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The Effectiveness of Bandotan Herb (*Ageratum Conyzoides* L.) as Blood Uric Acid Levels Reduction in Mencit with Allopurinol Comparison

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Abstract

The pain and swelling in the joints is one of the symptoms of high levels of uric acid in the blood. Although currently on the market have been widely circulated synthetic chemical drugs to lower uric acid, but often cause various side effects, so it is necessary to find an alternative medicine of natural ingredients to lower Uralic acid levels in rational with relatively minor side effects. Traditionally herb bandotan (*Ageratum conyzoides* L.) are used for various treatments among them for stiff healing, eliminate swelling, and pain. The pain and sciatica is likely to be due to the high levels of uric acid in the blood, then to scientifically proves the presence of a relationship of aches and pains with a decrease in uric acid in the blood necessary to test the effectiveness of herbal extracts bandotan to decrease blood uric acid levels male mice. Extraction is done by percolation using 80% ethanol. The study begins with phytochemical screening test performed on fresh herbs, botanicals and herbal extracts bandotan ethanol. Decreased levels of uric acid is measured by using a measuring device Easy Touch® uric acid levels in the blood of male mice hyperuricemia induced by administration of potassium bromate 0.5 mg / kg. The data obtained were analyzed by analysis of variance (ANAVA) followed by analysis of Least Significant Difference Test (LSDT) using the least squares difference with a 99% confidence level. Phytochemical screening result looks the same class of chemical compounds in fresh herbs, botanicals and herbal extracts ethanol bandotan, namely alkaloids, flavonoids, tannins, triterpenoids / steroids; and essential oils. The result of the effect of decreasing uric acid levels showed there has been a reduction in the dose of 50 mg / kg, but is still too small, and according to the results of statistical test Analysis of Varian (ANOVA) and test Least Significant Difference Test (LSDT) dose of 100 mg / kg body weight have an effect reduction in uric acid levels were not significantly different with allopurinol dose of 10 mg / kg.

Keywords: Herb bandotan ethanol extract, phytochemical screening, Uric acid levels, Allopurinol.

1. Introduction

Last few years, there are so many people claimed by the doctors suffering from disease that caused by the level of uric acid in blood. This disease is marked by pain especially in bone joint area for the sufferers. The pain is caused by the arthritis. The arthritis is caused by crystal accumulation in the joints area with high level of uric acid in blood [1]. Now days, several medicines which reduce level of uric acid have been circulated, but it contained synthetic chemicals which inflict the various side effects that adverse health so need to find alternative medicine from nature to reduce the level of uric acid in blood with easy side effects.

One of natural ingredients from plant which often used traditionally to reduce arching rheumatic pain, muscle pain and eliminate swelling is bandotan herb (*Ageratum conyzoides* L.). Moreover, bandotan herb is also used to stop the bleeding, menstruation pain, laxative urine, gas laxative, anti-diarrhea and uterine tumors, ulcers, and eczema.

This plant has several synonyms, namely *Ageratum cordifolium*, *Ageratum album*, *Ageratum*

odoratum, *Ageratum latifolium*. It is also known as *billy goat weed, goat weed, tropical white-weed, sereno, erva de Sao Joao, sheng hong ji, bastard agrmony, celestine, eupatoire bleue, white weed, floss flower, chuva, baume, bouton, menstrasto*. In Indonesia is known by using cultural language, such as *bandotan, herba tombak, siangit, tomak jantansiangik kahwa, rumput tahi ayam* (Sumatera), *babandotan, bandotan, bandotan, jukut bau, ki bau, berokan, wedusan, dus wedusan, dus bedusan, tempuyak* (Java), *dawet, lawet, rukut manooe, rukut weru, sopi* (Sulawesi) [2].

It is found that various functions of bandotan herb which is traditionally used in society; especially like stew which has been proved empirically as aching rheumatic pain and swelling in the joints reduction and it is so potential developed as uric acid reduction, but scientifically there is no research proved. The use of bandotan herb by stew is not quite practical and needed big volume, hard usage in storage and distribution so it is more practical in extract formed.

However in the effective research as uric acid reduction which is tested to animal experiments of course need a little volume. Therefore, need extract formed to minimize the volume.

In extract production, it is done by several processes, start from simplicia drying until extract making which probably get damaged or lose the content of chemical compounds class, so to measure the chemical compounds in extract, need to do phytochemical screening from fresh herb, dry simplicia and its ethanol extract.

Based on this, researcher does the test of phytochemical screening from fresh herb, simplicia, ethanol extract from bandotan leaf, and also does some effective test of ethanol extract of bandotan herb as level blood uric acid reduction to animal experiment male mencit induced for increasing the uric acid with 200 mg/kg BB of calcium bromate given.

1.1. Bandotan Plant (*Ageratum conyzoides* L.)

Bandotan (*Ageratum conyzoides* L.) from Asteraceae class, is a weed season plant, growing upright, forming branches and hairy. The length of bandotan stem is about 30-90 cm, the leaf is oval wide (like egg), face to face and cross each other, in the edge of herb is jagged and rather long stalk. Its flower is shaped cup and organized in header, coloring white purple. Its seeds are numerous wrapped in the sheath, white hair in the end of seeds. This plant is multiplied by seed, grows wild in the open place moist soil or somewhat protected, in the grass field, even in yards of the lowland to an altitude of 2500 m above sea level. Its presence is often undesirable because it was considered an eyesore [3].

This plant has several synonyms, namely Ageratum cordifolium, Ageratum album, Ageratum odoratum, Ageratum latifolium. And it is known as billy goat weed, goat weed, tropical white-weed, sereno, erva de Sao Joao, sheng hong ji, bastard agrmony, celestine, eupatoire bleue, white weed, floss flower, chuva, baume, bouton, menstrasto. In Indonesia, this plant ethnically is so called as *bandotan, herba tombak, siangit, tomak jantansiangik kahwa, rumput tahi ayam (Sumatera), babandotan, bandotan, bandotan, jukut bau, ki bau, berokan, wedusan, dus wedusan, dus bedusan, tempuyak (Java), dawet, lawet, rukut manooe, rukut weru, sopi* (Sulawesi) [4].

Character and Functions

The taste of bandotan herb is quite bitter, hot and neutral. This plant is used widely by society for traditional treatment in various parts of world because its function as stimulants, eliminate swelling, fever reducer, anti-toxin, to stop the bleeding, menstrual emetic, laxative urine, wind laxative, anti-diarrhea, tonic, uterine tumors, ulcers, and eczema. In Brazil, it is often used to treat colic, colds, fever, diarrhea, rheumatism, and used as a tonic. Even, Brazil Medicine Centre recommends as anti-rheumatic drug. In Africa, it is used to treat pneumonia, wounds and burns. In traditional society of India use it for bactericidal, anti-dysentery, and antibiotics.

In Indonesia, bandotan is known as the wound healing, inflammation (swelling), intestinal inflammation, itching, fever, abdominal pain, chest pain, and trachoma. Various experiments of traditional use of bandotan as medicine supported by scientists and already carried out some research to prove its functions scientifically.

As inflammation drugs, the researchers in Technology Institute of Bandung have made the ointment with material of bandotan extract. The ointment is effectively sure to reduce inflammation and side effect so it is more secure than other anti-Flammarion that circulated in market.

Nowadays, there are so many kinds of medicine use to reduce inflammation. The point is the medicines are divided into 2 groups, namely: Group I (i.e.: cortisone and dexamethasone) and Group non-Steroidal (i.e.: salicylic acid, mefenamic acid, and phenylbutazone)

However, synthetic drugs that can cause side effects, especially when used repeatedly for a long time. Anti-inflammatory steroids for example, can lead to decreased immunity to infection, osteoporosis, muscle atrophy and fatty tissue, increase intra-ocular pressure, and is diabetic. The non-steroidal anti-inflammatory class can lead to bleeding stomach ulcers, kidney disorders, and anemia. The side effects that arise are because of the inhibition of the cyclooxygenase enzyme that affects the

formation of thromboxane and prostaglandin. The effect disruption of this enzyme is a disorder of the stomach.

Chemical Ingredients

Bandotan Herb contains alkalaoida, amino acids, organasid, essential oils cumarin, stigmasterol, tannins, sulfur, and potassium chloride [2], seskuiterpen, hidrosinat acids, steroids, alkaloids, and terpenoids [3].

Plant Systematic

Division : Spermatophyta
Sub division : Angiospermae
Class : Dicotyledoneae
Order : Asterales
Family : Asteraceae
Genus : Ageratum
Species : *Ageratum conyzoides*

Figure 1: Bandotan Plant

Benefits of bandotan herb

Some of the benefits of fruits bandotan for health, among others: treat gout, cure diabetes, relieve flu symptoms, seizures or stiffness in the digestive tract due to gastritis and diarrhea, as an antibacterial or antiseptic, lowers high blood pressure, lowering uric acid levels in the blood, to overcome the infection, anti-tumor, improve endurance, so do not get sick, relieve headaches, prevent and cure cough and inflammation resolve. Herbaceous plants bandotan also efficacious among others, to reduce high blood pressure.

Taxonomy bandotan

In systematic grow herbs; carrots are classified as follows (Indonesian Wikipedia, encyclopedia):

Kingdom : Plantae (Plants)
Subkingdom : Tracheobionta (Plants vascular)
Super Division : Spermatophyta (Plants Produce seeds)
Division : Magnoliophyta (Plants flowering)
Class : Magnoliopsida (dashed two / dikotil)
Order : Malvales
Family : Muntingiaceae
Genus : Muntingia

In Indonesia, it is called as bandotan. In some areas, it is known with few names: Jakarta named cherry, Madura called baleci. Other names in some countries is Datiles, aratiles, manzanitas (Philippines); Mat Sam (Vietnam); Khoom sômz, takhôb (Laos); takhop farang (Thailand); krâkhôb goods (Cambodia); and kerukup siam (Malaysia), Capulin blanco, cacaniqua, nigua, niguito (Spain); Jamaican cherry and cherry Singapore (English). Dutch first call Japanse kers ("Japanese cherry")

Chemical contents of bandotan herb

Chemical constituents in herb bandotan are saponins, flavonoids, polyphenols, and essential oils. In every 100 grams of fruit bandotan water-containing 77.8 grams of protein 0384 gram, fats 1:56 grams, carbohydrates 17.9 g, fiber 4.6 g, ash 1:14 grams, calcium 124.6 mg, phosphorus 84 mg, iron 1:18 milligrams, carotene, 0.019 grams, tannin 0065 gram, 0.037 grams riboflavin, niacin 0.554 grams, and 80.5 milligrams of vitamin C.

1.2. Uric Acid

Uric acid is a crystalline acid, the end product of normal metabolism of purines (derivative form nucleoprotein), which is a component of nucleic acids contained in the nucleus of cells of the body. Purines naturally present in the body because it is contained in foods such as meat, fish, and offal [5].

Uric acid has been known since ancient Greece. The disease is known as gout or gout. The word comes from the Latin *gout / guttan* which mean droplets. The disease is known as the disease of the rich at the time thought to be caused by the presence of toxins that falls drop by drop in the joints [6].

Gout is a metabolic disease characterized recurrent acute arthritis due to deposition of monosodium urate in joints and cartilage, can also occur in the formation of uric acid kidney stones. Gout is associated with high levels of uric acid in the serum, a poorly soluble compound which is the end product of purine metabolismo [7].

Gout can be divided into primary forms (90 percent) and secondary (10 percent). Primary gout is gout cases where the cause is unknown or due to abnormalities in the body's metabolic processes. Secondary Gout is a case of the cause can be known or obstacles result from the disposal of uric acid as a side effect of certain drug and alcohol addiction [8].

The Formation of Uric Acid

Humans change purine nucleosides (adenosine and guanine) into uric acid. First of all adenosine experiencing deaminated into inosine by the enzyme adenosine deaminase, inosine catalyzed by the enzyme nucleoside purine phosphorylase, will release the compound ribose 1-phosphate and the purine bases which produce hypoxanthine which in turn form xanthine in a reaction catalyzed by the enzyme xanthine oxidase, and xanthine oxidized into uric acid catalyzed by the enzyme xanthine oxidase [9].

The metabolism of uric acid formation takes place in the liver. Uric acid itself is not a substance harmful to the body as it can in excreted from the body naturally. Uric acid levels are normal for women ranged from 2.4 to 5.7 mg / dl for men ranged from 3.4 to 7 mg / dl. The mechanism involves the kidney and intestinal excretion. Uric acid is formed in the liver that is secreted into the kidneys. In the kidney, a process of screening and uric acid is one that is filtered. The filtering process in the kidneys aims to reduce uric acid levels in the body to remain stable, the circumstances in which uric acid levels in excess body known as hyperuricemia [1].

Caused of Gout

Factors that influence as a cause of gout [10] are: Hereditary factors with a history of gout in the family tree. Increased levels of uric acid are caused by a diet high in protein and foods rich in purines. As a result of excessive alcohol consumption, because alcohol is one source of purine can also inhibit disposal through the kidneys.

The resistance of the removal of uric acid is due to certain diseases, especially renal impairment. Other factors are such as stress and high blood pressure.

Gout Disease Stages

Gout attack generally felt suddenly without prior symptoms and begins at night with prime locations joints toes, heels, knees, wrists and ankles, elbows and fingers. There are four stages of gout [11], namely:

a. **Asymptomatic stage:** At this stage there is an increase in uric acid levels, but it is not accompanied by pain and not formed of urate crystals in the bladder.
b. **Acute phase:** At this stage the joint experiencing severe pain accompanied by a burning sensation. Acute arthritis attacks usually occur suddenly at night making the patient waking from sleep. These attacks culminated in a short time and disappear within ten days.
c. **Chronic phase:** In the chronic phase, tofus in crystal formed after about 10 years of the first attack. These events usually appear when the disease is ignored. In this stage, the attack usually happens 5-6 times in a year. The pain lasts longer and is constantly up to some joints, such as the tip of my toes, ankles, knees, elbows, and wrists were swollen.
d. **Chronic Phase with Tofus:** After more than 10 years, the patients are hard lumps of uric acid crystals in the joints and some needle-shaped leaves of the ear. Joints are often affected are the joints are often under pressure, such as the big toe joint, knee, and elbow and finger joints.

Treatment of Acute Gout Attacks

Acute gout attacks are usually treated with high doses of NSAIDs. Colchicine can be used as the alternative that is as effective as NSAIDs. Colchicine relieves pain and inflammation of gouty arthritis dramatically within 12-24 hours, without altering the metabolism or excretion of uric acid and no other analgesic effect. Colchicine produces anti-inflammatory effects by binding the intracellular protein tubulin, thereby preventing polymerization into microtubules and causes inhibition of leukocyte migration and phagocytosis. Also inhibit the formation of leukotrienes B4 [7].

Long-Term Treatment

Long-term treatment is meant to address the high levels of uric acid. The treatment is performed after the acute attack ends. Up to now there is no special medication that can reduce excessive levels of uric acid in the blood. The usual drugs are drugs that can spur removal of uric acid through the kidneys like probenezid, can also be given a drug that inhibits the formation of uric acid such as allopurinol [2].

Potassium chromate as Inducers

Potassium bromate is a compound that has been declared by the Institute for Research on Cancer as a carcinogen. In the latest research it is known that potassium bromate also increase uric acid levels in the body. The study was motivated by the ability of potassium bromate that can damage tissue in the kidneys that causes kidney failure. The mechanism of increased uric acid is believed to be closely linked to the nature of potassium bromate as a very powerful oxidizer. Potassium bromate increases oxidation reactions in the body that causes the formation of uric acid from the breakdown of protein compounds. In addition, potassium bromate also increases the activity of the enzyme xanthine oxidase in the efforts to establish a blood uric acid [12].

2. Research Method

2.1. Materials

The plant material is a herb bandotan fresh and were old, carboxyl methyl cellulose (CMC), allopurinol, potassium bromate, ethanol, sodium chloride, Pb (II) acetate, iron (III) chloride, mercury (II) chloride, potassium iodide, iodine , α-naphthol, citric acid, bismuth nitrate, ether, chloroform, isopropanol, methanol, anhydrous sodium sulfate, ethyl acetate, magnesium powder, zinc powder, hydrochloric acid, toluene, sulfuric acid,

2.2. Tools

The glass tools in a lab are used in this experiment with a balance of electricity (Mattler Toledo), the balance of animals digital (Tanita), blender (National), a pipette, oral sonde, filter paper, hot plate, tool measuring blood uric acid levels Nesco® Multicheck, mortars and stamper, a set of distillation equipment for determination of water content (Azeotropi), rat cage, microscopes, glass objects, cover glass, rotavapour (Buchi), freeze dryer (Edwars), percolator.

2.3. Stages of labor

a. The collection of herbs and dried powder of bandotan into powder simplicia, phytochemical screening, and the water content is determined by means azeotropi.
b. Making perexion
c. Making extracts, percolation method with 80% ethanol.
d. Murine induced by potassium bromate in NaCl 0.9% dose of 200 mg / kg intraperitoneally to an increase in blood uric acid levels.
e. Decreased effectiveness test levels of uric acid from the ethanol extract of the herb bandotan,

2.4. Intake and Preparation of Animal Experiments

Animal experiment used in this study is 2-3 months old male mice weighing 25-30 g. Before the trial began in advance of mice, it is maintained for 1 week in a good cage to match its environment [13] fedding pellets.

2.5. Testing the effectiveness Decreased levels of uric acid

Male mencit that had been prepared for the experiments conditioned for one week before testing was conducted. Then it is fasted for 18 hours prior to the tests yet to be given a drink.

On the day of testing, the initial uric acid levels checked each mouse by using gauges blood uric acid levels Nesco® Multicheck, blood was collected from the mice. Then it is induced by potassium bromate in NaCl 0.9% dose of 200 mg / kg intraperitoneally to an increase in blood uric acid levels.

After 10 days the rats were tested levels of uric acid, and then divided into five groups each group consisting of 6 animals, namely:

Group 1: as a blank CMC suspension given 2 ml of 0.5%
Group 2: for comparison given the suspense Allopurinol dose of 10 mg / KgBW
Group 3: supplied with herbal extracts bandotan suspension 25 mg / KgBW
Group 4: given the herbal extracts bandotan suspension 50 mg / KgBW
Group 5: supplied with herbal extracts bandotan suspension 75 mg / KgBW

Each animal has induced gout given test material suitable treatment groups. Then check the uric acid levels do return after 1 hour; 2 hours; 3 hours; and 4 hours. The data obtained were statistically tested by ANOVA (analysis of variants) and LSD (least Significant Difference).

3. Research Result

3.1. Phytochemical Screening

Results of phytochemical screening showed class of chemical compounds contained in herbal bandotan fresh, simplicia herb bandotan and ethanol extract herb bandotan is the same that class of alkaloids, flavonoids, steroids, essential oils and tannins, means no damage materials during the manufacturing process simplicia and extracts. The presence of the chemical content of the compound, especially flavonoids, steroids, and tannin is potentially the ethanol extract of the herb bandotan have the ability to lower uric acid.

Table 1: The result of uric acid reduction

% decreased in Uric acid level					
Time	**Control (CMC)**	**Extract (25 mg/kg BW)**	**Extract (50 mg/kg BW)**	**Extract (75 mg/kg BW)**	**Allopurinal (25 mg/kg BW)**
1st Hour	0	29.40±3.77	46.10±4.81	50.99±11.35	60.85±5.53
2nd Hour	0	43.22±9.89	59.03±3.90	70.29±7.30	70.29±4.26
3rd Hour	0	51.35±7.84	72..02±7.73	79.94±11.09	88.68±2.77
4th Hour	0	61.21±8.53	83.25±9.78	90.27±9.25	91.54±2.59

3.2. Effectiveness of Test Results Decreased levels of uric acid

Based on the data, it can be seen that the percentage reduction in uric acid levels in the blood of mice is more quickly at a dose of extract with a concentration of 50mg / KgBW and 75 mg / KgBW compared with a concentration of 25 mg / KgBW. It showed that the ethanol extract of the herb bandotan can lower blood uric acid levels because it looks increasingly higher doses of ethanol extract of herb bandotan suspension is given, the greater the effect of decreasing the blood uric acid levels in mice were tested. The experimental results can be seen in Table 1.

Table 1 above shows that there are differences in the percentage of decrease in blood uric acid levels in animals given ethanol extract of the herb bandotan suspension with various concentrations.

The data is obtained from the testing of anti-hiperasam uratemia continued testing statistically using ANOVA one way to see whether there is any difference in the effect of decreasing uric acid levels significantly among all groups of animals treated with the test materials with differences in various concentrations, then if there is a difference continued LSD (least significant difference) to see whether there is a significant difference between the test material with one another. ANOVA test results can be seen in Table 2 as follows:

Table 2: The Result of ANOVA Test

Time	F0	F-table	
		5%	1%
1st Hour	234.96	2,76	4,18
2nd Hour	350.57	2,76	4,18
3rd Hour	405.55	2,76	4,18
4th Hour	460.98	2,76	4,18

Table 2 shows that from hour to 1 to 4, obtained F0 price is greater than F-table, the percent decrease in uric acid blood of animals differ significantly from one another. Hence continued LSD test results are in Table 3 below:

Table 3: The Result of LSD Test

Time	Treatment	% decreased in KT	Difference with			
			CMC	Simvastatin	Extract 2%	Extract 4%
1st day	CMC	1.54	-	-	-	-
	Simvastatin	58.54	57	-	-	-
	Extract 2%	27.48	25.93	31.06	-	-
	Extract 4%	49.72	48.18	8.82	22.24	-
	Extract 6%	51.01	49.47	7.53	23.54	1.29
$BNT_{0.005}$ =0.214				$BNT_{0.01}$ =0.291		
3rd day	CMC	4.1	-	-	-	-
	Simvastatin	70.98	66.87	-	-	-
	EEDM 2%	37.17	33.07	33.8	-	-
	EEDM 4%	66.92	62.82	4.05	29.75	-
	EEDM 6%	67.59	63.49	3.38	30.42	0.67
$BNT_{0.05}$ =0.268				$BNT_{0.01}$ =0.363		
7th day	CMC	19.78	-	-	-	-
	Simvastatin	100	80.22	-	-	-
	Extract 2%	59.18	39.4	40.82	-	-
	Extract 4%	90.18	70.41	9.81	31.01	
	Extract 6%	90.28	70.51	9.71	31.12	0.11
$BNT_{0.05}$ =0.245				$BNT_{0.01}$ =0.331		
11th day	CMC	49.9	-	-	-	-
	Simvastatin	100	50.1	-	-	-
	Extract 2%	100	50.1	0	-	-
	Extract 4%	100	50.1	0	0	-
	Extract 6%	100	50.1	0	0	0
$BNT_{0.05}$ =0.166				$BNT_{0.01}$ =0.225		

Seen in Table 3 that The LSD above show that until the third hour of the impairment testing of uric acid are very significant differences with each other of all groups in the test. In the fourth hour of testing it appears that there are no significant differences in test results of the group given the extract 75mg / kg with allopurinol group given 10 mg / kg. While the results of the other groups still looks a very significant difference.

Overall it can be concluded that the ethanol extract of the herb bandotan have activity lowers blood uric acid levels from animals tested for their very significant differences with the control group of animals given only 0.5% CMC suspension only, and the effect of decreasing the levels of uric acid good is the group given 75 mg extract / kg for not differ significantly from that given Allopurinol 10 mg / kg.

4. Discussion

Based on the overall test results prove that:

The results of the preliminary investigation of chemical constituents of fresh herbs, botanicals powder and ethanol extract herb bandotan (Ageratum conyzoides) contain the same compound, namely: glycosides, flavonoids, steroid / triterpenoida and tannins.

Extract herb bandotan (Ageratum conyzoides) can lower blood uric acid levels. The best dose is 75 mg/KgBW, because on the fourth hour do not differ significantly from the administration of allopurinol 10 mg / KgBW.

The ethanol extract herb bandotan been shown to have efficacy decrease in blood uric acid levels in mice, so it can be developed into drugs decrease uric acid levels alternatives from natural materials, for this needs to be done further research, include toxicity tests, and test product development, including clinical trials on volunteers in order

to extract the drug reduced levels of uric acid from natural materials which rational, easy to obtain, easy to use with relatively minor side effects

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