Development Of Instant Granules Containing Sappan Wood (Caesalpinia Sappan L) And Temu Mangga (Curcumma Mangga Valeton & Zipp) Extract Combination As Antimotility

Trisna Permadi, Swasono R. Tamat, Kartiningsih

Abstract: Indonesia is one of countries which as plants that have medicinal properties. Sappan wood (Caesalpinia sappan L) and temu mangga (Curcumma mangga Valeton & zipp) are native plants to Indonesia, which have antimotility property. Sappan wood and temu mangga contains flavonoids, saponins, tannins, steroids / triterpenoids and volatile oil which considered provide antimotility activity. This study begins with the maseration using ethanol 70% then evaporated and spray dryed. The various ratio of extract combination were formulated into instant granules. The granules were tested for phisicochemical properties and hedonic score, and the antimotility activity using colonic transit time method. All the granules complied with the phisicochemical properties of granules and the hedonic score. The best antimotility activity obtained in granules containing sappan wood and temu mangga extract 21:9, with intestinal transit percentage (60,07%) did not significantly different from the normal control (ANOVA one-way unstacked at α = 0,05).

Index Terms: antimotility, Caesalpinia sappan, Curcumma mangga, extract, instant granules, sappan wood, temu mangga.

INTRODUCTION

Diarrhea is an increased frequency and decreased of faeces when compared with normal individuals, in other words diarrhea is flaccid or liquid defecation than occurs 3 times or more within 24 hours [1]. Diarrhea is a disease caused by microorganisms infection including bacteria, viruses, parasites, protozoa, and fecal oral transmission. Diarrhea can affect all age of groups and various social groups, both in developed and development countries, and closely related to poverty and an unhygienic environtment [2]. Diarrhea is still a problem in developing countries such as Indonesia. Based on the pattern of causes of death of all ages, diarrhea is ranked 13th with a proportion of 3.5% of all death, whereas based on infectious disease, diarrhea is ranked 3rd after tuberculosis and pneumonia in Indonesia, diarrhea is the highest cause of infant and child mortality with a proportion of deaths of 31.4% and 25.2% [3]. In the case of diarrhea there is intestinal hypermotility which causes the movement of food and fluid in the intestine to increase and absorption in the large intestine is disrupted so that frequent defecation occurs. This can be overcome by administering drugs that reduce intestinal motility. The administration of this drug serves to suppress intestinal peristalsis so that it can reduce the frequency of defecation of diarrhea patients [3]. In developing countries, the majority of people living in rural areas often use traditional medicine in the treatment of all types of diseases including diarrhea. Indonesia is a developing country that has biodiversity in the form of plants and animals that are 80% efficacious. Among these plants that are commonly used to threat diarrhea are sappan wood and temu mangga, which are the main ingredients of traditional diarrhea medicines [4][5]. Sappan wood (Caesalpinia sappan L) is a shrub that is often used as traditional medicine in Asia, especially for tumors and cancers. In traditional Javanese medicine, sappan wood is used as the main ingredient of wedang secang taken to reduce disease such as : tuberculosis (TB), diarrhea, dysentry, antidote, medicine for internal and external wounds, threatment after childbirth, cataracts, ulcers, rheumatism, cold and fatigue [6]. Various study of sappan wood have been carried out by several researchers to determine the effectiveness of sappan wood as antidiarrheal drug. The content of tannin and gallic acid in sappan wood has the potential as anti-diarrhea and dysentry, and the content of essential oils from sappan wood also has the potential as anti-microbial diarrhea causing microbes such as E. Coli, Shigella, Salmonella, and Campylobacter [7]. Temu mangga (Curcumma mangga) is a derivative of the Zingiberaceae tribe which has characteristics such as tumeric but is white, and have a taste like a mixture of carrots and manggoes. Temu mangga is commonly used in Java as a cooking spice and also as a traditional medicine to relieve abdominal pain, fever, adn cancer. Several studies have also concluded that temu mangga has antioxidant, antitumor, antifungal, and anti alergic activity [8]. Temu mangga extract has been used as antacids and anti ulcers in herbal hospital in Indonesia. The content of tannin, turmeron and terpenoids from temu mangga has the potential to be antidiarrheal, and effective for protection against hyperacidity and gastric ulcers. Curcumin compounds have also been studied to have anti cancer activity against cervical cancer, colon cancer, breast cancer and lung cancer [9]. Diarrhea drugs circulating in pharmacies are usually in the form of capsules and tablets. But these preparations are very difficult for children and toddlers to consume, even they are reluctant to drink them. This can cause diarrhea treatment for children to be difficult, so it is necessary to make preparations by formulating secang wood extract and temu mangga into soluble granule preparations which have antimotility effects. This is to facilitate children and toddlers in consuming it, so that it can reduce the number of diarrhea sufferers. In this study sappan wood and temu mangga extract were made instant granule preparations with the right dose, low moisture content so that the stability of active ingredients was better, and individually packaged which made it easier for consumers to be carried out in their activities. Soluble granules are chosen because of their practical shape, good taste, and in accordance with high doses. This study carried out several analyzes, namely chemical analysis, physical analysis and organoleptic tests. 70% ethanol extract of sappan wood and temu mangga formulated into instant granules using factorial design 2^2 with two factors, concentration of sappan wood

extract and temu mangga extract so that the optimum formula which produces effective instant granule as in-vivo antimotility by using the intestinal transit method in male white mice DDY strains.

METHODS

Eextract Preparation

Simplicia powder was extracted by kinetic maceration with 70% ethanol solvent, then filtered. The collected filtrate was concentrated by vacuum evaporator then evaporated on a water bath at 50˚C until a thick extract was obtained. The thick extract was then dried by spray dying to obtain dry extract powder.

Granules Formulation

Formulas were made with various active ingredient combinations. These granules were made with wet granulation method, with sappan wood and temu mangga extract as active ingredient, PVP as a binder, sucrose as sweetener and filler, and banana essen as a flavor enchancer, the size ofthe comparison used is shown at table 1.

Table 1. *Instant granule combinattion formulas*

Ingredients	F1	F2	F3	F4
Sappan wood extract	21	16	10	8
Temu mangga extract	9	7	19	15
Banana essence	5	5	5	5
PVP	1	1	1	1
Sucrose	Until 100%			

Sucrose, sappan wood extract, temu manggaextract and PVP were mixed in one container, then the mixture was homogenized while adding banana essence little by little. The mixture is then sprayed with 96% alcohol while being pumped to a compact mass. Granule mass was sieved with 12 mesh sieve, then dried in an oven at 40˚C for 1 hour. Sifted again with a mesh sieve 14.

Hedonic Test

Hedonic test was carried out on 28 healthy adult volunteers with the parameters tested including aroma, color and taste. The sample was one sachet (5 gr) garnule dissolved in 100 mL of drinking water. The scale of the value used the numeric value with a value 1 to 5, value of 1 states very dislike, value 2 states dislike, value 3 states neutral, value 4 states like, and value 5 states love it.

Measurement of Antimotility Activity

In the first minute all groups were given preparations according to the treatment group orally. Forty-five minutes later the animal was given an active charcoal suspension, at sixty-five minutes the mice were sacrificed by dislocated cervical bone and the intestine was removed carefully. The intestine is stretched on the operating table, then the length of the intestine taken by active charcoal is measured and compared with the length of the whole intestine.

RESULTS

The dry extracts obtained was tested for its phisical and chemical properties to see the caracteristics of teh extracts. The flow rate and the angle of repose of the extract showed that the extracts was cohesive (<1.6 g/s), with moisture content that met with the rquirements of natural ingredients which was <10%. As for the full characteristics of the dried extract shown at table 2.

Table 2. *Dry extract characteristic*

Test	Sappan wood	Temu mangga
Organoleptic Texture Color Smell Taste	 Powder Brown Typical smell Bitter	 Powder Cream Typical smell Bitter
Flow rate **Angle of repose**	Cohesive 23,15 (Very good)	Cohesive 25,58 (Good)
Moisture content	4,88 %	6,73 %

The dried extract was then formulated into instant granules with various combination. All granule formulas obtained have a light brown color with a distinctive aroma of temu mangga adn sweet taste with a bitter aftertaste, all granules also meet the phisical requrement granules. As for the overall characteristics of the granules made can be seen in table 3.

Table 3. *Instant granules characteristic*

Parameters	F1	F2	F3	F4	Criteria
Taste	Sweet	Sweet	Sweet	Sweet	Not bitter
Moisture content (%)	3.33	3.33	3.30	3.80	3 – 5
Flow rate (g/s)	4.72	3.82	5.92	6.23	4 – 10
Angle of repose (°)	19.71	19.99	18.05	18.21	< 25
Time to dissolve (minutes)	1.08	1.10	1.17	1.02	< 5

For hedonic test, instant granule is then made into a solution with a concentration of 5% in drinking water, all formula has a red color solutions with a distinctive aroma of temu mangga and sweet taste with a bitter after-taste. As for the results of the hedonic test can be seen in table 4.

Table 4. *Hedonic test results*

Formula	Color	Aroma	Taste
F1	$3,5^{a}$	$4,0^{a}$	$2,4^{a}$
F2	$3,4^{a}$	$3,7^{b}$	$3,0^{a}$
F3	$3,7^{b}$	$3,0^{c}$	$2,4^{b}$
F4	$3,6^{b}$	$3,5^{d}$	$2,9^{b}$

- *Trisna Permadi & Kartiningsih, Faculty of Pharmacy University of Pancasila, Indonesia, PH- (021) 7864727. E-mail: trisnaffup@gmail.com*
- *Swasono R. Tamat, Radioisotop and Radiopharmaca Development Centre, BATAN, Indonesia. E-mail : swasonotamat@gmail.com*

Hedonic scalling scoring:
5 = Very like it
4 = Like it
3 = Quite like it
2 = Don't like it
1 = Very don't like it

Antimotility activity test was carried out on 28 male white mice DDY strain (divided into 7 groups), where in the normal group only given aquadest, the negative group was induced by oleum ricini and given Loperamid HCl, the positive group induced by oleum ricini, group F1 to F4 induced by oleum ricini and given supension F1 to F4 instant granules, each mice then given active charcoal as a marker, and length of intestine that is passed by active charcoal ratio against intestinal length entirely was measured. The results can be seen in table 5.

Table 5. *Antimotility activity test results*

Group	Ratio
Normal	58,61[a]
Negative	45,79[b]
Positive	86,11[c]
F1	60,07[a]
F2	66,13[d]
F3	55,03[e]
F4	55,34[e]

DISCUSSION

Diarrhea is the result of an imbalance between the mechanism of absorption and secretion in the digestive tract, accompanied by acceleration that results in a lot of fluid being wasted with feces. In some diarrhea the secretion mechanism is more dominant, while other diarrhea is hypermotility. The use of castor oil as an inductor of diarrhea in this study is due to autacoid and prostaglandin is one of the causes of diarrhea in humans. The release of ricin oleic acid from castor oil results in irritation and inflammation of the intestinal mucosa, which releases prostaglandin which stimulates motility and secretion [10]. Diarrhea increases motility, secretion and decreases absorption from the gastrointestinal tract, where these effects cause loss of a lot of electrolytes (especially Na+) and water [11]. Foster and Cox stated that diarrhea is a result of increased movement of the gastrointestinal tract, which is followed by a decrease in the transit time of feces in the colon. Any ingredients that reduce gastrointestinal movements and or reduce secretions have antidiarrheal activity [12]. In this study F1 to F4 granules showed a decrease in faecal transit time in the colon compared to positive control (mice that had been induced by oleum ricini) but not as strong as the activity of the negative control (mice that had been treated with Loperamid HCl). The antimotility activity of F3 and F4 has a cross active charcoal ratio that is smaller than normal control (58.61%) which is 55.03% and 55.34%. Based on data from the Ministry of Health of the Republic of Indonesia in 2011, giving antimotility drugs (such as Loperamid HCl) resulted in 1% of deaths in children [3], therefore F3 and F4 were not recommended as antimotility in children because they feared constipation. The antimotility activity of granules is estimated because the extract increases NaCl and water reabsorption by reducing intestinal motility as indicated by a reduction in intestinal active charcoal crossings. The antimotility activity of the extract can also occur because protein denaturation forms tannat protein, tannat protein makes the intestinal mucosa more resistant and reduces secretion. Secretory diarrhea is associated with activation of the Cl-channel, resulting in Cl-depletion of cells, loss of Cl- resulting in excessive water secretion to the intestinal lumen, extracts thought to inhibit the secretion of water into the lumen by reversing this process [10]. The antimotility activity is estimated to be due to the presence of tannins, flavonoids, saponins, steroids and / or triterpenoids found in the sappan wood extract and temu manga. Tannin can provide antidiarrheal activity through protein precipitation in enterocytes, reducing peristalsis and intestinal secretion. Sesquiterpen lactone is a group of compounds with anti-inflammatory activity that has the ability to relax smooth muscles thereby reducing gastrointestinal stress, even though the antidiarrheal activity of these terpenoids is known but the mechanism of action is unknown. Flavonoids and terpenoids are also known to inhibit autocoid and prostagladin release, which will reduce motility and secretion caused by castor oil [10]. Based on the results of the analysis of antimotility activity data using one-way (unstacked) ANOVA, it was found that F1 antimotility activity was not significantly different from the normal group, while the antimotility activity of F3 & F4 was not significantly different but both exceeded normal controls so it was not recommended. Based on the antimotility activity test, it was found that the granule formula that gave the best antimotility activity was F1 with the combination of sappan wood and temu mangga extract 21 : 9.

CONCLUSION

This study findings also sugested that sappan wood and temu mangga extract combination can be formulated into standardized herbal medicine by Indonesia regulation in the form of instant granules. This study also showed that color, aroma and taste of all granule formulas were acceptable by panelist. Granules with a combination ratio of sappan wood extract : temu mangga extract (21:9) have the best antimotility activity, with colonic transit time ratio of 60.07% which is not significantly different from normal control.

ACKNOWLEDGMENT

The authors wish to thank Ratna Djamil, Shirly Kumala and Nelly uyo. This work was supported in part by a grant from Mr. Tabligh.

REFERENCES

[1] Hura R, Suhatri, Elisma, Vahrozi H. "Uji aktivitas Antidiare Ekstrak Kulit Buah Duku (Lansium membranaceum (Kosterm.) Mabb) Pada Mencit Putih Jantan". National Conference Proceedings and Workshop "Perkembangan Terkini Sains Farmasi dan Klinik IV". pp. 268-272, 2014.
[2] Otimenyin S, Uzochukwu D. "Spasmolytic and anti-diarrhea effects of the bark of Erythrina senegalensis and root of Kigeliaafricana". Asian Journal of Pharmaceutical and Clinical Research. Vol. 3(4). pp. 11-14, 2010.
[3] Ministry of Health of the Republic of Indonesia. "Situasi Diare di Indonesia". Buletin Jendela Data dan Iinformasi Kesehatan. Triwulan II. 2011.
[4] Rahmawati F. "Kajian potensi wedang uwuh sebagai minuman fungsional". National Conference "Wonderfull Indonesia" PTBB FT UNY. pp. 619-631, 2011.

[5] Nuratmi B, Nugroho Y, Sundari D. “Efek antidiare jus temu putih (Curcuma zedoaria Rosc.) dan temu mangga (Curcuma mangga Val.Et. Zipp.) pada tikus putih”. Media Penelitian & Pengembangan Kesehatan (Litbangkes) Vo. XVI, No. 1. pp. 29-34, 2006.
[6] Badami S, Moorkoth S, Suresh B. “Caesalpinia sappan a medicinal and dye yielding plant”. Natural Product Radiance vol 3(2) March – April. pp. 75-82, 2004.
[7] Rina O, Ibrahim S, Dharma A, Afrizal, Wirawan C. “Screening for active agent to anti-diarrhea by an evaluation of antimicrobial activities from three fractions of sappan wood (Caesalpinia sappan. L)”. Der Pharma Chemica 8(19). pp. 114-117, 2016.
[8] Malek S, et al. “Phytochemical and cytotoxic Investigations of Curcuma mangga rhizomes”. Molecules ISSN 1420-3049 Vol. 6. pp. 4539-4548, 2011.
[9] RSUPN Cipto Mangunkusumo. “Informatorium Obat Herbal Rumah Sakit Umum Pusat Nasional DR. Cipto Mangunkusumo”. pp 145-146, 2012.
[10] Chitme, Havagiray R, Ramesh C, Sadhna K. “Studies on anti-diarrheal activity of calotropis gigantea R.BR. in experimental animals”. J Pharm Pharmaceutical Science 7(1). pp. 70-75, 2004.
[11] Rang H.P, Dale M.M, Ritter J.M, Moore P.K. “Pharmacology” Fifth Edition. Churchill. 2003.
[12] Foster R.W. “Basic Pharmacology”. pp. 45-47, 1983.
[13] Adjirni, B Nuratmi, Sa’roni Sa. “Efek Antidiare Kayu Secang (Caesalpinia Sappan L) Pada Tikus Putih”. Warta Tumbuhan Obat Indonesia Vol. 4 No 3. 1998.
[14] J.T Dipiro, R. L. Talbert, et al. “Pharmacotherapi Handbook. (6th edition)” Mc Graw-Hill. pp. 617-632, 2006.
[15] A Fahrial Syam. “Pengobatan Diare yang Tepat”. EGC. Jakarta. 2006.
[16] HC Ansel. “Pengantar Bentuk Sediaan Farmasi” translated by Farida Ibrahim. Universitas Iindonesia Press. pp. 261-271, 2005.
[17] H.G Vogel. “Drug Discovery and Evaluation Pharmacologycal Assays”. Springer-Verley Berlin, Deidelbarg. New York. page 1243. 2002.
[18] Departemen Kesehatan Republik Indonesia. “Parameter Standar Umum Ekstrak Tumbuhan Obat” Direktorat Jenderal Pengawasan Obat dan Makanan. Jakarta. pp. 3-27. 2000.
[19] Badan Pengawas Obat dan Makanan Republik Indonesia. “Persyaratan Mutu Obat Tradisional”. No. 12. 2014.