apart except for the negative control group. This scab release process together with the

dryness of the wound. This marks has been the growth of new cells in the skin that helps speed up the release of scab and merapatnya wound edges (Aponno et al, 2014).

The last stage in the healing process of burns is the maturation phase (remodeling), occurs at the time of the release of visible scab and new skin tissue. In this phase, the cells are still active role of fibroblasts and collagen that will help provide elasticity, suppleness and moisture. Long maturation phase depends on the damage caused to the skin for a period of 1 month to 2 years.

4. Conclusion

Ethanolic Extract of avocado leaves concentration 20%, 35% and 50% have activity against burn healing in male mice, the views from the observation day 1 until day 14 shows the percentage of healing of burns, respectively for 86%, 88 % and 90%.

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Alcohol on Adolescent and Health Impacts

Rosmala Nur, Rasyka Nurul, I Putu Dedy Budiastra

Public Health Study Program, Faculty of Medicine and Health Sciences, University of Tadulako

ABSTRACT

Alcohol consumption is currently one of the adolescents problems whose numbers tend to increase from year to year. The result is that in addition can compromise the security of the environment such as the rise of juvenile gangs, sexual misconduct, rampant of thuggish could also impact on the health of adolescents. The purpose of this study was to determine the factors associated with alcohol consumption and its impact on the health of adolescents in Palu City, Central Sulawesi, Indonesia. This study used mixed research method were quantitative and qualitative research. Samples for this study were 65 teens, domiciled in the 8th Neighbourhood, 8th Hamlet, BTN Citra Pesona Indah, Talise Urban Village, SubdistrictMantikulore, Central Sulawesi Province, Indonesia, whereas qualitative sample amounted to 5 informants that teens who still consumedalcohol. The results showed a significant relationship between motive curious with alcohol consumption (P = 0.001), the opportunity with alcohol consumption (P = 0.001), inferiority with the alcohol consumption (P = 0.001), and emotional with alcohol consumption (P = 0.001). All of 5 informants said that they felt the effects for consumed alcohol such as decreased body resistance, easily hurted, lazy woke up, often felt asleep in class, vomited and coughed up blood. The conclusion was that there was influence between the motives of curiosity, inferiority, and emotional occasion for alcohol consumption and its impact on the health of adolescents in Palu.

Keywords: Adolescent, Alcohol, Health

ABSTRAK

Konsumsi alkohol saat salah satu masalah remaja yang jumlahnya cenderung meningkat dari tahun ke tahun. Hasilnya adalah bahwa selain dapat mengganggu keamanan lingkungan seperti munculnya geng remaja, pelecehan seksual, maraknya premanisme juga bisa berdampak pada kesehatan remaja. Tujuan dari penelitian ini adalah untuk mengetahui faktor-faktor yang terkait dengan konsumsi alkohol dan dampaknya pada kesehatan remaja di Kota Palu, Sulawesi Tengah, Indonesia. Metode penelitian campuran Penelitian ini menggunakan yang kuantitatif dan penelitian kualitatif. Sampel untuk penelitian ini adalah 65 remaja, yang berdomisili di 8 Sekitar, 8 Hamlet, BTN Citra Pesona Indah, Talise Kelurahan, SubdistrictMantikulore, Provinsi Sulawesi Tengah, Indonesia, sedangkan sampel kualitatif sebesar 5 informan bahwa remaja yang masih consumedalcohol. Hasil penelitian menunjukkan hubungan yang signifikan antara motif penasaran dengan konsumsi alkohol (P = 0,001), kesempatan dengan konsumsi alkohol (P = 0,001), rendah diri dengan konsumsi alkohol (P = 0,001), dan emosional dengan konsumsi alkohol (P = 0,001) . Semua dari 5 informan mengatakan bahwa mereka merasakan efek untuk consumedalcohol seperti daya tahan tubuh menurun, mudah hurted, malas bangun, sering merasa tertidur di kelas, muntah dan batuk darah. Kesimpulannya adalah bahwa ada pengaruh antara motif rasa ingin tahu, rendah diri, dan kesempatan emosional untuk konsumsi alkohol dan dampaknya pada kesehatan remaja di Palu.

Kata kunci : Anak Remaja, Alkohol, Kesehatan

*Corresponding author : Rosmala Nur, Email : malanur@yahoo.com

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1. INTRODUCTION

Alcohol was the substance most frequently abused human, alcohol obtained from the fermentation of honey, sugar, juice or tubers. From the fermentation, could be obtain alcohol to 15% but with the distillation process could be produce alcohol levels higher even reached 100%. The maximum blood alcohol level reached 30-90 minutes. The maximum blood alcohol level reached 30-90 minutes. Once absorbed, the alcohol/ethanol distributed to all of tissues and body fluids. With increased levels of alcohol in the blood of people will be euphoria, but with the decline of people can become depressed (Centre For Disease Control and Prevention 2014). Alcohol is a drink that can cause drinkers get drunk and lost consciousness. Alcohol can damage the mind, so that people become abnormal (Clark 2005). The effects after consuming alcohol can be felt immediately within a few minutes only, but the effect varies depending on the amount/level of alcohol consumed. In small amounts, alcohol produces a feeling relaxed, and the user will be easier to express emotions, such as joy, sadness and anger.

The alcohol content above 40 grams per day for men or for women above 30 grams per day can cause damage to the organ/body part of the drinker. For example, damage of soft tissues in the oral cavity, around the throat, and in the digestive system (in the stomach). Human organs most vulnerable due to alcohol is the liver (Donovan 2004) and (Nur 2015).

Report of the World Health Organization (WHO) on alcohol and health in 2013 said as many as 320,000 people aged 15-29 died worldwide each year caused from alcohol-related. This number reached 9% of all deaths in that age group. Alcohol in the western world had become common and socially acceptable and almost consumed every day ((Fahmi 2013).

Data collected by BNN (National Narcotics Agency) Indonesia until 2013 illustrated the significant increase in the pattern of substance abuse including alcohol over the last five years. In 2013 occurred 42.213 cases of drug abuse, 31.708 cases of abuse of psychotropic and 9.346 cases of abuse of addictive substances, from previous data in 2008 occurred 28.118 cases of drug abuse, 21.318 cases of abuse of psychotropic and 4.639 cases of abuse of addictive substances. Abuse of drugs grouped by formal education in 2013 where junior high school and senior high school ranks first with 72.934 cases, elementary school with 6.346 cases, and colleges with 3.987 cases,(Kusmaryadi 2013).

Data obtained from the official Neighbourhood 08 RW 08 BTN Citra Pesona Indah village TalisesubdistrictMantikulore are

adolescents aged 14-25 years amounted to 178 people. Of these, there are some teenagers as the alcohol collected from government RT 08 RW 08, 2013. With the above background, researchers interested in conducting research on "Relations Alcohol Consumption and Effects on Adolescent Health BTN Citra Pesona Indah RT 08 RW 08 Sub Talise subdistrict Mantikulore Palu ".

A. Factors Influenced the Consumption of Alcohol and Its Impact for Adolescent Health

Consumed alcohol is one form of social deviation. Social distortion that occurs in adolescents will not just appear when there is no pull factor or a motivating factor. Pull factors are outside oneself, while the driving factor comes from the self or family that allows a person to perform such deviations (Marshall 2009).

Adolescent can fall into an alcohol problem since it is influenced by the neighborhood association as follows (Joseph, 2009).

1. Adolescent who are drinking alcohol always has a "user group". Initially adolescent just try for family or friends who use it, but no later becomes a habit.
2. In adolescents who re "disappointed" with their condition and families. Often be preferred to sacrifice anything for the sake of good relations with their peers.
3. The existence of "call" or "bid" of friends and the many movies and entertainment facilities that give examples of "modern social models" usually encourage adolescent to drink alcohol as a group.

4. If adolescent have become accustomed to drinking alcohol and being easy to get it, then they will wear themselves so that they will be hooked. Use of alcohol among adolescent in general because the alcohol is promising something that is a sense of enjoyment, comfort and pleasure as well as serenity.although it is perceived as false. Deviations are caused by socialization imperfect good relationships in the community and family life in which they considered unsatisfactory so that they seeking escape outside the house to find a friend who can provide protection and recognition of the existence of themselves. Irregularities committed through abuse of drugs and alcohol, usually a person will not do this directly, but invited by a group of their friends to try first to prove that they have become adults. Over time the person will get recognition from their peers and become part of the group (Marshall 2009).

According of (Hutagalung 2008), factors that influence alcohol consumption among adolescemt, among others:

1. The social Environment

a. Curious Motives

That adolescent always have a nature always want to know everything that is not known

negative impacts or less. For example, want to know what it's like alcohol.

b. Opportunity

Because of busy parents and families with their respective activities or as a result of a broken home familiy, lack of affection and so on, then in the event they are trying to find an escape by drinking alcohol.

2. Personality

a. Inferiority

Because they can not cope with feelings of inferiority in the community, they demonstrate the existence themselves, then use alcohol so get what conceivable, among others, more active, more courageous and so forth.

b. Emotional

Emotional ofadolescent in general are still unstable if at the time of puberty. At that time they usually want to loose the bonds of rules imposed by parents for their personal life, so that it causes a personal conflict. In an attempt to escape from the personal conflicts, they seek refuge in drink alcohol in order to reduce the saturation of the rules given by the parents.

2.3 Impact of Consuming Alcohol for Health

Now, consuming alcohol is like being a part of the lifestyle of some communities in Indonesia. Starting from a mere trial and error, many of which later end up addicted to this one type of drinks. Alcoholhas different levels. For example, beer and soda alcohol (1-7% alcohol), wine (10-15% alcohol), and alcohol or commonly called the spirit (35-55% alcohol). The concentration of alcohol in the blood is achieved within 30-90 minutes after drinking. During this time, the negative effects of excessive alcohol consumption the most widely known is drunk, and that too may disappear by itself. But it turned out negative effects do not stop there. Not just cause drunk, but alcohol also has other negative effects such as damage to the body's metabolic system of the human body which then cause addiction and damage to some elements of the brain.

Alcohol is one of the drinks containing addictive substances (alcohol). Alcohol abuse will have an impact that is not good for a person's physical and psychological health. According to the result of the impact of substance abuse or addictive to the user are (White et al. 2008) dan (Mercken et al. 2010)

a. Personality broken

b. Behavior (lying, manipulation)

c. The mindset of the typical (in a hurry)

d. Violation of norms

e. Physical (shivering, sleepless nights sleep in the daytime).

For those who are pregnant and if you consume alcohol the result is fatal, because the nutrients to the fetus will be disrupted, so that later the baby was born in a state of less than perfect, however, because the health of the fetus is diet and behavior of mother (Hutagalung 2008) and (Martino & Kovalchik 2015).

Signs are caused by the consumption of alcohol and similar drugs, normally would cause the courage leads to rude behavior, grumpy, irritable and brutal acts. Another impact of the consumption of addictive substances is on one's social life such as: inability to socialize with non-drinkers, often in conflict with others, the inability of the social functions such as work or school a mess, drop out of school and the low scores of report cards.

When viewed in terms of health, alcohol is also greatly impact the health of a person. Alcohol into the body can cause irritation of the digestive tract such as the stomach and intestines that can cause bleeding. Injured gastric ulcer disease can cause bowel perforated while will cause disruption of the absorption of food so that the body becomes thin ((Jackson 2002) .

Those affected by GMO usually experience changes in behavior, such as want to fight or commit other acts of violence, are not capable of judging reality, impaired social function, and interrupted his work. Physiological changes also occur, such as the walk way that is not upright, flushing, or crossed eyes. Psychological changes experienced by drinkers for example irritable, talk rubbish, or loss of concentration ((Krosnick et al. 2006). Those who are already addicted usually experienced a phenomenon called alcohol withdrawal syndrome, that fear stop drinking alcohol. They will often trembling and heart palpitations, anxiety, restlessness, depressed, and many hallucinations (Krosnick et al. 2006).

2. METHODS

2.1 Types of Research

This research used mixed methods research is quantitative research with survey method where researchers conducted a direct approach to the adolescents to determined the factors that influenced adolescents in consuming alcohol. While examined the impact of consuming alcohol on adolescents health, researchers used a qualitative research (independent and dependent variables) were observed at the same time by using research instruments were questionnaires and in-depth interviews (Machfoedz 2013)

The research design used a cross sectional where researchers conducted measurements or observations at the same time or at a time (Machfoedz 2013) .

2.2 Location and Time Research

This research was conducted in the 8th Neighbourhood, 8th Hamlet, BTN Citra Pesona Indah, Talise Urban Village, Subdistrict Mantikulore, Central Sulawesi Province, Indonesia in January 2015.

2.3 Population and Samples

a. Quantitative Research

The population in this study were all teenagers in 8th Neighbourhood, 8th Hamlet, BTN Citra Pesona Indah, Talise Urban Village, Subdistrict Mantikulore totaling 178 people. For quantitative methods, sample size was calculated using the Slovin's formula (Notoatmodjo 2003), as follows:

$$n = \frac{N}{1 + N(d)^2}$$

Description :

n = Amount of samples

N = Large populations

d2 = The error rate (10%)

From this formula, the number of samples obtained by 65 people.

The sampling technique in this study used simple random sampling that all populations had an equal opportunity to be sampled by means of raffle samples (Suyanto and Salama, 2011). In this study, the authors took a sample by writing the names of the teenagers in the paper and then rolled up and inserted into the container and then carried out the draw. If already obtained samples, the researchers seek addresses of respondents to filled the questionnaires.

b. Qualitative research

The number of informants who were interviewed in depth was determine using snowball sampling technique was a sampling technique that was originally small in number, then the sample was tell to choose their friends to serve as informants. Making temporary initial informants where the number of samples can be grown in research, tailored to the needs of research in line with the clear focus of research and had reached the saturation level (redundancy), which at the time with the addition of the informants will no longer provided significant new information. The number of initial informants were 5 teens who consumed alcohol were each taken from one sample in junior high school, one sample senior high school, one sample in college, 1 sample in work, and one sample that did not work. Thus variation so that the information extracted informant will get varied answers anyway. Determination of the initial informants had the following inclusion criteris (Sugiyono 2010): teenagers who still consumed alcohol, teenagers who wanted to be informants, a teenagers who had the time for questioning and teenagers who were not known by researchers.

2.4 Data Collection

2.4.1 Primary Data

Data obtained directly from the informants through interviews and questionnaires.

2.4.2 Secondary Data

Data obtained in the 8th Neighbourhood, 8th Hamlet, BTN Citra Pesona Indah, Talise Urban Village, Subdistrict Mantikulore, Central Sulawesi Province, Indonesia from the form of data on the number of teenagers.

2.5 Data analysis

Analysis of the data used are:

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2.5.1Univariate Analysis

Univariate analysiswas conducted to determinethe frequencydistributionof eachvariable studiedbothindependent variablesandthe dependent variable using a computer.

2.5.2AnalysisBivariate

This analysis was conducted to determine the effect of independent variables and the dependent variable through cross-tabulation with statistical test Chi-square (X^2), with a confidence level of 95 % and asignificance level of 0.05.

For qualitative research, data analysis using

Opportunities	Amount	Percentage (%)
Low	31	47.7
High	34	52.3
Total	65	100.0

methods interactive model developed by Miles and Huberman. Component analysisi ncluding data collection, data reduction, data presentation, and conclusion/verification. The stages of data analysis interactive model (Sugiyono 2010) .

3. RESULTS AND DISCUSSION

3.1 Results of Quantitative Research

3.1.1 Univariate Analysis

a. Curious Motives

Curious Motives	Amounts	Percentage (%)
Low	25	38.5
High	40	61.5
Total	65	100.0

Inferiority	Amount	Percentage (%)
Low	21	32.3
High	44	67.7
Total	65	100.0

The results of interviews with informants to obtained data about the motives of the informants would like to know can be seen in Table 5.1.

Table 3.1: Distribution of Informants According Curious Motives of Adolescents to Alcohol Consumption

Based on Table 3.1, as many as 65 informants had high curious motive number as many as 40 people (61.5 %).

b. Opportunity

Results of interviews about the opportunity can be seen in Table 3.2.

Table 3.2: Distribution of Informants According Adolescents's Opportunities to Alcohol Consumption

According to the Table 3.2, from 65 informants who had high opportunity many as 34 people (52.3 %).

c. Inferiority

Results of interviews about feelings of inferiority can be seen in Table 3.3.

Table 3.3: Distribution of Informants According Adolescents's Feelings of Inferiority to Consumption of Alcohol

According to the Table 3.3, from 65 informants who had high sense of inferiority as many as 44 people (67.7%).

d. Emotional

Results of interviews about the emotional can be seen in Table 5.4.

Table 3.4: Distribution of Informnts According to Adolescents's Emotional to Consumption of Alcohol

Emotional	Amount	Percentage (%)
Low	30	46.2
High	35	53.8
Total	65	100.0

According to the Table 3.4, from 65 informants who had high emotional as many as 35 people (53.8%).

e. Consumption of Alcohol

Results of interviews about the consumption can be seen in Table 3.5.

Table 3.5: Distribution of Informants According Alcohol Consumption in Adolescents

Alcohol Consumption	Amount	Percentage (%)
Not consumed	24	36.9
Consumed	41	63.1
Total	65	100.0

According to the Table 3.5, from 65 informants who consumed alcohol as many as 41 people (63.1%).

3.1.2 Bivariate Analysis

a. Effects of Curious Motives Adolescents to the Alcohol Consumption

To determined the efffects of curious motives about the alcohol consumption in adolescents can be seen in Table 3.6.

Table 3.6: Distribution Effect on Curious Motives to Alcohol Consumption in Adolescents

Curious Motives	Alcohol Consumption				Total		P Value	OR 95%
	Not consumed		Consumed					
	F	%	F	%	F	%		
Rendah	16	64.0	9	36.0	25	100.0	0.001	7.111 (2.307-21.919)
Tinggi	8	20.0	32	80.0	40	100.0		
Jumlah	24	36.9	41	63.1	65	100.0		

In Table 3.6 showed that informants who had the high curious motives were more likely to consumed alcohol with the proportion of 80.0. Based on the results of chi square test with P = 0.001 (P < 0.05), statistically significant influenced of curious motive with alcohol consumption in adolescents. When viewed from the odds ratio score (OR) = 7, meaning the

informants who had high curious motive had a chance to 7 times more likely to consumed alcohol, compared with informants who had the low motives curious.

b. The Effects of Opportunity to Alcohol Consumption

To determined the effects of opportunity to consumption of alcohol in adolescents can be seen in Table 3.7.

Table 3.7: Distribution Effect of Opportunities on Alcohol Consumption in Adolescents

Opportunites	Alcohol Consumption				Total		P Value	OR 95%
	Not consumed		Not consumed					
	F	%	F	%	F	%		
Low	21	67.7	10	32.3	31	100.0	0,000	21,700 (5,329-88,359)
High	3	8.8	31	91.2	34	100.0		
Total	24	36.9	41	63.1	65	100.0		

In Table 3.7 showed that informants who had the high opportunity, likely to consumed alcohol with the proportion of 91.2 %. Based on the results of chi square test with P value = 0.000 (P < 0.05) means that statistically there is a significant effect between opportunity with alcohol consumption in adolescents. When viewed from OR = 22 meant that informants who had the high opportunities had 22 times more likely to consumed alcohol, compared with informants who had the low oppportunity.

c. The Effects of Inferiority to Alcohol Consumption

To determined the effects of inferiority to the alcohol consumption in adolescents can be seen in Table 3.8

Table 3.8: Distribution The Effect of Inferiority to Alcohol Consumption in Adolescents

Inferiority	Alcohol Consumption				Total		P Value	OR 95%
	Not consumed		Not consumed					
	F	%	F	%	F	%		
Low	16	76.2	5	23.8	21	100.0	0.000	14.400 (4.072-50.921)
High	8	18.2	36	81.8	44	100.0		
Total	24	36.9	41	63.1	65	100.0		

In Table 3.8 showed that informants who had the low inferiority were more likely to consumed alcohol with the proportion of 81.8%. Based on the results of chi square test with P value = 0.000 (P < 0.05) meant that statistically there was significant relationship between low inferiority with the alcohol consumption in adolescents. When viewed from the OR = 14, meant informants who had higher inferiority had a chance 14 times more likely to consumed alcohol compared with informants who had low inferiority.

d. The Effects of Emotional to Alcohol Consumption

To determine the effects of emotional to alcohol consumption in adolescents can be seen in Table 3.9.

Table 3.9: Distribution of Emotional Effect to Alcohol Consumption Alcohol in Adolescents

Emotional	Alcohol Consumption				Total		P Value	OR 95%
	Not consumed		Not consumed					
	F	%	F	%	F	%		
Low	17	56.7	13	43.3	30	100.0	0.004	5.004 (1.677-15.170)
High	7	20.0	28	80.0	35	100.0		
Total	24	36.9	41	63.1	65	100.0		

In Table 3.9 showed that informants who had the high emotional were more likely to consumed alcohol with the proportion of 80.0%. Based on the results of chi square test with P value = 0.004 (P < 0.05) meant that statistically there was significant relationship between emotional with alcohol consumption in adolescents. When viewed from the OR = 5, meant that informants who had the high emotional had the opportunity five times more likely to consumed alcohol, compared with informants who had the low emotional.

3.2 Qualitative Research Results

3.2.1 Impact of Alcohol Consumption For Health

For the informants who consumed alcohol, there would be a change in them that was related to health. This interview was conducted to determined the feelings of informants, changes and disorders of the body as well as their ways to eliminated the habit of consumed alcohol.

a. First Experience of Consumed Alcohol

"Initially, when I consumed alcohol was good, but if too much enters the body usually caused headache, vomiting, nausea due to the influence of drink. But, over time so accustomed and fun. My problem to be forgotten" (A, 21th).

"The first I drank this, my body felt hot, my head felt dizzy, the body felt weak, I just was not powered, sluggish.."(KS, 21)

"The first my body was heat and then feel nauseous, dizzy"..(RD, 17th)

b. Perceived changes in the body for consumed alcohol

"The change were mybody resistance decreased, easily hurted, then I often excessive of sleep and I woke up late, I always want to sleep anymore time learninghours.(RD, 17th)

"The changes that I felt was my body thinner, because too much to drink. My friends had drink at night and when gathered with friends and then we stayed up. By stayed up, my weight being dropped drastically due to lacked of sleep and only drank alcohol..(A, 21th)

c. Disorders of the Body when Consumed Alcohol

"I've blood vomiting, blood cough, I had been treated in hospital. Now I often headache, dizziness, cough, sluggish."(RK, 18th)

d. The Efforts to Eliminated theAddiction with Alcohol

"I avoided friends who liked to drink and looked for something else, yes, my message is do not drink alcohol, drink water and healthy drinks only, not alcohol, you can drink alcohol but must be according to the rules."(A, 21th)

"Initially started from your self to no longer drank alcohol because I know that the alcoholist very damaging myself. the second, I tried to not get along with my friends who drank alcohol, I kept a distance from them, I just kept friends with them but if to be invited to drank alcohol I tried not to do.."(RD, 17th)

3.3 Discussion

3.3.1Quantitative Research

a. The Effects of Curious Motivesin Adolescents to AlcoholConsumption

Curious motives is a strong desire of adolescents to try new things that are not known positive and negative impacts. The results of the univariate analysis (Table 3.1) showed that informants who had the high curious motives more than those who had the low curious motives.

The results of the bivariate analysis showed that informants who had the high curious motives were more likely to consumed alcohol (Table3.6).

Statistically, there was the effects between curious motives about the alcohol consumption (P =0.001andOR=7). The results showed that high curoius motives had a very strong effects on the consumption of alcohol which had seventimes greater opportunity of went to consumed alcohol. This was possible due to the high teens want to know the motive of the alcohol then they will start to try and find an opportunity to consumed alcohol, because adolescent is a period that is mentally unstable so that most adolescent wanted to try something new. These desires should be restrained by adolescent before knew what the impact for themselves and their environment.Informants were first consumed alcohol seeing his friends consumed alcohol. Moreover, the insistence of friends that if it did not try the alcoholis considered disloyal to his peers.

The tendency of the results above acoording with Martino & Kovalchik (2015) and Turbin et al. (2000) that adolescent have always wanted to know the nature of everything that is not yet known or less negative impact. For example,want to know how the taste of alcohol. Adolescent who consume alcohol in general for drinks give a sense of pleasure, comfort, joy,and peace, and also most importantly can eliminate the burden and all the problems faced.

Similarly(Ari 2012) and (Kusmaryadi 2013)foundthat adolescentswho consumealcohol tendto followorsee their friendswhoconsumetoo.Usually, more their friendswhoconsume alcohol, also higher the curiosityof thealcohol. Peersgavean important influencein shapingbehaviorin adolescents. Adolescentbeforestarting something new, theywant to know howthe taste of alcohol. Itis motivatedby the frequentadolesentlookgoodsocial environmentofthe family andofthe peersenvironmentwhofrequentlyconsume alcohol.

a. The Effects of Opportunity to Alcohol Consumption

Opportunityis atimeobtainedbyadolescentsdue to lackof attentionfromfamilyorlack of affectionfrom parents. So thatadolescent behaviorcan not becontrolledfromthefamilyoftheadolescenthave the opportunitytodo thingsthat are notdesirable, such asalcohol consumption andso on.

The results ofthe univariate analysis(Table 3.2) showedthat informants whohad the high opprotunitymore than those whohadthe low opportunity. The results ofthe bivariateanalysisshowedthat informants whohad the high opportunity were more likely toconsumed alcohol(Table3.7). Statisticallythere wasthe influence ofa opportunityto thealcohol consumption(P =0.000andOR=22). The results showed that the high opportunity of having a very strong influence on consumption of alcohol with a

22 times greater opprotunity of going to consumed alcohol. It was possible that with the high opportunity that were so adolescent began to try new things like consumed alcohol which was able to eliminated boredom at home and the problems it faced. Opportunity to came due because of busy parents or lacked of supervision of parents, peers who also consumed alcohol, and as an escaped from lack of affection or eliminated the problem because of the downturn.

(Febrianty 2013) and (Bachtiar 2011) said andarguedthatbecause of busyparents andfamilies withtheir respectiveactivitiesoras a result ofa broken home, theybecomea lack of affection, heartbreak, and so on. So inthe eventadolescenttrying to findan escapeby drinkingalcohol. Adolescenthave not beenable to overcometheir problemwithpositive thinking, so that theway takenis a shortcutthattheir problemwillberesolved quicklyso thatnew problemsfor themselves andtheir families or eventhe surrounding environment.

(Hany 2010) and (Hawar & I 2011), in his article titled"AlcoholShould notbe Friend", foundthe supervision ofparents andthe surrounding communityto a large extentso that the adolescentbegan toconsumealcohol. Parents whojust thinkthatwithsufficientchildren is the most important thing. It was verywrongway, in addition tophysicalneeds, children also needlove fromparents,attention, andproblemoropportunityin conveyingtheir opinions, and parentsto be friends insharing.

b. The Effects of Inferiority to Alcohol Consumption

Inferiority is where a person hasa weakconfidencethatsomeone is afraidto get along, thenby consumingalcoholthat confidencegrows anda sense of inferioritywill disappearbecause of the influenceofalcohol.The results ofthe univariate analysis(Table 3.3) showedthatinformants who had the high inferioritycompared with those withlow inferiority.The results ofthe bivariateanalysisshowedthat informantswerefeeling inferiority were more likely toconsumed alcohol(Table3.8).

Statisticallythere wasthe effects ofopportunityto thealcohol consumption(P =0.000andOR=14). The results showed thathighinferiorityhada very strong influenceon consumptionof alcoholwith 14times greaterchance ofgoing to consumealcohol. This could happenbecause ofthe possibility ofinferioritywill greatly affectedadolescentin startinganassociationin their neighborhood. Adolescent wouldseekits own wayso thattheseshortcomingswere notknown byfriendsand environment. People with inferioritynotto got along, to competedandshowed their image, so as to showedwho they was,adolescent wouldduseany meansto be moredarein the mixsuch asconsumed alcohol, smokedorused drugs. With sodisadvantages thatadolescentwould not be seenby friendsand environment.

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In keeping with the findings above, (Martino & Kovalchik 2015) and (Hutagalung 2008) noted that to cover up feelings of inferiority in the association in the community and among their peers, so they used the alcohol so get what conceivable among others, more active, more bold, more expressive and etc.

According to (Aufseeser et al. 2006) and (Febrianty 2013), people were consuming alcohol will feel firmer, the euphoria, the problem goes away, so talk more than usual, feel more free in inter-personal relationships, so that adolescent who initially shy or afraid will feel more adventurous, without shame to mingle with their friends.

d. The Effects of Emotional to Alcohol Consumption

Emotional is the uncontrolled behavior of adolescentin life. Adolescentdo not like tobe restrainedbyrules thatrestricttheir association.The results ofthe univariate analysis(Table 3.4) showedthatinformants who hadhigh emotionalmore than those who hadlow emotional.The results ofthe bivariateanalysisshowedthat informants whohadhigh emotional were more likelytoconsumed alcohol(Table3.9).

Statisticallythere wasthe influence of inferiority to thealcohol consumption(P =0.004andOR=5). The results showedthathighinferiorityhada very strong effectson consumptionof alcoholwith5times greaterchance ofgoing to consumdalcohol. This trendmightoccurbecause ofthe emotionalwouldbringthemon apersonal conflict. On the one hand, there wererules thatmust be obeyed, andthe other sidethere wasa strong desireto be freefromthe rules,so thatthehigh emotionaladolescent could notthink clearlyandchose the wayof freedomin socializingwithout being dictatedbythe existing rules.

The findings aboveaccordingwith(Bott 2014) and (Hutagalung 2008), that adolescent emotionaltypical is still unstable,especiallyduringpuberty. At that timetheywanted toescapefrom the bonds ofthe rulesimposedby parents tosatisfytheir personal life, so thatit causesa personal conflicts. In an attemptto escape fromthepersonalconflict they seekrefuge indrinkingalcoholwith the aim toreduce the saturationof therules givenbythe parents.

(Centre For Disease Control and Prevention 2014) and (Kusmaryadi 2013) alsofoundadolescentweakness of mental due tothe high emotionalwouldeasily dothings that arenegativeso thatallthese negative influenceslead todrug abuseactivities, psychotropicoralcoholordangerous drugs.

3.3.2Qualitative Research

The results ofthe analysisof the opinions ofthe fiveinformantsshowed that afterconsumed alcohol, informants felt no changein their bodydue to alcohol. Afterconsumed alcohol, they werefree

ofproblems,freein socializing, though initiallyto felt dizzyornauseousbut over timebecameaccustomedand fun. But over time theybegan to appearnew problemsrelated tohealth.Theyfelt body resistancebegan to decline, easily hurted, the body started tothin, it was often too lateto get up early, alwayswanted to sleepespeciallyduring school hours, andthere wasalso a feelingsluggish.

(Kaya & Unalan 2010) and Bachtiar(2011), alcoholcontaining addictive substancesthatif consumedeven thoughfew willlead toaddictionoutstandingandwhen consumedcontinuouslywill cause nerves brain damagethat causeseasyto losesense,balance andsense of touch.

The same thingwas stated by(Mercken et al. 2010) and (Fahmi 2013)thatthe adverse effectsofdrinking alcoholtovarious organsin the body, from the brain, mouth, gastrointestinal tract, upto the large intestine. Drinking too much alcoholusuallycause a reactionof confusion, slowing ofreaction time, blurring ofvision, to a loss ofconcentration andmuscle coordination, whichcanmake a personan injuryorfatal accident. In addition, the use ofalcoholin a short timeandexcessivelycan causealcohol poisoningoralcohol intoxicationthatcould endanger lives.

Resultsin ashort period can be feltwith increasingheart rateandthe heart of thestatewill be weakenedand so can notworkoptimally.Thisactuallyhappensbecausealcohol candamage the cellsof the bodyandalsoincludingcells ofthe heart, resulting in heart performancewouldnot beoptimal (Martino & Kovalchik 2015) dan (Bachtiar 2011). For those who alreadyhave a wifeit isvery dangerousbecause if toooften consumealcohol cancausedecreasedsex arousaland willcauseimpotent(Bachtiar 2011).

Drinkingexcessive chronically can lead to damagebrain tissues, causing a power interruptionmemories, capabilityassessment, learning, andcertainmental disorders. Due to alcohol, the feeling ofsomeonebeing changed, peoplebecome irritableand disturbanceof attention tothe environment soexcludedfrom their social environmentandorremovedfrom their job. It also canpermanentlydamage thebrain tissues(Marshall 2009).

IV.CONCLUSIONS

Based on the results of research and discussion, it can be concluded as follows:
1.There was the effects ofcurious motives, opportunity, inferiority, emotionaltoalcohol consumptionin adolescents.
2.There wasthe effectsof alcohol consumptionon healthadolescentswhichdecreased body resistance, easily hurted, too lateto got up early, often sleepy, thin body, vomitedandcoughed up blood, andfelt sluggishwhenhad sex.

Suggestions

1.For adolescents, in order toavoidthe alcohol consumptionbecause it can damagehealth.
2.The government shouldrestrictalcoholdistributionin the

communityand alwayssupervise the useofalcoholin order notmisplaced.

3. Forthe parentsare expected tosupervisethe associationofchildrenfor fear ofconsumingalcohol, drugsandthe like.

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Analysis of The Patient Satisfaction Level to Pharmacist Service Quality in Four Pharmacies in Palu City With Using Servqual (Service Quality) Method

Olvi Irene Makadjadi*, Alwiyah Mukaddas, Muhamad Rinaldhi Tandah

Pharmacy Department, Faculty of Science, Tadulako University, Palu.

ABSTRACT

This research aimed to know about customer satisfaction level of service quality of pharmacist that connecting with five service quality dimensions pervade *Tangible, Reliability, Responsiveness, Assurance,* and *Emphaty* in four pharmachis of Palu city on January 2016 to March 2016. This kind research is non-experimental as quantitative descriptive research use questioner instrument with *Likert* scale. Customer satisfaction level measure by using *SERVQUAL (Service Quality)* method to five service quality dimensions that is *Tangible, Reliability, Responsiveness, Assurance,* and *Emphaty* and analyze with *Importance Performance Analysis (IPA)* and *Customer Satisfaction Index (CSI).* Based on the result of this research of 340 respondents shown that average value of discrepancy (Gap) -0,77 with compatibility level 83,49%. Cartesius diagram shown there are several things that have to increase by the pharmacist, but in whole manner customer satisfaction level has *CSI* value 77,95% by criteria satisfied.

Keywords: *CSI , IPA,* Pharmacist, Satistaction level, *SERVQUAL* Method

ABSTRAK

Penelitian ini bertujuan untuk mengetahui tingkat kepuasan pasien terhadap kualitas pelayanan apoteker yang dihubungkan dengan lima dimensi kualitas pelayanan yang meliputi *Tangible, Reliability, Responsiveness, Assurance,* dan *Emphaty* diempat apotek kota Palu pada bulan Januari 2016 sampai Maret 2016. Jenis penelitian ini non eksperimental berupa penelitian deskriptif kuantitatif dengan memakai instrumen kuesioner yang menggunakan skala *Likert.* Tingkat kepuasan pasien diukur dengan menggunakan metode *SERVQUAL (Service Quality)* terhadap 5 dimensi kualitas pelayanan yaitu meliputi *Tangible, Reliability, Responsiveness, Assurance,* dan *Emphaty* dan dianalisis dengan *Importance Performance Analysis (IPA)* dan *Customer Satisfaction Index (CSI).* Hasil penelitian dari 340 responden dengan rata-rata nilai kesenjangan (Gap) yaitu -0,77 dengan tingkat kesesuaian 83,49%. Diagram kartesius menunjukkan masih ada beberapa hal yang harus ditingkatkan oleh apoteker, tetapi secara keseluruhan tingkat kepuasan pasien memiliki nilai *CSI* 77,95% dengan kriteria puas.

Kata Kunci: Apoteker, *CSI , IPA,* Metode *SERVQUAL,* Tingkat Kepuasan

***Corresponding Author :** Olvi Irene Makadjadi, email : olviirene@yahoo.co.id

INTRODUCTION

Knowledge about the health of the world community, especially the drug is still very limited. Medication will only provide benefits if used in a way that is completely disposable and if stored properly. With the right knowledge, people will be able to gain maximum benefit from the drug and may minimize any undesirable things that can occur due to the use of a drug. One of the elements that have the expertise and can be a source of information about medicines is a pharmacist. However, the role of the pharmacist is now perceived not run as it should.

Pharmacists are considered not to act as informer drug and has not been able to act as a filter rational use of medicines, safe and affordable by the public (Rasdianah, 2011).

Research conducted by Ihsan (2014) in Kendari city pharmacies, showed that only 40% of pharmacists pharmacy manager (APA) ensure quality of service that manages pharmacy. This shows that the implementation of the pharmacy carried APA implications for the level of customer satisfaction in the evaluation of quality of service. While in the review of the level of customer satisfaction was 76.70% enough category. The quality of service for customer satisfaction, is the first step in the future success of the company. SERVQUAL method is one of the most well known method for measuring the quality in the service industry. The method introduced by Parasuraman, Zeithaml and Berry (1988), which has been widely used in research.

Based on the above background, the researchers are interested in doing research in some pharmacies town of Palu, in order to know the level of quality of services provided by pharmacists to patients.

RESEARCH METHODS

Types Of Research

This research is non-experimental research in the form of descriptive quantitative research instrument used in the form of questionnaires.

Research Sites

This study was conducted at four pharmacies Palu namely, pharmacy Natoro Farma, Kimia Farma 328 Megatama, Kimia Farma Dewi Sartika, and Kimia Farma PEL 25 Undata.

Population and Sample

The population in this study were all visitors / patients who redeemed a prescription at a pharmacy.

Sampling was done by purposive sampling. The number of samples taken by the number of research indicators which 17 indicators multiplied by 5 x 5 = 85 respondents, then multiplied by the number of pharmacy 4 x 85 = 340 total respondents overall sample. Sampling is based on inclusion and exclusion criteria as follows :

The inclusion criteria samples:

1. Patients aged 17-60
2. Patients who receive pharmacy services by pharmacists with a doctor's prescription
3. Patients who are not illiterate

Sample exclusion criteria:

1. Patients who are ill
2. Not willing to become respondents
3. Patients who first treatment and drug services

RESULT

Table1Characteristics Of Respondents

Data	Frequency	Percentage (%)
1. Gender		
Man	145	42,65
Woman	195	57,35
2. Age		
≤ 20 year	19	5,59
21 - 30 year	49	14,41
31 - 40 year	37	10,88
41 - 50 year	185	54,41
51 – 60 year	50	14,71
3. Education last respondent		
a. Not completed primary school	0	0
b. Primary School	6	1,76
c. Junior High School	10	2,94
d. Senior High School	158	46,47
e. College	166	48,82
4. Employment of respondents		
a. POLRI	10	2,94
b. ABRI	5	1,47
c. PNS	180	52,94
d. Retired	30	8,82
e. Student	25	7,35
f. Entrepreneur	50	14,71
g. Others	40	11,76
5. Visit		
a. 2-4 times	90	26,47
b. 4-6 times	103	30,29
c. 6-10 times	80	23,53
d. More than 10 times	67	19,71

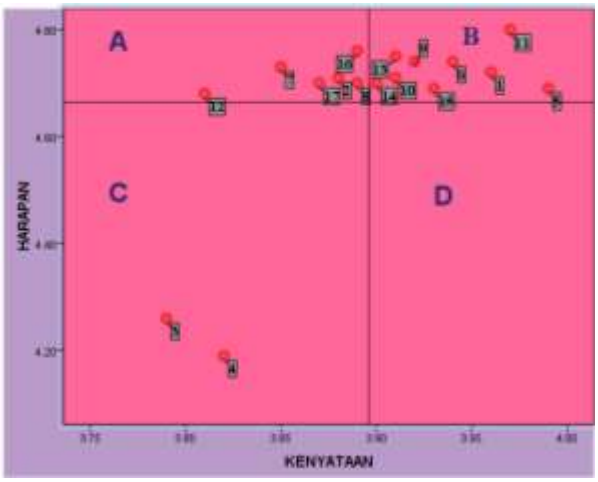
Table2
Average Item Expectations and Reality As Well As The Value Gap

Num	Indicator	Skor		$\bar{x}$	ȳ	Level Of Compliance (%)	Gap
		Reality (x)	Expectations (y)				
Tangible							
1.	The existence of a pharmacist in a pharmacy in every hour of	1345	1605	3,96	4,72	83,80%	-0,76

	service						
2.	Pharmacy board include the name and number SIK pharmacist pharmacists with clearly	1319	1600	3,88	4,71	82,44%	-0,83
3.	Pharmacists groomed and uniformed	1289	1450	3,79	4,26	88,90%	-0,47
4.	Pharmacists provide a copy of the recipe after the patient redeem some drugs or with a patient's request	1298	1425	3,82	4,19	91,09%	-0,37
Reliability							
5.	Pharmacist handed a prescription drug based on fast (less than 15 minutes)	1355	1595	3,99	4,69	84,95%	-0,71
6.	Pharmacists replace patented drugs (expensive) drugs to generic (cheap) with the approval of a doctor or patient	1341	1610	3,94	4,74	83,29%	-0,79
7.	Pharmacists can answer patients' questions both oral and written	1310	1607	3,85	4,73	81,52%	-0,87
Responsiveneess							
8.	Pharmacists directly serve the patient when the patient comes	1323	1597	3,89	4,70	82,84%	-0,81
9.	Pharmacists tell the old recipe is completed	1332	1611	3,92	4,74	82,68%	-0,82
10.	Pharmacists attention to the patient's complaints	1331	1601	3,91	4,71	83,14%	-0,79
Assurance							
11.	Pharmacists provide information on how to use / consumption of drugs	1351	1633	3,97	4,80	82,73%	-0,83
12.	Pharmacists provide an understanding about the side effects and drug interactions	1297	1590	3,81	4,68	81,57%	-0,86
13.	Pharmacists provide information related to illegal drugs	1331	1615	3,91	4,75	82,41%	-0,84
Emphaty							
14.	Pharmacists serve patients without discriminating patients	1327	1599	3,90	4,70	82,99%	-0,80
15.	Patient communication with pharmacists running smoothly	1335	1593	3,93	4,69	83,80%	-0,76
16.	Pharmacists always be friendly and courteous in serving patients	1321	1618	3,89	4,76	81,64%	-0,87
17.	Pharmacists are willing to be contacted whenever a patient in need of care	1315	1597	3,87	4,70	82,34%	-0,83

Table 3
Value Gaps Average and The Level Of Conformity For Each Dimension Servqual

Dimension *SERVQUAL*	Reality ($\bar{x}$)	Expectation ($\bar{y}$)	Gap	Level Of Compliance (%)
Tangible	3,86	4,47	-0,61	86,37%
Reliability	3,93	4,72	-0,79	83,25%
Responsiveneess	3,91	4,71	-0,81	82,89%
Assurance	3,90	4,74	-0,84	82,24%
Emphaty	3,90	4,71	-0,82	82,69%
Average	3,90	4,67	-0,77	83,49%



Picture 1 Cartesian Diagram and The Factors That Affect The Level Of Patient Satisfaction In Four Pharmacies In The Palu City Of Hammer

Table4Distribution Of The Indicators In Each Quadrant

Quadrant	Number Indicator
A	2, 7, 8, 12, 16, 17
B	1, 5, 6, 9, 10, 11, 13, 14, 15
C	3, 4
D	-

Table5*Customer Satisfaction Index* (CSI)

Num	Indicator	Mean Importance Score (MIS)	Weighting Factors (WFi)	Mean Satisfaction Score (MSS)	Weighted Score (WSi)
1.	The existence of a pharmacist in a pharmacy in every hour of service	4,72	0,06	3,96	0,24
2.	Pharmacy board include the name and number SIK pharmacist pharmacists with clearly	4,71	0,06	3,88	0,23
3.	Pharmacists groomed and uniformed	4,26	0,05	3,79	0,20

4.	Pharmacists provide a copy of the recipe after the patient redeem some drugs or with a patient's request	4,19	0,05	3,82	0,20
5.	Pharmacist handed a prescription drug based on fast (less than 15 minutes)	4,69	0,06	3,99	0,24
6.	Pharmacists replace patented drugs (expensive) drugs to generic (cheap) with the approval of a doctor or patient	4,74	0,06	3,94	0,24
7.	Pharmacists can answer patients' questions both oral and written	4,73	0,06	3,85	0,23
8.	Pharmacists directly serve the patient when the patient comes	4,70	0,06	3,89	0,23
9.	Pharmacists tell the old recipe is completed	4,74	0,06	3,92	0,23
10.	Pharmacists attention to the patient's complaints	4,71	0,06	3,91	0,23
11.	Pharmacists provide information on how to use / consumption of drugs	4,80	0,06	3,97	0,24
12.	Pharmacists provide an understanding about the side effects and drug interactions	4,68	0,06	3,81	0,23
13.	Pharmacists provide information related to illegal drugs	4,75	0,06	3,91	0,23
14.	Pharmacists serve patients without discriminating patients	4,70	0,06	3,90	0,23
15.	Patient communication with pharmacists running smoothly	4,69	0,06	3,93	0,23
16.	Pharmacists always be friendly and courteous in serving patients	4,76	0,06	3,89	0,23
17.	Pharmacists are willing to be contacted whenever a patient in need of care	4,70	0,06	3,87	0,23
Total		79,25	1,00	66,24	3,90
CSI = (*Weighted score total* : 5) x 100%					77,95%

DISCUSSION

Characteristics of respondents in table 1 showed that respondents with female sex as much as 195 (57,35%) more than the male respondents of 145 (42,65%). Based on the age range, the highest score at the age of 41-50 years amounted to 185 (54,41%) and the smallest value at age ≤ 20 years. Education respondents indicated that most respondents college education is 166 (48,82%) and the lowest education level of primary school is 6 (1,76%). The highest responder jobs are as many as 180 civil servants (52,94%) and the smallest is the armed forces by 5 (1,47%). Furthermore, respondents most visited 4-6

times numbered 103 (30,29%) and least visited more than 10 times the amount to 67 (19,71%).

Analysis Of Patient Satisfaction

1. *Importance Performance Analysis* (IPA)

a. The Results Of The Gap

A negative number would indicate that the respondents 'expectations are not met, while a positive number indicates that respondents' expectations are met (Baroroh, 2014). The results of the analysis of the gaps, it appears that the whole performance indicators remain below respondents' expectations for the results obtained indicate negative numbers all. In this method of measuring the level of conformity is required to determine how much the respondents are satisfied with the performance of the company, and how big the service providers understand what customers to the services they provide (Nugraha, 2014).The average value of the variable gap is -0,77 with a concordance rate of 83,49%.Some of the variables that are above the average value of the difference in weight is a variable that should be prioritized for repair (Table 3).The variables that need to be prioritized is Assurance and Emphaty, where the variable is the value of the gap between expectation and reality is large enough respondents felt above the average value of the gap. Assurance on the average variable rate of 4,74 expectancy an average rate of 3,90 true value of the difference -0,84 with a concordance rate of 82,24%.Furthermore Emphaty variable average rate expectations by 4,71 the average rate of 3,90 fact that there is a difference of -0,82 and a concordance rate of 82,69%. Furthermore, Responsiveness variable has a value difference of -0,81 and 82,89% compliance rate. Reliability followed variable value difference -0,79 to 83,25% compliance rate and the variable having the lowest value of the difference -0.61 namely Tangible with the greatest concordance rate of 86,37%.So, from these results it can be concluded that the lower the value of the gap, the higher the level of patient satisfaction.

b. Quadrant Analysis

Cartesian diagram illustrates the indicators that affect customer satisfaction. Divided into four quadrants A, B, C and D. The four quadrants are formed from vertical point to 4.67 (average expectations) and horizontal dots of 3.90 (average true).

Dimensions and indicators that go in quadrant a deemed to affect patient satisfaction, including elements of the services that are considered very important, but the pharmacist has not carried out according the patient as disappointing.In this quadrant there are four dimensions of which Tangible ie indicators board pharmacies include the name of the pharmacist and the number SIK pharmacist clearly (2), it is in because the patient wants to know the name of the pharmacist and the number SIK is needed to determine whether the pharmacist has a work permit or not,

considering the number of illegal practices which are being developed in the community. Completeness of information on the pharmacy board becomes important by patients. Dimensions of Reliability indicator that the pharmacist can answer questions patients either orally or in writing (7). This is due to lack of patient understanding of the drug makes patients often ask their pharmacists, but patients do not get a satisfactory answer, the limited time to be one cause, because pharmacists serve patients that much so it is difficult to explain in detail the information.Further dimensions Responsiveness with direct indicator of pharmacists serve patients when patients come in (8). This shows that the pharmacist has not been responsive to the patients who come to the pharmacy.The indicators included in the dimensions of Assurance that pharmacists provide an understanding about the side effects and drug interactions (12). This is because patients are generally only know the effects of drug therapy without understanding the side effects that can be caused from drug consumption, so it is this which makes the patient feel important to be able to understand it.Provision of information regarding side effects of medication should be more careful, because not to the information provided raises fears and worries to consume drugs, so use language that is easily understood by the patient and not just use a medical term that is difficult to understand. Besides, there should also be told to the patient how to cope with the symptoms of drug side effects that arise as measures that can reduce the side effects that arise and immediately contact a doctor.Indicators on the dimensions of Empathy that pharmacists always be friendly and courteous in serving patients (16) and pharmacists willing to be informed whenever a patient in need of care (17).A friendly attitude and manners make the patient feel comfortable, so that the patient will return to the same pharmacy for pharmacists good service.But, otherwise when the patient is not served by friendly patient will feel uncomfortable and will move to other pharmacies.In contrast to the results of research conducted by Baroroh (2014) concerning customer satisfaction with pharmacy services at a pharmacy Yogyakarta city where there is not any dimensions in this quadrant. These results indicate that each region has a pharmacist services different.

Later in the B quadrant are five dimensions in it.The first dimension Tangible with indicators of the presence of pharmacists in pharmacies in every hour of service (1).This is because the pharmacy is a place of research is a pharmacy that has a pharmacist at the time of service hours so this indicator is feasible there in quadrant B. The second dimension Reliability indicators pharmacist handing medicine based on prescription fast (less than 15

minutes) (5).In preparing the drug under prescription, the pharmacist is assisted by an assistant pharmacist, so that services can be faster preparation of drugs.Pharmacists replace patented drugs (expensive) drugs to generic (cheap) with the approval of a doctor or a patient (6).This is due to the income of each patient is not the same, so that in redeeming the drug, the patient would like to buy the drugs that have the same efficacy but has a relatively reach.Dimensions Responsiveness with indicators in which pharmacists tell the old recipe is completed (9). By knowing the wait time drug, the patient can adjust the time with other purposes.Especially for employees, so if tasted old, the patient can go and come back on the clock that has been informed by the pharmacist and indicators pharmacist attention to the patient's complaints (10), where the pharmacist showing gesture responsiveness and help the patient when the patient tells a complaint that he felt.Dimensions Assurance pharmacist indicators provide information on how to use / consumption of drugs (11) and pharmacists to provide information related to illegal drugs (13).The use of drugs affect the fast or slow a patient in the healing process.In this case the pharmacist have explained how the use of drugs that include rules of use.Empathy with the indicators and dimensions pharmacists serve patients without discriminating patients (14), and patient communication with a pharmacist running smoothly (15).These results indicate that the pharmacist does not see differences that exist in every individual that pharmacists serve patients without discriminating, so that communication between patients and pharmacists can work well.In this quadrant patients have been satisfied with the performance of pharmacists and should be maintained. The different results shown Baroroh (2014) in this quadrant there are only dimension Tangible and Empathy. In view of the many indicators that are in quadrant B shows the quality of service of the pharmacist in the pharmacy Palu town has been good.

Quadrant C Tangible dimension occupied only by pharmacists indicators groomed and uniformed (3) and pharmacists indicators provide a copy after the patient redeem some prescription medications or by request of the patient (4). This is due to the patient's lack of understanding about the rare copy of the recipe or to ask that this indicator is considered less important. Where the factors of less importance for patients, their implementation was also mediocre in this quadrant. While the results of the research Baroroh (2014), there is the dimension Assurance, Reliability, and Responsiveness in quadrant C.

Pada In quadrant D, contains a factor that is less important for the patient but the implementation is excessive. The results show that in this quadrant does not have a single dimension that is in it. So these results

indicate that the services of pharmacists in the city of Palu nothing excessive or exceed the expectations of patients.These results showed similar results with Baroroh (2014) that there is not any dimensions in this quadrant.

Based on the analysis above quadrant, shows that in the five dimensions of service quality that includes Tangible, Reliability, Responsiveness, Assurance and Empathy with several indicators in it outlined in quadrant A, exposing the patient dissatisfaction with the services of pharmacists. This is because at any specific indicators within these dimensions pharmacist care showed weakness experienced by the patient when it comes in the pharmacy until interaction with the pharmacist.

It can be concluded that every pharmacist in their respective areas have this level of service quality vary. Where the standard implementation of pharmacy services in advanced areas (Yogyakarta) and the growing area (Palu) is not the same. Thus, these results prove that the five dimensions of service quality that includes Tangible, Reliability, Responsiveness, Assurance, and Emphaty have a relationship with the level of patient satisfaction in Palu city pharmacy.

2. *Customer Satisfaction Index* (*CSI*)

Calculation Customer Satisfaction Index (CSI) scores using the average rate expectations and the perceived level of each indicator. Based on the calculations that have been done, the value of CSI by 77,95%. CSI value is obtained by dividing the total value of Weighted Score (WS) with a maximum scale used in this study is 5 and multiplying by 100%. The satisfaction index is in the range from 0,66 to 0,80 with the criteria of "satisfied" (Sukardi and Chandrawatisma, 2006).

CONCLUSIONS

1. Quality of care pharmacists on the dimensions of Tangible, Reliability, Responsiveness, Assurance and Empathy have a relationship with patient satisfaction level in four pharmacies Palu.
2. Results of value Customer Satisfaction Index (CSI) in four pharmacies amounted to 77,95% of Palu city. Where these values are in the range from 0,66 to 0,80 with the criteria are satisfied.
3. There are several indicators that a priority for repair, namely on the indicator number 2 (Tangible), 7 (Reliability), 8 (Responsiveness), 12 (Assurance), 16 (Empathy), 17 (Empathy).

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Meta-Analysis Using Mantel Haensel Case Study: Ewing Sarcoma Disease

Moch. Riski Almubarak*, Junaidi, Lilies Handayani

Statistics Department, Tadulako University

ABSTRACT

Meta-Analysis is a statistical technique that combining the results of two or more similar studies in order to obtain cumulatively composite data. Aplied on *meta-analysisewing sarcoma* patient data from five studies conducted to obtain an overall average the used of *Mantel-Haenszel* method. *Conprehensive Meta-Analysis* (CMA) Package is used to view the *odds ratio* and *risk ratio* of each study and its overall average conclusions. Manual calculation formula *Mantel-Haenszel*, then compare the results from the CMA package generally showed no significant difference.

Key Words : *Meta-Analysis, Ewing Sarcoma, Conprehensive Meta-Analysis* (CMA)*, Mantel-Haenszel, odds ratio, risk ratio.*

ABSTRAK

Meta Analisis merupakan suatu teknik statistika untuk menggabungkan hasil dua atau lebih penelitian sejenis sehingga diperoleh paduan data secara kumulatif. Pengaplikasian *meta analisis* pada data pasien *ewing sarcoma* dari lima studi dilakukan untuk mendapatkan rata-rata keseluruhan menggunakan metode *Mantel-Haenszel*. Paket *Conprehensive Meta-Analysis* (CMA) digunakan untuk melihat *odds ratio* dan *risk ratio* dari setiap studi beserta kesimpulan rata-rata keseluruhan. Perhitungan secara manual dengan rumus *Mantel-Haenszel* dilakukan, selanjutnya membandingkan hasil yang diperoleh dengan hasil dari paket CMA pada umumnya hasil yang diperoleh menunjukkan tidak terdapat perbedaan secara signifikan.

Kata kunci : *Meta Analisis, Ewing Sarcoma, Conprehensive Meta-Analysis* (CMA) *, Mantel Haenszel, odds ratio, risk ratio.*

***Corresponding author :** Moch Risky Almubarak, email : rizkytkj001@gmail.com

1. Introduction

Statistics is a science that is useful as a tool for analyzing the study data in various fields of science. In statistics there are various methods or techniques used to analyze the research data. One of the techniques or methods which combine and merge two or more similar studies or studies on the same topic (Suryanto, 2004).

Along with the many scientific studies that discuss the same topic with different characteristics and results contained in it, sometimes requires us to reassess the scientific study or commonly called the *literature review*. There are four methods in the *literature review,* the *narrative review, descriptive review, vote counting,* and *meta-analysis*. Of the four methods, *Meta Analysis* is a method that focuses on quantitative approach, which focused on the effect size (King & June, 2005).

Approaches to which can be used to calculate the *effect size* among other methods Inverse-Variance which is a method for obtaining estimates of effect size combined where each study is weighted by the variance, Method *mantel-haenszel* is a method of using the contingency table 2x2 where to line to categorical data, and *Peto* method is the method that often used to estimate combined odds ratio for a *meta-analysis* of clinical trials.

Currently, the *meta-analysis* are widely used in research in the world of health. either in the form of clinical trials and for research on diseases to reach a conclusion. One example of research on the disease cases *prognostic Significance of P16INK4a alteration for Ewing Sarcoma* (Honoki, et al, 2007).

Ewing sarcoma is a rare malignant tumor in which cancer cells can be found in bone or soft tissue. Ewing sarcoma was first described in 1921 by Dr. James Ewing (1866 - 1943), where the disease is different from the types of lymphoma and other cancers. Ewing sarcoma can also metastasize to other places such as the bone marrow, lungs, kidneys, liver, adrenal gland, and other soft tissues.

There are many studies that discuss the disease *ewing sarcoma* or bone cancer, including Huang, et al (2005); Lopes-Guerrero, et al (2001); Maitra, et al, (2001); Tsuchia, et al (2000); and Kovar, et al (1997) and Junaidi, et al (2012). From the description that has been presented authors are interested in combining and analyzing studies of disease ewing sarcoma using a meta-analysis with*mantel-haenszel* method, namely using *odds ratio*, *risk ratio* by looking at the characteristics of the patients metastatic *ewing sarcoma*.

2. Theoretical basic

Meta-analysis can be defined as the analysis of the collection of statistical analysis of the results very much from single studies with the aim of integrating the results of these studies (Glass, 1976). Anwar (2005) named that the *meta-analysis* is a statistical technique for combining the results of two or more similar studies in order to obtain the data alloy cumulatively.

According Suryanto (2004) *meta-analysis* is the study by analyzing data derived from primary studies. The results of the analysis of the primary studies used as the basis for accepting or supporting the hypothesis, reject or abort the hypothesis proposed by some researchers.

Meta-analysis is a technique used to summarize the results of quantitative research by

looking for the value of the *effect size*. *Meta-analysis* allows for combining the results are diverse and attention to sample size and *effect size*, which *effec size* used was the *odds ratio* and *risk ratio*.

Odds are the odds ratio of successful events with opportunities to fail. Based on 2x2 contingency table, odds ratio is the odds ratio in the experimental group with odds in the control group (Agresti, 2002).

According to Altman, (1991) calculate the *odds ratio*, *standard error*, and 95% confidence intervals as follows.

$$OR = \left(\frac{(a \times d)}{(b \times c)} \right) \quad (1)$$

with a *standard error* of the *log odds ratio* becomes

$$SE\left\{\ln(OR)\right\} = \sqrt{\frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d}} \quad (2)$$

and 95% confidence intervals are

$$95\%CI = \exp\left(\ln\left(OR\right) - 1{,}96 \times SE\left\{\ln\left(OR\right)\right\}\right) (3)$$

for the lower limit of the confidence interval and for the upper limit of the confidence interval.

$$95\%CI = \exp\left(\ln\left(OR\right) + 1{,}96 \times SE\left\{\ln\left(OR\right)\right\}\right) \quad (4)$$

Risk ratio is the ratio chance events that occurred in the experimental group to the control (Agresti, 2002). According to Altman, (1991) calculate the *risk ratio*, *standard error*, and 95% confidence intervals as follows.

$$RR = \left(\frac{\left(\frac{a}{(a+b)} \right)}{\left(\frac{c}{(c+d)} \right)} \right) \quad (5)$$

with a standard error *log risk ratio* becomes

$$\text{Log Risk Varians} = \left(\frac{\left(\frac{b}{a} \right)}{(b+a)} \right) + \left(\frac{\left(\frac{d}{c} \right)}{(d+c)} \right) \quad (6)$$

$$\text{Log Risk SE} = \sqrt{\text{LogRiskVarians}} \quad (7)$$

and 95% confidence intervals are

$$95\%CI = \exp\left(\ln\left(RR\right) - 1{,}96 \times SE\left\{\ln\left(RR\right)\right\}\right) \quad (8)$$

for the lower limit of the confidence interval and the upper limit of the confidence interval

$$95\%CI = \exp\left(\ln\left(RR\right) + 1{,}96 \times SE\left\{\ln\left(RR\right)\right\}\right) \quad (9)$$

Odds ratio estimator and the combined *risk ratio* of each variable called the *mantel-haensel odds ratio* and *risk ratio* as follows:

$$OR_{MH} = \left(\frac{\sum_{i=1}^{k} \frac{a_i \times d_i)}{n_i}}{\sum_{i=1}^{k} \frac{b_i \times c_i}{n_i}} \right) \quad (10)$$

Where the *standard error* of the *mantel-haenszel odds ratio*, Deeks & Higgins (2010).

$$SE\left\{\ln(OR_{MH})\right\} = \sqrt{\frac{1}{2}\left(\frac{E}{R^2} + \frac{F+G}{R \times S} + \frac{H}{S^2} \right)} (11)$$

Untuk setiap stratum :

$$R = \sum_{i=1}^{k} \left(\frac{(a_i \times d_i)}{N_i} \right) \; S = \sum_{i=1}^{k} \left(\frac{(b_i \times c_i)}{N_i} \right)$$

$$E = \sum_{i=1}^{k} \left(\frac{(a_i + d_i)a_i \times d_i}{N_i^{\,2}} \right) \; F = \sum_{i=1}^{k} \left(\frac{(a_i + d_i)b_i \times c_i}{N_i^{\,2}} \right)$$

$$G = \sum_{i=1}^{k} \left(\frac{(b_i + c_i)a_i \times d_i}{N_i^{\,2}} \right) \; G = \sum_{i=1}^{k} \left(\frac{(b_i + c_i)b_i \times c_i}{N_i^{\,2}} \right)$$

and 95% confidence intervals are

$$95\%CI = \exp\left(\ln\left(OR_{MH}\right) - 1,96 \times SE\left\{\ln(OR_{MH})\right\}\right) \quad (12)$$

for the lower limit of the confidence interval and the upper limit of the confidence interval.

$$95\%CI = \exp\left(\ln\left(OR_{MH}\right) + 1,96 \times SE\left\{\ln(OR_{MH})\right\}\right) \quad (13)$$

and 95% confidence intervals are

$$RR_{MH} = \left(\frac{\sum_{i=1}^{k} \frac{a_i(c_i + d_i)}{n_i}}{\sum_{i=1}^{k} \frac{c_i(a_i + b_i)}{n_i}} \right) \quad (14)$$

Where the *standard error* of the *mantel-haenszel odds ratio*, Deeks & Higgins (2010).

$$SE\left\{\ln(RR_{MH})\right\} = \sqrt{\frac{R}{(R \times S)}} \quad (15)$$

$$P = \sum_{i=1}^{k} \left(\frac{\left(\left(n_{1i} \times n_{2i}\right)(a_i + c_i)\right) - \left((a_i \times c_i) \times N_i\right)}{{N_i}^2} \right)$$

$$R = \sum_{i=1}^{k} \left(\frac{\left(a_i \times n_{2i}\right)}{N_i} \right) \quad S = \sum_{i=1}^{k} \left(\frac{\left(c_i \times n_{1i}\right)}{N_i} \right)$$

and 95% confidence intervals are

$$95\%CI = \exp\left(\ln\left(RR_{MH}\right) + 1,96 \times SE\left\{(RR_{MH})\right\}\right) \quad (16)$$

for the lower limit of the confidence interval and the upper limit of the confidence interval.

$$95\%CI = \exp\left(\ln\left(RR_{MH}\right) + 1,96 \times SE\left\{\ln(RR_{MH})\right\}\right) \quad (17)$$

3. Research methodology

Next on the variables used in this study consisted of two variable intervention (odds of death by metastasis) and variable control (chance of dying without metastasis).

The data used in this research is secondary data, ie journal associated with the disease ewing sarcoma. While the types of data used in this research is quantitative data, that is data in the form of values of individual studies that will be taken as related research data.

Steps in the analysis for each research purposes are as follows:

1. Steps to analyze similar studies by calculating the *odds ratio* manually, namely:
   a. *Odds ratio* determines the average overall conclusion by the formula

$$OR_{MH} = \left(\frac{\sum_{i=1}^{k} \frac{(a_i \times d_i)}{n_i}}{\sum_{i=1}^{k} \frac{(b_i \times c_i)}{n_i}} \right)$$

   b. To process research data with the application CMA (*Comprehensive Meta Analysis*)
   c. Analyzing the results of the end user and the program to get a conclusion.
2. The steps to get the average value of the whole which is the conclusion of several studies on the disease *ewing sarcoma* in patients with metastases at diagnosis, and without metastasis at diagnosis with meta-analysis.
   a. *Risk Ratio* determines the value of each research manually with the formula.

$$RR = \left(\frac{\left(\frac{a}{(a+b)}\right)}{\left(\frac{c}{(c+d)}\right)} \right) = Nilai\ Risk\ Ratio$$

   b. Determining risk ratio average overall conclusion by the formula

$$RR_{MH} = \left(\frac{\sum_{i=1}^{k} \frac{a_i(c_i + d_i)}{n_i}}{\sum_{i=1}^{k} \frac{c_i(a_i + b_i)}{n_i}} \right)$$

c. To process research data with the application CMA (*Comprehensive Meta Analysis*)

d. Analyzing the results of the end user and the program to get a conclusion.

4. Results and Discussion

4.1 Calculation of *odds ratios* of each study

- **Study of Huang, et al (2005)**

Table 4.1 Results of 2x2 contingency *odds ratio*

Ewing Sarcoma Desease	Huang,dkk, 2005	
	Is death	Not is death
with Metastasis	5	1
Withhout Metastasis	13	41
	60	

By using equation (1) is obtained:

$$OR_{Huang} = \frac{5 \times 41}{1 \times 13} = \frac{205}{13} = 15{,}77$$

From the manual calculation of the value of the *odds ratio* in the study Huang, et al (2005) obtained the value of the *odds ratio* of 15.77. In the study Lopes-Guerrero, et al (2001) in the same manner showed 21.00. In the study Maitra, et al (2001) showed 4,125. In the study Wei, et al (2000) didapakan 15.333 results. In the study Kovar, et al (1997) also showed calculating the odds ratio of 1.6.

4.2 The average yield of the overall value of the*Mantel-HaensZel odds ratio*

The average yield *mantel-haensZel* value *odds ratio* of five studies.

Table 4.2 Results 2 × 2 contingency *odds ratio mantel–haensel*

Desease *Ewing Sarcoma*	*odds ratio mantel haensel*	
	Is death	Not is death
With Metastasis	30	14
Without Metastasis	31	87
	162	

By using equation (9) is obtained:

$$OR_{Mantel-Haensel} = \frac{\frac{30 \times 87}{162}}{\frac{14 \times 31}{162}} = \frac{\frac{2610}{162}}{\frac{434}{162}} = \frac{16{,}11}{2{,}679} = 6{,}0$$

4.3 *Odds ratio* using average overall CMA

CMA (*Conprehensive Meta-Analysis*) is one of several data processing applications in the field of statistics, where the CMA itself is used in the field of health, especially in the case study used meta-analysis to find the value of the *odds ratio and risk ratio* by using a *forest plot.*

The results of each study using the CMA program when compared with the manual there are differences but not significant.

Table 4.3 Value *odds ratio* of the results of manual calculations and program CMA

No	Studi	*Odds ratio*	
		Manual	CMA
1	Huang, (2005)	15,77	15,769
2	Lopes G, (2001)	21,00	21,000
3	MaitraG, (2001)	4,12	4,125
4	Wei, (2000)	15,333	15,333)
5	Kovar, (1997)	1,6	1,600
6	$OR_{mantel-haensel}$	6,0	5,967

Tabel 4.4 Value confidence intervals of the results of manual calculations and program CMA

Study	*Confidence Interval Odds Ratio*	
	Manual	CMA
Huang, (2005)	(1,141 – 147,513)	(1,686 – 147,509)
Lopes G, (2001)	(0,924-477,256)	(0,924 – 477,229)
MaitraG, (2001)	(0,495 – 34,342)	(0,493 – 34,900)
Wei, (2000)	(1,61 – 145,744)	(1,611 – 145,901)
Kovar, (1997)	(0,326 – 7,835)	(0,326 – 7,848)
$OR_{mantel-haensel}$	(2,882 – 12,615)	(2,472 – 14,399)

From table 4.3 and 4.4 Average yield for the *odds ratio* value either manually or with the CMA program, on the study of Huang (2005) obtained a yield of 15.77 with a confidence interval of 1.41 to lower limits and 147.513 for the upper limit of the program CMA itself obtained a yield of 15.769 with a confidence interval of 1.686 for the lower limit and upper limit of 147.509. From the results of calculations there are differences but not significant.

Studies Lopes-Guerrero (2001) obtained a yield of 21.00 with a confidence interval (0.924 to 477.256) for the CMA program itself obtained yield was 0.924 with a confidence interval, (0.924 to 477.229). Based on the results of the second well of the program as CMA and the manual there are differences but not significant.

In a study Maitra, (2001) obtained a yield of 4.12 with a confidence interval (0.495 to 34.342), the CMA program obtained results with a confidence interval 4.125 (0.924 to 34.900). The second is based on the calculation results, it can be seen that the results of both calculations are differences but not significant.

Wei Study, (2001) obtained at 15.333 with a confidence interval (1.61 to 145.744) at the CMA program obtained a yield of 15.33 with a confidence interval (1.611 to 145.901). From the results of the calculations in Table 4.3 and Table 4.4 can be seen the difference between the results of calculations. From these results it can be seen a second difference calculation result but not significant.

on the study of Kovar, (1997) obtained a yield of 1.6 with a confidence interval (0.326 to 7.835) at the CMA program itself obtained yield was 1.600 with a confidence interval (0.326 to 7.848). From the results of the calculations both manually and the CMA program in Table 4.3 and Table 4.4 there are differences but not significant.

From table 4.7 odds ratio results obtained with the *mantel-haensel* fixed model with a confidence interval of 6.0 (2.882 to 12.615). At the CMA program obtained yield was 5.967 with a confidence interval (2.472 to 13.499). Based on the output of the 4.7 picture CMA and manual calculations above can be seen the results of each study where the results of the program and manual calculation of 0.884 of these differences did not reach pesentase that could make the results be biased to the upper limit of the confidence interval. So to say the results of the calculations are correct. The purpose of calculating the 95% confidence level on *ewing sarcoma* disease with and without metastasis at diagnosis that the interval (2.882 to 12.615) will load the average results of all studies that the more influential sixfold disease death rates *ewing sarcoma*.

4.4 Calculation of *risk ratio* for each study

• Study of Huang, et al (2005)

Table 4.5 Results of 2x2 contingency *risk ratio*

Ewing Sarcoma Desease	Huang,dkk, 2005	
	Is death	Not is death
with Metastasis	5	1
Without Metastasis	13	41
	60	

By using equation (5) is obtained

$$RR_{Huang} = \frac{\frac{(5)}{(5+1)}}{\frac{(13)}{(13+41)}} = \frac{\left(\frac{5}{6}\right)}{\left(\frac{13}{54}\right)} = \frac{0,833}{0,240} = 3,470$$

manual calculation for the value of *risk ratio* on research Huang, et al (2005) obtained the value of *risk ratio* of 3.470. In the study Lopes-Guerrero, et al (2001) in the same manner showed 7.00, on research Maitra, et al (2001) showed 2,222, the study Wei, et al (2000) didapakan result of 3.05, the research Kovar, et al (1997) also showed calculating risk ratio of 1.30.

4.5 Results The overall average value *Mantel-Haenselodds ratio*

The following will be given the average yield of the overall risk ratio of 6 studies using the *mantel-haensel.*

Table 4.6 Results of 2 × 2 contingency *risks ratiomantel haensel*

Ewing Sarcoma Desease	*risk ratio Mantel Haensel*	
	Is death	Not is death
With Metastasis	30	14
Without Metastasis	31	87
	162	

By using equation (10) is obtained:

$$RR_{Mantel-Haensel} = \frac{\frac{30\times(31+87)}{162}}{\frac{31\times(30+14)}{162}} = \frac{\frac{30\times118}{162}}{\frac{31\times44}{162}} = \frac{\frac{3540}{162}}{\frac{1364}{162}} = \frac{21,851}{8,419} = 2,59 = 2,6$$

4.6 *Risk ratio* value using the average overall CMA

The overall value comparison of average risk ratio manual and CMA program.

Table 4.7 Value risk ratio of the results of manual calculations and program CMA

Study	*risk ratio*	
	Manual	CMA
Huang, (2005)	3,46	3,462
Lopes G, (2001)	7,00	7,000
MaitraG, (2001)	2,222	2,250
Wei, (2000)	3,05	3,048
Kovar, (1997)	1,30	1,300
$OR_{mantel-haensel}$	2,6	2,603

Table 4.8 Value confidence intervals of the results of manual calculations and program CMA

Study	*Confidence Interval Odds Ratio*	
	Manual	CMA
Huang, (2005)	(1,912 – 6,27)	(1,912 – 6,267)
Lopes G, (2001)	(0,494 – 99,067)	(0,494 – 99,113)
MaitraG, (2001)	(0,747 – 6,783)	(0,747 – 6,779)
Wei, (2000)	(1,621 – 5,7266)	(1,621 – 5,728)
Kovar, (1997)	(0,534 – 3,164009)	(0,534 – 3,167)
$OR_{mantel-haensel}$	(1,810 – 3,738184)	(1,896 – 3,921)

From 4:16 on the study table Huang obtained a yield of 3.46 with a confidence interval (1.912 to 6.27). At the CMA program for the study of Huang obtained yield was 3.462 with a confidence interval (1.912 to 6.267). From the results it can be seen that there is a difference. So it can be concluded that although there are differences between manual calculation and CMA program but not significant. The purpose of these calculations with a confidence level of 95% is expected that the interval 1.912 to

6.27 would load the overall average of the results of the study Huang, (2005).

In a study of Lopes-Guerrero obtained yield was 7.00 with a confidence interval of (0.494 to 99.067). At the CMA program for the study of Lopes-Guerrero obtained yield was 7.000 with a confidence interval (0.494 to 99.113). From these results it can be seen that no significant difference in the two results of the calculation, namely manual and use the CMA program. So with a 95% confidence interval (0.494 to 99.067) are expected to represent all the research on the study of Lopez-Guerrero (2001).

In a study of 2,222 Maitra obtained results with confidence intervals (0.747 to 6.783). At the CMA program obtained yield was 2.250 with a confidence interval of (0.747 to 6.779). From the results of both studies calculations manually and CMA program there are differences but not significant. So we can say that the outcome was appropriate because the level of concordance between the user and the CMA program is identical, despite differences but not significant. With a confidence level of 95% is expected to represent the entire results of the study Maitra, (2001).

In a study of Wei diproleh result of 3.05 with a confidence interval 1.621 to 5.7266 for the lower limit and upper limit. At the CMA program for the study of Wei obtained yield was 3,048 with a confidence interval of 1.621 to 5.728 for the lower limit and upper limit. From these results it can be seen that the difference between the results of calculations either manually or using the CMA program. So we can conclude that the results are identical but insignificant and the 95% confidence level that the interval (1.621 to 5.7266) are expected to represent the entire results of the study Wei, (2000).

In a study of Kovar obtained yield was 1.30 with a confidence interval of (0.534 to 3.164009). At the CMA program obtained results with a confidence interval 1.300 (0.534 to 3.167). From the results it can be seen that is not much difference between the two calculation results. So we can say that the results of the calculations manually and there are differences in the program but are not as significant. With a 95% confidence level that the confidence interval (0.534 to 3.164009) representing all the results of the study Kovar, (1997).

On the results of average overall *risk ratio* with *Mantel-Haensel* method obtained yield was 2.6 with a confidence interval of 1.810 for the lower limit and 3.738184 for the upper limit. At the CMA program obtained yield was 2.603 with a confidence interval 1.896 to 3.921 for the lower limit and upper limit. Where the average yield to risk ratio value with a yield of 2.603 with a level of 95% confidence interval 1.896 up to 3.921. From the results of manual calculations and CMA program can be seen the difference was not significant. The purpose of the results of these calculations is the 95% confidence level is desirable that the interval (1.810 to 3.738184) will load the average results of all studies on diseases ewing sarcoma diagnosed with and without metastasis. From manual calculations and CMA program to risk ratio value of 2.6 or can be said of patients with metastases have doubled the chance of dying than

without metastasis compared with patients who did not have metastases at diagnosis.

5. Conclusion

From the analysis above, both the results of manual calculations and program output although there are differences but not significant. Five studies that analyze the outcome of the chance of dying with and without metastasis of 162 patients, of research Huang, et al, (2005) resulted in an odds ratio of 15.77, on research Lopez-Guerrero, et al (2001) in the same way RESULTS 21.00. In the study Maitra, et al (2001) obtained a yield of 4.125 while the research Wei, et al, (2000) resulted in an odds ratio of 15.333. Recently the research Kovar, et al (1997) obtained results of calculation of the odds ratio of 1.6.

The fifth result of the above it can be concluded that more die diagnosed with metastasis than those without metastasis undiagnosed, with the p-Value = 0.000 for average overall odds ratio P-value*mantel-haensel*, and α = 0.05 it can be said that the value of α is greater than the value of p-value to the conclusion that more that died with metastasis compared with those without ewing sarcoma metastatic disease. Figure 4.2 dish up value odds ratios with 95% confidence interval for a great look which death by metastasis or no metastasis at the time dignosis with a fixed p-value*mantel-haensel* odds ratio obtained from the equation 2:10 was 5.967 (95% CI, 2.472 to 14.400; P value = 0.000 <α = 5%) showed statistically significant. The mortality rate is higher or poorer prognosis for patients who have metastases compared with patients who did not have metastases at diagnosis.

Further risk ratio is used to see the comparison between the intervention and control groups. In Figure 4.3 presents how much influence metastasis in the intervention group or the control of the disease ewing sarcoma. Of the five studies with a number of patients as many as 162 people, using the CMA program (Conprehensive Meta-Analysis) on (or confidence interval CI 95%) obtained a fixed value *mantel-haenzel risk ratio* 2.603 (95% CI, 1.896 to 3.921) where the value of P- value = 0,000 <α = 5% (figure 4.3) showed a statistically significant, the average rate higher death or a worse prognosis for patients ewing sarcoma that had metastasized compared with patients ewing sarcoma who have metastases at diagnosis.

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Ordinary Logistic Regression to Analyze Factors Affecting Graduation Status of Mathematics Student in The Faculty Of Mathematics And Natural Sciences, Tadulako University

Iut Tri Utami, Fadjryani, Lilies Handayani

Statistics Department, Tadulako University

ABSTRACT

Grade Point Average (GPA) is the average credit score which is a unit of the final value that describes the value of the learning process of each semester. There are several factors that affect GPA and status graduation of mathematics student such as gender, origin, university test, senior high school status, parents occupation and income of parents. This research was conducted in the Mathematics Departement, Tadulako University to analyze the factors that affect graduation status of mathematics student using Ordinary Logistic Regression (OLR) method. The research revealed that Pseudo R-Square 84.5%. This indicates that the predictor variables are able to explain the variation of graduation status of mathematics student amounted to 84.5%.

Keywords: ordinary logistic regression, grade point average, graduation status

ABSTRAK

Prestasi Kumulatif (IPK) adalah nilai kredit rata-rata yang merupakan unit dari nilai akhir yang menggambarkan nilai dari proses belajar setiap semester. Ada beberapa faktor yang mempengaruhi IPK dan status kelulusan siswa matematika seperti jenis kelamin, asal, tes universitas, status SMA, orang tua pendudukan dan pendapatan orang tua. Penelitian ini dilakukan di Matematika Departement, Universitas Tadulako untuk menganalisis faktor-faktor yang mempengaruhi status kelulusan siswa matematika menggunakan metode Ordinary Logistic Regression (OLR). Penelitian ini mengungkapkan bahwa Pseudo R-Square 84,5%. Hal ini menunjukkan bahwa variabel prediktor mampu menjelaskan variasi status kelulusan siswa matematika sebesar 84,5%.

Kata kunci : Regresi logistic ordinary, IPK, Status kelulusan

***Corresponding author :** Iut Tri Utami, email : triutami.iut@gmail.com

1. Introduction

GPA is an indication of a student's academic achievement at a college or university, calculated as the total number of grade points received over a period divided by the total number of credits awarded. Students who earn high GPA indicates that the student is able to attend college well and conversely but the student with the lower GPA show that the student is not able to follow the lecture well. Moreover, in the real world many companies are recruiting qualified employees with the conditions determined by the company, one of which is the value of GPA which must achieve certain minimum value. In connection with the value of GPA which is required when applying for a job, do not be surprised if the company listed value GPA high enough as one of the requirements to apply for jobs at the agency. Based on the diverse backgrounds of students as well as many other factors in their daily life as a student, it is possible GPA students achieved at the end of the semesters are influenced by various factors, both internal and external factors. Internal factors include motivation, learning, talent and health. While external factors, namely family, campus, community and the environment (Dalyono, 1997).

This research was conducted in the Mathematics department, faculty of Mathematics and Natural Sciences, Tadulako University to analyze the factors that affect graduation status of Mathematics student using ordinal logistic regression method. Ordinary logistic regression analysis was used to analyze the data with categorical response variable (nominal) with continuous and categorical predictor variables. Research on the factors affecting the GPA has been done by Putriaji Hendikawati (2011) and Karyanus Daely, et al (2013) by using factor analysis.

2. Theoretical basic

A regression model is commonly used to study relationships between multiple independent and dependent variables and to determine significant independent variables related to a dependent variable. Basically, there are two common categories of regression models: the linear regression model and the logistic regression model. The decision to choose linear regression or logistic regression depends on the measurement scale of a dependent variable. If a dependent variable is expressed on an interval scale, a linear regression is more appropriate to be used. If a dependent variable is a binary/dichotomous data, a logistic regression provides more meaningful results (Agresti, 2002).

The OLR model is an extension of a logistic regression that is especially used to analyze nominal or ordinal data. The OLR method is the most appropriate and practical technique to analyze the effect of independent variables on a rank order dependent variable because the dependent variable cannot be assumed as normally distributed or as interval data (Lawson & Montgomery, 2006). The OLR model fit depends on the number of independent variables and the selected link function that are decided during the model-building phase. The selected link function in the model describes the effect of the independent variables on the rank order dependent variable.

Considering $J+1$ ordered categories, cumulative probabilities, cumulative odds and cumulative logits are defined by

$$P(Y \le j|\, x) = \frac{\exp(\alpha_j + \sum_{k=1}^{p} \beta_k x_k)}{1 + \exp(\alpha_j + \sum_{k=1}^{p} \beta_k x_k)}$$

$$P(Y \le j|\, x) = \pi_1(x) + \pi_2(x) + \cdots + \pi_j(x)$$

$$odds = \frac{P(Y \le j|\, x)}{1 - P(Y \le j|\, x)} = \frac{\pi_1(x) + \cdots + \pi_j(x)}{\pi_{j+1}(x) + \cdots + \pi_{J+1}(x)}$$

$$logit\ P(Y \le j|\, \overset{x}{\rightarrow}) = ln \frac{P(Y \le j|\, x)}{P(Y > j|\, x)} = \alpha_j + \sum_{k=1}^{p} \beta_k x_k$$

where $j = 1,2, \ldots, J$.

Researchers may assess the performance of an ordinal logistic model based on its model fitting statistics and the accuracy of the predicted classification (Chen & Hughes, 2004). The model-fitting statistics, such as Pearson and Deviance goodness-of-fit statistics, measure the model fit based on the expected and observed frequency for each occurrence. In addition, to measure the strength association between independent and dependent variables, the model statistics that depends on the likelihood ratio, such as the pseudo R square, may also be used. The way to interpret pseudo R square in an ordinal regression model is similar to that of the R square in linear regression models. It represents the success of the model in explaining variations in the data or the proportion of variation in the outcome variable accounted for by the independent variables.

3. Research methodology

This study aims to analyze GPA of undergraduate Mathematic students year of 2014 - 2015. This data was obtained from Tadulako University Academic Board. The data consist of several predictors such as gender (X_1), origin (X_2), university test (X_3), senior high school status (X_4), parents occupation (X_5) and salary (X_6). The original response variable for this study is GPA. Detail of variables in the GPA data is available in Table 1.

Table 1. Predictor Variables

Variable	Definition
Gender (X_1)	1 = male 2 = female
Origin (X_2)	1 = from Palu 2 = outside Palu
University Test (X_3)	1 = PMDK 2 = SPMB 3 = Local
Senior High School Status (X_4)	1 = public school 2 = private school
Parents Occupation (X_5)	1 = civil servant 2 = Policeman/National army 3 = entrepreneur 4 = Pensionary 5 = Farmer/Fisherman 6 = Others
Income (X_6)	1 = < Rp.1.000.000 2 = Rp. 1.000.000 – Rp. 3.000.000 3 = > Rp. 3.000.000

In OLR, we need to have ordinal-scaled response variable. The response variable is GPA which has ratio scale of measurement, we need to convert the GPA into three scaled ordinal variable, namely :

1 = GPA 3.51 – 4.00 = Excellent
2 = GPA 2.76 – 3.50 = Very Good
3 = GPA 2.00 – 2.75 = Good

Steps in the analysis for each research purposes are as follows:

1. Analyze the characteristics of GPA student using descriptive analysis
2. Fit the data using OLR method
3. Calculate and interpret the classification accuracy of the model.
4. Make conclusions and suggestions.

4. Results and Discussion

Characteristics of GPA of Mathematics student can be shown in Figure 1. Most predicate graduation of Mathematics student year 2014-2015 was very good with a percentage of 93%. While the percentage of the title of graduation of excellent and good their respective are 3% and 4%. In all the predictor variables indicate the most title of graduation is very good, it can be shown in Table 2-7.

Figure 1. Percentage of Title of graduation of Mathematics Student year 2014-2015

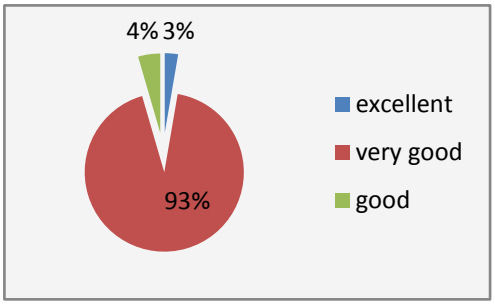

Table 2. Characteristics based on title of graduation and Gender

		Y			Total
		excellent	very good	good	
male	Count	2	22	2	26
	Percentage	7.7	84.6	7.7	
female	Count	1	81	3	85
	Percentage	1.2	95.3	3.5	
	Total	3	103	5	111

Table 3. Characteristics based on title of graduation and Origin

		Y			Total
		excellent	very good	good	
Palu	Count	2	47	3	52
	Percentage	3.8	90.4	5.8	
other	Count	1	56	2	59
	Percentage	1.7	94.9	3.4	
	Count	3	103	5	111

Table 4. Characteristics based on title of graduation and University test

		Y			Total
		excellent	very good	good	
PMDK	Count	3	10	0	13
	Percentage	23.1	76.9	0.0	
SPMB/ SNMPTN	Count	0	59	0	59
	Percentage	0	100	0	
Local	Count	0	34	5	39
	Percentage	0	87.2	12.8	
	Count	3	103	5	111

Table 5. Characteristics based on title of graduation and High school status

		Y			Total
		excellent	very good	good	
public school	Count	3	95	5	103
	Percentage	2.9	92.2	4.9	
private school	Count	0	8	0	8
	Percentage	0	100	0	
	Count	3	103	5	111

Table 6. Characteristics based on title of graduation and Parents Occupation

		Y			Total
		excellent	very good	good	
civil servant	Count	2	23	0	25
	Percentage	8	92	0	
policeman	Count	0	20	1	21
	Percentage	0	95.3	4.8	
enterpreneur	Count	1	28	2	31
	Percentage	3.2	90.3	6.5	
pensionary	Count	0	13	0	13
	Percentage	0	100	0	
farmer	Count	0	8	1	9
	Percentage	0	88.9	11.1	
others	Count	0	11	1	12
	Percentage	0	91.7	8.3	
	Count	3	103	5	111

Table 7. Characteristics based on GPA and Income

		Y			Total
		excellent	very good	good	
< 1 juta	Count	0	19	3	22
	Percentage	0	86.4	13.6	
1 juta - 3 juta	Count	2	53	0	55
	Percentage	3.6	96.4	0	
> 3 juta	Count	1	31	2	34
	Percentage	2.9	91.2	5.9	
	Count	3	103	5	111

The test conducted by OLR by entering all of the predictor variables used in this study. Then do partial test of each variable. The next step is to establish a logit function is used to make the function of the opportunities in each category the response variable.

Table 8. Parameter Estimates

Variable	Categorical	Estimate	Exp (B)	Sig
Title of graduation	Constanta 1 Constanta 2	5.135 8.193	169.86 3615.55	0.083* 0.112
Gender	Male	0.226	1.25	0.013*
Origin	Palu	0.121	1.13	0.006*
University test	PMDK SPMB	-1.392 -0.410	0.25 0.66	0.096* 0.042*
Senior High School Status	Public School Private School	0.244 0.503	1.28 1.65	0.006* 0.780
Parents Occupation	Civil servant Policeman/National Army Enterpreneur Pensionary Farmer/Fisherman	2.048 2.358 2.151 2.442 0.192	7.75 10.57 8.59 11.50 1.21	0.023* 0.030* 0.025* 0.031* 0.003*
Income	< Rp. 1.000.000 Rp. 1.000.000 – Rp. 3.000.000	2.452 -0.170	11.61 0.84	0.032* 0.003*

*Significant to 10%

It turned out that the partial test or β coefficient significance test on each variable, there are predictor variables that are not significant to 10%. Partial testing odds ratio value obtained in Table 8 for predictor variable of gender, for example, exp (1.482) = 4.402 which means that students with male gender have 4.402 chances times greater than female.

Table 9. Model fitting

Model	G^2	Chi Square	df	Sig	Decision
Intercept only Final	561.14 447.89	113.252	75	0.000	Reject H_o

Ordinal logistic regression models have been known. For β coefficient significance test values together, then tested the G^2 or Likelihood Ratio Test, it can seen in Table 9.

$G^2(x) = 5.135 + 0.226\ X_{11} + 0{,}121\ X_{21} - 1.392\ X_{31} - 0.410\ X_{32} + 0{,}244\ X_{41} + 2{,}048\ X_{51} + 2{,}358\ X_{52} + 2.151\ X_{53} + 2{,}442\ X_{54} + 0{,}192\ X_{55} + 2{,}452\ X_{61} - 0{,}170\ X_{62}$

On testing simultaneously, Table 9 shows that the G^2 value of 447.892, which means that $G^2 > \chi^2_{(0.1;75)}$ and obtained a decision to reject H_0, It means that the value of the coefficient β significantly to the regression model ordinal logistic regression.

Table 10. Pseudo R-Square

Cox and Snell	.113
Nagelkerke	.845
McFadden	.195

Link function: Logit.

Based on the results of Pseudo R-square value in Table 10 obtained Nagelkerke 84.5%. This indicates that the predictor variables are able to explain the variation of title of graduation mathematics student amounted to 84.5%.

5. Conclusion

Most characteristics of Mathematics students indicates that the title of graduation was very good. All predictor variables showed that the most title of graduation was very good. By testing simultaneously, the factors that influence are gender, origin, university test, parents occupation, and income. In the testing individual gender, origin, university test, parents occupation, and income. The

accuracy of the classification of the models simultaneously obtained by 84.5%, which means it's pretty good.

Suggestions in further research is necessary to review. The university test is a significant factor in the title of graduation. Hence the need for the calculation of the percentage of the number of students coming from different paths opened by Tadulako university. There are another several contributing factors that may affect the title of graduation prediction models.

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Autoregressive Integrated Moving Average (Arima) Modelling to Forecast Rainfall In Palu

Adliansyah A. Sidora*, Junaidi, Lilies Handayani

Statistics Department, Tadulako University

ABSTRACT

Rainfall is the most important elements of the climate specifically in Indonesia which has a very large variation compared to other climate elements. This study aims to forcasting rainfall in Palu using Autoregressive Integrated Moving Average (ARIMA). Rainfall data is collected from the period 1 January 2009 to 31 October 2016 at Station Meteorology and Geophysics Agency (BMKG) Palu and is processed using Minitab application to see it's pattern the ARIMA model. ARIMA modeling steps initially stationary test of data, the model identification, parameter estimation, verification of the model and it is then followed by forecasting. The results showed that ARIMA $(1,1,1)(1,1,3)^{12}$ with a significance test model parameters and *overfitting.*

Keywords: Rainfall, ARIMA, and *Overfitting*.

ABSTRAK

Curah hujan merupakan unsur iklim paling penting khususnya di Indonesia yang memiliki variasi sangat besardi bandingkan unsur iklim lainnya. Penelitian ini bertujuan untuk meramalakan curah hujan di Kota Palu menggunakan metode Autoregressive Integrated Moving Average. Data curah hujan di kumpulkan dari periode 1 Januari 2009 sampai 31 Oktober 2016 di Stasiun Badan Meteorologi dan Geofisika (BMKG) Kota Palu dan diproses menggunakan aplikasi minitab untuk dilihat polanya dalam model ARIMA. Tahap pemodelan ARIMA di mulai dari pengujian stasioneritas data, identifikasi model, estimasi parameter, verifikasi model dan di lanjutkan dengan peramalan. Hasil penelitian menunjukan model ARIMA yaitu $(1,1,1)(1,1,3)^{12}$ dengan uji signifikasi parameter model dan *overfitting*.

Kata kunci :Curah hujan, ARIMA dan *Overfitting.*

***Corresponding author :** Adliansyah A. Sidora, Email : adliansyah21untad@gmail.com

1. Intoduction

Rainfall climate is the most important element in indonesia have a variety of very greater than element other climate. In general the size of the rainfall vary according to the height of place as influence geografik.The rainfall down in indonesia in general and cities Palu in particular, varying from month to month and even from season to season within one year (asdak 1995).To minimize impacts generated by rainfall are erratic by provided information on the risks of extreme weather as a prediction rainfall in an area in a particular period.The importance of predicted rainfall this is useful to avoid arousing loss for human life.This is the background of the this research, especially for cities Palu.

Time series analysis is a quantitative method to determine the pattern of past data that has been collected regularly. Time series analysis is one method of forecasting is to explain that observation on a variable row is seen as a realization of a random variable distributed together.

One method of time series analysis ie Autoregressive Integrated Moving Average (ARIMA). Several studies using ARIMA models will be undertaken by the Wijaya (2008) to predict the air the monthly temperature in Jakarta, DjoniHatidja (2011) to predict the stock price of PT. TelkomselTbk in Manado and AnieLusiani (2011) for modeling rainfall in Bandung. Based on these studies, the authors try to do modeling Autoregressive Integrated Moving Average (ARIMA) for forecasting the average rainfall in the city of Palu.

2. Theoretical basic

Also known as the ARIMA time series analysis method Box-Jenkins.ARIMA very good accuracy for short-term forecasting, while for long-term forecasting accuracy of forecasting unfavorable. Usually it will tend to be flat (flat / constant) for a sufficiently long period. Autoregressive modeling Integrated Moving Average (ARIMA) model that is fully independent ignores the variables in making the forecast. ARIMA uses past and present values of the dependent variables to produce accurate short-term forecasting. ARIMA suitable if the observation of the time series (time series) are statistically correlated with each other (dependent).

The purpose of this model is to determine the statistical relationship between variables predicted both the historical value of the variable so that forecasting can be done with that model. A key assumption that must be met in time series model is the assumptionstationary. However, nonstationary series can be transformed into a stationary series with distinction (differencing).

Seasonal ARIMA model is generally formulated with the notation:

$$\boldsymbol{ARIMA} = (\boldsymbol{p}, \boldsymbol{d}, \boldsymbol{q})(\boldsymbol{P}, \boldsymbol{D}, \boldsymbol{Q})^{\boldsymbol{s}} \quad (1)$$

with,

$(\boldsymbol{p}, \boldsymbol{d}, \boldsymbol{q})$ = Part there are not seasonal model

$(\boldsymbol{P}, \boldsymbol{D}, \boldsymbol{Q})$ = Seasonal art model

$\boldsymbol{s}$ = The number of seaosonal model

Generally an ARIMA model to a time series data $\boldsymbol{X_t}$ is as follows (Makridakis et al, 1999):

$\phi\ B\ (1-B)^d X_t = \theta(B)\varepsilon_t \quad ; \varepsilon_t \sim N(0, \sigma_t^2 \quad (2)$

The above equation can be written by the operator backshift ($\boldsymbol{B}$), becomes:

$\boldsymbol{1 - B^d 1 - \phi_1 B + \phi_2 B^2 - \cdots - \phi_p B^p X_t = (1 + \theta 1 B - \theta 2 B 2 + \ldots + \theta q B q X t}$(3)

Thus obtained:

$1 - B^d X_t - \phi_1 X_{t-1} - \phi_2 X_{t-2} - \ldots - \phi_p X_{t-p} = \varepsilon_t + \theta_1 \varepsilon_{t-1} + \theta_2 \varepsilon_{t-2} + \cdots + \theta_q \varepsilon_{t-q}$ (4)

The study will analyze and determine the optimum form an ARIMA model to forecast monthly precipitation in the period of years to come. The benefit of this research is to extend the application of scientific development, especially in the field of mathematical statistics and mathematical models of rainfall obtaining Palu city that can serve as a comparison against an existing model. Processing of data to complete the modeling and quantitative forecasting assisted by several software among others SPSS, Minitab, and Microsoft Excel. Especially for forecasting with time series analysis in this study, use Minitab software for computer software has a complete facility for problems ARIMA.

3. Research methodology

The data used for this paper is secondary data from 1 January 2009 to 31 October 2016 (monthly data).

A time series model is said to be good if it was in accordance with reality. In other words, if the error (error) the smaller models, the model could be said to be good (Iriawan, 2006). Data analysis was performed using ARIMA method with the help of statistical software is MINITAB. Steps for implementing the method ARIMA respectively are:

a). Stationary testing of data

Stationary data is data that has an average and variance are constant over time.

b). Model identification

While the model identification was done by comparing the distribution coefficients and coefficients autokolerasi partial autokolerasi actual theoretical distribution.

c). Estimasi Parameter Model

The next stage after the initial model ($\boldsymbol{p, d, q}$) is determined by estimating the *AR* and *MA* parameters that exist in the model. This estimate could use a simple least squares technique, the estimation method is not linear and the method of MLE (maximum likelihood estimation), Yule Walker, Durbin Watson, etc. The method used is that if the data most appropriate to the circumstances. At this stage of the estimation, mathematical calculation technique is relatively complex, so the researchers used the help of Minitab software. Significance test using the reference parameter hypothesis as follows:

H_0: Parameter is not significant

$\boldsymbol{H_1}$: Significant Parameter

Critical areas: $\boldsymbol{H_0}$ rejected if the p-value < α = 0.05 (significant models / feasible to use).

d). Verification of the model

Testing the feasibility of the model can be done in several ways:

1. Overfitting made if necessary wider models.

2. Test the residual (error term). Systematically residuals can be calculated by subtracting the data forecast results with the original data. ARIMA model selection methods performed by observing the autocorrelation coefficient distribution and partial autocorrelation coefficients.
   - Autocorrelation coefficient

     The correlation coefficient indicates the direction and the relationship the two variations so that describe what happens to one variable when a change in another variable
   - Partial autocorrelation

     Partial autocorrelation coefficient measures the degree of closeness of the relationship between $\boldsymbol{X_t}$ with $\boldsymbol{X_{t-k}}$,where as the effect of the time lag of 1, 2, 3, and so on up to $\boldsymbol{k-1}$ was constant.

e). Using Selected Model for Forecasting.

4. Results and Discussion

Rainfall data in Palu of the period 1 January 2009 until 31 October 2016 processed using Minitab software in order to obtain the following results.

a). Stationary testing data is used to determine if the data that has been stationary or not stationary seen from the plot trend data

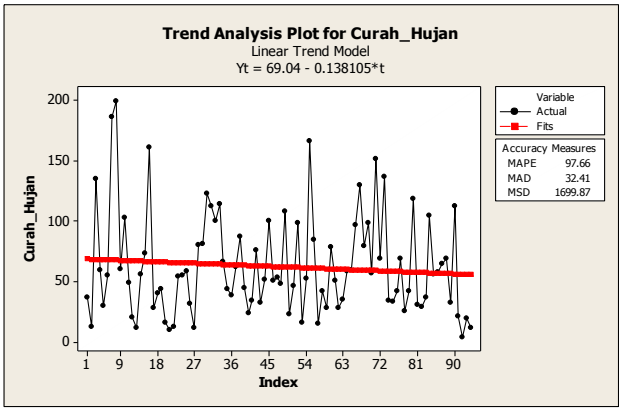


Figure 1. Plot *Trend*

From a visual graph, it turns out the data is not stationary and necessary transformation. Then the Box Cox transformation Figure 2 can be seen the value of lambda = 0,17. Smaller than a transformation that needs to be done again.

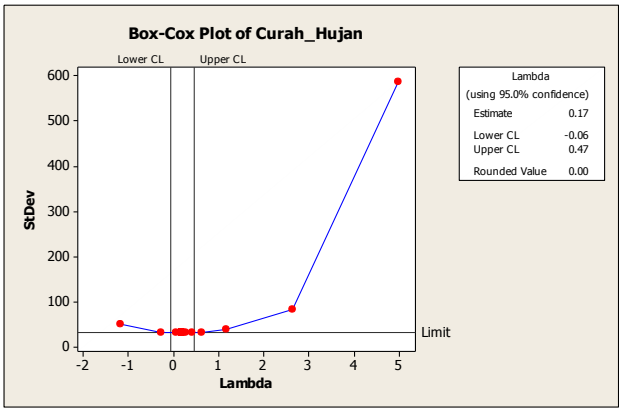


Figure 2. Plot Transformation Box Cox

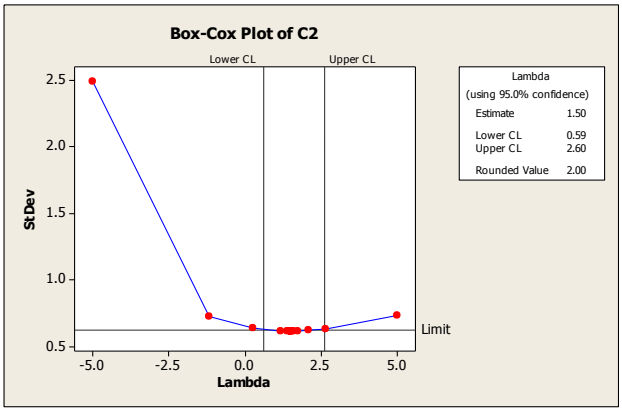
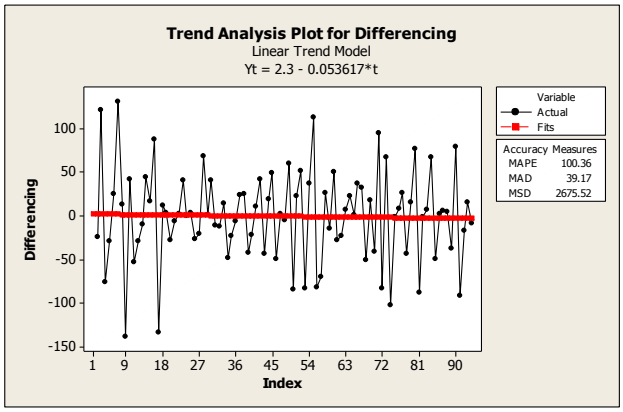


Figure 3. Plot Transformation Box Cox

Then after doing another Box Cox transformation can be seen the value of lambda = 1.50 greater than one so don't to need for transformation, but because the data is not stationary it is necessary to differencing.



Gambar 4. Plot *Trend*

Plot trend of results above that the data has been stationary average and variance are constant over time.

b). While the model identification

Determination of the model while ARIMA (p, d, q)done by identifying the plot *Autocorrelation Function* (ACF) and Partial *Autocorrelation Function* (PACF) of monthly rainfall data in Palu from 1 January 2009 to 31 October 2016. Here is a plot of ACF and PACF monthly rainfall in Palu after one distinction.

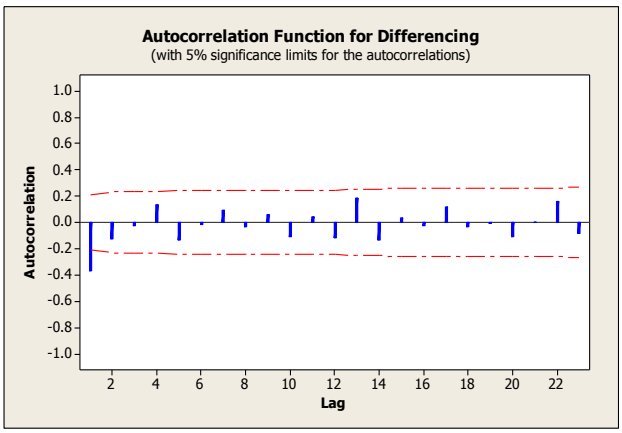


Figure 5. Plot ACF

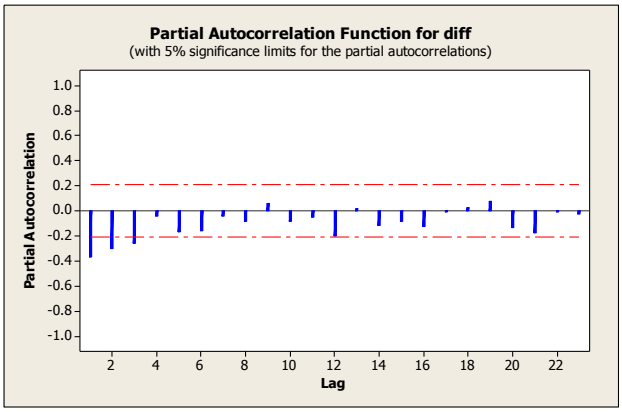


Figure 6. Plot PACF

Based on the data PACF plot shows the difference in the pattern of MA (Moving Average) of order 3, *MA* (3) that are not seasonal. Order *MA* assumed value of r_3 which are beyond the limits of significance autocorrelation. Seasonal patterns are still visible on the values of the autocorrelation data is adrift thus strengthening the process *MA* (3) which is seasonal. There is one value of autocorrelation in ACF plot is very significant that the first lag so it is assumed the existence of a pattern *AR* (*Autoregressive*) of the order of one or *AR* (1) is not seasonal. Based on this, while the

model is ARIMA (1,1,3)(0,1,3)^{12}, with d = 1 and s = 12.

c). While the model parameter estimation

To estimate the parameters in the model while, the first step is to describe the model ARIMA (1,1,3)(0,1,3)^{12} to shape :

$$(\mathbf{1}-\boldsymbol{\phi_1 B})(\mathbf{1}-\boldsymbol{B})(\mathbf{1}-\boldsymbol{B})^{\mathbf{12}}\boldsymbol{X_t} = (\mathbf{1}-\boldsymbol{W_1 B})(\mathbf{1}-\boldsymbol{\psi_1})^{\mathbf{12}}(5)$$

with,

$(\mathbf{1}-\boldsymbol{\phi_1 B})$ = *AR* (1) is not seasonal

$(\mathbf{1}-\boldsymbol{B})$ = The distinction is not seasonal

$(\mathbf{1}-\boldsymbol{B})^{\mathbf{12}}$ = Seasonal distinction

$(\mathbf{1}-\boldsymbol{W_1 B})$ = *MA* (3) is not seasonal

$(\mathbf{1}-\boldsymbol{\psi_1})^{\mathbf{12}}$ = *MA* (3) seasonal

The above model involves three parameters: $\boldsymbol{\phi_1}$ as *AR* (1) is not seasonal, $\boldsymbol{W_1}$ as *MA* (3) are not seasonal and $\boldsymbol{\psi_1}$as*MA* (3) seasonal. With the help of Minitab program, three parameter estimation results are obtained as follows :

ARIMA (1,1,3)(0,1,3)^{12}

Final Estimates of Parameters					
Type		Coef	SE Coef	T	P
AR	1	-0.7841	0.7531	-1.04	0.301
MA	1	-0.1456	0.7579	-0.19	0.848
MA	2	0.6543	0.5339	1.23	0.224
MA	3	0.1830	0.1465	1.25	0.216
SMA	12	1.2397	0.1217	10.19	0.000
SMA	24	-0.5682	0.1773	-3.20	0.002
SMA	36	0.0525	0.1688	0.31	0.757
Constant		-0.3422	0.3683	-0.93	0.356

Differencing: 1 regular, 1 seasonal of order 12
Number of observations: Original series 94, after differencing 81
Residuals: SS = 114320 (backforecasts excluded)
MS = 1566 DF = 73

d). Verification of the model

- Significance coefficient (parameter)

Significance coefficient of each parameter can be seen in the final estimate of the parameter table (*final estimates of parameters*). for pattern(*Type*) AR (1), Minitab results showed that *p*-value = 0.301>α = 0.05 (not significant models / unfit for use). And so on for other patterns. This shows the weakness of the role of these patterns against the model.

- *Overfitting*

In the verification of the model, the models need to be raised broader (overfitting) to get the best data. For example, raised ARIMA models:

ARIMA (1,1,2)(0,1,3)^{12}

Final Estimates of Parameters					
Type		Coef	SE Coef	T	P
AR	1	-0.3544	0.2716	-1.30	0.196
MA	1	0.4726	0.2395	1.97	0.052
MA	2	0.5856	0.2156	2.72	0.008
SMA	12	1.2864	0.1178	10.92	0.000
SMA	24	-0.5201	0.1733	-3.00	0.004
SMA	36	0.0046	0.1696	0.03	0.978
Constant		-0.14712	0.01082	-13.60	0.000

Differencing: 1 regular, 1 seasonal of order 12
Number of observations: Original series 94, after differencing 81
Residuals: SS = 96537.3 (backforecasts excluded)
MS = 1304.6 DF = 74

ARIMA (1,1,2)(0,1,3)^{12} is not significant because the p-value of each parameter is greater than α.

ARIMA (0,1,2)(1,1,3)^{12}

Final Estimates of Parameters					
Type		Coef	SE Coef	T	P
SAR	12	-0.9871	0.0458	-21.54	0.000
MA	1	0.6133	0.1216	5.04	0.000
MA	2	0.2923	0.1245	2.35	0.022
SMA	12	0.3896	0.1326	2.94	0.004
SMA	24	0.7043	0.1757	4.01	0.000
SMA	36	-0.4570	0.1783	-2.56	0.012
OConstant		-0.2960	0.1438	-2.06	0.043

```
Differencing: 1 regular, 1 seasonal of order 12
Number of observations:  Original series 94,
after differencing 81
Residuals:     SS =  103239 (backforecasts
excluded)
               MS =  1395   DF = 74
```

ARIMA $(0,1,2)(1,1,3)^{12}$significant because the p-value of each parameter is smaller than α.

ARIMA $(1,1,1)(1,1,3)^{12}$

Final Estimates of Parameters					
Type		Coef	SE Coef	T	P
AR	1	0.2328	0.1154	2.02	0.047
SAR	12	-1.0001	0.0389	-25.73	0.000
MA	1	1.0416	0.0179	58.18	0.000
SMA	12	0.3038	0.1266	2.40	0.019
SMA	24	0.7557	0.1610	4.69	0.000
SMA	36	-0.3367	0.1582	-2.13	0.037
Constant		-0.37350	0.04307	-8.67	0.000

```
Differencing: 1 regular, 1 seasonal of order 12
Number of observations:  Original series 94,
after differencing 81
Residuals:     SS =  97514.6 (backforecasts
excluded)
               MS =  1317.8   DF = 74
```

ARIMA $(1,1,1)(1,1,3)^{12}$ significant because the p-value of each parameter is smaller than α.

So after a lot of models in overfitting get. However, based on the p-value and the value of SSE most small get optimum model is ARIMA $(1,1,1)(1,1,3)^{12}$.

- Residual test

  The forecast results at the end of the verification testing residual values obtained by subtracting the data forecast results with the original data. After the residual value is known, calculation of the autocorrelation coefficient value of the residual value. If the values of correlation coefficients of residuals for different time lag is not significantly different from zero, the model is considered adequate to be used as a forecasting model. Data from the forecast used to starting from the period November 2016 to December 2017 so that the residual value calculation result data obtained from the difference with the original data forecast period September 2015 to October 2016. In the picture below shows the residual value (residual) models and partial absence of significant autocorrelation. So, ARIMA $(1,1,1)(1,1,3)^{12}$ is the model that corresponds to the original data.

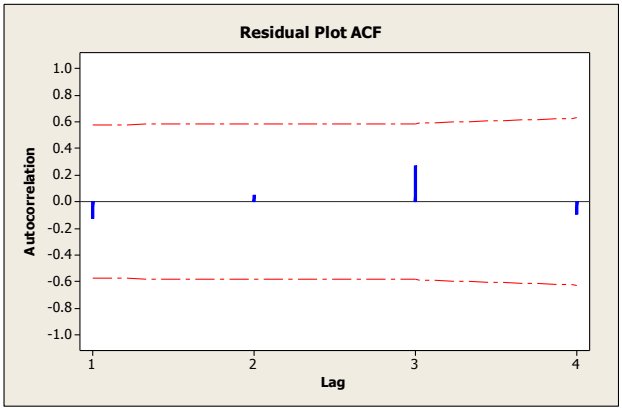


Figure 7. Plot ACF Data Residual

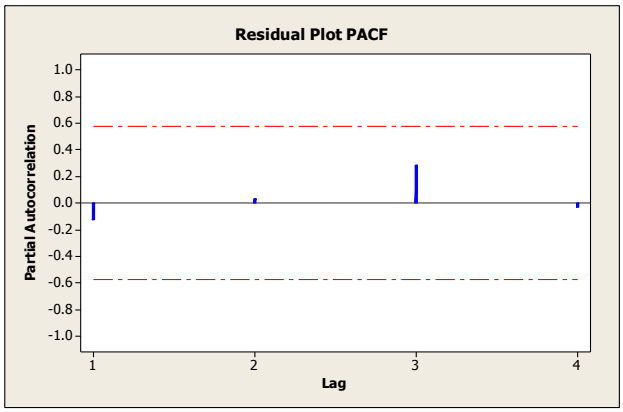


Figure 8. Plot ACF Data Residual

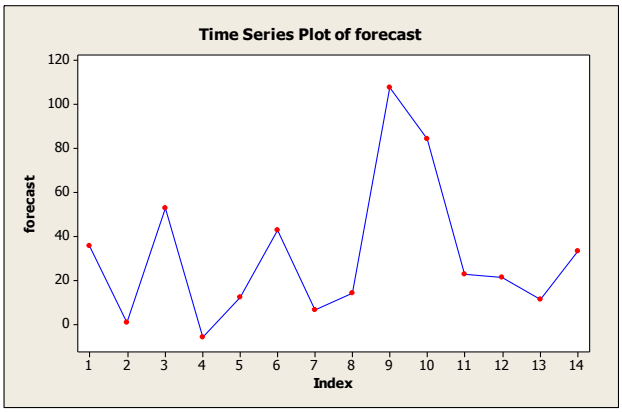


Figure 9.Forcast Data Plot

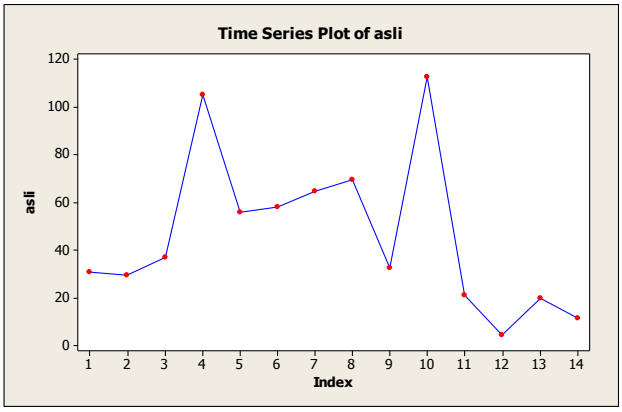
e). Forecasting

Based on the optimum model of ARIMA $(1,1,1)(1,1,3)^{12}$ obtained Palu rainfall forecasts for November 2016 to December 2017 is:

Table 1. Estimated Rainfall in Palu (mm)

Month	Years	
	2016	2017
January		53.10
February		5.74
Marc		12.26
April		42.72
May		6.47
June		14.32
July		107.86
August		84.54
September		22.67
October		21.52
November	35.77	11.39
December	1.04	33.51

Visualization results forecast rainfall in Palu is presented in the form of curves and also presented the original data curve 1 last year (the period from September 2015 to October 2016) in Figure 9 and 10.



Gambar 10. Plot The Original Data

The highest rainfall inPalu at the period November to December 2016 came in November, which is 35,77 mm and the lowest rainfall occurs in December is 1,04 mm. In 2017 the highest rainfall occurs in July is 107,86 mm and the lowest rainfall occurs in February 5,74 mm.

5. Conclusion

From the research process by the method of ARIMA on rainfall data Palu period January 2009 to October 2016 concluded that :

a). Optimum models for forecasting rainfall Palu one years to come (the period

November 2016 to December 2017) is ARIMA $(1,1,1)\ (1,1,3)^{12}$..

b). Based on the results of forecasting overall highest rainfall occurred in July 2017, while the lowest rainfall in December 2016.

c). The level of accuracy of precipitation forecast results still need to be developed with further research, such as the modification of the model is expected to be more in accordance with the conditions of rainfall in the city of Palu.

Acknowledgment

Thanks to the two lecturers who are willing to take the time, junaidi M.Sc., P.hD as first counselor and Lilies Handayani as second counselor. as well as statistical studies program chairman Nur'eni, S.Si., M.Si, as well as all lecturers on the courses of statistics and statistical studies Program Staff.

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Formulation and Optimation of Nanoemulsion Extract of Brown Rice (*Oriza nivara*)

Nur Ain Thomas*, Rani Hiola, Rifkah Anggai

Faculty of Sport and Health Science, State University of Gorontalo

ABSTRACT

Nanoemulsion has an advantage as a medicine in both transdermal and dermal route as well as decreasing the barrier *diffusion* from stratum corneum also increasing the rate of active substances through skin as a *permeation enhancers.* The extract of brown rice is proven to have an anti-oxidant effect with its compound; the flavonoid. This compound is needed as an alternate use of anti-oxidant by utilizing the available resources. An effective yet formulated distribution system formulated in certain dosage form is, however, necessary to ease the application process of the brown rice extract with an anti-oxidant effect. Thus, the extract of brown rice is made into nanoemulsion. This research attempts to invent a formulation and optimization of nanoemulsion of brown rice extract (Oriza Nivara). The optimization of nanoemulsion basis by varying the ratio of surfactant and co-surfactant is the first phase of this study. In the optimization of sweet basis, almond is used as the oil as well as surfactant tween 80 and PEG 400 as co-surfactant. Afterward, a particle size analysis is conducted by using PSA. The filled nanoemulsion basis proceed to the evaluation of physic stability which cover the evaluation of organoleptic, centrifugation, and *freezethaw* in 30 days. The stable basis, based on the physic stabilityevaluation, is progressed to the formulation of nanoemulsion of brown rice extract. The results indicates that the physical formulation of nanoemulsion of brown rice extract is stable without any phase split, the pH of the dosage form is filling the skin's pH, the viscosity is good during the distribution evaluation, also during 30 days, the dosage form is stable according to the *freezethaw* test.

Keywords : formulation, optimization, nanoemulsion, brown rice extract.

ABSTRAK

Nanoemulsion memiliki keunggulan sebagai obat baik transdermal dan rute dermal serta mengurangi difusi penghalang dari stratum korneum juga meningkatkan tingkat zat aktif melalui kulit sebagai permeasi enhancer. Ekstrak beras merah terbukti memiliki efek anti-oksidan dengan senyawa tersebut; flavonoid. Senyawa ini diperlukan sebagai penggunaan alternatif anti-oksidan dengan memanfaatkan sumber daya yang tersedia. Sistem distribusi belum dirumuskan efektif diformulasikan dalam bentuk sediaan tertentu, bagaimanapun, diperlukan untuk mempermudah proses penerapan ekstrak beras merah dengan efek anti-oksidan. Dengan demikian, ekstrak beras merah dibuat menjadi nanoemulsion. Penelitian ini mencoba untuk menciptakan formulasi dan optimalisasi nanoemulsion ekstrak beras merah (Oriza Nivara). Optimasi secara nanoemulsion dengan memvariasikan rasio surfaktan dan co-surfaktan adalah tahap pertama dari penelitian ini. Dalam optimasi dasar manis, almond digunakan sebagai minyak serta surfaktan tween 80 dan PEG 400 sebagai co-surfaktan. Setelah itu, analisis ukuran partikel dilakukan dengan menggunakan PSA. dasar nanoemulsion diisi melanjutkan ke evaluasi stabilitas fisik yang meliputi evaluasi organoleptik, sentrifugasi, dan freezethaw dalam 30 hari. Dasar yang stabil, berdasarkan stabilityevaluation fisik, yang maju ke perumusan nanoemulsion ekstrak beras merah. Hasil menunjukkan bahwa formulasi fisik nanoemulsion ekstrak beras merah stabil tanpa fase split, pH bentuk sediaan mengisi pH kulit, viskositas yang baik selama evaluasi distribusi, juga selama 30 hari, bentuk sediaan stabil menurut tes freezethaw.

Kata kunci: formulasi, optimasi, nanoemulsion, ekstrak beras merah.

*Corresponding author : Nurain Thomas, email : nurain.thomas@gmail.com

1. Introduction

The brown rice extract (*Oryzanivara*) was proofed to have an anti-oxidant effect, decreasing LDL and increasing HDL, also to prevent the lipid oxidation process. This is similar to the research of Chang and Bardenas (1965) that the brown rice contain anthocyanin in addition to the carbohydrate, fat, protein, fiber, and mineral. According to Damanhuri (2005), anthocyanin is a red-colored pigment in the pericarp and tegmen (skin layer) of the rice or in every parts of unhulled rice (gabah).

The extract of brown rice (*Oryzanivara*) which contain natural compound, in this regard, is lacking of the physical form if it is being used topically due to the difficulty of the extract to penetrate the inner layer of the skin and also the lack of comfort during the usage.Undoubtedly, an effective yet formulated system in a certain preparation, to achieve an optimal therapy, is necessary to facilitate the application of the brown rice extract that has anti-oxidant effect. Therefore, the brown rice extract is being made in nanoemulsion preparation.

The nanoemulsion is a developed form of emulsion preparation, which has high solubilization. This can increase the biovailability in a medicine. The nanoemulsion is favorable because of its good stability and increasing the absorption of the active substant in topical application. The nanoemulsion preparation has a clear, and transparent form that can turn this into a valuable thing aesthetically. According to the Schoenwald and Elnagan (1989)nanoemulsion can be applied topically. The nano-sized particle enable the nanoemulsion to go through human skin's layers and decreasing the process of abrasion.

This research aims to formulate stablenanoemulsion preparation from the extract of brown rice (*Oryzanivara*) physically.

2. Methodology

Tools

Most of the tools in the lab; they are: spoon, horn, chemical glass (*Pyrex*), stir bar (*Pyrex*), glass wire equipment (*Pyrex*), rotary evaporator (*Heidolf*®), analytic balance (*Precisa*®), test tube, electric mixer, viscometer, pH meter, centrifugation, particle size analyzer (Nano Delsa TM C, Beckman Coutler), digital microscope (Dino Lite), a set of blender, vial, tube racks, mortar, stamper, porcelain dish.

Materials

Several materials used are brown rice (Oryzanivara), 96%ethanol, sweet almond oil, PEG 400, ethanol, tween 80, citric acid, sodium citrate, a-tocopherol, DMDM hydantoin, NaOH, HCl, and dust magnesium.

Procedure of Research

Preparation

The brown rice sample is being cleaned and being mashed by a blender until become powder with smooth texture.

Extraction

The brown rice powder is pondered up to 4000 grams and being poured into a maceration vessel; ethanol 96% is then being added until the powder is submerged perfectly. The mixed powder is being stirred with a *magnetic stirrer*; leave it on for 24 hours. Afterward, filter the powder with paper filter to get the liquid extract and then it is being concentrated by *rotary evaporator* tool until the texture turns thick. Dry the extract by dryer machine; set up the temperature to 50^{o}C.

Phytochemical Screening

A total of 1 gram of extract of red rice (Oryzanivara) is poured in the test tube, diluted with a few drops of 70% alcohol, and a few drops of 10% NaOH is added into it. The positive results of flavonoid compounds are shown in red constant.

The Optimization of the Basis of Nanoemulsion

The process of making nanoemulsion preparation starts with optimizing oil and water with a mixture of surfactant and co-surfactant. This process is done by mixing both the surfactant and co-surfactant (mixture 1), and add the sweet almond oil; stir it with magnetic stirrer with 200rpm of speed to form a homogeneous mixture (mixture 2). Pour the water to the mixture 2 and stir it until the texture turn into homogeneous. There is an observation for each physical appearance basis formula in 24 hours prior to proceeding to centrifugation test.

Particle Size Analyzer

After the optimization of nanoemulsion basis, the basis with clear color is being processed further by conducting an analysis regarding the particle size by using *Particle* Size*Analyser,Delsa™ Nano*.

Nanoemulsion Ethanol Brown Rice Extract

Based on the results of optimization of nanoemulsion with various kinds of surfactant and co-surfactant in nanoemulsion basis that gives clear appearance proceeded to the process of formulation of brown rice nanoemulsion extract that is shown in the following table.

Physical Evaluation of Nanoemulsion Preparation of Brown Rice Extract (*OryzaNivara*)

1. **pH Evaluation**
   The pH of the preparation can be measure by using potentiometric (pH meter). This is done for 30 days, whereas the pH is measured in the storage in a room temperature.
2. **Viscosity Evaluation**
   The measurement is done by *Viscometer Brookfield*. The vessel is filled with ± 250 mL of preparation that will be tested; a spindle is being installed accordingly until the border of the spindle is dipped into the preparation. Turn on the motor and let the spindle spin until the reading process is stable.
3. **Freeze Thaw Evaluation**
   The nanoemulsion preparation is kept at low temperature (5^{o}C) for 24 hours, it is further removed and placed at 40^{o}C for 24 hours; this process is counted as 1 process. This experiment is done for seven cycles.
4. **Evaluation Centrifugation**
   The nanoemulsion preparation is being putted into a centrifugation tube and then being centrifuged at 3750 rpm for 30 minutes. This test depict the stability of nanoemulsion due to the effect of gravity equivalent for a year.

3. Result

Phytochemical Screening Test

The flavonoid test in brown rice (Oryzanivara) ethanol extract is due in three methods namely NaOH, *Wilstarter*, and *Bate-smith* that shows the color change to red, constant, or orange as depicted in the following table.

Table 3. Phytochemical Screening Results

Compound	Methods	Reagent	The Results of the Test	Details
Flavonoid	NaOH	NaOH 10%	red	(+)
	Wilstater	HCl + Mg	red	(+)
	Bate-smith	HCl	orange	(+)

Optimization of Nanoemulsion Basis

The phase of optimization of nanoemulsion basis is done by varying the concentration of both surfactant – co-surfactant and there is a visible basis with clear physical appearance in F10 and F11 as shown in the table as follows.

Table 4. The Optimization of Nanoemulsion Basis; The Comparison between Oil and Surfactant and Co-surfactant Mixed

Ingredient	Formula %										
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
	1:1	1:2	1:3	1:4	1:5	1:6	1:7	1:8	1:9	1:10	1:11
Sweet almond oil	5	5	5	5	5	5	5	5	5	5	5
Tween 80	3,5	7,5	10,5	12,5	15	17,5	20	22,5	25	27,5	30
PEG 400	1,5	2,5	4,5	7,5	10	12,5	15	17,5	20	22,5	25
Water	100	100	100	100	100	100	100	100	100	100	100
Results	K	K	K	K	K	K	K	K	AK	J	J

Notes:
AK : a little bit muddy
K : muddy
J : clear

Table 5. The Formulation of Nanoemulsion Ethanol Brown Rice Extract (*Oryza nivara*)

Material	Formula %		
	$F_{10}A$	**$F_{10}B$**	**$F_{10}C$**
	1:10	1:10	1:10
Ethanol extract of brown rice	**5**	**10**	**15**
Sweet almond oil	5	5	5
Tween 80	27,5	27,5	27,5
PEG 400	22,5	22,5	22,5
α tokoferol	0,05	0,05	0,05
Citric acid	0,324	0,324	0,324
Citric natrium	1,79	1,79	1,79
DMDM hydantoin	0,1	0,1	0,1
Water	100	100	100

The evaluation of physical stability of nanoemulsion preparation of brown rice extract

Inorganoleptic observation, the nanoemulsion preparation of ethanol extract of brown rice (*Oryzanivara*) shows physical appearance as translucent red color, homogenous, and possess distinct tween smell, as described by the following table

Table 6. Organoleptic observation

Observation	**5%**	**10%**	**15%**
Organoleptic	RedTranslucent Distinct tween smell Homogenous	RedTranslucent Distinct tween smell Homogenous	RedTranslucent Distinct tween smell Homogenous

pH Evaluation

The result of pH evaluation of nanoemulsion preparation of ethanol extract of brown rice (*Oryzanivara*) shows no change in pH level during periods of storage on T_0 until T_{30} in temperature ranged from 15-30^{o}C, as seen in the following table:

Table 7. pH evaluation

Time/T (days)	**pH**		
	5%	**10%**	**15%**
0	7,15±0,04	7,19±0,03	7,11±0,01
5	7,14±0,04	7,13±0,02	7,15±0,03
1/0	7,20±0,01	7,15±0,02	7,15±0,03
15	7,17±0,05	7,14±0,01	7,13±0,02
20	7,17±0,04	7,17±0,02	7,11±0,01
25	7,16±0,01	7,14±0,02	7,14±0,04
30	7,21±0,01	7,14±0,03	7,22±0,01

Evaluation Viscosity

Results of the evaluation of the viscosity of the preparation nanoemulsi ethanol extract of red rice (Oryza nivara) showed no change in viscosity during storage at T0 until T30 at 15-30^{o}C temperature which can be seen in the following table.

Table 8. Viscosity Evaluation

time/T (days)	**Viscosity**		
	5%	**10%**	**15%**
0	1.108 ±4,04	1.106±4,58	1.109±3,05
5	1.120±7	1.122±3,05	1.124±3,21
10	1.128±3,05	1.128±2,64	1.123±3,51
15	1.121±3,78	1.127±1	1.132±4,16
20	1.125±2	1.110±8,5	1.133±3,60
25	1.122±4,16	1.125±2,08	1.172±1,52
30	1.107±5,29	1.190±3,05	1.105±3,05

Freeze thaw evaluation

Freeze thaw evaluation is the evaluation in which the preparation is exposed in seven different cycles (an exposure to temperature of 40^{o}C and 4^{o}C, each in 48 hours, per cycle) and further observed the change in pH level and viscosity of the preparation.

Table 9.pH evaluation on temperature5^{o}C and 40^{o}C

Time/T (days)	pH		
	5%	10%	15%
0	7,02 ±0,01	7,14±0,01	7,16±0,01
5	7,17 ±0,01	7,12±0,01	7,19±0,01
10	7,15 ±0,02	7,15±0,03	7,09±0,01
15	7,10 ±0,01	7,12±0,01	7,2±0,03
20	7,14 ±0,01	7,14±0,03	7,16±0,03
25	7,15±0,01	7,12±0,01	7,14±0,03
30	7,22±0,01	7,13±0,03	7,20±0,01

Table 10. Viscosity evaluation on temperature 5^{o}C dan 40^{o}C

Time/ T (days)	Viscosity		
	5%	10%	15%
0	1.127±3,05	1.119±2	1.109±2,08
5	1.121±4,58	1.119±2,08	1.190±2
10	1.129±2	1.126±3,05	1.125±2
15	1.133±5,29	1.125±2	1.129±2,51
20	1.124±3,05	1.126±3,05	1.122±3,78
25	1.126±5,50	1.123±2	1.122±2,64
30	1.121±1,52	1.124±3,60	1.123±3,05

Centrifugation evaluation

The result of centrifugation evaluation of nanoemulsion preparation of ethanol extract of brown rice (*Oryzanivara*) with speed of 3000 rpm during 15 minutes shows no splitting phase, as seen in the graph.

Table 12. Centrifugation evaluation

	Physical appearance		
	5%	10%	15%
Result	-	-	-

Information: (-) : Not splitting

4. Discussion

Nanoemulsion is a developed form of emulsion preparation, known for being stable and increasing the absorption of active substance in topical application. Nanoemulsion preparation is mainly used in topical application with local or systemic effect. The aim of this study is to formulate nanoemulsion preparation from stable brown rice extract (*Oryzanivara*).

The first step on this research is to grind the brown rice, followed with extraction by maceration method applied within 3x24 hours, the solvent is replaced each hour until the filtrate is colorless. The diluted extract then is tested by phytochemical screening test, which Nohong (2009) claimed as a proper method to uncover the existence of secondary metabolite substances of plants. The table 4 shows that brown rice extract is positive in containing flavonoid substance observed by*Wilstater* and *Bate-Smith* method, and few drops of 10% NaOH reactor. The extraction result is concentrated with rotary evaporator and dried in oven in a temperature of 50^{o}C.

The next optimization of nanoemulsion base, consisting of oil mixed from surfactant – co-surfactant and water. The base optimization is conducted by creating 11 formulas by variating surfactant concentrate, i.e., Tween 80 as surfactant and PEG 400 as co-surfactant. As seen in table 4those are variated from low to high concentrate ratio by observing the physical appearance of the base that shows clearness. The result of base optimization in table 4 shows a turbid appearance on formula 1 – formula 9, in contrary, Formula 10 (tween 80 27,5%, PEG 400 22,5% and F11 (tween 80 30%, PEG 400 25%) show clear appearance. Turbid appearance happens because the surfactant is not able to lower the surface tension, layer the surface of oil globule as a dispersed phase, and co-surfactant to increase the activity of surfactant in layering gaps between surfactants on the surface of globule, in which Malakar (2011) claimed that nanoemulsion preparation occurs because of the précised ratio, oil, mixture of surfactant – co-surfactant, and water. The base showing clear appearance is

processed by analysis of particle size by using Delsa™ Nano tool, with the test result that shows nanoemulsion preparation on Formula 10 has 23,4 nm diameter of globule.

Afterwards, the process continues to the phase of creation of nanoemulosion preparation of ethanol extract of brown rice (*Oryzanivara*). The table 5 explains that the nanoemulsion preparation shows lucent physical appearance by variation of 5%, 10%, and 15%. The preparation then is proceeded to stability test. (which involves pH test, viscosity test, freeze thaw test, and centrifugation test) Purnamasari (2012) once argued that it is needed to evaluate the nanoemulsionpreparation in order to determine the parameter before and after stability test, thus one can determine the physical stability of the preparation. Started by organoleptic test (involves color, smell, and homogeneity of the nanoemulsion preparation), the table 6 signifies there are three formulation of the preparation that possess traits of translucent red, homogenous, and has distinct smell of tween. Afterwards, the preparation then was tested for its pH stability and viscosity in a temperature of 15-30^{o} Celsius. The test resulted that the pH level of the preparation during T_0-T_{30} was approximately ±7. It was appropriate with the pH level of physiological liquid of body, which is about 7,34-7,45. On the other hand, the table 8 depicts that the viscosity level is about ±1000. Purnamasari (2012) mentioned that the nanoemulsion preparation shows traits of pseudoplastic fluid, nearly similar to Newtonian fluid. This is due that nanoemulsion preparation has very small particle size, similar to a single solution, resulting in low viscosity. During freeze thaw stability test, the pH level and viscosity of the preparation were observed in two conditions, each in 40^{o}C and 5^{o}C during seven cycles or a month. The result was depicted in table 9, where the pH level of the preparation was 6-7 and the viscosity was ±1.000. Husni (2014) asserted that there was no signs of phase splitting such as sedimentation, break, or inflation during freeze thaw test. This indicated that the preparation is stable either in low or high temperature. The test result is analyzed by *Annava* statistical analysis to observe significant changes from each formula in every test, given that a significant change is (α=5%)= 0,05, resulting in no significant changes. As seen in table 12, the evaluation result of naanoemulsion preparation of ethanol extract of brown rice by using centrifugation tool (in 3000 rpm speed) shows no phase splitting in the preparation. This test was done to measure the stability of the preparation during one year duration.

5. Conclusion

Based on the result, brown rice extract can be formulated into a physically stable nanoemulsion preparation. It is needed to conduct further researches as an antiwrinkle. An irritation test also needed to be conducted to provide better explanation

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Emulgel Formulation of Purified Leaf Extract of Cherry (*Muntingia calabura* L) and Antibacterial Activity Test on *Staphylococcus aureus*

Masyithah Maghfirah[1*], Abd Rahman Razak[2] , Yuliet[1]

[1]Department of Pharmacy, Faculty of Sciences, Tadulako University, Palu
[2]Department of Chemistry, Faculty of Sciences, Tadulako University, Palu

ABSTRACT

Research on the antibacterial activity test of emulgel of purified leaves extract of cherry (*Mutingia calabura* L) on the growth of *Staphylococcus aureus* had been done. This study aims to determine the effect of the use of Carbopol 940 and glycerin on the physical quality and stability of emulgel of purified leaves extract of cherry, as well as the interaction of the use of Carbopol 940 and purified glycerin in emulgel extract and to determine the inhibition of emulgel of purified leaves extract of cherry against *Staphylococcus aureus*. Purified leaves extract of cherry was obtained by maceration using 96% ethanol and then purified by n-hexane and ethyl acetate. The study design used a completely randomized design with 2 factors: factor A is the concentration of Carbopol 940 which consists of 4 levels (0.5%, 1%, 1.5% and 2%) and factor B is a glycerin which consists of 4 levels (10%, 15%, 20% and 25%). Evaluation of the stability include organoleptic, homogenity, pH, viscosity, and dispersive power and antibacterial activity test. The results showed that the use of Carbopol 940 and glycerin affected the physical quality and stability of emulgel of purified leaves extract of cherry, as well as there was interaction between carbopol 940 and glycerin in emulgel of purified leaves extract of cherry. Emulgel of purified leaves extract of cherry with concentration of 1.5% carbopol and 10% glycerin (A3B1) have inhibitory activity against *Staphylococcus aureus* with inhibition diameter of 17.75 mm.

Keywords: purified extract, cherry leaves, Glycerin, Carbopol 940, *Staphylococcus aureus*.

ABSTRAK

Penelitian tentang uji aktivitas antibakteri emulgel ekstrak terpurifikasi daun kersen (*Mutingia calabura* L) terhadap pertumbuhan bakteri *Staphylococcus aureus* telah dilakukan. Penelitian ini bertujuan untuk mengetahui pengaruh penggunaan carbopol 940 dan gliserin terhadap mutu fisik dan stabilitas emulgel ekstrak terpurifikasi daun kersen, serta interaksi penggunaan carbopol 940 dan gliserin dalam emulgel ekstrak terpurifikasi dan mengetahui daya hambat emulgel ekstrak terpurifikasi daun kersen terhadap bakteri *Staphylococcus aureus.* Ekstrak terpurifikasi daun kersen diperoleh dengan cara maserasi menggunakan etanol 96% kemudian dilakukan purifikasi dengan n-heksan dan etil asetat. Desain penelitian menggunakan rancangan acak lengkap pola faktorial dengan 2 faktor yaitu faktor A adalah konsentrasi carbopol 940 yang terdiri dari 4 taraf (0,5%, 1%, 1,5% dan 2%) dan faktor B adalah gliserin yang terdiri dari 4 taraf (10%, 15%, 20%, dan 25%). Evaluasi stabilitas sediaan mencakup uji organoleptis, uji homogenitas, uji PH, uji

viskositas, uji daya sebar dan uji aktivitas antibakteri. Hasil penelitian menunjukkan bahwa penggunaan carbopol 940 dan gliserin mempengaruhi mutu fisik dan stablitas emulgel ekstrak terpurifikasi daun kersen, serta terdapat interaksi penggunaan carbopol 940 dan gliserin dalam emulgel ekstrak terpurifikasi daun kersen. Emulgel ekstrak terpurifikasi daun kersen dengan konsentrasi carbopol 1,5% dan gliserin 10% (A3B1) memiliki daya hambat terhadap bakteri *Staphylococcus aureus* dengan diameter daya hambat sebesar 17,75 mm.

Kata kunci: Ekstrak Terpurifikasi, Daun Kersen, Gliserin, Carbopol 940, *Staphylococcus aureus*

*Corresponding author : Masyithah Maghfirah, email : masyithah_maghfirah@yahoo.com

1. Introduction

The skin is the largest organ in the human body and is the primary line of defense against infection from outside. The skin has its own immune system is destroyed by microorganisms (Davies, 1998). Human life in nature are always in contact with microorganisms, bacteria, viruses, fungi, parasites and various forms of life. Infection occurs when microorganisms enter the body causing various disturbances of normal physiology of the body causing infectious diseases. Infectious diseases have the ability to spread to other people healthy so that the population of patients can be extended (Adrian, 2009).

Infectious diseases is one of the problems in the health sector that continues to grow. Infection is a major cause of disease in the world, especially in the tropics, such as Indonesia because of low environmental sanitation so that support to grow subur.Penyakit microbial infections in humans and animals can reduce health of the body resulting in a decrease in productivity and reproducibility even death (Adrian, 2009).

Staphylococcus aureus is one of a group of bacteria that can cause various diseases as a result of infection vary in body tissues such as skin infections. *Staphylococcus aureus* causes a variety of infections purulent (suppurative diseases) and toksinosis. *Staphylococcus aureus* is a major pathogenic bacteria in humans. *Staphylococcus aureus* is coagulase-positive, which differentiates it from other species. Almost everyone has experienced a variety of *Staphylococcus aureus* infection during their lifetime, from severe food poisoning or minor skin infections, to infections that can not be cured (Darwani, 2009).

The bacteria also cause intoxication and the occurrence of various infections such as pimples, boils, pneumonia, empyema, endocarditis or fester on the body manapun.Leukosidin, bacterial toxins can be lethal in human white blood cells affected by the bacterial toxin can ini.Infeksi also caused by direct contamination of wounds, for example in post-surgical wound infections by *Staphylococcus aureus* or infections after trauma. The bacteria are spread and bacteremia, the clinical picture is similar to that seen in the clinical picture of other infections through the bloodstream (Darwani, 2009).

There is a trend back to nature among the public led to the therapeutic use of natural materials more attractive as compared to the synthetic chemicals or semisintesis.Daun

cherry also called Muntingia calabura Lmemiliki contain tannins, flavonoids, polyphenols and saponins which can be used as an antibacterial (Mintowati, et al 2013). Previous research has been done on the test antibacterial activity of extracts and fractions of leaves cherry at a concentration of 10%, 20%, and 40% against *Staphylococcus aureus* showed that extracts and fractions has antibacterial activity against bacteria test except the fraction of n-hexane (Yuliani, 2014).

Purified extract that is an outcome that just sum up the selective extraction of compounds useful as small as possible and limiting substances that are not needed as components of substances involved tersari ballast. In the purification process used solvent n-hexane and ethyl acetate with the aim to attract non-polar components.

Purified extract of leaves of cherry formulated in dosage emulgel to increase the effectiveness of the use of leaf cherry as antibakteri.Sediaan emulgel as antibacterials are still rare, and its use is still more desirable emulgel terbatas.Penggunaan dosage when compared with emulsion or gel preparation only. Gel has the advantage of relatively high water content so as to provide the humidity that is cool and gives comfort to the skin (Mitsui, 1997) .Sedangkan emulsion has the advantage could form a mutually immiscible perfomed be able to come together to form a homogeneous preparation danstabil (Magdy 2004). In the oil phase emulsion systems are functioning as an emollient or occlusive will prevent evaporation so that the water content in dalamkulit can be maintained. Increased oklusivitas of the oil phase of the emulsion system will increase the hydration of the stratum corneum and this is associated with a reduced diffusion barrier bagizat dissolved. Hence the emulsion system in emulgel dosage forms will provide a high penetration of the skin (Block, 1996).

Gelling agent plays an important role in making emulgel because the gel system can increase the viscosity of dosage. Humectant may serve to maintain the consistency of moist preparations, namely to keep the water content at emulgel. According to Islam et al. (2004), Carbopol 940 is a gel forming material which has a high viscosity at low concentrations. Glycerin is a humectant that is derived from plant fats, so the glycerin safely used in topical preparations (Rowe, Sheskey and Quiin 2009; Highland, 2011).

2. Experimental

Extraction

Dried cherry leaves as much as 4.648 grams was inserted into the maceration jar and added 27 L of ethanol 96% so that the powder is submerged. Left for 3 x 24 hours and then closed stirring occasionally. After 3 days filtered to obtain a filtrate. Then the filtrate obtained was concentrated by rotary evaporator to obtain a thick extract.

Extracts Purification

Cherry leaf extract as much as 753 g diluted with enough ethanol was added in 1490 mL of distilled water and further homogenized, purified again with n-hexane solvent was added 1233 mL using a separating funnel, be repeated 3 times until the green color disappear. Insoluble fraction of purified n-hexane solvent is added back to 1233 mL ethyl acetate and purified again using a separating funnel 3 times, the end result is called refining purified extract.

Phytochemical screening

a. Flavonoids test

Weighed 0.1 g of purified extract of leaves of cherry added 0.2 g Mg powder, then added 5 mL of concentrated hydrochloric acid. If the form of orange, red or yellow indicate the presence of flavonoids (Harbone, 1987).

b. Phenolic test

Weighed 0.1 g of purified extract of leaves of cherry Add 5 mL of 1% FeCl3, if there is a change in green, red, purple, blue / black showed phenolic compounds (Harbone, 1987).

c. Saponin test

Weighed 0.1 g cherry leaf extract purified water is adde and dheated. The solution was cooled then shaken. Appearance lather for 30 seconds showed saponin (Herbone, 1987).

d. Steroids/Terpenoid test

A total of 0.1 purified extract of leaves of cherry added 1.25 mL of ethanol and then heated and filtered. The filtrate was evaporated and then added ether. Ether layer pipette and tested. If the reagent is added Lieberman Buchard and formed as many as 3 drops red / purple, positive for triterpenoids. If the green color is formed, it is positive for the steroid (Harbone, 1987).

e. Alkaloid test

Dissolved 0.1 g of purified extract of leaves of cherry with a few ml of 2N sulfuric acid and filtered. Then the filtrate was tested by adding one or two drops of reagent Mayer, Wagner and Dragendorff different in a test tube. A positive reaction is characterized by the deposition of a white or yellowish in reagent Mayer, the appearance of red-black color on the reagent Wagner, and the orange precipitate at reagent Dragendorff (Harbone, 1987).

f. Tanin test

Weighed 0.1 g of purified extract of leaves of cherry added 10 mL of distilled water, filtered and the filtrate was added reagents FeCl 1% as much as 5 mL. Dark blue or black color indicates the presence of tannins (Harbone, 1987).

Formulation of Emulgel

Emulgel purified extract of leaves of cherry made according to a formula contained in Table 3.1, each formula is made as much as 50 grams three times replication.

Table 1. Basic formula of emulgel of purified leaves extract of cherry (*Muntingia calabura* L)

Ingredients	Concentration (100%)
Purified extract	10
Carbopol 940	**0,5 – 2 (according to treatment)**
Trietanolamin	1,5
Parafin cair	2
Tween 80 dan span 80	3
Gliserin	**10 – 25 (according to treatment)**
Metil paraben	0,2
Propil paraben	0,02
Aquadest ad	100

Method for production of emulgel of purified leaves extract of cherry

Carbopol 940 was developed in 11 mL of distilled water until fluffy. The oil phase and the water phase was prepared separately by mixing each component at 60 ° C. The oil phase was added to the water phase is then mixed and ground until homogeneous by heating at a temperature of

70-80^{o}C (Jain, 2010). Mixing is continued without heating for 2 minutes to form an emulsion. The emulsion is formed is then mixed with Carbopol 940 which has inflated and then crushed until homogeneous. TEA is added to a pH of 4 to 6.5.

Stability Test of Emulgel

Organoleptic test

Organoleptic evaluation visually, from the smell and color, by the way to smell and observe the color change in dosage. Performed on days 0, 7, and 14 after manufacture emulgel.

Homogenity test

Viewing the size of the particles on the slide, to determine the presence of coarse particles on sediaan.Sediaan emulgel smeared on a glass slide and then visually observed particle size is done on days 0, 7, and 14 after manufacture emulgel.

Viscocity test

The viscosity measurements using a vikometer (Brookfield) by way emulgel put in a container and mounted on a portable Viscotester. Viscosity emulgel known by watching the numbers on the screen viscometer. This test is performed on days 0, 7 and 14. days after emulgel made.

Dispersive power test

Dispersive power test conducted by emulgel weighed weighing 1 g and placed in the middle of a round glass scale. Round glass top and weights with a total weight of 125 g is placed on emulgel, allowed to stand for one minute, noting diameter distribution is done on days 0, 7, and 14 after manufacture emulgel (Garg, 2002).

pH test

Evaluation of pH using a pH meter (Consort C561) which was calibrated using standard buffer solution pH 4, 10, and 7, then the tool was added to the preparation emulgel pH. PH measurements carried out on days 0, 7, and 14 after the making of emulgel.

Antibacterial Activity Test

Staphylococcus aureus is taken as 1 ml and then added media NA sterile still warm 20 ml put in a petri dish and then homogenized and allowed to solidify, and then made a hole resembling the well, then pipette emulgel extract purified leaf cherry antibacterial many as 100 mL and then put into wellbore which has been marked in accordance concentrations of each and then incubated at 37ºC for 24 hours. Measurement of the inhibition zone formed around the disc using a caliper.

Data analysis

Data were analyzed by completely randomized design factorial pattern with a degree of confidence of 95% ($\alpha = 0.05$). This test is used to determine the effect of variations in the concentration of Carbopol 940 and glycerin on the quality of physical preparation and diameter area emulgel inhibition against *Staphylococcus aureus*. Pengolahan data is done using software SPSS 16.

3. Result and Discussion

Simplicia cherry leaves as much as 4648 grams was extracted by maceration method using ethanol 96% as much as 27 L. results obtained cherry leaf extract ethanol condensed as much as 753 grams. The yield obtained is 16.20% (w / w).

Purification

Based on the results of cherry leaf extract purification process using n-hexane and ethyl acetate, purified extract obtained as much as 270.39 grams with the results of yield of 35.91% (w / w).

Phytochemical Screening

Phytochemical screening includes checking for the presence of several groups of secondary

metabolites such as flavonoids, phenolics, saponins, steroids, terpenoids, alkaloids and tannins. Based on testing that has been done shows that the purified extract positive cherry leaf contains flavonoids, phenolics, saponins, triterpenoids, alkaloids, and tannins (Appendix 3). This class of compounds that have the potential as an antibacterial. Screening results can be seen in Table 3:

Table 3. Results of phytochemical screening purified extract of leaves of cherry

group Compounds	Positive results	results Identification
Flavonoid	The solution is red, orange or yellow	+
Fenolik	The solution is green, red, purple, blue or black	+
Saponin	formed foam	+
Steroid	Green solution	-
Triterpenoid	The solution is red or purple	+
Alkaloid	Precipitates a white solid (Mayer), red-black solution (Wagner), or precipitate orange (Dragendorff)	+
Tanin	The solution was dark blue or black	+

Description: + = Extract contains a class of compounds tested
- = Extract not contain compounds tested

Evaluation of Stability Emulgel

The results of organoleptic inspection of preparations emulgel cherry leaf extract is done at 16 formula in which each formula replicated three times. Inspection is done visually. Observations can be seen in Table 4 below:

Table 4 Results of organoleptic test Emulgel purified extract of leaves of cherry (*Muntingia calabura* L)

Formula		days to		
		0	7	14
A1B1	color	ct	Ct	Ct
	aroma	+	+	+
A2B1	color	c	C	C
	aroma	+	+	+
A3B1	color	c	C	C
	aroma	+	+	+
A4B1	color	cm	Cm	Cm
	aroma	+	+	+
A1B2	color	ct	Ct	Ct
	aroma	+	+	+
A2B2	color	c	C	C
	aroma	+	+	+
A3B2	color	c	C	C
	aroma	+	+	+
A4B2	color	cm	Cm	Cm
	aroma	+	+	+
A1B3	color	ct	Ct	Ct
	aroma	+	+	+
A2B3	color	c	C	C
	aroma	+	+	+
A3B3	color	c	C	C
	aroma	+	+	+
A4B3	color	cm	Cm	Cm
	aroma	+	+	+
A1B4	color	ct	Ct	Ct
	aroma	+	+	+
A2B4	color	c	C	C
	aroma	+	+	+
A3B4	color	c	C	C
	aroma	+	+	+
A4B4	color	cm	Cm	Cm
	aroma	+	+	+

Information: color: (ct) = dark brown
aroma: (+) = distinctive aroma extract
(c) = brown
(cm) = light brown
aroma: (+) = distinctive aroma extract

The observation of the 16 formula organoleptic observed visually show that all preparations have color and aroma remain stable during 14 days of storage at room temperature.

Homogeneity test

The results of the examination of homogeneity emulgel estrak purified preparations cherry leaf is done at 16 formula in which each formula is replicated three kali. Pemeriksaan done visually. Observations can be seen in Table 5 below:

Table 5 Homogeneity emulgel preparations purified extract of leaves of cherry

Formula	Hari ke-		
	0	7	14
A1B1	+	+	+
A2B1	+	+	+
A3B1	+	+	+
A4B1	+	+	+
A1B2	+	+	+
A2B2	+	+	+
A3B2	+	+	+
A4B2	+	+	+
A1B3	+	+	+
A2B3	+	+	+
A3B3	+	+	+
A4B3	+	+	+
A1B4	+	+	+
A2B4	+	+	+
A3B4	+	+	+
A4B4	+	+	+

Description: (+) = homogeneous

(-) = Not homogeneous

Viscosity test

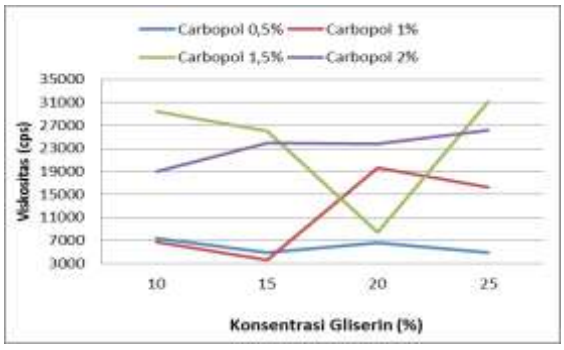

Figure 1 Interaction between Carbopol and glycerin concentration on viscosity grades

Figure 1. shows the interaction because there are pieces line indicated by the graph. The highest viscosity values contained in the formula A3B4 (Carbopol 940 concentration of 1.5% and 25% glycerin). While the lowest viscosity values in the formula A2B2 (940 Carbopol concentration of 1% and 15% glycerin).

Scatter Power Test

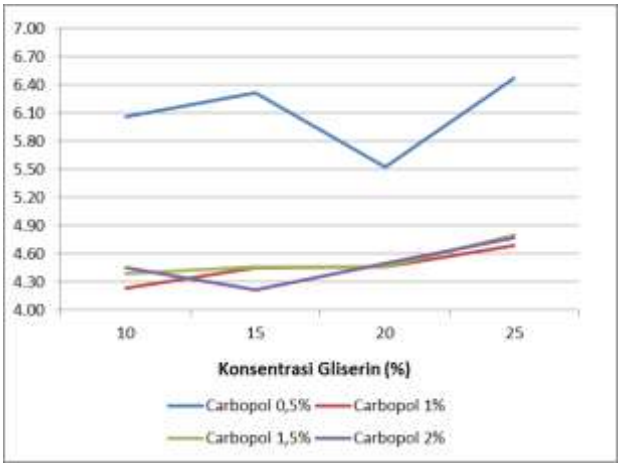

Figure 2 Interaction between Carbopol and glycerin concentration against the value of the spread

Figure 2 shows the interaction between the concentration of Carbopol 940 1%, 1.5%, and 2% to the concentration of glycerin because there are pieces line indicated by the graph. While the concentration of Carbopol 940 0.5% did not have any interaction due to a concentration of 0.5% lines do not intersect with another line. Value of the scatter is highest in the formula A1B4 (Carbopol 940 concentration of 0.5% and 25% glycerin). While the value of the scatter in the formula A4B2 lowest (2% concentration Carbopol 940 and 15% glycerol).

pH test

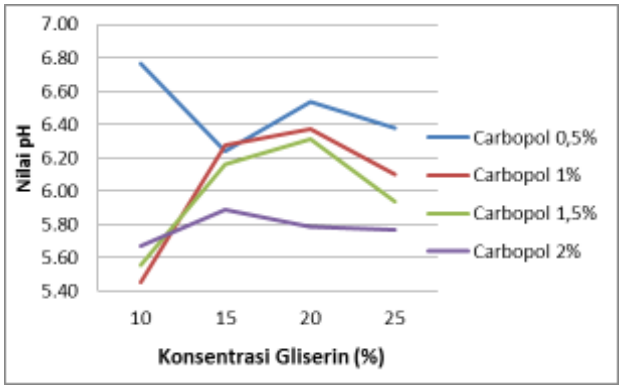

Figure 3 Interaction between Carbopol and glycerin concentration of the pH value

Figure 3 shows the interaction because there are pieces line indicated by the graph. The pH value is highest in the formula A1B1 (Carbopol 940 concentration of 0.5% and 10% glycerin). While the value of the formula A2B1 lowest pH (concentration of 1% Carbopol 940 and 10% glycerol).

Antibacterial Activity Test

The results of antibacterial activity test preparation emulgel purified extract of leaves of cherry performed on the best formula is Carbopol concentration of 1.5% glycerine 10% (A3B1) with three repetitions replication. Observations can be seen in Table 6 below:

Table 6 Results of Antibacterial Activity Test preparations Emulgel purified extract of leaves of cherry (Muntingia calabura L) Against *Staphylococcus aureus* Bacteria.

treatment	Inhibition area diameter (mm)			Average
	1	2	3	(mm)
A3B1	17,75	18,00	17,50	17,75
Extract	17,78	18,00	18,02	17,93

5. Conclusions

1. The use of Carbopol 940 and glycerin affect the physical quality and stability emulgel purified extract of leaves of cherry.
2. Interaction use of Carbopol 940 and glycerin in emulgel purified extract of leaves of cherry.
3. Emulgel cherry leaf extract purified with Carbopol concentration of 1.5% and 10% glycerin (A3B1) have inhibitory against *Staphylococcus aureus* with inhibition diameter of 17.75 mmAcknowledgment

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Preparation and Antioxidant Activity Test of Drug Combination Skin Tea Mangosteen (*Garcinia mangostana* L.) and Rosella (*Hibiscus sabdariffa*)

Farah Diba S*, Jamaluddin, Evi Sulastri

Department of Pharmacy, Faculty of Mathematics and Natural Sciences, Tadulako University

ABSTRACT

The purpose of this study was to determine the effect of the combination of cider rosella flower petals and mangosteen rind in the preparation of medicinal teas to its antioxidant activity (Value IC_{50}). Both sari created by the extraction process digestion method using water-soluble. Preparations medicinal tea made within 5 formula by comparison sari rosella flower petals and mangosteen rind as follows F1 (100:0ml) F2 (25:75ml), F3 (50:50ml), F4 (75:25ml), F5 (0:100ml). Physical stability test was conducted on the organoleptic test, pH test, and test the clarity during 14 days of storage. Meanwhile test the antioxidant activity using DPPH method were then analyzed using linear regression equations, and physical stability testing methods were statistically analyzed using *paired samples T-test*. The results showed the fifth formula medicinal tea has a good physical stability during storage of 14 days, and the IC_{50} value of the five formulas included in the category of very powerful antioxidant activity. And from the formula of the highest is F5 2,60 ppm and from the results of the combination of cider rosella flower petals and mangosteen rind on a formula F3 has antioxidant activity (Value IC_{50}) is the highest of 3.87 ppm.

Key words: Medicine Tea, Mangosteen (*Garcinia mangostana*), Roselle (*Hibiscus sabdariffa* L), Antioxidants.

ABSTRAK

Tujuan penelitian ini adalah untuk mengetahui pengaruh kombinasi sari kelopak bunga rosella dan kulit buah manggis dalam sediaan teh obat terhadap aktivitas antioksidannya (Nilai IC_{50}). Kedua sari dibuat dengan proses ekstraksi metode digesti menggunakan pelarut air. Sediaan teh obat dibuat dalam 5 formula dengan perbandingan sari kelopak bunga rosella dan kulit buah manggis sebagai berikut F1 (100:0ml) F2 (25:75ml), F3 (50:50ml), F4 (75:25ml), F5 (0:100ml). Uji stabilitas fisik yang dilakukan meliputi uji organoleptis, pengujian pH, dan uji kejernihan selama 14 hari penyimpanan. Sementara itu uji aktivitas antioksidan menggunakan metode peredaman DPPH selanjutnya dianalisis menggunakan persamaan regresi linear, dan pengujian stabilitas fisik dianalisis secara statistik menggunakan metode *paired samples T test.* Hasil penelitian menunjukkan kelima formula teh obat memiliki stabilitas fisik yang baik selama penyimpanan 14 hari, dan nilai IC_{50} dari kelima formula termasuk dalam kategori aktivitas antioksidan yang sangat kuat. Dan dari hasil formula yang tertinggi ialah F5 sebesar 2,60 ppm dan dari hasil kombinasi sari kelopak bunga

rosella dan kulit buah manggis pada formula F3 memiliki aktivitas antioksidan (Nilai IC_{50}) tertinggi sebesar 3,87 ppm.

Kata kunci: Teh Obat, Manggis (*Garcinia mangostana* L.), Rosella (*Hibiscus sabdariffa*), Antioksidan.

***Corresponding author :** Farah Diba, email : farah.diba9937@gmail.com

1. Introduction

Antioxidants serve to neutralize free radicals that atoms and electrons unpaired electron pair gain and become stable. The existence of antioxidants can protect the body from a variety of degenerative diseases and cancer. Besides antioxidants also help suppress the aging process / antiaging (Andriyanti, 2009).

The mangosteen fruit (Garcinia mangostana) is a tropical fruit that is popular with the people of Indonesia. Generally people are eating the fruit, the fruit skin is discarded. At the time of harvest, mangosteen rind waste can be utilized as food products and beverages and pharmaceuticals which have potential antioxidant activity alami.Kulit mangosteen fruit has antioxidant activity obtained from phenol compounds such as xanton (Asep et al, 2012).

The statement was supported by research Indra et al, (2011) which states that the mangosteen rind IC50 value of 8.667 ppm. Dyahnugra et al, (2015) reported that from an extract of mangosteen rind has antioxidant activity of 84.42% and total phenol by 41,12mg / g sample.

Besides mangosteen rind, other plants that have high antioxidant activity is rosella flower petals. Essential ingredients contained in rosella flower petals is the pigment anthocyanin. The anthocyanin pigments that form a reddish purple color at rosella flower petals that act as antioxidants (Mardiah, 2009).

Based on the results of research conducted by Ningrum, D. (2012) suggest that the ability of dried rosella flower petals to capture free radicals DPPH (1,1-diphenyl-2-picrylhydrazyl) amounted to 75.59%, and total phenol of 6.491 ± 0.34 mg / g. Research from Lukitaningsih et al (2013) reported that the rosella (Hibisbus sabdariffa L.) has the ability to capture a radical DPPH was quite good with IC50 value of 74.21 ppm, and total anthocyanin in the extract was found to be 4.86 ± 0.02 mg / mL.

The combination of mangosteen rind and rosella flower petals on the research is intended to produce a medicinal tea preparations are acceptable (acceptable) and is stable during storage with high antioxidant activity in the preparation of medicinal teas. Tea drug is used in preparations for oral administration, which is made by mixing the drug pig or extract (liquid extract) with tea or adding another excipient materials (Goeswin, A, 2007). Research Utomo, et al (2008) reported a combination of antioxidant activity assay ant nest extract and black tea extracts with DPPH generate IC50 values in the ratio of 1: 1 with the highest antioxidant activity of 2.3925 ppm. Meanwhile Larasati (2015) to test the antioxidant activity of the combination syrup and extract of mangosteen rind soursop leaves, each 50: 50ml has the highest antioxidant activity of 71.76%, the ratio of 75: 25ml amounted to 55.75%, the ratio of 25: 75ml of 57.92%. This suggests that the variation of the combination of extracts can produce different antioxidant activity in preparation.

Based on the above problems do research antioxidant activity of the combination of extracts of mangosteen rind and rosella flower petals in the form of medicinal tea formulations UV-Vis spectrophotometry.

2. Experimental

2.1 Sampling technique

The main material used in this study were obtained mangosteen rind of plantation residents in the village Poleganyara Poso district and rosella flower petals obtained from residents in the village plantations Sidera District of Sigi. The mangosteen fruit and rosella chosen should be fresh and intact.

2.2 Sample Processing Method (Atmajasari, D, 2014)

First of all the first mangosteen fruit is washed, after it was separated from the rind of mangosteen fruit, then the inner skin of the mangosteen fruit is scraped and washed clean. As for rosella flowers, flowers are still fresh removed the seeds and then washed clean, each weighed 1000 grams for each treatment, then cut into small pieces, then blended each ingredient by adding water where the comparison samples and water (2 : 1), and then heated at 40 ° C for 10 minutes and then filtered to obtain juice, after it was examined.

2.3 Identification Test Compound (Harborne, 1987)

Phenolic Test

Taken each 1 ml juice mangosteen rind and rosella flowers, and put into a test tube, add 5 drops of 5% FeCl3 solution and shaken strongly. The formation of blue-black color after the addition of 5% FeCl3 showed phenolic compounds.

Flavonoid Test

Taken each 1 ml juice mangosteen rind and rosella flowers, and put into a test tube, add 0.2 grams of magnesium powder, then add 1 ml concentrated HCl and shaken strongly. If the form of orange, red or yellow in the solution shows the presence of flavonoids.

Anthocyanins Test

Taken each 1 ml juice mangosteen rind and rosella taken and put into a test tube. 2M HCl is added to taste, then heated 1000C for 5 minutes. Positive results indicate anthocyanins in case of red color in the solution.

Xanton Test

Taken each 1 ml juice mangosteen rind and rosella taken and put into a test tube, and then enter the Mg powder and concentrated HCl added to taste, then shaken until the powder dissolves Mg. The positive results shown by the formation of red, yellow or orange.

Formula of Medicine Tea

Bahan	Formula					Kegunaan
	F1	F2	F3	F4	F5	
Sari Bunga rosella (ml)	100	25	50	75	0	Bahan dasar
Sari Kulit buah manggis (ml)	0	75	50	25	100	Bahan dasar
Sukrosa(%)	20	20	20	20	20	Pemanis
Natrium Benzoat (g)	0,5	0,5	0,5	0,5	0,5	Pengawet
Aquadest (ml)	Hingga 150ml	Hingga 150ml	Hingga 150ml	Hingga 150ml	Hingga 150ml	Pelarut

Preparation of Drug Tea (Larasati, 2015). Preparations medicinal tea made with the composition of the combination juice mangosteen rind and petals as shown in Table 4, where F1 (100%: 0) F2 (25: 75%), F3 (50: 50%), F4 (75: 25%) , F5 (0: 100%). The initial stage is taken each drug concentration ratio tea, after it added sucrose and sodium benzoate, the mixture is stirred until homogeneous, then put water up to 150 ml. Preparations have been so incorporated respectively into a brown glass bottle containers.

2.4 Tea Antioxidant Activity Test Drugs.

Making Parent DPPH solution (0.5 mM)

Weighed 4.9 mg DPPH, then put in a 25 ml flask, plus ethanol pro analysis up to the mark and shake. Making the solution Blanko 20 ml pipette stem DPPH solution, put in a flask and added ethanol to 100 ml pro analysis.

Uptake Measurement Blanko

Pipette 4 ml of the reference solution, then homogenized and left to stand for 30 minutes then measured absorbance at a wavelength of 517 nm.

Making the Test Solution

A total of 10 mg medicinal teas p.a dissolved in 10 ml of ethanol, wherein the concentration of 1000 ppm were obtained. Further dilution storied, by pipette 1 ml of each dilution and enter into a 10 ml measuring flask, to obtain a concentration of 0.01 ppm, 0.1 ppm, 1 ppm, 10 ppm and 100 ppm. Then from any concentration of 2.5 ml pipette then added 2.5 ml of DPPH solution. Subsequently allowed to stand for 30 minutes and measured absorbance at 517 nm wavelength.

Comparative solution of Vitamin C

Weighed as much as 10 mg of vitamin C, diluted with ethanol pro analysis of up to 10 ml, which concentration is 1000 ppm were obtained. Next do the multilevel dilution, by pipette 1 ml of each dilution and enter into a 10 ml measuring flask, to obtain a concentration of 0.01 ppm, 0.1 ppm, 1 ppm, 10 ppm and 100 ppm. Then from any concentration of 2.5 ml pipette then added 2.5 ml of DPPH solution. Subsequently allowed to stand for 30 minutes and measured absorbance at 517 nm wavelength.

2.5 Evaluation of Medicinal Tea preparations

Personality Appearance (Soekarto, 1981)

Observed all formulas in terms of taste, color, aroma and shape during the storage period of 14 days.

Measurement of pH (Sativa, 2006)

Preparation is done by entering a medicinal tea into the container, and its pH is measured by using a pH meter previously calibrated using buffer solutions at pH 4 and pH 7.

Test clarity (Lachman, 2008)

Inspection is done by using a round bottom test tubes, colorless, transparent, and made of glass neutral, then the container illuminated from the side by using two black and white background. Background black in use to investigate the dung-colored while the white background to a dark-colored impurities.

2.6 Data analysis

Data obtained on organoleptic observation, clarity test, and testing pH, analyzed descriptively for 14 days. While the data of antioxidant activity using DPPH method and to determine the amount of antioxidant activity (IC50) using the linear regression equation. While paired sample t test was used to determine differences in pH within an interval of 14 days.

3. Results and Discussions

Tests carried out on pollen antioxidant rosella flower petals and mangosteen rind

formulated in medicinal tea preparations. Medicinal tea made by combining rosella flower petals and mangosteen rind, which is intended to produce an acceptable dosage (acceptable) and is stable during storage with high antioxidant activity in the preparation of medicinal teas.

Evaluation of the stability of the medicinal tea preparations include tests antoksidan to see the IC50 value, the identification of compounds, pH test, test the clarity and organoleptic observations which consist of flavor, color, aroma, and shapes to see views generated from medicinal tea. Based on the results of organoleptic evaluation for 14 days (Table 3.1), it can be observed that all the formula has not changed either in terms of taste, color, aroma and shape during the storage period of 14 days.

Sediaan	Sifat Organoleptik							
	Rasa		Warna		Aroma		Bentuk	
	H-0	H-14	H-0	H-14	H-0	H-14	H-0	H-14
F1	Asam	Asam	Merah	Merah	Aroma khas	Aroma khas	Cair	Cair
F2	Manis dan sedikit sepat	Manis dan sedikit sepat	Orange kecoklatan	Orange kecoklatan	Aroma khas	Aroma khas	Cair	Cair
F3	Manis	Manis	Merah kecoklatan	Merah kecoklatan	Aroma khas	Aroma khas	Cair	Cair
F4	Manis dan sedikit sepat	Manis dan sedikit sepat	Merah	Merah	Aroma khas	Aroma khas	Cair	Cair
F5	Sepat	Sepat	Orange kecoklatan	Orange kecoklatan	Aroma khas	Aroma khas	Cair	Cair

Table 3.2

Sediaan	Nilai Rata-rata (n=2) Uji pH±SD	
	Hari ke-0	Hari ke-14
F1	2.98±0.05	3.14±0.04
F2	3.68±0.04	3.84±0.13
F3	3.32±0,00	3.49±0.05
F4	3.06±0.04	3.30±0.007
F5	4.26±0,00	4.42±0.13

Keterangan :
F1 = Rosella:Manggis (100:0)
F2 = Rosella:Manggis (25:75)
F3 = Rosella:Manggis (50:50)
F4 = Rosella:Manggis (75:25)
F5 = Rosella:Manggis (0:100)

The pH value of tea according to (SNI, 1992) which is between 3.5-4.0. In this study, the formula F2 to F5 formula has qualified pH. In the formula F1 base ingredients 100% rosella flower petals have a low pH value is 2.94. This is because the high acid content that is contained on the resulting pH rosella flower tea drug dosage to be low. This is in line with the results of Rienoviar (2010) reported that the pH value obtained from rosella syrup ranged from 2.61 to 2.67. The pH value of the preparations related to the tea shelf life because it affects the organoleptic assessment and product content of microorganisms. Products that have an acidic pH will not be overgrown by bacteria or microbes that are not resistant to acids (Winarno, 1992).

Table 3.3

Sediaan	Uji Kejernihan (n=2)	
	H-0	H-14
F1	+	+
F2	++++	++++
F3	+++	+++
F4	++	++
F5	++++	++++

Keterangan :
F1 = Rosella:Manggis (100:0)
F2 = Rosella:Manggis (25:75)
F3 = Rosella:Manggis (50:50)
F4 = Rosella:Manggis (75:25)
F5 = Rosella:Manggis (0:100)

\+ : Jernih +++ : Keruh
++ : Agak Keruh ++++ : Sangat Keruh

Test the clarity of the preparation shows that the higher the concentration of mangosteen rind in the preparation of tea drugs, the more turbid appearance stocks. This is because the concentration of mangosteen rind xanton on high, where the compound is not water soluble xanton that causes the display looks cloudy medicinal tea preparations (Nugroho, 2008).

Table 3.4

Sediaan	Nilai IC_{50} (n=2)
F1	13.14 ppm
F2	7.70 ppm
F3	3.87 ppm
F4	11.31 ppm
F5	2.60 ppm

Testing the antioxidant activity of the combination drug tea extract rosella flower petals and mangosteen rind is done by using DPPH (1,1-diphenyl-1-picrylhydrazyl), DPPH is one method that is fast, simple, and economical, which can be used to measure the ability of antioxidants contained in food or beverages.

That the IC50 value of F1 to F5 shows a very strong antioxidant activity. While medicinal teas best combination of rosella flower petals and mangosteen rind is contained in the formula F3 (Rosella: Manggis 50:50) is 3.87 ppm. This indicates that the synergy or mutually supportive balance between xanton and anthocyanin compounds that work as antioxidants compared to other combination formulas with different concentration ratio. The synergistic nature is possessed antioxidant properties when added to the other primary antioxidants increases the antioxidant activity, but in a state of their own also have a higher antioxidant activity.

4. Conclusions

Based on observations made, it can be summed up as follows:

a. Tea drug combination rosella flower petals and mangosteen rind has good physical stability during storage of 14 days.

b. IC50 value of the five formulas included in the category of very powerful antioxidant activity. Formula dosage combination medicinal tea rosella flower petals and mangosteen rind highest antioxidant activity (IC50 value) is F3 (50:50) of 3.87 ppm.

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Synthesis and Characterization of Sodium carboxymethyl Cellulose (Na-CMC) from Sweet Corn Cob (*Zea mays-saccharata* S) and its Application in Suspension

Listya Sushmita S[1*], Ni Ketut Sumarni [2] , Evi Sulastri [1]

[1]Department of Pharmacy, Faculty of Sciences, Tadulako University, Palu
[2]Department of Chemistry, Faculty of Science, Tadulako University, Palu

ABSTRACT

This research aims to know the characterization of Sodium Carboxymethyl Cellulose (Na-CMC) from sweet corn cob (*Zea mays -saccharata* S*)* and its effect to physical character in suspension. The first process of synthesis Na-CMC is isolation of cellulose from sweet corn cob (*Zea mays-saccharata* S). After that, the cellulose convert into Na-CMC by reaction alkalization using 15% NaOH and reaction carboxymethylation using 5g sodium monochloroacetate (NaMCA). The result of Na-CMC will be characterization consists of identification test and characterization test. Subsequently, formulation of suspension with Na-CMC from sweet corn cob (*Zea mays-saccharata* S *)* at concentrations variation i.e F1 (0,25%), F2 (0,5%), F3 (0,75%), F4 (1%) and F5 (2%), then evaluation physical consist of organoleptic test, pH, viscosity, displaced volume, and sedimentation volume. The characterization of Na-CMC from sweet corn cob (*Zea mays-saccharata* S*)* are pH 6,89 ± 0,04, viscosity grade medium, 8% ± 2 water content, 0,72 ± 0,15 degree of substitution (DS), and 99,62% ± 0,08 purity. The evaluation physical of suspension in formulation suspension F1 until F5 showed that difference significant between physical character of suspension and increase concentrations of Na-CMC for pH test, viscosity, and sedimentation volume but did not give difference significant for displaced volume. So, increase concentrations of Na-CMC from sweet corn cob (*Zea mays-saccharata* S*)* have effect for physical character of suspension.

Key Word : Sweet corn cob (*Zea mays-saccharata* S*)*, Characterization Sodium Carboxylmethyl Cellulose (Na-CMC), Suspension, Evaluation physical of suspension.

ABSTRAK

Penelitian ini bertujuan untuk mengetahui karakterisasi Natrium Karboksimetil Selulosa (Na-CMC) tongkol jagung manis (*Zea mays-saccharata* S*)* dan pengaruhnya terhadap sifat fisik sediaan suspensi. Sintesis Na-CMC dimulai dari isolasi selulosa tongkol jagung manis (*Zea mays-saccharata* S), selulosa selanjutnya melalui proses alkalisasi menggunakan larutan NaOH 15% dan karboksimetilasi menggunakan 5 gram Natrium Monokloroasetat (NaMCA) untuk membentuk Na-CMC. Na-CMC yang diperoleh dikarakterisasi yang terdiri atas uji identifikasi dan uji karakterisasi. Selanjutnya dilakukan formulasi suspensi dengan variasi konsentrasi Na-CMC tongkol jagung manis (*Zea mays-saccharata* S) yaitu F1 (0,25%), F2 (0,5%), F3 (0,75%), F4 (1%) dan F5 (2%). Hasilnya kemudian dievaluasi fisik meliputi pengujian organoleptis, pH, viskositas, volume terpindahkan, dan volume sedimentasi. Hasil karakterisasi Na-CMC tongkol jagung

manis (*Zea mays-saccharata* S) yaitu pH 6,89 ± 0,04, Viskositas grade medium, Kadar air 8% ± 2, Derajat Subtitusi (DS) 0,72 ± 0,15, dan kemurnian 99,62% ± 0,08. Hasil sifat fisik sediaan suspensi menunjukan formula suspensi F1 hingga F5 pada pengujian pH, viskositas dan volume sedimentasi yaitu terdapat perbedaan signifikan sifat fisik suspensi seiring bertambahnya konsentrasi Na-CMC. Sedangkan pada volume terpindahkan yaitu tidak terdapat perbedaan signifikan. Sehingga disimpulkan penambahan Na-CMC tongkol jagung manis (*Zea mays-saccharata* S) berpengaruh terhadap sifat fisik sediaan suspensi.

Kata Kunci : Tongkol jagung manis (*Zea mays-saccharata* S), Karakterisasi Natrium karboksimetil selulosa (Na-CMC), Suspensi, Evaluasi fisik suspensi.

***Corresponding author :** Listya Sushmita S, email : listya12farmasi@gmail.com

1. Introduction

Corn is one of the palawija crops that grow in almost all regions in Indonesia. Based on data from the Central Bureau of Statistic (BPS) Central Sulawesi province, corn production in Central Sulawesi in the last seven years has risen from the year 2008 amounted to 136 907 tons up to 170 022 tons in 2014. Along with the increased production of corn, it can not be denied that the existence of corn waste will also increase. The one of corn waste is corn cob. Corn cob is part of corn without grain kernel. Most people just assume corn cob as a junk or as an animal feed (Pujiani et al, 2013).

The growth of the pharmaceutical industry in Indonesia is increasing, but more than 90% of raw materials pharmaceutical industry is still import from a few countries that make dependence availability of raw materials. So, that the Indonesian government plans to draw up a strategy to strengthen the local industrial raw materials (Kemenperin.go.id). According to the the Central Bureau of Statistic (BPS) Foreign Trade, the availability of raw materials Na-CMC is still import into Indonesia amount 3752 tons or US $ 13 million in 2015.

Na-CMC can be synthesized from chemical modification of cellulose is generally derived from wood. However, the increased use of wood as a source of cellulose relates to the global environment condition so that the world must regulate supply and demand for this material to be maintained its balance (Sudirjo, 1996). Based on this, it is necessary to use alternative sources of cellulose to reduce the exploitation of using wood and support government programs in an effort to use local raw materials by utilizing the natural resources of Indonesia.

The research from Lestari et al (2013), corn cob can be used as raw material to form Na-CMC because contains cellulose amount 62.80% with percent yield amount 99.52%. Meanwhile, research from Melisa (2014) use varieties sweet corn cobs with % yield of cellulose amount 36.165% and the % yield of Na-CMC amount 73.45%. So, to guarantee the quality of Na-CMC from corn cobs it is necessary characterization is consists of two tests i.e identification tests include organoleptic test, morphology, solubility, foam test, precipitate formation, color reaction and characterization test include pH test, viscosity, water content, degree of substitution (DS) and purity.

Na-CMC in pharmaceutical industry used as excipient in pharmaceutical form. In

suspension form, Na-CMC used as a suspending agent to reduce the rate of settling by the increasing the viscosity because to desired characteristic of suspension is must settle slowly (Lachman L, et al, 2008).

Based on this, it is necessary to do research on the effects of physical character of the suspension with the use of excipent Na-CMC from sweet corn cob (Zea mays saccharata-S) as a suspending agent and its characterization to ensure the quality.

2. Experimental

2.1 Materials and Methods

2.1.1 Isolation of Cellulose (Melisa,2014)

25 g Sweet corn cobs powder was soaked with 10% NaOH at ratio of powder to solvent 1 : 10 (w/v) for 1 x 24 hours. After that, filtered using a filter cloth. The residue obtained is then washed with distilled water up to 3 times and then filtered again

2.1.2 Bleaching of Cellulose (Hutomo, G ; 2012)

Cellulose was diluted with 125 mL of NaOCl 6% and add 500 ml of distilled water, heated at 70°C for 60 minutes, then washed with distilled water and filtered to remove residual NaOCl. The results of filter are then diluted 250 ml of 3% sodium metabisulfite and adding 250 ml of distilled water and then heated at 60°C for 180 minutes. After that, washed with distilled water and filtered. Cellulose is then put into a petri dish, and then dried at 60°C in an oven to constant weight. Furthermore, calculated the yield of Cellulose.

2.1.3 Synthesis Na-CMC

Synthesis of Na-CMC using methods Adinugraha, et al (2005) with modifications methods by Lestari, et al (2013). 5 g cellulose of sweet corn cobs was added 100 ml of isopropanol while stirring using a magnetic stirrer. After that, alkalized at temperature room for 1 hour by added slowly 20 ml of 15% NaOH. After alkalization is over, amount 5 g sodium monokloroasetat (NaMCA) was adeed slowly. Set temperature to 55°C in carboxymethylation process and the reaction continue for 3 hours. Subsequently ,the mixture is filtered and the slurry soaked with methanol for 24 hours, then neutralized with glacial acetic acid added to pH 6-8. Na-CMC was thus obtained by washing and filtering with 70% ethanol for 4 times and dried at 60°C in an oven until its weight is constant. Furthermore, calculated the yield of Na-CMC.

2.1.4 Characterization of Na-CMC

Characterization of Na-CMC consist of Identification test i.e organoleptic, solubility, foam test, precipitate formation, and color reaction were determined by method of the JECFA (2000) and morphology using by *Scanning electron microscope* (SEM) Characterization test i.e pH was determined by method of Wijayani,et al (2005) and viscosity, water content, degree of subtitution (DS) and purity were determined by the ASTM D1439-94 standard method (ASTM, 1994).

2.1.5 Formulation of Suspension

Material	Formulation							Function
	K (+)	K (-)	F1	F2	F3	F4	F5	
Paracetamol	1,5 g	1,5 g	1,5 g	1,5 g	1,5 g	1,5 g	1,5 g	Therapeutic agent
Na-CMC	2%	-	0,25%	0,5%	0,75%	1%	2%	Suspending Agent
Tween 60	1%	1%	1%	1%	1%	1%	1%	Wetting agent
Propylenglycol	15%	15%	15%	15%	15%	15%	15%	Humektan
Propyl Paraben	0,05%	0,05%	0,05%	0,05%	0,05%	0,05%	0,05%	Preservative
Methyl Paraben	0,2%	0,2%	0,2%	0,2%	0,2%	0,2%	0,2%	Preservative
Aquades	Added until 60 ml							vehicle

Source : Rowe, et al (2009) and Niazi (2004)

K+ = control formulation with Na-CMC comersil

K- = control formulation without Na-CMC

2.1.6 Evaluation physical of suspension

Evaluation physical consist of organoleptic test, pH, viscosity, displaced volume (Dirjen POM, 1995) and sedimentation volume (Ogaji et al, 2012).

3. Results and Discussion

Isolation of cellulosa from powder sweet corn cob are soaking with 10% NaOH solution to dissolve the non-cellulose component is lignin and hemicellulose are generally non-cellulose components who soluble in aqueous alkali so that the cellulose will be acquired (Lestari,et al,2013; putera,2012). Bleaching is process to remove lignin which still produce a brown color in the slurry and bleach the isolation product . In bleaching process consists of two stages, bleaching with NaOCl which acts as an oxidator which can oxidize the structure of lignin and sodium metabisulfite to reduce the structure of lignin that is soluble in water (Lestari, et al, 2013). The Persen yield of sweet corn cob cellulose produced is 54,04% ± 2,61.

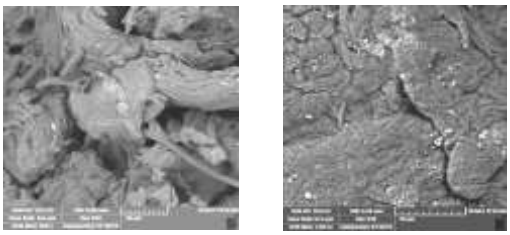
There are two main reactions in order to convert cellulose into Na-CMC: the first procedure is alkalization using NaOH solution and the second reaction is followed by carboxymethylation using reagen Sodium monochloroacetic (NaMCA) (Saputra,et al, 2014). Synthesis of Na-CMC from corn cob refer to Lestari,et al(2013) research, which the good result in optimization of the synthesis Na-CMC by using 15% NaOH solution and 5 grams NaMCA. The Persen yield of Na-CMC sweet corn cob produced is 91,23%±2,63.

Characterization of Na-CMC

Characterization of Na-CMC from sweet corn cob consist of identification test and characterization test.

Table 1. Identification results of Na-CMC sweet corn cob

Identification	Identification result
Organoleptic	Granul, slightly yellowish, odourless.
Morphology	Irregular shape, coarse and curve interface.
Solubility	Coloid form, soluble in water, insoluble in ethanol.
Foam test	When shaking : no layer of foam appears.
Precipitate formation	A precipitate appears when reaction with 5% $CuSO_4$.
Color reaction	A red colour develops at the interface.



(a) (b)

Fig 1. Morphology Na-CMC (a) magnification 500x (b) magnification 2000x

Identification test is the initial screening to identify Na-CMC which distinguishes it from the other product. The identification results showed that the product formed from modified cellulose from sweet corn cob is Na-CMC.

Table 2. Characterizartion of Na-CMC sweet corn cob

Parameter	Result
pH (1%)	6,89 ± 0,04
Viscosity	Grade medium
Water content	8% ± 2
Degree of Subtitution	0,72 ± 0,15
Purity	99,62% ± 0,08

pH test to show the quality of Na-CMC because it affects the viscosity Na-CMC. The results of pH as shown in Table 2 that meet standart of SNI (6-8) and USP (6,5 - 8,0). Na-CMC solution pH stable at pH 2-10, precipitation occurs at a pH below 2, and the viscosity can be reduced if the pH above 10 (Rowe, et al; 2009).

The results of water content as shown in table 2 that meet standart of USP (≤ 10%). The water content affects the stability of Na-CMC are both related to the chemical reaction and contamination of microorganisms (Wijayani et al; 2005).

The testing of degree of substitution (DS) to know the amount of carboxymethyl groups are replaced with hydroxyl groups in the glucose unit to forming sodium carboxymethylcellulose (Na-CMC) (Dow pharmaandfood, 2014). The results of degree of substitution (DS) Na-CMC from sweet corn cob that meet standart of SNI (0.7 to 1.2). DS 0.72 ± 0.15 which indicates an average of 7 carboxymethyl groups are substituted per 10 anhydroglucose unit of cellulose (Kamal; 2010).

The testing of purity Na-CMC to see the amount of side product form in process synthesis Na-CMC. The side product from synthesis Na-CMC is sodium Chlorida (NaCl). The Results of purity Na-CMC sweet corn cob that meet standart of SNI ≥ 99.5% with NaCl content is ≤ 0.5%.

Viscosity of Na-CMC sweet corn cob is viscosity grade medium, to knowing the grade variation of viscosity Na-CMC concentration so that know the quantity concetration it can be used to increase the viscosity of a solution (Rowe et al; 2009).

Formulation and evaluation physical of suspension

Suspension formulations made using five variations concentrations of Na-CMC sweet corn cob i.e F1 (0.25%), F2 (0,5%), F3 (0.75%), F4 (1%), and F5 (2 %)

Table 3. Organoleptic of suspension

Formula	Organoleptic
K+	Solution dispersion, turbid, slightly odour
K-	Solution dispersion, turbid, slightly odour
F1	Solution dispersion, turbid, slightly odour
F2	Solution dispersion, turbid, slightly odour
F3	Solution dispersion, turbid, slightly odour
F4	Solution dispersion, turbid, slightly odour
F5	Solution dispersion, turbid, slightly odour

Table 4. Evaluation result of pH, viscosity, and displaced volume (average ± SD, n=3)

Formula	pH	Viscosity (Cp)	Displaced volume
K+	6,85 ± 0,29	229,2 ± 65,70	99,44% ± 0,97
K-	5,37 ± 0,04	11,3 ± 0,50	98,89% ± 0,97
F1	6,10 ± 0,02	33,3 ± 0,70	98,89% ± 1,92
F2	6,60± 0,03	41,7 ± 1,29	99,44% ± 0,97
F3	6,14± 0,13	48,3 ± 0,61	99,17% ± 0,83
F4	6,36 ± 0,03	55,2 ± 0,8	98,89% ± 0,97
F5	6,55 ± 0,23	106,9 ± 29,14	99,44% ± 0,97

Table 5. Evaluation result sedimentation volume

Formula	F (days)		
	0	7	14
K+	1	1	1
K-	1	1	1
F1	1	0,18 ±0,07	0,17±0,06
F2	1	0,34±0,05	0,28±0,02
F3	1	0,39±0,03	0,37±0,03
F4	1	0,58±0,05	0,55±0,03
F5	1	0,86±0,07	0,79±0,06

Evaluation physical of formulation suspension F1-F5 on testing pH, viscosity, and sedimentation volume is a significant difference (<0,05)between the physical character of suspension with increasing concentrations of Na-CMC sweet corn cobs. While the displaced volume that is not give significant difference (>0,05). So the addition of

Na-CMC sweet corn cobs affect the physical character of suspension preparation

4. Conclusions

The characterization of Na-CMC from sweet corn cob (*Zea mays-saccharata* S*)* are pH 6,89 ± 0,04 , viscosity grade medium, 8% ± 2 water content, 0,72 ± 0,15 degree of substitution (DS), and 99,62% ± 0,08 purity and Na-CMC sweet corn cob as a suspending agent in formulation suspension affect physical character of suspension.

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Microencapsulation of Super Red Dragon Fruit (*Hylocereus costaricensis* (F.A.C.Weber) Britton & Rose) Peels Extract by Simple Coacervation Method

Evi Sulastri, Yusriadi, and Muzayyinah*

Department of Pharmacy, Faculty of Sciences, Tadulako University, Palu

ABSTRACT

The encapsulation is puposed to protect the super red dragon fruit (*Hylocereus costaricensis*) peels extract from environmental conditions that can cause damage. Encapsulation is performed using simple coacervation method. The lumpy extract of super red dragon fruit peels was obtained by maceration method using methanol:HCl (9:1). The lumpy extract then encapsulated using gelatin with varying concentrations extract:gelatin are 1:2 (formula 1), 1:3 (formula 2) and 1:5 (formula 3) at a speed of 750 rpm. The microcapsules were obtained characterized include water content test, measurement of entrapment efficiency, particle measurement, morphological observation of microcapsules, and the antioxidant activity test by DPPH method. The IC_{50} of microcapsules F1, F2, and F3 respectively was 13.5 ppm, 15 ppm and 30.23 ppm. This research result the microcapsules with matrix type, particle size in the range of 41-45 μm, water content 2-4%, and the maximum entrapment efficiency is 80%.

Key words: Betacyanin, Gelatin, *Hylocereus costaricensis*, Microcapsule, Simple Coacervation

ABSTRAK

Enkapsulasi ini dilakukan dengan tujuan untuk melindungi ekstrak kulit buah naga super merah *(Hylocereus costaricensis)* dari kondisi lingkungan yang dapat merusaknya. Enkapsulasi dilakukan dengan metode koaservasi sederhana *(Simple Coacervation).* Ekstrak kental kulit buah naga super merah diperoleh dengan metode maserasi menggunakan pelarut metanol:HCl (9:1). Ekstrak kental kemudian di enkapsulasi menggunakan penyalut gelatin dengan variasi konsentrasi ekstrak:penyalut sebesar 1:2 (formula 1), 1:3 (formula 2), dan 1:5 (formula 3) pada kecepatan 750 rpm. Mikrokapsul yang dihasilkan dikarakterisasi meliputi uji kadar air, pengukuran efisiensi penjerapan, pengukuran partikel, pengamatan morfologi mikrokapsul, serta dilakukan uji aktivitas antioksidan mikrokapsul dengan metode DPPH. Nilai IC_{50} mikrokapsul F1, F2, dan F3 berturut-turut adalah 13,5 ppm, 15 ppm dan 30,23 ppm. Penelitian ini menghasilkan mikrokapsul dengan tipe matriks, ukuran partikel dalam rentang 41-45 μm, kadar air 2-4%, dan efisiensi penjerapan maksimal sebesar 80%.

Kata Kunci: Betasianin, Gelatin, *Hylocereus costaricensis*, Koaservasi Sederhana, Mikrokapsul

***Correspondent author :** Muzayyinah, email : muzayyinahmona@gmail.com

1. Introduction

Hylocereus sp. is one source of pigment betalain namely betasianin. Betalain pigment has a pharmacological effect as anticancer, antihiperlipidemia, antimicrobial and antioxidant (Gengatharan *et al*, 2015). From 100 g of red dragon fruit peels were extracted obtained total betacyanin is 515.20 g/100 g (Priatni and Pradita, 2015). However, the stability of betalain pigment can be affected by several factors such as light, pH, and temperature can affect the production process or storage. According to Reshmi, S.K. *et al*, (2012), an increase in pH, temperature or light exposure can damage the betacyanin molecule. To overcome betacyanin instability caused by environmental influences, it can be done by microencapsulation techniques to minimize the environmental impact on the stability of the extract, so it can facilitate the process of formulation if it will be created as a pharmaceutical preparation.

Microencapsulation is a technique in which droplets of liquid, solid particles or gas entraped in an encapsulating agent. Overall, the material will be covered by the coating material or covered in homogeneous or heterogeneous matrix to form a microcapsule with many uses (Ghosh, 2006).

One of an encapsulation method which is simple and can be accomplished using conventional equipment is coacervation method (Agnihotri *et al*, 2004). Coacervation is a process where the aqueous colloid solution is separated into two liquid phases, one of which is rich of colloid (cocervate) and other poor of colloids (Martins, 2012).

Gelatin show high ability as a coating agent on the microencapsulation process. This is demonstrated by Maji *et al* (2006) in study of microencapsulation of *Zanthoxylum limonella* oil with gelatin as a coating agent showed that encapsulation efficiency reaching up to 98%. In addition, gelatin also biodegradable, non-toxic and non-irritant.

Based on the description above, in this study conducted microencapsulation of super red dragon fruit (*Hylocereus costaricensis*) peels extract by simple coacervation method using gelatin as a coating agent.

2. Experimental

2.1 Materials and Methods

Sample Preparation

Super red dragon fruit is washed and taken it peels. The peels of super red dragon fruit cut into small sections and ready to be extracted.

Extraction

800 g of super red dragon fruit peels macerated using 96% methanol and 1% HCl with a volume ratio 9: 1 of 1000 ml for 3x24 hours at room temperature, then filtered and the filtrate is collected. The filtrate obtained was evaporated with a rotary vacuum evaporator at a temperature of 400^0 C to obtain a thick extract.

Antioxidant Activity Test of Super Red Dragon Fruit Peels Methanol Extracts by DPPH Method

10 mg super red dragon fruit peels extract put in a flask and added with 10 ml of ethanol pro analysis to obtain a concentration of 1000 ppm. Next do the dilution by pipette 0.5 ml, 0.4 ml, 0.3 ml, 0.2 ml, 0.1 ml, and 0.05 ml sample from the stem solution sample. Then each put in a 10 ml flask and added with ethanol pro analysis in order to obtain a concentration of 100 ppm, 80 ppm, 60 ppm, 40 ppm, 20 ppm and 10 ppm.

Subsequently pipette 2.5 ml of each concentration was then put into a test tube and added with 2.5 ml of DPPH solution blank. Then allowed to stand for 30 minutes and measured the absorbance at 517 nm wavelength.

Do the same way to measure the antioxidant activity of the super red dragon fruit peels extract microcapsules.

The percentage of antioxidant activity can be calculated with the following formula :

$$\% \text{ inhibition} = \frac{\text{blank abs} - \text{sample abs}}{\text{blank abs}} \times 100\%$$

Formulation of Microcapsules

Microcapsules made by following the method of Maji *et al* (2006) as follows: extract and corn oil are mixed in advance and then added span 80 (A). Gelatin dissolved in distilled water (B). A mixture added gradually to the B mixture under continous stirring with a speed of 750 rpm for 30 minutes to form an emulsion. Temperature is set at 40^0C. Then a sodium sulfate solution was added gradually to form coaservate. The temperature is lowered until it reaches 5^0C, then glutaraldehyde added gradually to form Then the temperature is increased again up to 40^0C and stirred for 2-3 hours. After 1x24 hours, the microcapsules were separated by filtered. The residue obtained was dried by freeze dried method.

Table 1. Super red dragon fruit peels extract microcapsule formula

		Formula		
Materials	**Uses**	**1**	**2**	**3**
Extract (g)	Active ingredient	1	1	1
Gelatin (g)	Coating agent	2	3	5
Glutaraldehid (ml)	Crosslinking agent	0,1	0,3	0,5
Sodium sulfat (%)	Coacervate inducing agent	20	20	20
Distilled water (ml)	Solvent	50	50	50
Span 80 (ml)	Emulsifier	0,15	0,15	0,15
Corn oil (ml)	Oil phase	4	6	10

Microcapsules Characterization

a. Entrapment Efficiency

An entrapment efficiency measurement is done by comparing the total content of betacyanin in each gram of microcapsules to the total content of betacyanin in each gram of extract.

1 g of microcapsules and extract diluted perfectly with 25 ml of distilled water. 5 ml of stem solution sample put into the flask and added with 10 ml distilled water. Absorption was measured at 538 nm wavelength using Uv-Vis spectrophotometer.

$$\text{Entrapment efficiency} = \frac{\text{total content in each gram of microcapsules}}{\text{total content in each gram of extract}} \times 100\%$$

b. Water content test

Water content test was done by using a moisture balance. It is preheated for 10 minutes. 1 g of microcapsules were placed in an aluminum container evenly. The temperature is set at 105^0C then measured. The result on the moisture balance is recorded as the water content of the microcapsules.

$$\text{Total content} = \frac{A \times MW \times DF \times 1000}{E \times l}$$

Where : A = absorbance at 538 nm
MW = molecular weight of betacyanin (550 g/mol)
DF = dilution factor
E = mean molar absorbtivity ($6,5 \times 10^4$ L/mol in H_2O)
l = path length (1,0 cm)

c. Particle size analysis

Particle size analysis performed using a light microscope equipped with a micrometer. A number of microcapsules dispersed in a VCO then dripped into a deck glass. The observations were made under a microscope by repeating 3 times and set the particle size

.

d. Morphological characterization of the microcapsules by scanning electron microscope (SEM)

Microcapsules morphological analysis carried out using a SEM (Scanning Electron Microscope). Samples were placed on the sample holder and then examined the morphology seen in the intensity of 10 kV.

3. Results and Discussion

In coacervation method, microencapsulation process takes in three steps under continuous stirring. The first step is the formation of emulsions, which are used span 80 as emulsifier. After the formation of the emulsion, the second step is the process wherein the polymer coating the core material. It is induced by the addition of sodium sulfate to promote the phase separation which will produce coaservate (the part that rich in colloids). The third step is the stabilization of the coating material. To stabilize the coating that has enveloped the core material, the addition of glutaraldehyde that can cause crosslink reaction between the aldehyde group of glutaraldehyde with the amino groups of gelatin. Furthermore coaservate formed filtered and then dried by freeze dry method to obtain super red dragon fruit peels extract microcapsules.

Water Content

Table 2. The result of water content test

Mikrocapsules	The mean value of water content (%) ± SD
F1	2,63 ± 0,28
F2	2,52 ± 0,27
F3	4,43 ± 0,35

ANOVA statistical test results showed that there were significant differences in the water content of the data of each formula. Differences in water levels obtained may be affected by the water content of the active substance or coating agent that used. The more of the coating agent is used it also increases the moisture content which is obtained. The water content of the gelatin which used as a coating agent in this formula is 10.39% and the water content of the extract which used as an active ingredient in this formula is 1.38%. It is also in line with research conducted by Febriyenti *et al* (2013)

which showed that an increase in the water content of the microcapsules along with the increasing concentration of coating used, wherein the core material and the coating ratio of 1:1 has a water content of 2.6% and the core material and the coating ratio of 1:2 has a water content of 3.6% in the formulation of microcapsules Gliquidone using ethyl cellulose as coating agent. Ethyl cellulose is known have a water content of 8.91%.

Particle Size

Table 3. The result of particle size analysis

Mikrocapsules	The mean value of particle size (μm) ± SD
F1	41,05 ± 18,24
F2	45,69 ± 7,06
F3	45,71 ± 3,74

The amount of coating agent that used in microencapsulation also affect the particle size of microcapsules. The more coating agent that is used, the particle size will increase due to the thickness increases of the walls of the microcapsules are formed. It is also in line with research conducted by Comunian *et al* (2013) which showed that the particle size of the microcapsules produced from the core material and the coating ratio of 1:1 is 71.10 μm smaller than the core material and the coating ratio of 1:2 is 81.91 μm. In addition, the particle size can also be influenced by the stirring speed used in making microcapsules. If a large stiring speed is used, the particles size produced will be small. The particle size of microcapsules resulting by simple coacervation methods is 20-200 μm (Richard *et al*, 2000).

Morphology of Microcapsules

Microcapsules morphological observation using SEM (Scanning Electron Microscope) and light microscopy showed that the morphology of super red dragon fruit peels extract microcapsules have an irregular shapes with a matrix type. It shows that the core material has been entrapped in microcapsule coating. Matrix type is the type of microcapsules containing a core material uniformly dispersed in the coating agent (Thies, 1996).

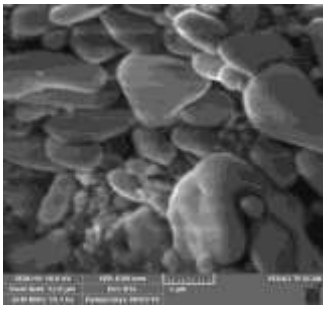

Figure 1. SEM results of super red dragon fruit peels extract microcapsules

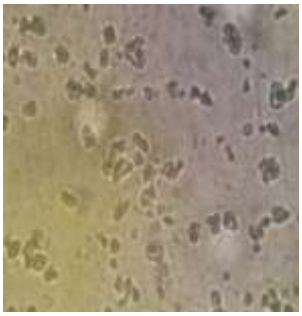

Figure 2. The morphology of the microcapsules by observation using a light microscope magnification 100 times.

Entrapment Efficiency

Table 4. The result of entrapment efficiency measurement

Mikrocapsules	The mean value of entrapment efficiency (%) ± SD
F1	21,84 ± 1,28
F2	72,91 ± 5,82
F3	80,52 ± 0,74

ANOVA statistical test results showed significant differences in the entrapment efficiency value of each formula microcapsules. Encapsulation efficiency can be influenced by the amount of coating agent that used, with increasing the concentrations of coating agent that used, the encapsulation efficiency will be increase. This is due the growing possibility of a coating agent for coat the core material. It is also demonstrated in a study conducted by Maji *et al* (2006) which states that along with the increase of the total polymer used, the encapsulation efficiency will increase. In the study, encapsulation efficiency of *Zanthoxylum limonella* oil with gelatin coating agent using coacervation methods varied between 59.10%±1.11 to 98.20±1.13%.

Antioxidant Activity

Table 5. The result of antioxidant activity test by DPPH method

Sample	IC_{50} (ppm) (n=3)
Extract	23,4
F1	13,5
F2	15
F3	30,23

The test results showed that the antioxidant activity super red dragon fruit peels has a very strong antioxidant activity (IC_{50} value <50 ppm). Their antioxidant activity is caused by the betacyanin pigment content that is betanin on super red dragon fruit peels extract. Based on the study of Rebecca *et al* (2010) showed that the samples of red dragon fruit contain a pigment betanin which was analyzed by HPLC, and contains a total polyphenols is 86.10 mg/0,5 g of extract with EC_{50} values of 2.90 mM. The total content of betacyanin obtained in this study was 21.61 mg/L. Betalain compounds can act as an antioxidant by donating electrons from the N atom to neutralize free radicals which can cause oxidation processes.

4. Conclusions

Super red dragon fruit (*Hylocereus costaricensis*) peels extract can be encapsulated by simple coacervation methods using a gelatin as coating agent and produce microcapsules with matrix type, particle size in the range of 41-45 μm, water content 2-4%, and the maximum entrapment efficiency is 80%.

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Formulation and Characterization of *Eleutherine bulbosa* antioxidant cream

Husnul Warnida[*] and Henny Nurhasnawati

Akademi Farmasi Samarinda
Jalan Abdul Wahab Syahranie 226, Air Hitam, Samarinda

ABSTRACT

Exposure of the skin to ultraviolet (UV) radiation from the sun has various adverse effects, photoaging and skin cancer are of great concern. The ability of botanical antioxidants for prevention of photocarcinogenesis and photoaging had been widely known. Bawang tiwai (*Eleutherine bulbosa*) is traditionally used by the native people of Kalimantan for cancer treatment. The ethanolic extract of bawang tiwai originated from Banjarbaru district, South Kalimantan had strong antioxidant activity. The objective of the study was to formulate *Eleutherine bulbosa* extract into cream and evaluate its scavenging activity. Antioxidant activity of *Eleutherine bulbosa* cream was assessed by 2-diphenyl-1-picrylhydrazyl (DPPH) method. The *Eleutherine bulbosa* extract was incorporated into five cream formulas in varied concentration of emulsifying wax and cetyl alcohol. Evaluation of cream including physical appearance, pH, viscosity, stability, and microbial growth test. The result showed that *Eleutherine bulbosa* cream has antioxidant activity and good physicochemical quality.

Keywords: antioxidant, cream, *Eleutherine bulbosa*, photoaging, photocarcinogenesis, skin care

ABSTRAK

Kulit yang terpapar sinar UV dalam waktu lama akan mengalami berbagai efek samping, di antaranya penuaan dini dan kanker kulit. Antioksidan yang terkandung dalam tumbuh-tumbuhan dapat mencegah penuaan dini dan kanker kulit. Secara tradisional, bawang tiwai (*Eleutherine bulbosa* Mill. Urb) digunakan oleh Suku Dayak Kalimantan untuk pengobatan berbagai jenis penyakit, salah satunya kanker. Ekstrak etanol bawang tiwai yang berasal dari kota Banjarbaru, Kalimantan Selatan, memiliki efek antioksidan kuat. Penelitian ini bertujuan memformulasi ekstrak etanol bawang tiwai dalam bentuk krim perawatan kulit dengan variasi emulsifying wax dan cetyl alcohol. Evaluasi krim meliputi parameter organoleptis, pengukuran pH, daya sebar, viskositas, stabilitas, dan uji pertumbuhan mikroorganisme. Hasil penelitian menunjukkan bahwa krim ekstrak bawang tiwai memiliki aktivitas antioksidan, stabilitas, dan sifat fisika kimia yang baik.

Kata Kunci: antioksidan, *Eleutherine bulbosa*, kanker kulit, krim, penuaan dini, perawatan kulit,

*Corresponding author : Husnul Warnida, email : hwarnida@gmail.com

1. Introduction

Photoaging is a term that denotes the gross and microscopic cutaneous changes induced by chronic and repeated sun exposure. Since photoaging is extrinsic aging produced mainly by ultraviolet (UV) light, one may infer that photoaging could be prevented and regulated (Miyachi, 1995). Reactive oxygen species (ROS) is the major pathogenic agents for connective tissue alteration in photoaging and induce changes in gene expression pathways related to collagen degradation and elastin accumulation (Scharffetter–Kochanek, 2000).

Skin is constantly exposed to ROS from the environment, such as air, solar radiation, ozone, and other air-borne pollutants, or from the normal metabolism, primarily from the mitochondrial respiratory chain wherein excess electrons are donated to molecular oxygen to generate superoxide anions (Rhie, 2001). The damaging effects of higher concentrations of ROS generated in vitro and in vivo after UVA and UVB irradiation of the skin (Scharffetter–Kochanek, 2000). Increased ROS generation can overwhelm antioxidant defense mechanisms, resulting in oxidative stress and oxidative photodamage of proteins and other macromolecules in the skin (Afaq, 2006).

The novel strategies were needed to reduce the occurrence of skin cancer and delay the process of photoaging. One approach is through photochemopreventive agents such as botanical antioxidants. Botanical antioxidants have been shown to be associated with reduced incidence of ROS mediated photocarcinogenesis and photoaging (Afaq, 2006). This has generated a great interest in the screening of plants for antioxidant properties.

Eleutherine bulbosa is an Iridaceae popularly known in the Kalimantan, Indonesia as bawang tiwai, bawang dayak, dan bawang sabrang. The red bulbs are traditionally used by Dayak tribe living in Kalimantan to cure various type of illness such as cancer, high blood pressure, diabetes mellitus, cholesterol, and ulcers. This plant is originated from South America. Other species from this genus for example are *Eleutherine americana*, *Eleutherine palmifolia*, and *Eleutherine plicata* (Kuntorini and Nugroho, 2010; da Silva Malheiros *et al*, 2015) Ethanol extract of *Eleutherine bulbosa* originated from South Kalimantan had strong antioxidant activity with IC_{50} 25.3339 ppm (Kuntorini and Astuti, 2012)

The objectives of the study were to formulate *Eleutherine bulbosa* extract into cream and to evaluate antioxidant capacity and physicochemical characterization of cream.

2. Experimental

2.1 Materials and Methods

2.1. Sample collection

Eleutherine bulbosa was obtained from Melak village, Kutai Barat district, East Kalimantan, Indonesia and was identified and authenticated by a botanist of Mulawarman University.

Figure 1. *Eleutherine bulbosa* (Mill) Urb.

2.2. Chemicals

2,2-diphenyl-1-picrylhydrazyl (DPPH) was obtained from Sigma Aldrich Co. St Louis, USA.

Ascorbic acid was obtained from Bratachem. All other chemicals used were of analytical grade.

2.3. Pharmaceutical excipients

Pharmaceutical excipients used for preparation of cream such as olive oil (*oleum olivarum*), cetyl alcohol, emulsifying wax, propylene glycol, sodium lactate, rose fragrance oil (*oleum rosae*), nipagin, nipasol, distilled water (*aqua destillata*) were of Farmakope Indonesia quality.

2.4. Extraction of Plant Material

Eleutherine bulbosa bulbs were air-dried at room temperature for 2 weeks and were grinded to a coarse powder (mesh 40). The dried powder of *Eleutherine bulbosa* bulb (250 g) was macerated in 2.5 L of ethanol 95% at room temperature for 48 hours. The extract was concentrated using a rotary evaporator with the water bath set at 50°C to obtain semi solid mass (yield: 11,6 %w/w).

2.5. Formulation of antioxidant cream

Olive oil, shea butter, cetyl alcohol, nipasol, and emulsifying wax were heated to 70°C (oil phase). Sodium lactate, nipagin, and distilled water were heated to 75°C (water phase). The water phase slowly poured into the oil phase. The mixture was stirred with stick blender until turning creamy, thick, and homogenous. *Eleutherine bulbosa* bulb ethanolic extract was diluted with propylene glycol and then the cream base was added and carefully mixed. The fragrance was added at 45°C.

The formula is shown in Table 1.

Table 1. Composition of antioxidant cream

Materials	**quantity (gram)**				
	f A	f B	f C	f D	f E
E. bulbosa extract	6	6	6	6	6
olive oil	15	15	15	15	15
shea butter	5	5	5	5	5
emulsifying wax	3	4	5	6	7
cetyl alcohol	6	5	4	3	2
propylene glycol	3	3	3	3	3
sodium lactate	1	1	1	1	1
fragrance rose oil	1	1	1	1	1
Nipagin	0.18	0.18	0.18	0.18	0.18
Nipasol	0.02	0.02	0.02	0.02	0.02
distilled water	60	60	60	60	60

2.6. Evaluation of Cream

The modified procedures (Aswal, 2013) were used to evaluate the antioxidant cream.

2.6.1. Physical appearance/visual inspection

The cream was observed for color, odor and appearance.

2.6.2. Determination of pH

About 0.5 g of cream was weighed and dissolved in 50 ml of distilled water and its pH is measured.

2.6.3. Determination of Emulsion Type (dye test)

The scarlet red dye was mixed with the cream. A drop of the cream was placed in microscopic slide, covered with a cover glass and examined under microscope. If the disperse globules appear red and the ground is colorless, the cream is O/W type. The reverse condition occurs in W/O type cream i.e. the disperse globules appear colorless in the red ground.

2.6.4. Viscosity

The viscosity of cream was determined by Brookfield viscometer using spindle no 7.

2.6.6. Stability Studies

Stability study was carried out as per ICH guidelines. The cream filled bottle was kept in humidity chamber maintained 30±2°C with 65±5% RH for two months. After then samples were analyzed for the physical properties.

2.6.6. Test for microbial growth

The formulated creams were inoculated on the plates of Mueller Hinton agar media by a streak plate method. The plates were incubated in incubator at 37°C for 24 hours. After the incubation period, plates were taken out and the microbial growth was compared with the control plate (Muthukumarasamy *et al*, 2016).

2.6.7. Antioxidant activity of the cream

2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging activities of the cream was investigated following a modified method of Mishra (2014).

1 g of cream was extracted with ethanol 95%, then shaken rapidly for 5 min. The extract was filtered and the filtrate was collected. Briefly, 1 ml methanolic solution of DPPH (40 ppm) was added to 10 ml filtrate dissolved in ethanol at different concentration (150 - 350 ug/mL). Absorbance was recorded at 518 nm (Shimadzu, UV/Vis spectrophotometers). Ethanol was used as a blank, Ascorbic acid was used as standard. The scavenging activity was calculated using the equation: %scavenging activity = {(A518 control – A518 sample) / A518 control} x 100.

3. Results and Discussion

a. Evaluation of the Cream

Physical properties of cream including physical appearance, pH, viscosity, and spread ability are shown in table 2. All formulas had pleasant odor and light brownish color. The formulated cream was not greasy on skin and was easily removed by washing with tap water. The pH of cream was 5, which is good as a skin pH. The viscosity of cream was in range 6790-14155 centipoises which indicated that cream is easily spreadable.

The dye test confirms that all formulations were O/W type emulsion cream. When the formulations were kept for 2 months, it was found that there were not any particular changes in the color and consistency of the cream.

Table 2. Physicochemical Evaluation of the Cream

Parameter	**Formula**				
	A	**B**	**C**	**D**	**E**
appearance	light brown	light brown	light brown	light brown	light brown
odor	Good	good	good	good	good
Viscosity	6790	7435	9460	10055	14155
stability (2 months)	Stable	stable	stable	stable	stable
microbial growth	<100 colonies	<100 colonies	<100 colonies	<100 colonies	<100 colonies

b. Free Radical Scavenging Activity

The DPPH test provides information on the reactivity of the test compounds with a stable free radical. DPPH gives a strong absorption band at 518 nm in visible region. When the odd electron becomes paired off in the presence of a free radical scavenger, the absorption reduces and the DPPH solution is decolorized as the color changes from deep violet to light yellow. The degree of reduction in absorbance measurement is indicative of the radical scavenging (antioxidant) power of the extract.

Plants having significant medicinal values have often been found to be rich in phenolics and to have high antioxidant potentials (*Afolabi* et al, 2007). *Eleutherine bulbosa* is traditionally used by people

of Dayak as medicine for various. Kuntorini and Astuti (2010) showed that ethanolic extract of *Eleutherine bulbosa* bulbs have strong antioxidant acitivity. Chemical analysis of bulbs was proving the presence of naphthoquinones and anthraquinones, especially the eleuterina, eleuterol (Paramapojna *et al*, 2008), and eleuterinona (Xijing *et al*, 2009).

The antioxidant activity of phenolics is due to their redox properties which allow them to act as reducing agents, metal chelators and free radical quenchers (Rice-Evans *et al*, 1996). The secondary metabolites such as phenolics and flavonoids from plants have been reported to be potent free radical scavengers.

Formulated cream C exhibited DPPH scavenging activity of 41.34% followed by formula A, D, B, and E whose scavenging activities were 39.9%, 34.77%, 34.7%, and 31.23%, respectively.

The IC_{50} of the formulated cream C, A, D, B, E and ascorbic acid values were found to be 435.5, 456.27, 499.46, 514,0, 584.9 and 11.50 µg/mL, respectively. No significant differences of IC_{50} values between formulas A, B, C, D, and E.

Antioxidant activity of formulated cream was very low compare to Kuntorini and Astuti (2010). It indicated the release of active component of *Eleutherine bulbosa* extract from cream base was not maximized.

There were many factors that influenced the low release of active compound from antioxidant cream. One of them was the solvent for extraction cream. We used ethanol, a semi solar solvent. Apparently, ethanol was not completely dissolved the active component of *Eleutherine bulbosa* extraxt.

Another factor was the thickness of antioxidant cream due to the high level of cetyl alcohol and cetearyl alcohol. Erös *et al* (1994) confirmed a reciprocal relationship exists between the logarithm of viscosity and the quantity of drugs released.

4. Conclusions

Cream of *Eleutherine bulbosa bulb* extract had antioxidant activity and good physicochemical properties. Further research is required to improve the activity and stability of cream.

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