

Diuretic Effect on Combination of Celery Herb (*Apium graveolens* L.) and Bay Leaf (*Syzygium polyanthum* W.) Ethanol Extract Towards Wistar Male Mice (*Rattus norvegicus* L.)

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Abstract. Celery (*Apium graveolens* L.) and Bay (*Syzygium polyanthum* Wight) contain active compound of flavonoid which can obstruct reabsorption of Na and water until increase diuretic effect. This research aims to know diuretic effect combinations from celery leaf and bay leaf ethanol extract 70% toward Wistar Male Mice using Lipschitz test. The research design is experimental with *posttest only control group design* by dividing the mice into normal group, hydrochlorothiazide group 25 mg/KgBB, control CMC-Na 0,5%, and combinations of celery and bay leaf ethanol extract treatment group. Those were made in 3 variances combinations doses which are; 1.125 mg/KgBB:6.25 mg/KgBB (combination-1), 2.25 mg/KgBB:12.5 mg/KgBB (combination-2), and 4.5 mg/KgBB:25 mg/KgBB (combination-3) and also 2 single doses of celery extract 4,5 mg/KgBB and bay leaf 25 mg/KgBB. Diuretic effect is determined by a diuretic index and Lipschitz value. Urine volume is analyzed with ANOVA and continued analyzing with non parametric Kruskal-Wallis and Mann Whitney. The results of diuretic effect combinations from celery and bay leaf ethanol extract showed that the three combinations have diuretic effect with value index in series from the smallest dose combinations are; 1,83, 1,86, 2,09 at 5 hours and 1,73, 1,75, 2,02 at 24 hours. Lipschitz values are 0,78, 0,79, 0,89 at 5 hours observation and 0,79, 0,79, 0,913 at 24 hours. Diuretic energy are ; 69,84%, 72,48%, 94,12% at 5 hours and 65,79%, 67,79%, 93,15% at 24 hours. Based on the test results of diuretic effects, combinations of celery and bay leaf ethanol extract have diuretic effect and combination-3 which is the closest to hydrochlorothiazide.

Introduction

Plants utilization for diseases-treatment purpose has long history, our ancestors from ancient era had used plants as important part in maintaining health. Those natural ways of treatment usually using potions from nature based on the previous usage experiences and from the nature mostly were from plants. Parts of plants such as; root, rhizome, trunk, bark, leaf, until seed and flower of a plant [1]. The plants that people often use for natural treatment are celery plant and bay leaf. Celery (*Apium graveolens* Linn) is a plant that is often found

everyday because it is usually used as food flavoring. Traditionally, people have utilized it for hypertension treatment. Celery has several efficacies which are as antioxidant, anticancer, antiplatelet and antihyperdemic, antihypertension, and also diuretic [2]. Bay leaf (*Syzygium polyanthum* Wight) is also a plant that is familiar in society used as traditional food flavoring, people have utilized it in the treatment of various diseases, one of them are hypertension and cholesterol. Part of the plant used is the leaf that has several merits as antipirai, antihyperlipidemia, antidiabetes, antihypertension, and able to indrease urine production [3].

Diuretic medical plants are medical plants that have efficacies which can exuviate urine or called diuretic. Diuretic is a kind of medicine that can increase water volume and natrium excreted by body through urine. Urinary output is mainly used to decrease fluid accumulation which is caused by the enhancement of the outer cells fluid volume that can cause edema and hypertension, [4]. Celery leaf contains compound such as apigenin, apiin, and 3-n-buthyptalide functions as vasodilator to increace blood stream in kidney thus result in natrium excretion, chloride and water which result in decreasing extracellular volume [5]. Celery leaf ethanol extract contains flavonoid 24,71 mg/100 gram analyzed with kuertesin comparison [6]. Celery leaf ethanol extract have diuretic percentage of 61,1% up to 116,6%, so, it is considered that celery ethanol extract can provide diuretic effect [7]. Bay leaf contains tannin, flavonoid with main component of fluoretin and kuersetin. Bay leaf ethanol extract contains total flavonoid for $1,67 \pm 0,02$ (g-QE/100 g extract) [8]. Bay leaf ethanol extract combines with sow thistle (*Sonchus Arvensis* L) can increase cumulative urine volume for 50.15% within 3 days [9].

Based on celery and bay leaf efficacies, combination of two is expected can provide better diuretic effect so that it can be used as a good therapy in several diseases that require fluid excretion from body through urine, especially in hypertension.

Material and Method

Plant. Celery herb (*Apium graveolens* L.) and bay leaf (*Syzygium polyanthum* W.) were obtained from Yogyakarta city.

Preliminary Extraction. Celery and bay leaf used were old enough and ready to be harvested. The leaves were washed with running water, then dried by aerated in a place protected from the direct sunlight until it was not wet. The leaves then were dried using oven. After it was dry, each of simplisia was pulverized until smooth. Making celery and bay leaf extract ethanol, each of them used maceration method, the ratio sample and solvent were 1:10. Celery and bay leaf, each of them were soaked using 70 % of ethanol for 24 hours and mixed with *stirrer* for first 6 hours. After that, the macerate was separated from pulp using paper filter until it was attained liquid extract. Remaceration was conducted for 24 hours with ratio 1:2. Macerate was collected and vaporized using *rotary vaporizer* until it was attained thick extract. Each of the extracts was re-vaporized in above *waterbath* to decrease fluid level inside.

Tested animals. Tested animals used were male Wistar mice with 2-3 month old, weighted 130-200 gram. Tested animals were placed in the cage for 7 days and provided with food and

water *ad libitum*. Placement before research was conducted for acclimatization of laboratory environment.

Diuretic Effect. The method used was Lipschitz [10] with modification on the usage of Hydrochlorotiazide as reference group. Hydrochlorotiazide 25 mg, celery herb and bay leaf ethanol extract were suspended into CMC-Na 0.5% for oral injection to tested animals. Injection dose combinations of EEHS and EEDS are ; 1,125 mg/KgBB + 6,25 mg/KgBB (combination 1), 2,25 mg/KgBB + 12,5 mg/KgBB (combination 2), and 4,5 mg/KgBB + 25 mg/KgBB (combination 3) and also single dose of EEHS 4,5 mg/KgBB and EEDS 25 mg/KgBB. CMC-Na 0,5% and aquadest were used as control group. Tested animals were satisfied for 18-24 hours before they were injected and kept giving a drink. After being satisfied, as much 5 mL/100 gramBB was rendered orally toward tested animals to replace the lost fluid during the tested animals were satisfied [11]. As much of 40 mice were selected randomly and divided into 8 groups. Each group consisted of 5 mice which were treated as follows:

- Group I : Normal group, tested animals were supplied with Aquadest orally.
- Group II : Control group, tested animals were supplied with suspension CMC-Na 0,5% orally.
- Group III : Hydrochlorotiazide group 25 mg/KgBB in CMC 0.5% orally.
- Group IV : Tested animals were supplied with suspension of celery leaf extract with dose of 4.5 mg/KgBB orally.
- Group V : Tested animals were supplied with suspension of bay leaf extract with dose of 25 mg/KgBB orally
- Group VI : Tested animals were supplied with suspension combination 1 (dose 1.125 mg/KgBB : 6.25 mg/KgBB) orally.
- Group VII : Tested animals were supplied with suspension combination 2 (dose 2.25 mg/KgBB : 12.5 mg/KgBB) orally.
- Group VIII : Tested animals were supplied with suspension combination 3 (dose 4.5 mg/KgBB : 25 mg/KgBB) orally.

After the treatment, tested animals were placed inside metabolit cage. Urine were collected in a vessel and it was measured at the 5th hour and 24th hour after rendering test material. The attained urine volume data was used as diuretic parameter calculation such as diuretic index, lipschitz value, and diuretic energy (%).

Statistics Analysis. Urine volume data was analyzed with SPSS (version 25.0) which is normality test used Kolmogorov-Smirnov, *homogeneity of variances* used Levene test, it was continued with Kruskall-Wallis and Mann-Whitney to see the differences among groups.

Result and Discussion

Extraction Result. In the research, thick extract from celery leaf extract was 177,185 grams from a total of 2.6 kg of simplicia powder and 112.44 grams of bay leaf viscous extract from a total of 2.2 kg of simplicia powder. Rendemen was obtained by comparing the initial weight of simplicia with the final weight of the extract produced. Rendemen produced from celery leaf ethanol extract was 6,815% and from bay leaf ethanol extract was produced rendemen as much as 5,111%.

Diuretic Effect Testing Result. Diuretic effect preparation test was determined from significant indication of urine volume test animal and diuretic effect energy can be found from

index calculation result and Lipschitz diuretic activity value. Diuretic effect in this research can be seen from the average urine volume value \pm SD and every treatment group at time at 5 hours and 24 hours observations. The result of average urine volume \pm SD of each group at 5 hours observation can be seen in Table 1.

Table 1. Average of Cumulative Urine Volume (ml/Kg) for 5 hours and 24 hours observation time

Group	Dose (mg/KgBB)	Urine Volume (mL/Kg)	
		5 Hours	24 Hours
Normal	-	31,08 \pm 2,01	41,30 \pm 2,04
CMC-Na 0,5%	-	33,53 \pm 1,77	43,20 \pm 1,92
Hydrochlorotiazide	25	73,46 \pm 3,14 ^a	91,25 \pm 3,60 ^a
Celery Exctract	4,5	41,39 \pm 2,29 ^a	55,11 \pm 2,05 ^a
Bay Extract	25	55,78 \pm 0,82 ^a	69,56 \pm 0,79 ^a
Combination 1	1,125 + 6,25	56,95 \pm 3,43 ^a	71,63 \pm 3,01 ^a
Combination 2	2,25 + 12,5	57,83 \pm 2,34 ^a	72,50 \pm 2,44 ^a
Combination 3	4,5 + 25	65,08 \pm 1,10 ^a	83,35 \pm 3,32 ^a

Information : letter *superscript* in the line shows the actual difference (P<0,05) toward the normal group.

From Table 1, it can be seen that each group at 5 hours and 24 hours observations had different urine volumes. There were volume enhancement in every treatment groups compared with normal control group and control CMC-Na 0,5%, it indicates that there were diuretic effect in every test conducted, whether on single dose of celery leaf ethanol extract, single dose bay leaf ethanol extract, and dose of combinations celery and bay leaf ethanol extract. The highest urine volume was in hydrochlorotiazide group followed by the combination of group 3. To see the different average of cumulative urine volume in every group at 5 hours and 24 hours observations can be seen in graphic figure 1.

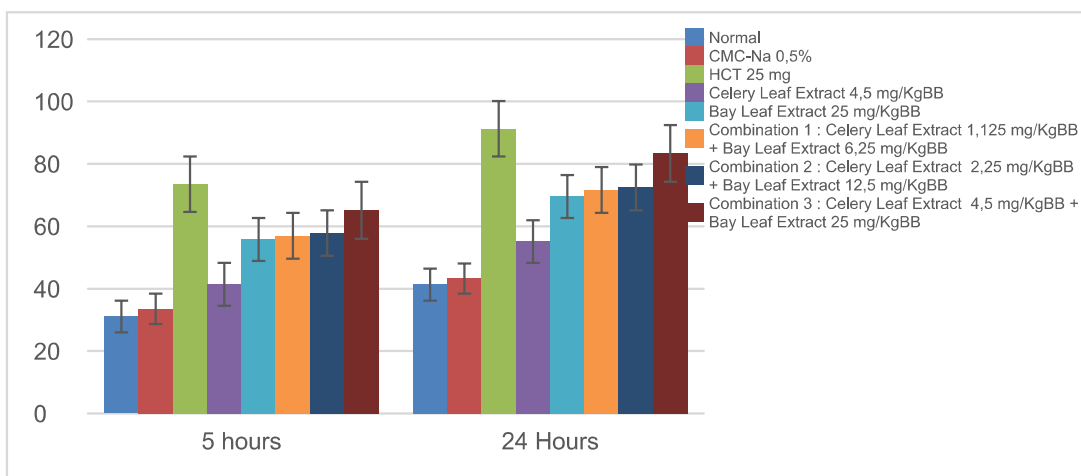


Fig. 1. Graphic of Average Cumulative Urine volume (mL/Kg) in every group at the at 5 hours and 24 hours observation

From the graphic presented in Figure 1, it can be seen that there were urine volume enhancement in every group at 5 hours to 24 hours observations. Combinations of groups I, II, and III had an average increasing in urine volume compared with single dose group, both

ethanol extract of celery leaf or bay leaf. This showed that the combination can increase the volume of urine excreted.

Then the data was analyzed statistically. The result showed that urine volume data was distributed normally. Testing used Mann-Whitney was conducted to see the significance between two groups. Significance relation between each treatment group in the observation time at 5 hours can be seen in Table 2 and the significance relation between each treatment group in the observation time at 24 hours can be seen in Table 3.

Table 2. Significance between each group treatment in 5 hours time

Treatment Group	Normal	HCT	Combination 1	Combination 2	Combination 3
CMC-Na 0,5%	TS	-	-	-	-
Hydrochlorotiazide	S	-	S	S	S
Dose 1	S	S	S	S	S
Dose 2	S	S	TS	TS	S
Combination 1	S	S	-	TS	S
Combination 2	S	S	TS	-	S
Combination 3	S	S	S	S	-

Table 3. Significance relation between every group treatment in 24 hours time

Treatment Group	Normal	HCT	Combination 1	Combination 2	Combination 3
CMC-Na 0,5%	TS	-	-	-	-
Hydrochlorotiazide	S	-	S	S	S
Dose 1	S	S	S	S	S
Dose 2	S	S	TS	S	S
Combination 1	S	S	-	TS	S
Combination 2	S	S	TS	-	S
Combination 3	S	S	S	S	-

Information:

Dose I : Celery Leaf Ethanol Extract 4,5 mg/KgBB (EEDSd)

Dose II : Celery Leaf Ethanol Extract 25 mg/KgBB (EEDSm)

Combination I : EEHS 1,125 mg/KgBB + EEDS 6,25 mg/KgBB

Combination II : EEHS 2,25 mg/KgBB + EEDS 12,5 mg/KgBB

Combination III : EEHS 4,5 mg/KgBB + EEDS 25 mg/KgBB

S : Significant

TS : Not Significant

Based on Table 2 and Table 3, it can be found that combination 3 was significantly different ($P \geq 0,05$) to two groups of single dose and two other combination groups, but it was different significantly ($P \leq 0,05$) toward hydrochlorotiazide group both at 5 hours and at 24 hours observations. While combination 1 and combination 2 were not significantly different

($P \leq 0,05$) which stated that both diuretic effects were not much different. Dose 1 had significant difference ($P \geq 0,05$) to the group of dose 2 and the three combinations. Furthermore, dose 2 was not significantly different towards combination of group 1 and combination 2 at 5 hours observation and significantly different toward group of combination 1 at 24 hours observation. This shows that ethanol extract bay leaf with dose 25 mg/KgBB had diuretic effect which almost had the same with combination 1 and combination 2.

Control group CMC-Na 0,5% was not different significantly ($P \geq 0,05$) to the normal group because CMC-Na 0,5% did not affect diuretic. This case shows that CMC-Na 0,5% did not influence diuretic effect of celery and bay leaf ethanol extract. Group of single dose celery leaf and bay leaf extract, and also combination of groups I, II, and III were stated as had diuretic effect, however the closest to hydrochlorotiazide group was the combination of group 3. This also shows that celery and bay leaf extract had diuretic effect because they contained flavonoid which can cause urinacy enhancement, where the working mechanism was by obstructed Na^+ , K^+ , Cl^- reabsorption, thus made electrolyte enhancement in the body, then becomes diuretic [12].

Diuretic activity was determined by using diuretic parameter which were diuretic index, Lipschitz values, diuretic energy (%) Diuretic Index, Lipschitz value, and diuretic energy of every group at 5 hours and 24 hours observations, it can be seen in Table 4.

Table 4. Diuretic Index, Lipschitz Value, and Diuretic Percentage Energy and Diuretic Energy of every Gorup at 5 hours and 24 Hours Observations.

Group	Dose (mg/KgBB)	Diuretic Index		Lipschitz Value		Diuretic Value (%)	
		5 Hours	24 Hours	5 Hours	24 Hours	5 Hours	24 Hours
Normal	-	1	1	-	-	-	-
CMC-Na 0,5%	-	1.08	1.05	0.46	0.47	0	0
Hydrochlorotiazide	25	2.36	2.21	1	1	119.09	111.14
Celery Extract	4,5	1.33	1.33	0.56	0.60	23.44	27.56
Bay Extract	25	1.79	1.68	0.76	0.76	66.37	60.99
Combination 1	1,125 + 6,25	1.83	1.73	0.78	0.79	69.84	65.79
Combination 2	2,25 + 12,5	1.86	1.75	0.79	0.79	72.48	67.79
Combination 3	4,5 + 25	2.09	2.02	0.89	0.91	94.12	93.15

Diuretic Index is a result from comparison of the test group urine volume with the normal group urine volume. Diuretic index is used as parameter to measure activity of a diuretic compound. Activity of a diuretic compound can be categorized into several levels according to its diuretic index values which are: strong type in index if the value is greater than 1,50; in medium type if the index values is between 1,00 until 1,50; weak type if the diuretic index is below 0,72 [13]. Strong diuretic activity is showed by hydrochlorotiazide control group, combination 1, combination 2, and combination 3, and ethanol extract celery leaf and single dose bay leaf ethanol extract with index diuretic more than 1,50 in both time observations. Diuretic activity is showed by celery leaf ethanol extract single dose with diuretic index of

1,33. From the three combinations, diuretic index with the closest to hydrochlorothiazide is combination group 3, which is 2,09. To see the different level of diuretic effects in each group at 5 hours and 24 hours observations can be seen in table Figure 2.

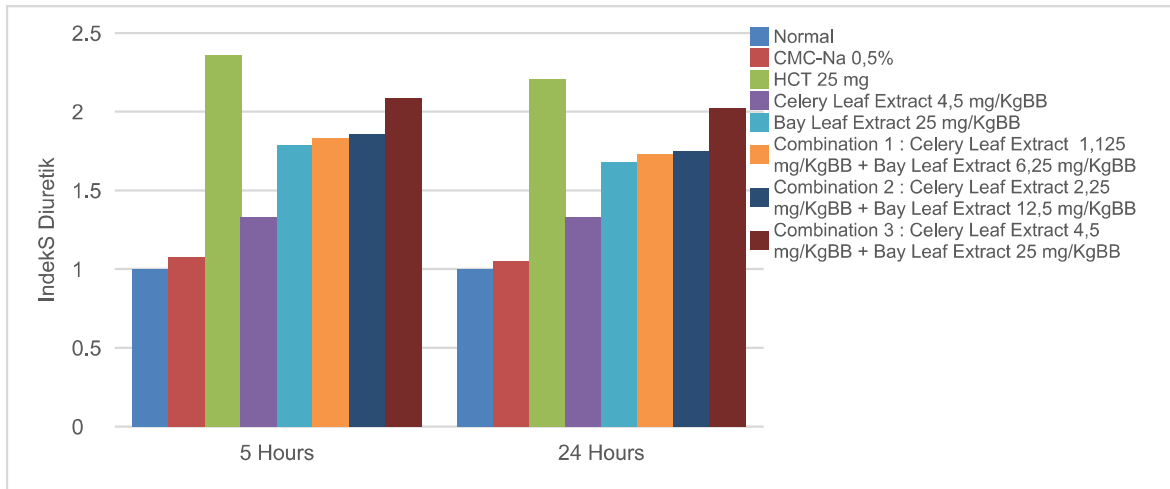


Fig. 2. Graphic of Diuretic Index of Every Group at 5 Hours and 24 Hours Observations.

Lipschitz value is urine volume comparison test group to hydrochlorothiazide group to know diuretic energy test group compared with hydrochlorothiazide [13]. Based on the data presented in Table 4, hydrochlorothiazide group has Lipschitz value: 1 and it is used as comparison within calculation. The smallest Lipschitz values in single dose group of celery leaf ethanol extract is 0,56 at the first 5 hours and getting increased becomes 0.60 at 24 hours observation time. It can be concluded that celery leaf ethanol extract with dose 4,5 mg/KgBB had activity 56% at 5 hours observation and 60% at 24 hours observation compared with the hydrochlorothiazide. Bay leaf ethanol extract with dose of 25 mg/KgBB has Lipschitz value : 0,76, thus diuretic activity to hydrochlorothiazide is 76%. Both of combination 1 and 2 have slightly differences, those are 0,78 and 0,79 at 5 hours observation, and 0,79 at 24 hours observation. While combination 3 is the highest and the closest to comparison which are: 0,89 at 0-5 hours and 0,991 at 0-24 hours observation, in which it has diuretic activity as 89% and 91% compared with hydrochlorothiazide. Hydrochlorothiazide is an antihypertension medicine thiazide type which works on tubulus distal and hamper natrium chloride *co-transporter*, so it causes diuretic effect [14]. To know the differences in each Lipschitz group's at 5 hours and 24 hours observations can be seen in Graphic Figure 3.

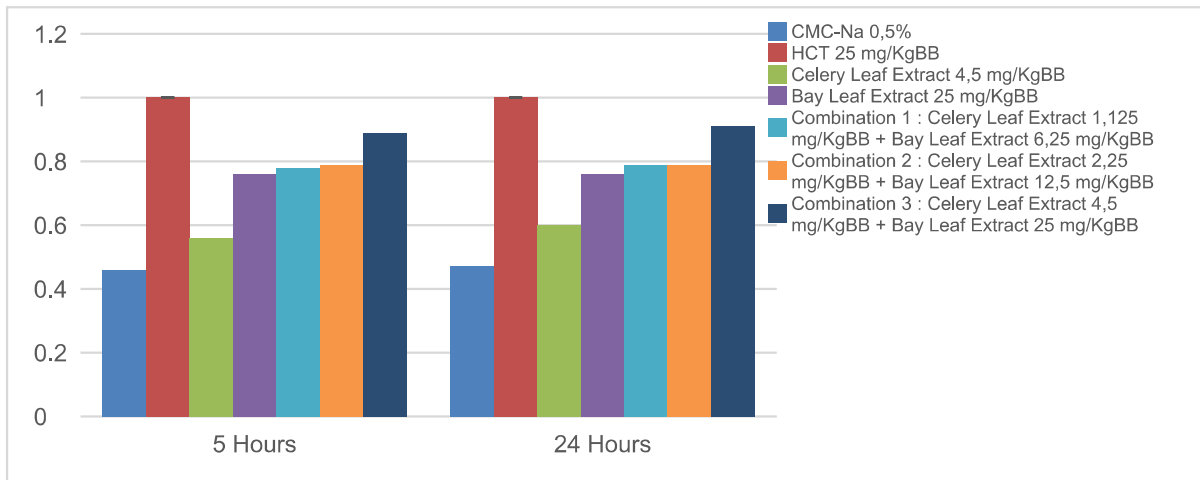


Fig. 3. Lipschitz Value every Group at 5 hours and 24 hours observations.

Diuretic Energy Percentage is urine volume comparison percentage treatment group with CMC-Na 0,5% group. Diuretic energy describes percentage of urine increasing volume compared with negative control group. The higher diuretic energy, the more diuretic effectivity get increased. Table 4 has presented diuretic percentage data of every group in both time observations which are; 119,09% and 111,14%. This because hydrochlorotiazide is a drug that posses diuretic effect and it has been used publicly for antihypertension therapy.

From the three combinations, diuretic energy in a series from the smallest combinations are ; 69,84%, 72,48%, 94,12% at 5 hours observation and 65,79%, 67,79%, 93,15% at 24 hours observation. From the outcome, it shows that there were enhancement of diuretic energy along with the increasing of extract celery and bay leaf combination dose. This makes clear that the greater dose used, the content of active flavonoid inside is getting more and more and increases urine excretion. Combination 3 has the biggest diuretic energy in among the three combinations, so, it is stated that the diuretic energy is the closest to hydrochlorotiazide. To see the different diuretic energy percentage in every group at 5 hours and 24 hours observations can be seen on the graphic of Figure 4.

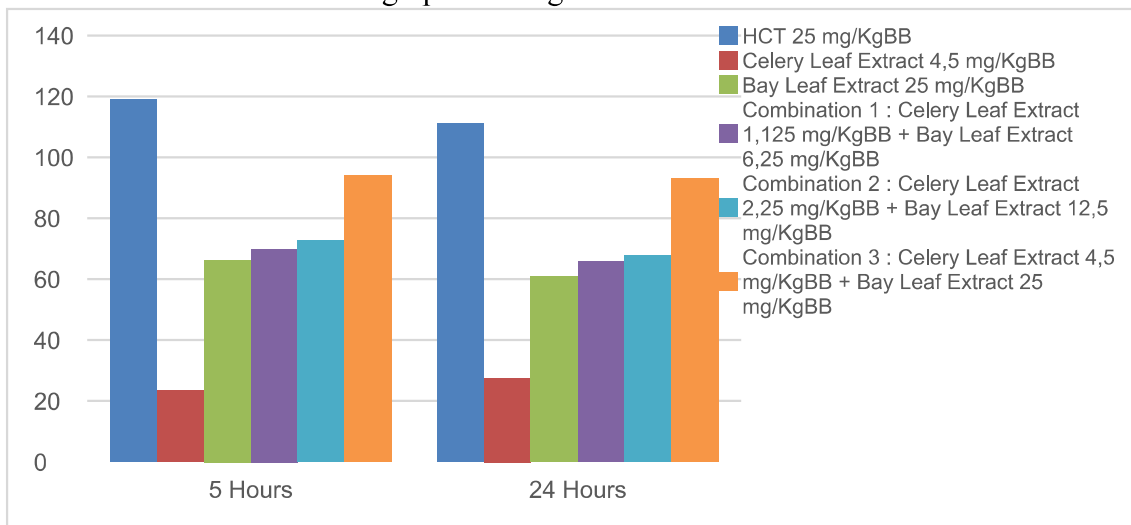


Fig. 4. Diuretic Energy Every Group in Observation Time 5 Hours and 24 Hours

Single dose of celery extract has the smallest diuretic energy which is 23,44% at 5 hours observation and 27,56% at 24 hours observation. This might be happened because of extract dose was too small which was 4,5 mg/KgBB. However, diuretic energy produced by the celery extract single dose was greater than previous research. Celery leaf ethanol extract with dose of 80 mg/KgBB produce diuretic energy as 61,1% and kept increased into 88,8% and 116,6% in dose 80 mg/KgBB and 160 mg/KgBB [7]. Diuretic effect produced by the celery leaf ethanol extract has been predicted because it contains flavonoid inside. Celery leaf ethanol extract contains flavonoid 24,71 mg/100 gram which was analyzed used kuersetin comparison [6].

Single dose bay leaf 25 mg/KgBB can produce diuretic energy as 66,37% at 5 hours observation and 60,99% at 24 hours observation. Celery leaf ethanol extract dose 50 mg/KgBB has diuretic effect, it was indicated with urine volume increasing compared with control [15]. The other research reported that celery leaf ethanol extract and sow thistle with dose 200 mg/KgBB can provide diuretic energy as 50,15% within 3 days [9]. Bay leaf ethanol extract contains flavonoid with total : $1,67 \pm 0,02$ (g-QE/100 g extract). This shows that in the research on bay leaf ethanol extract with dose 25 mg/KgBB really consists of diuretic effect because it contains flavonoid inside.

CONCLUSION

1. Combinations of celery leaf and bay leaf ethanol extract have diuretic effect with diuretic index value in series from combination 1, 2, 3 are 1,83, 1,86, and 2,09 in observation time at 5 hours; 1,73, 1,75, and 2,02 at 24 hours observation. Diuretic energy in series from the smallest dose combinations are 69,84%, 72,48%, 94,12% in observation 5 hours; 65,79%, 67,79%, 93,15% at 24 hours combination.
2. The most effective dose combination as diuretic is the combination 3 which is celery leaf ethanol extract 4,5 mg/KgBB + bay leaf ethanol extract 25 mg/KgBB.

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Journal: «**Advanced Materials Research**»
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Diuretic Effect on Combination of Celery Herb (*Apium graveolens* L.) and Bay Leaf (*Syzygium polyanthum* W.) Ethanol Extract Towards Wistar Male Mice (*Rattus norvegicus* L.)

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Keywords: Ethanol Extract, *Apium graveolens*, *Syzygium polyanthum*, hydrochlorothiazide, Lipschitz

Abstract. Celery (*Apium graveolens* L.) and Bay (*Syzygium polyanthum* Wight) contain active compound of flavonoid which can obstruct reabsorption of Na and water until increase diuretic effect. This research aims to know diuretic effect combinations from celery herb and bay leaf ethanol extract 70% toward Wistar Male Mice using Lipschitz test. The research design is experimental with *posttest only control group design* by dividing the mice into normal group, hydrochlorothiazide group 25 mg/kg, control CMC-Na 0.5%, and combinations of celery herb (CHEE) and bay leaf ethanol extract (BLEE) treatment group. Those were made in 3 variances combinations doses which are; 1.125 mg/kg:6.25 mg/kg (combination-1), 2.25 mg/kg:12.5 mg/kg (combination-2), and 4.5 mg/kg:25 mg/kg (combination-3) and also 2 single doses of CHEE 4.5 mg/kg and BLEE 25 mg/kg. Diuretic effect is determined by a diuretic index and Lipschitz value. Urine volume is analyzed with ANOVA and continued analyzing with non parametric Kruskal-Wallis and Mann Whitney. The results of diuretic effect combinations from CHEE and BLEE showed that the three combinations have diuretic effect with value index in series from the smallest dose combinations are; 1.83, 1.86, 2.09 at 5 hours and 1.73, 1.75, 2.02 at 24 hours. Lipschitz values are 0.78, 0.79, 0.89 at 5 hours observation and 0.79, 0.79, 0.913 at 24 hours. Diuretic energy are ; 69.84%, 72.48%, 94.12% at 5 hours and 65.79%, 67.79%, 93.15% at 24 hours. Based on the test results of diuretic effects, combinations of CHEE and BLEE have diuretic effect and combination-3 which is the closest to hydrochlorothiazide.

Introduction

Plants utilization for diseases-treatment purpose has long history, our ancestors from ancient era had used plants as important part in maintaining health. Those natural ways of treatment usually using potions from nature based on the previous usage experiences and from the nature mostly were from plants. Parts of plants such as; root, rhizome, trunk, bark, leaf, until seed and flower of a plant [1]. The plants that people often use for natural treatment are celery plant and bay leaf. Celery (*Apium graveolens* Linn) is a plant that is often found everyday because it is usually used as food flavoring. Traditionally, people have utilized it for hypertension treatment. Celery has several efficacies which are as antioxidant, anticancer, antiplatelet and antihyperdemic, antihypertension, and also diuretic [2]. Bay leaf (*Syzygium polyanthum* Wight) is also a plant that is familiar in society used as traditional food flavoring, people have utilized it in the treatment of various diseases, and one of them are hypertension and cholesterol. Part of the plant used is the leaf that has several merits as antipirai, antihyperlipidemia, antidiabetes, antihypertension, and able to indrease urine production [3].

Diuretic medical plants are medical plants that have efficacies which can exuviate urine or called diuretic. Diuretic is a kind of medicine that can increase water volume and natrium excreted by body through urine. Urinary output is mainly used to decrease fluid accumulation which is caused by the enhancement of the outer cells fluid volume that can cause edema and hypertension, [4]. Celery herb contains compound such as apigenin, apiin, and 3-n-buthyptalide functions as vasodilator to increase

blood stream in kidney thus result in natrium excretion, chloride and water which result in decreasing extracellular volume [5]. Celery herb ethanol extract contains flavonoid 24.71 mg/100 gram analyzed with kuertesin comparison [6]. Celery leaf ethanol extract have diuretic percentage of 61.1% up to 116.6%, so, it is considered that celery ethanol extract can provide diuretic effect [7]. Bay leaf contains tannin, flavonoid with main component of fluoretin and kuersetin. Bay leaf ethanol extract contains total flavonoid for 1.67 ± 0.02 (g-QE/100 g extract) [8]. Bay leaf ethanol extract combines with sow thistle (*Sonchus Arvensis* L) can increase cumulative urine volume for 50.15% within 3 days [9].

Based on celery herb and bay leaf efficacies, combination of two is expected can provide better diuretic effect so that it can be used as a good therapy in several diseases that require fluid excretion from body through urine, especially in hypertension.

Material and Method

Plant. Celery herb (*Apium graveolens* L.) and bay leaf (*Syzygium polyanthum* W.) were obtained from Yogyakarta city.

Preliminary Extraction. Celery herb and bay leaf used were old enough and ready to be harvested. The leaves were washed with running water, then dried by aerated in a place protected from the direct sunlight until it was not wet. The leaves then were dried using oven. After it was dry, each of simplisia was pulverized until smooth. Making celery herb and bay leaf extract ethanol, each of them used maceration method, the ratio sample and solvent were 1:10. Celery and bay leaf, each of them were soaked using 70 % of ethanol for 24 hours and mixed with *stirrer* for first 6 hours. After that, the macerate was separated from pulp using paper filter until it was attained liquid extract. Remaceration was conducted for 24 hours with ratio 1:2. Macerate was collected and vaporized using *rotary vaporizer* until it was attained thick extract. Each of the extracts was re-vaporized in above *waterbath* to decrease fluid level inside.

Tested animals. Tested animals used were male Wistar mice with 2-3 month old, weighted 130-200 gram. Tested animals were placed in the cage for 7 days and provided with food and water *ad libitum*. Placement before research was conducted for acclimatization of laboratory environment. All studies were approved by the Research Ethics Committee Ahmad Dahlan University (Ethical Approval Number 011805079).

Diuretic Effect. The method used was Lipschitz [10] with modification on the usage of Hydrochlorotiazide as reference group. Hydrochlorotiazide 25 mg, CHEE and BLEE were suspended into CMC-Na 0.5% for oral injection to tested animals. Injection dose combinations of EEHS and EEDS are ; 1.125 mg/kg + 6.25 mg/kg (combination 1); 2.25 mg/kg + 12.5 mg/kg (combination 2); and 4.5 mg/kg + 25 mg/kg (combination 3) and also single dose of CHEE 4.5 mg/kg and BLEE 25 mg/kg. CMC-Na 0.5% and aquadest were used as control group. Tested animals were satisfied for 18-24 hours before they were injected and kept giving a drink. After being satisfied, as much 5 mL/100 gram was rendered orally toward tested animals to replace the lost fluid during the tested animals were satisfied [11]. As much of 40 mice were selected randomly and divided into 8 groups. Each group consisted of 5 mice which were treated as follows:

- Group I : Normal group, tested animals were supplied with Aquadest orally.
- Group II : Control group, tested animals were supplied with suspension CMC-Na 0.5% orally.
- Group III : Hydrochlorotiazide group 25 mg/kg in CMC 0.5% orally.
- Group IV : Tested animals were supplied with suspension of CHEE with dose of 4.5 mg/kg orally.
- Group V : Tested animals were supplied with suspension of BLEE with dose of 25 mg/kg orally

- Group VI : Tested animals were supplied with suspension combination 1 (dose 1.125 mg/kg: 6.25 mg/kg) orally.
- Group VII : Tested animals were supplied with suspension combination 2 (dose 2.25 mg/kg: 12.5 mg/kg) orally.
- Group VIII : Tested animals were supplied with suspension combination 3 (dose 4.5 mg/kg: 25 mg/kg) orally.

After the treatment, tested animals were placed inside metabolit cage. Urine were collected in a vessel and it was measured at the 5th hour and 24th hour after rendering test material. The attained urine volume data was used as diuretic parameter calculation such as diuretic index, lipschitz value, and diuretic energy (%).

Statistics Analysis. Urine volume data was analyzed with SPSS (version 25.0) which is normality test used Kolmogorov-Smirnov, *homogeneity of variances* used Levene test, it was continued with Kruskal-Wallis and Mann-Whitney to see the differences among groups.

Result and Discussion

Extraction Result. In the research, thick extract from CLEE was 177.185 grams from a total of 2.6 kg of simplicia powder and 112.44 grams of bay leaf viscous extract from a total of 2.2 kg of simplicia powder. Rendemen was obtained by comparing the initial weight of simplicia with the final weight of the extract produced. Rendemen produced from CHEE was 6.815% and from BLEE was produced rendemen as much as 5.111%.

Diuretic Effect Testing Result. Diuretic effect preparation test was determined from significant indication of urine volume test animal and diuretic effect energy can be found from index calculation result and Lipschitz diuretic activity value. Diuretic effect in this research can be seen from the average urine volume value \pm SD and every treatment group at time at 5 hours and 24 hours observations. The result of average of cumulative urine volume for 5 hours and 24 hours observation time of each group can be seen in Table 1.

Table 1. Average of Cumulative Urine Volume (mL/kg) for 5 hours and 24 hours observation time

Group	Dose (mg/kg)	Urine Volume (mL/kg)	
		5 Hours	24 Hours
Normal	-	31.08 \pm 2.01	41.30 \pm 2.04
CMC-Na 0,5%	-	33.53 \pm 1.77	43.20 \pm 1.92
Hydrochlorotiazide	25	73.46 \pm 3.14 ^a	91.25 \pm 3.60 ^a
CHEE	4.5	41.39 \pm 2.29 ^a	55.11 \pm 2.05 ^a
BLEE	25	55.78 \pm 0.82 ^a	69.56 \pm 0.79 ^a
Combination 1	1.125 + 6.25	56.95 \pm 3.43 ^a	71.63 \pm 3.01 ^a
Combination 2	2.25 + 12.5	57.83 \pm 2.34 ^a	72.50 \pm 2.44 ^a
Combination 3	4.5 + 25	65.08 \pm 1.10 ^a	83.35 \pm 3.32 ^a

Information: ^a letter *superscript* in the line shows the actual difference (P<0.05) toward the normal group.

From Table 1, it can be seen that each group at 5 hours and 24 hours observations had different urine volumes. There were volume enhancement in every treatment groups compared with normal control group and control CMC-Na 0.5%, it indicates that there were diuretic effect in every test conducted, whether on single dose of CHEE, single dose BLEE, and dose of combinations. The highest urine volume was in hydrochlorotiazide group followed by the combination of group 3. To see the different average of cumulative urine volume in every group at 5 hours and 24 hours observations can be seen in graphic fig. 1.

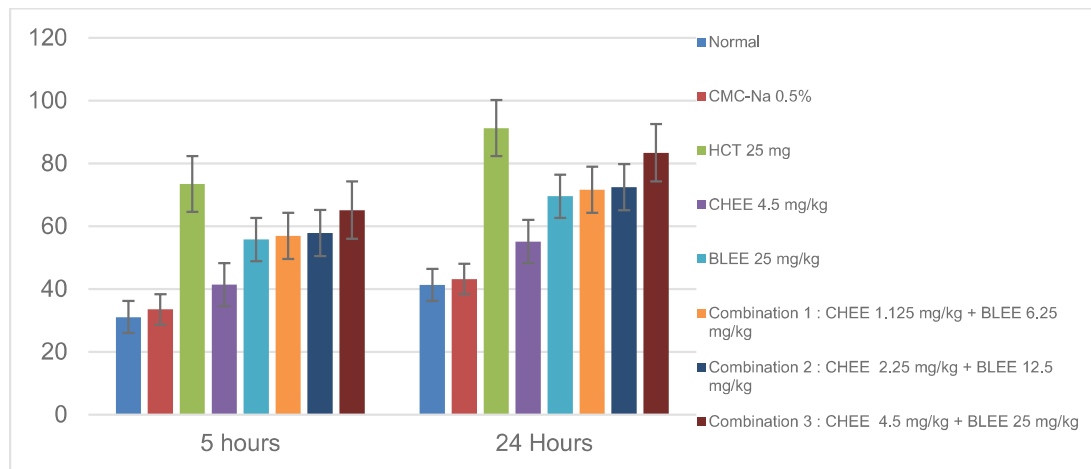


Fig. 1. Graphic of Average Cumulative Urine volume (mL/Kg) in every group at the at 5 hours and 24 hours observation

From the graphic presented in Fig. 1, it can be seen that there were urine volume enhancement in every group at 5 hours to 24 hours observations. Combinations of groups I, II, and III had an average increasing in urine volume compared with single dose group, both CHEE and BLEE. This showed that the combination can increase the volume of urine excreted.

Then the data was analyzed statistically. The result showed that urine volume data was distributed normally. Testing used Mann-Whitney was conducted to see the significancy between two groups. Significancy relation between each treatment group in the observation time at 5 hours can be seen in Table 2 and the significancy relation between each treatment group in the observation time at 24 hours can be seen in Table 3.

Table 2. Significancy between each group treatment in 5 hours time

Treatment Group	Normal	HCT	Combination 1	Combination 2	Combination 3
CMC-Na 0.5%	NS	-	-	-	-
Hydrochlorotiazide	S	-	S	S	S
Dose 1	S	S	S	S	S
Dose 2	S	S	NS	NS	S
Combination 1	S	S	-	NS	S
Combination 2	S	S	NS	-	S
Combination 3	S	S	S	S	-

Table 3. Significancy relation between every group treatment in 24 hours time

Treatment Group	Normal	HCT	Combination 1	Combination 2	Combination 3
CMC-Na 0.5%	NS	-	-	-	-
Hydrochlorotiazide	S	-	S	S	S
Dose 1	S	S	S	S	S
Dose 2	S	S	NS	S	S
Combination 1	S	S	-	NS	S
Combination 2	S	S	NS	-	S
Combination 3	S	S	S	S	-

Information:

Dose I : Celery Herb Ethanol Extract 4.5 mg/kg (CHEE)

Dose II : Bay Leaf Ethanol Extract 25 mg/kg (BLEE)

Combination I : CHEE 1.125 mg/kg + BLEE 6.25 mg/kg

Combination II : CHEE 2.25 mg/kg + BLEE 12.5 mg/kg
 Combination III : CHEE 4.5 mg/kg + BLEE 25 mg/kg
 S : Significant
 NS : Not Significant

Based on Table 2 and Table 3, it can be found that combination 3 was significantly different ($P \geq 0.05$) to two groups of single dose and two other combination groups, but it was different significantly ($P \leq 0.05$) toward hydrochlorotiazide group both at 5 hours and at 24 hours observations. While combination 1 and combination 2 were not significantly different ($P \leq 0.05$) which stated that both diuretic effects were not much different. Dose 1 had significant difference ($P \geq 0.05$) to the group of dose 2 and the three combinations. Furthermore, dose 2 was not significantly different towards combination of group 1 and combination 2 at 5 hours observation and significantly different toward group of combination 1 at 24 hours observation. This shows that BLEE with dose 25 mg/kg had diuretic effect which almost had the same with combination 1 and combination 2.

Control group CMC-Na 0.5% was not different significantly ($P \geq 0.05$) to the normal group because CMC-Na 0.5% did not affect diuretic. This case shows that CMC-Na 0.5% did not influence diuretic effect of CHEE and BLEE. Group of single dose CHEE and BLEE, and also combination of groups I, II, and III were stated as had diuretic effect, however the closest to hydrochlorotiazide group was the combination of group 3. This also shows that celery and bay leaf CHEE and BLEE had diuretic effect because they contained flavonoid which can cause urinary enhancement, where the working mechanism was by obstructed Na^+ , K^+ , Cl^- reabsorption, thus made electrolyte enhancement in the body, then becomes diuretic [12].

Diuretic activity was determined by using diuretic parameter which were diuretic index, Lipschitz values, diuretic energy (%) Diuretic Index, Lipschitz value, and diuretic energy of every group at 5 hours and 24 hours observations, it can be seen in Table 4.

Table 4. Diuretic Index, Lipschitz Value, and Diuretic Percentage Energy and Diuretic Energy of every Group at 5 hours and 24 Hours Observations.

Group	Dose (mg/kg)	Diuretic Index		Lipschitz Value		Diuretic Value (%)	
		5 Hours	24 Hours	5 Hours	24 Hours	5 Hours	24 Hours
Normal	-	1	1	-	-	-	-
CMC-Na 0.5%	-	1.08	1.05	0.46	0.47	0	0
Hydrochlorotiazide	25	2.36	2.21	1	1	119.09	111.14
CHEE	4.5	1.33	1.33	0.56	0.60	23.44	27.56
BLEE	25	1.79	1.68	0.76	0.76	66.37	60.99
Combination 1	1,125 + 6,25	1.83	1.73	0.78	0.79	69.84	65.79
Combination 2	2,25 + 12,5	1.86	1.75	0.79	0.79	72.48	67.79
Combination 3	4,5 + 25	2.09	2.02	0.89	0.91	94.12	93.15

Diuretic Index is a result from comparison of the test group urine volume with the normal group urine volume. Diuretic index is used as parameter to measure activity of a diuretic compound. Activity of a diuretic compound can be categorized into several levels according to its diuretic index values which are: strong type in index if the value is greater than 1.50; in medium type if the index values is between 1.00 until 1.50; weak type if the diuretic index is below 0.72 [13]. Strong diuretic activity is showed by hydrochlorotiazide control group, combination 1, combination 2, and combination 3, and CHEE and single dose BLEE with index diuretic more than 1.50 in both time observations. Diuretic activity is showed by CHEE single dose with diuretic index of 1.33. From the three combinations, diuretic index with the closest to hydrochlorotiazide is combination group 3, which is 2.09. To see the

different level of diuretic effects in each group at 5 hours and 24 hours observations can be seen in table Fig. 2.

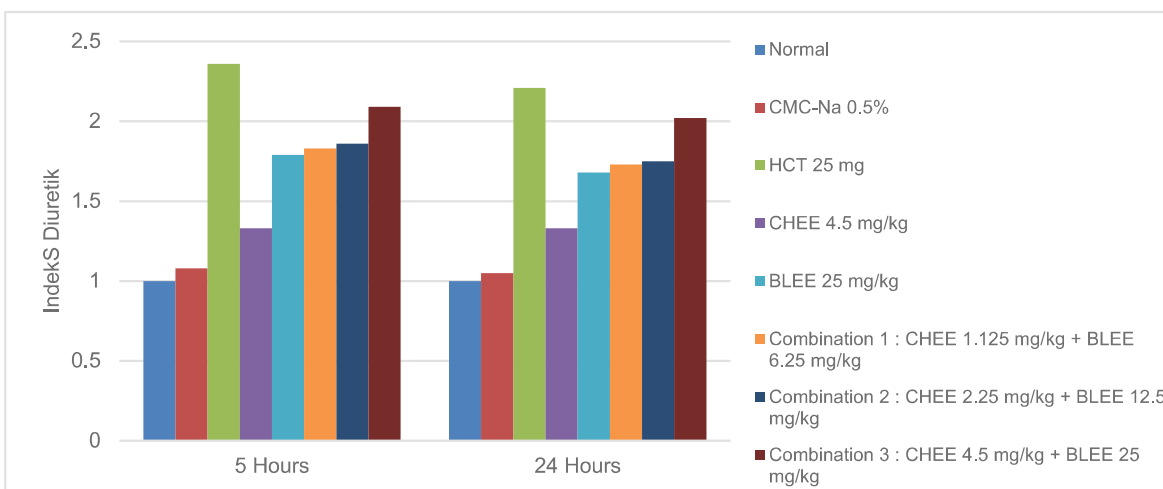


Fig. 2. Graphic of Diuretic Index of Every Group at 5 Hours and 24 Hours Observations.

Lipschitz value is urine volume comparison test group to hydrochlorotiazide group to know diuretic energy test group compared with hydrochlorotiazide [13]. Based on the data presented in Table 4, hydrochlorotiazide group has Lipschitz value: 1 and it is used as comparison within calculation. The smallest Lipschitz values in single dose group of CHEE is 0.56 at the first 5 hours and getting increased becomes 0.60 at 24 hours observation time. It can be concluded that CHEE with dose 4.5 mg/kg had activity 56% at 5 hours observation and 60% at 24 hours observation compared with the hydrochlorotiazide. BLEE with dose of 25 mg/kg has Lipschitz value : 0.76, thus diuretic activity to hydrochlorotiazide is 76%. Both of combination 1 and 2 have slightly differences, those are 0.78 and 0.79 at 5 hours observation, and 0.79 at 24 hours observation. While combination 3 is the highest and the closest to comparison which are: 0.89 at 0-5 hours and 0.991 at 0-24 hours observation, in which it has diuretic activity as 89% and 91% compared with hydrochlorotiazide. Hydrochlorotiazide is an antihypertension medicine thiazide type which works on tubulus distal and hamper natrium chloride *co-transporter*, so it causes diuretic effect [14]. To know the differences in each Lipschitz group's at 5 hours and 24 hours observations can be seen in Graphic Fig. 3.

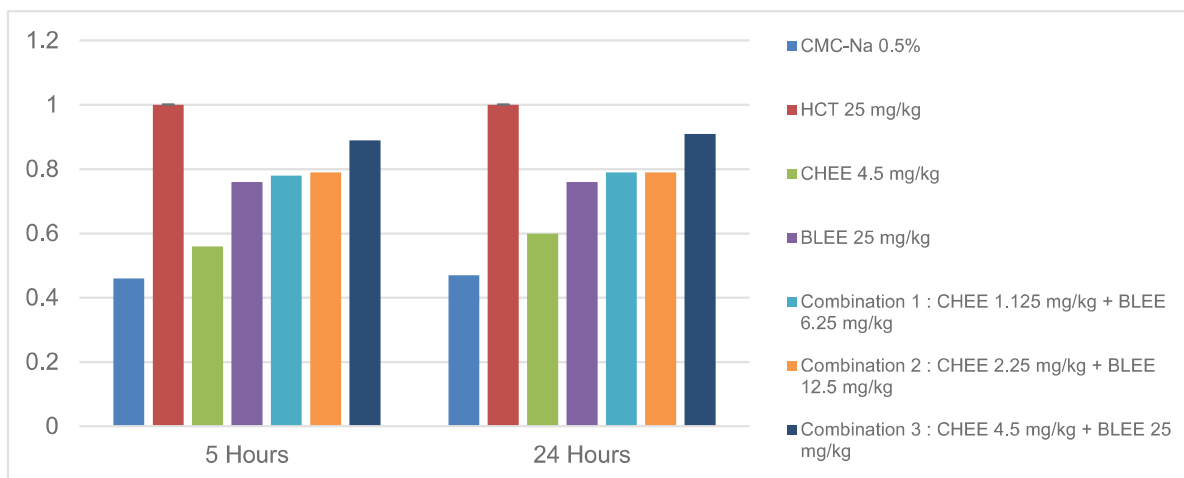


Fig. 3. Lipschitz Value every Group at 5 hours and 24 hours observations.

Diuretic energy percentage is urine volume comparison percentage treatment group with CMC-Na 0.5% group. Diuretic energy describes percentage of urine increasing volume compared with negative control group. The higher diuretic energy, the more diuretic efectivity get increased. Table 4 has

presented diuretic percentage data of every group in both time observations which are; 119.09% and 111.14%. This because hydrochlorotiazide is a drug that posses diuretic effect and it has been used publicly for antihypertension therapy.

From the three combinations, diuretic energy in a series from the smallest combinations are; 69.84%, 72.48%, 94.12% at 5 hours observation and 65.79%, 67.79%, 93.15% at 24 hours observation. From the outcome, it shows that there were enhancement of diuretic energy along with the increasing of CHEE and BLEE combination dose. This makes clear that the greater dose used, the content of active flavonoid inside is getting more and more and increases urine excretion. Combination 3 has the biggest diuretic energy in among the three combinations, so, it is stated that the diuretic energy is the closest to hydrochlorotiazide. To see the different diuretic energy percentage in every group at 5 hours and 24 hours observations can be seen on the graphic of Fig. 4.

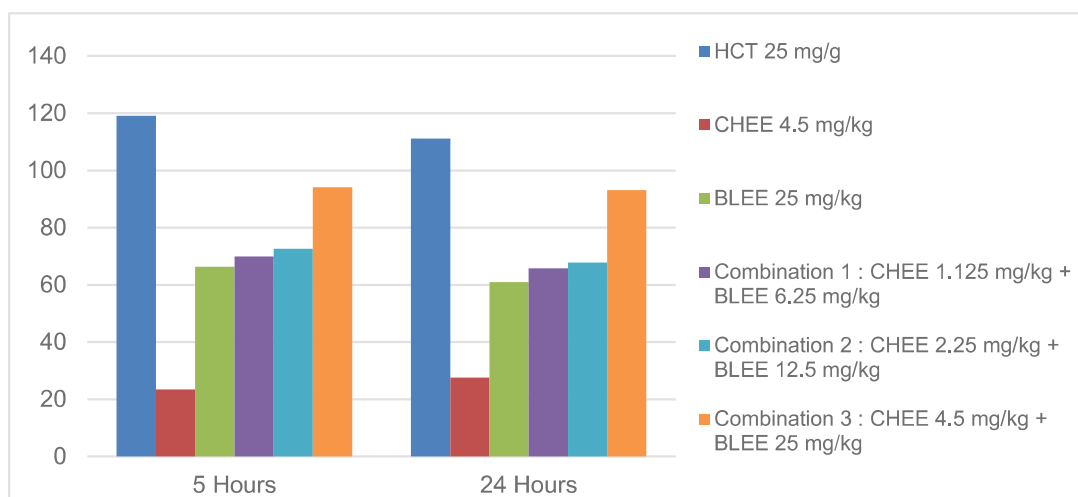


Fig. 4. Diuretic Energy Every Group in Observation Time 5 Hours and 24 Hours

Single dose of CHEE has the smallest diuretic energy which is 23.44% at 5 hours observation and 27.56% at 24 hours observation. This might be happened because of extract dose was too small which was 4.5 mg/kg. However, diuretic energy produced by the celery extract single dose was greater than previous research. CHEE with dose of 80 mg/kg produce diuretic energy as 61.1% and kept increased into 88.8% and 116.6% in dose 80 mg/kg and 160 mg/kg [7]. Diuretic effect produced by the CHEE has been predicted because it contains flavonoid inside. CHEE contains flavonoid 24.71 mg/100 gram which was analyzed used kuersetin comparison [6].

Single dose BLEE 25 mg/kg can produce diuretic energy as 66.37% at 5 hours observation and 60.99% at 24 hours observation. BLEE dose 50 mg/KgBB has diuretic effect, it was indicated with urine volume increasing compared with control [15]. The other research reported that BLEE and sow thistle with dose 200 mg/KgBB can provide diuretic energy as 50.15% within 3 days [9]. BLEE contains flavonoid with total: 1.67 ± 0.02 (g-QE/100 g extract). This shows that in the research on BLEE with dose 25 mg/kg really consists of diuretic effect because it contains flavonoid inside.

Conclusion

Combinations of celery herb (CHEE) and bay leaf ethanol extract (BLEE) have diuretic effect with diuretic index value in series from combination 1, 2, 3 are 1.83, 1.86, and 2.09 in observation time at 5 hours; 1.73, 1.75, and 2.02 at 24 hours observation. Diuretic energy in series from the smallest dose combinations are 69.84%, 72.48%, 94.12% in observation 5 hours; 65.79%, 67.79%, 93.15% at 24 hours combination. The most effective dose combination as diuretic is the combination 3 which is CHEE 4,5 mg/kg + BLEE 25 mg/kg.

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