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Juice of Noni Fruit (*Morinda citrifolia* L) and Its Effect to Reduce Pain

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ABSTRACT

The purpose of this research is to find out the effect of Noni juice (*Morinda citrifolia*) to decrease pain. The research design was using laboratory experiment, with Randomized Post-test only control group design. The population was adult female guinea pigs (Rattus norvegicus) Wistar strain, while the sample was a part of the population with the number of guinea pigs is 36. Random sampling was used. The samples were divided into 6 groups based on randomized allocation technique. Group 1 was the negative control group, was given distilled water 6 ml/BW 100g per sonde, group 2 is the positive control group which was given asetosal at a dose of 0.6 mg/10g BW personde and the treatment group were given a ripe noni fruit juice each with a dose of 2 ml/100g BW, 4 ml/100g BW, 6 ml/100g BW, and unripe noni with the dose of 4 ml/100g BW. The guinea pigs were induced to the pain using 1.5% acetic acid in peritoneal. After treatment, the changes on pain responses were observed by observing their writhing responses (writhing Reflex Test or abdominal constriction test) every 5 minutes for 30 minutes. The average value of the number of guinea pigs that got twisted fruit juice and asetosal was compared with the group that received only distilled water per sonde. Data analysis was conducted by analysis of variance test one-way ANOVA and LSD (Least significant Difference). The analysis showed that there were significant differences in pain responses between the control group and the treatment group ($p = 0.000$ or $p < 0.05$) with good average value of guinea pigs writhing were given unripe noni juice with the dosage of 4 ml/100 GBW (x=4,47). Conclusion: The results of this analysis show that there is an influence of noni juice to decrease pain in guinea pigs.

KEYWORDS: noni juice, pain response, guinea pigs

INTRODUCTION

Studies and research on Noni continues to be done by various research institutions and universities. In the field of biochemistry, it has been discovered that noni fruit contains xeronine and its precursor (proxeronine) in great amount [1]. Proxeronine colloid is a type of acid that does not contain sugar, amino acids or nucleic acids as other colloids with relatively large molecular weight, more than 16,000. If consuming proxeronine, then xeronine levels in the body will increase. In the human body (intestine), proxeronase enzymes and other substances will change proxeronine into xeronine, which is one of the important substances to regulate specific functions of proteins and cells of the human body. Hawaii University researchers (1993) managed to separate substances of Noni scopoletin. Scopoletin substances have medicinal properties, and experts believe that scopoletin is one of the substances contained in Noni fruit that can bind serotonin, one of the essential chemicals in the human body. Scopoletin serves to widen the channels of the blood vessels and blood circulation. The compound of scopoletin (hydroxy-methoxy-coumarin) is very effective as an anti-inflammatory agent. The ability of Noni as an analgesic substance has been known in the history of traditional medicine, that's why this plant is called "a painkiller tree" or "a headache tree". Scientific research has proven beneficial effects of Noni to cope with the pain. In 1990, the researchers found a significant relationship between the dose of Noni juice extract with analgesic activity on guinea pigs (generally, the more used, the more powerful is the analgesic effect). The mechanism of noni is to relieve pain. A theory from Dr. Ralph Heinicke (a famous biochemist from the U.S.) says that xeronine is one instrument to relieve pain. This is attributed to the ability of the protein to normalize xeronine on abnormal cells, including cells of the brain tissue, as the source of pain. Some cases of chronic pain such as constant headaches, nerve pain in muscles and joint pain can be cured after taking Noni juice. Dr. Joseph Betz, a chemical researcher from the FDA (Food and Drug Association) from division of the Natural Products Canter for Good Safety and Applied Nutrition in the U.S. says that some experiments have shown that Noni juice can soothe muscle movement.

Waha MG, [2] and Peter PI [3] describe that one of the important alkaloid found in Noni fruit is xeronine. Xeronine also produced by the human body in a limited number that serves to activate enzymes and regulate the function of proteins in the cell. Xeronine was first discovered by Dr. Ralph Heinicke (a biochemist). Although Noni fruit contains very little xeronine, but it also contains ingredients to form (precursor) xeronine, namely proxeronine in large number. Proxeronine colloid is a type of acid that does not contain sugar, amino acids or

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INTRODUCTION

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nucleic acids as other colloids with relatively large molecular weight, more than 16,000. When we consume proxeronine, then the xeronine levels in the body will increase. In the human body (intestine), proxeronase enzymes and other substances will transform into xeronine proxeronine. The xeronine main function is to regulate the shape and rigidity (hardness) of specific proteins contained in the cell. It is important to remember when these proteins function abnormally, then our bodies will experience health problems.

World Noni Research Foundation (WNRF) explains that noni fruit inhibits the action of enzymes Cyclooxygenase (COX). COX enzyme is composed of two types of COX 1 and COX -type 2. At the time of injury, illness or trauma, it leads active COX2 enzyme to produce prostaglandins that cause pain and inflammation while the opposite occurs in COX1 enzyme that protects the stomach and kidney from the risk of damage or injury. Noni has the ability to selectively inhibit COX2 enzyme activity so that prostaglandins are not formed. Other ingredients of noni fruit is scopoletin, it is an antihistamine that provides anti-inflammatory effects [4].

Dyatmiko W, *et al* [5] conducted a study on guinea pigs, with the aim of the study to determine the effect of anti inflammation of dried Morinda citrifolia linn fruit administered orally to guinea pigs. The dosage given in group I was the control group dosage, group II was the group given a dose of the test material as much as 1500 mg/kg body weight of mice or 2100 mg/kg body weight of guinea pigs and group III was the group given Indomethacin with the dose of 10 mg/kg body weight of guinea pigs or asetosal at a dose of 190 mg/kg body weight of guinea pigs, with each group consisting of 8 guinea pigs. The results showed no significant difference to the amount of writhing of the 3 groups. Asetosal can lower the overall pain by 64.79 %, while the experimental group was given material that can decrease the pain by 59.41 %. The results of this test material qualify as an analgesic drug that is able to reduce pain by 50 %.

Dysmenorrhea is menstrual pain that can cause a woman must have a break or result in reduced performance and reduced activities of daily living [6]. The incidence of menstrual pain in Indonesia is estimated to reach nearly 55 % of women of at childbearing age who are tormented by pain during menstruation, and 10 % had severe symptoms that require bed rest. The incidence of primary dysmenorrhea types in Indonesia is around 54.89 %, while the rest are those with secondary type [7]. Dysmenorrhoea or painful menstruation occurs due to an imbalance of progesterone hormone in the blood causing pain arises, but it certainly associated with ovulation. During the luteal phase, the release of too much prostaglandin F2α (PGF2α) can increase uterine contractions and causes uterine arteriolar vasospasm, resulting in ischemia and lower abdominal cramps [8]. The increasing production of prostaglandin F2α (PGF2α) and prostaglandin E2 (PGE2) or the ratio of PGF2α: PGE2 which is not sufficient will increase the resting tonus uterus, myometrium contractile pressure, the frequency of the pressure of the uterus, and uterine contractions arithmic. These abnormalities would cause vasoconstriction, ischemia and hypoxia uterus, which all cause pain. In general, 50-60% of women require analgesic medication to overcome this problem of dysmenorrhoea [9]. The usual treatment given to reduce pain during menstruation is a non-steroidal anti-inflammatory medication (such as ibuprofen, naproxen and mefenamic acid). Most drugs are anti-inflammatory non-steroidal (NSAID) that are effective in treating primary dysmenorrhea in 70-90 % of cases, but they also have negative side effects, while the use of non- pharmacological methods have not shown high effectiveness in reducing menstrual pain [10].

The use of noni fruit for medication has been done widely and is believed to have many health benefits. Some cases of chronic pain such as constant headaches, nerves pain in muscles and joint pain can be cured after taking Noni juice. Empirically, noni also have properties to treat pain during menstruation, but it has never been proven scientifically. In the first phase of this study the researcher wants to find out the effects of noni fruit juice to decrease pain in guinea pigs with the expectation that the results of this study can be used as an ingredient for phase II study on the effects of noni fruit juice against menstrual pain. The results of this study are expected to provide information and develop the knowledge related to the use of medicinal plants/herbs as an alternative to overcome the problem of pain during menstruation and obtaining proven products. The purpose of the study was to determine the content of active ingredient in noni fruit juice and to analyse the effect of noni juice (*Morinda citrifolia*) to decrease pain on guinea pigs.

MATERIALS AND METHODS

Place and Time of the Research

The study was conducted at the Laboratory of the Nutrition Department of Health Polytechnic of Malang and at the Chemistry Laboratory, University of Muhammadiyah Malang. The study was conducted from May until October 2012.

Steps of the Research

Materials for the research: Noni fruit is made in the form of natural juices. The making of noni juice is made each day with a single dose of 30g/200g BW of guinea pigs/day.

Research Procedures

The design of this research is an experimental laboratory with Randomized Post-test only controls group design. The sample in this study is the adult female guinea pigs (*Rattus norvegicus*) Wistar strain, with criteria (1) weight: 100-150 g, (2) ± 2-3 months old, (3) in a healthy physical condition, (4) taken randomly from animal breeding unit in Malang as many as 36 guinea pigs. The ampling technique used in this study was Randomized Simple Random Sampling. The sample is further divided into 6 groups in a complete random (randomized allocation). They are: Group 1: Treatment with distilled water given 6 ml/100g BW per sonde, Group 2: Treatment by administering asetosal at a dose of 0.6 mg/10g BW personde, Group 3: treatment by administering ripe noni juice with the dose of 2 ml/100g BW personde, Group 4: Treatment by administering ripe noni juice with the dose of 4 ml/100g BW personde, Group 5: Treatment with administering ripe noni fruit juice with the dose of 6 ml/100g BW personde, Group 6: Treatment with giving unripe noni fruit juice with the dose of 4 ml/100 GBW personde. The study was conducted in two stages, the first stage was preparation, female guinea pigs at the age of 2-3 months got acclimatization, meaning that they were treated in the same conditions to adapt for 1 week under laboratory conditions, and then they were randomized into 6 groups, the second phase of the study began after the implementation of acclimatization until the observations of the guinea pigs writhing.

After adaptation and randomization, the guinea pigs in all groups were induced with chemicals that are 1.5% acetic acid at a dose of 1 ml intra-peritoneal with the intention of causing abdominal pain and muscle spasms. Before being induced, the guinea pigs in all groups were previously fasted for 6 hours, then were given natural Noni fruit juice. Noni fruit juice is made by fruit juicer, given per sonde with the dose of 2, 4 and 6 ml/100g BW (for group 3 until 5) and unripe noni with the dose of 4 ml/100g BW (for group 6).

Table 1. Operational definitions of Variables

No	Variables	Operational definitions	Measurement	Data Scale	Categories
1	Noni fruit juice provision	The administration of unripe and ripe noni fruit in the form of natural juice per sonde to guinea pigs groups with a dose of 2, 4 and 6 ml/100 g BW	Measurement glass in millilitres	-	-
2	Pain decrease	The alteration in pain respond by observing guinea pigs writhing (*Writhing Reflex Test* atau *Abdominal Constriction Test*) after induced with acetic acid 1.5% of 1 ml intra peritoneal. It is continued by pain respond observation every 5 minutes for 30 minutes. The average value of guinea pigs writhing which get fruit juice and asetosal is compared to the groups which only got distilled water per sonde.	The observation of its writing in every 5 minutes	Ratio Ordinal	The average differences of guinea pigs writhing frequency among groups Pain decrease is visualized (the difference of guinea pigs writhing value among group 2 to 6 with group 1 is as the following: • Excellent: pain respond decrease is about 75% up • Good: pain respond decrease is more than 50 - 74% • Not good enough: pain respond decrease is about 25 - 49% • Bad: pain respond decrease is less than 25%

Processing and data analysis techniques

Data processing was conducted by editing, coding, scoring and tabulating the data. The data were analysed as follows: (1) Test Descriptive Statistics. To determine the characteristics of the measured data variables include the mice BW, the value of guinea pigs writhing per group, in the form of average value and standard deviation in all groups, (2) a test for checking the normality of distribution using one-sample Kosmogorov-Smirnov, to determine whether the data distribution do not differ from normal data distribution. Theis test was performed on the data of mice guinea pigs BW and guinea pigs writhing from all groups. (3) Homogeneity test of the initial data with one-way ANOVA test. If $p>0.05$, then the data from the population has the same level of homogenyity [11]. The test was performed on the data of initial BW (pre) in all groups, (4) Test inferential statistics. Data analysis on pain decrease using frequency value and the average value of writhing in each group with the ratio scale, and then tested by one-way analysis of variance/ANOVA, then to determine the level of significance of differences between the groups, it must be followed by LSD (Least significant Difference). (5) Presentation of Research Data. The data were presented in the form of frequency distribution tables and results analysis.

For the data of decrease rate in pain, it was qualitatively visualized with ordinal data scale by observing the average difference between the writhing of each group of guinea pigs which were given noni fruit juice (group 3 to 6) with an average value of guinea pigs writhing in group that was given only distilled water drink

(group 1). The visualization category is as follows: (1) Excellent: if there is 75 % reduction in pain response, (2) Good: if the reduction in pain response is over 50-74 %, (3) Not good enough: if the reduction in pain response is 25-49 %, and (4) Bad: if the reduction in pain response is less than 25 %

RESULTS

The Result of Content Identification of Noni Fruit

Based on the analysis using chromatography method with High Performance Liquid Chromatography (HPLC) to identify of the active substance contents in noni fruit juice in the chemist laboratory of the Faculty of Mathematics, University of Muhammadiyah Malang, it was found out that noni fruit juice contains xeronine (mg/kg) which was classified as colloidal compounds, with the amount of content as many as 893.960 ppm (ripe noni) and 1339.254 (unripe noni). The results of the analysis can be seen in Table 2 below:

Table 2 Content of xeronine on ripe and unripe noni fruit

Treatment	Repetition	Xeronine content (ppm)
Unripe noni fruit	1	1339.254
	2	1336.486
Ripe noni fruit	1	893.960
	2	802.591

Descriptive analysis

Data of writhing frequency test. Descriptive analysis of the writhing frequency test data on negative control group with distilled water provision per sonde (P1), positive control by administering asetosal per sonde (P2), giving noni juice per sonde with each dose of 2 ml (P3), 4 ml (P4), 6 ml (P5) and unripe noni fruit juice of 4 ml (P6) can be seen in Table 3 below:

Table 3. the average value of guinea pigs writhing frequency on groups P1 to P6

Treatment	Average value of guinea pigs writhing test frequency for 5 minutes during 30 minutes						
	First 5 minutes	Second 5 minutes	Third 5 minutes	Fourth 5 minutes	Fifth 5 minutes	Sixth 5 minutes	Average
P1	14.50	17.00	20.67	20.17	18.50	20.00	18.47
P2	9.83	9.33	7.67	9.50	7.17	6.50	8.33
P3	7.33	7.33	6.50	7.17	6.50	6.33	6.86
P4	6.00	6.83	5.33	8.67	6.50	7.17	6.75
P5	5.67	5.83	6.17	4.83	6.00	5.83	5.72
P6	4.00	4.33	4.67	4.83	3.67	5.33	4.47
Average	**7.88**	**8.44**	**8.50**	**919**	**8.05**	**8.52**	**8.43**

As described in table 3 above, it can be seen that there is an effect of noni fruit juice to the frequency of guinea pigs writhing. The average value of writhing frequency shows that, in the treatment group that were given noni juice (P3, P4, P5, P6) the average of writhing frequency lowered there times or more (X=6.86; X=6.75; X=5.72; X=4.47) compared to the negative control group (P1) with the administration of distilled water 6 ml/100 GBW (X=18.47) with the lowest stretching frequency in the group P6 that was given unripe noni fruit juice with the dose of 4 ml/100 GBW. Writhing frequency in the treatment group with the administration of noni juice is still lower than the positive control group (P2) given asetosal 1.5% (X=8.33).

Normality Test Results

The data used to test the normality of the data is the average frequency of guinea pigs writhing for 30 minutes in each group (P1 to P6) using Kosmogorov-Smirnov one-sample normality test.

Table 4. The result of *Kosmogorov-Smirnov one-sample normality test* on data P1 to P6

Treatment group	Frequency of guinea pigs writhing test (p)
P1	0.878
P2	0.803
P3	0.731
P4	0.982
P5	0.696
P6	1.000

The Results of Kosmogorov-Smirnov test for normality of the sample can be seen in Table 4. above, it shows the value of p > 0.05 for all the data so that the significance of the frequency of guinea pigs writhing test in each group are normally distributed.

Homogeneity Test Results

The data used to test the homogeneity of the data is the average frequency of guinea pigs writhing test in each group (P1 to P6) within 5 minutes for 30 minutes using one-way ANOVA Levene test. The test results demonstrate the value of p>0.05 for the average score of writhing frequency test (p=0.991), which means that all the data is homogeneous, as shown in Table 5 below.

Table 5. Results of Lavene anova homogeneity test on group P1 to P6

Treatment	Frequency of guinea pigs writhing test	
	Average ± SD	P levene
P1	7.88 ± 3.77	0.991
P2	8.44 ± 4.50	
P3	8.50 ± 6.04	
P4	9.19 ± 5.71	
P5	8.05 ± 5.25	
P6	8.52 ± 5.65	

Analysis Variance Writhing Frequency Test Data

The results of analysis of variance on guinea pigs writhing frequency test data between treatment groups. The level of significance of differences in frequency data between negative control group with distilled water provision of ml/100g 6 BW per sonde (P1), positive control group by administering asetosal mg/10g 0.6 BW per sonde (P2), the group which are given ripe noni juice per sonde with each dose is 2 ml (P3), 4 ml (P4), 6 ml (P5) and unripe noni per sonde with a dose of 4 ml can be detected through ANOVA statistical test.

Table 6. the result of anova test on guinea pigs writhing test frequency among groups P1 to P6

Group	N	(X)	SD	P
P1	6	18.47	2.36	0.000
P2	6	8.33	1.39	
P3	6	6.86	0.46	
P4	6	6.75	1.14	
P5	6	5.72	0.46	
P6	6	4.47	0.59	

The test results indicate the levels of significance with p = 0.000 (p < 0.05) so that Ho is rejected, which means that there are significant differences in frequency between the groups of mice writhing test P1 to P6 are as shown in Table 6 and Figure 1.

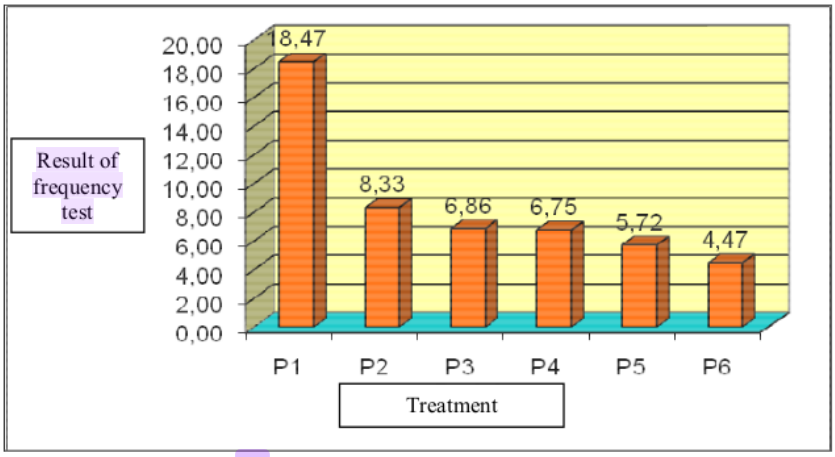

Figure 1 Result of frequency test on mouse geliat

The results of LSD Test on guinea pigs writhing frequency test among treatment groups

Statistical test followed by LSD Post Hoc Tests, to determine between which groups differed significantly in terms of the frequency of writhing test of guinea pigs for 30 minutes . Average difference was significant at $\alpha < 0.05$.

The result of LSD Post Hoc Tests shows a significant difference in the frequency of guinea pigs writhing test for 30 minutes between the negative control group (administration of distilled water) with a group given ripe noni fruit juice with a dose of 2 ml/100 grBW, 4 ml/100 grBW, 6 ml / 100grBW ($p = 0.000$) and given unripe noni with a dose 4 ml/100grBW dose ($p = 0.000$).

The frequency of guinea pigs writhing test was not significantly different between the positive control (administration of asetosal) with the group given ripe noni fruit juice with a dose of 2 ml/100grBW ($p = 0.053$), while the group which is given noni juice with a dose of 4 ml/100grBW, 6 ml/100grBW and 4 ml/100 grBW of unripe noni juice is significantly different (p-value = 0.039, $p = 0.001$, and $p = 0.000$).

The writhing frequency of guinea pigs was not significantly different between treatment groups which were given ripe noni fruit juice 2 ml, 4 ml and 6 ml with $p = 0.882$, $p = 0.170$ and $p = 0.130$, but they differ significantly in the group given the unripe noni juice at the dosage of 4 ml with a significance value of $p = 0.000$, while the ripe noni 6 with ml dose did not differ significantly ($p = 0.098$)

Reduction in pain after treatment

The results of measurements of pain in guinea pigs could be quantitatively seen in guinea pigs writhing test frequency in the negative control group, positive control group (administration of aspirin) and treatment group (administration of noni fruit juice with various doses) in the table. The data on the rate of pain decrease can be qualitatively visualized with ordinal data scale by looking at the average difference between the writhing of each group of guinea pigs that were given noni fruit juice (group 3 to 6) with an average value of guinea pigs writhing in the group given only distilled water drink (group 1). The visualization category are as follow (1) Very good: if the rate for pain reduction is 75% up, (2) Good: if the rate of pain reduction is more than 50-74 %, (3) Not good enough: if the rate of pain reduction is 25-49% and (4) bad: if the rate of pain reduction is less than 25%. Interpretation for pain reduction data can be seen in Table 7 as follows:

Table 7 pain respond decrease in each treatment group

Treatment	Frequency of guinea pigs writhing test compared to group P1 (F=18,47)	Pain decrease respond(%)	Category
P1	18.47	0.00	Bad
P2	8.33	54.89	Good
P3	6.86	62.86	Good
P4	6.75	63.46	Good
P5	5.72	69.02	Good
P6	4.47	7579	Very good

Based on table 4.9 above, it can be seen that the treatment groups with the administration of noni juice (P3, P4, P5 and P6) had shown reduction in pain responses in a good rate and in a very good rate when compared to the negative control group (P1) and a positive control group (P2).

DISCUSSION

The content of Noni Fruit substances

The research on the effects of noni juice to decrease pain here is an experimental laboratory research, using adult female guinea pigs (*Rattus norvegicus*) Wistar strain. It was intended to find out about corelation between substances in noni fruit with pain response, particularly its analgesic effect. So far there has been no research on the effects of ripe and unripe noni fruit juice to pain response. The previous research had learnt about the effects of noni fruit extract against pain.

Noni fruit contains an alkaloid compound that the human body needs to activate enzymes and regulate and establish the structure of proteins, they are Xeronine and proxeronin (*xeronine precursor*) [9]. Waha MG [2] and Peter PI [3] describe one important alkaloid found in Noni fruit, it is xeronine. Xeronine is also produced by the human body in a limited number that serves to activate enzymes and regulate the function of proteins in the cell. Xeronine was first discovered by Dr. Ralph Heinicke (a biochemist). Although the Noni fruit contains very little xeronine, but it contains ingredients forming (precursor) xeronine, namely proxeronine in large numbers. Proxeronine colloid is a type of acid that does not contain sugar, amino acids or nucleic acids as other colloids with relatively large molecular weight, more than 16,000. When we consume proxeronine, the xeronine levels in the body will increase. In the human body (intestine), proxeronase enzymes and other substances will transform into xeronine proxeronine. Xeronine main function is to regulate the shape and rigidity of specific proteins

contained in the cell. It is important to remember when these proteins function abnormally, and then our bodies will experience health problems.

In this study, phytochemical test of ripe and unripe noni fruit juice shows that the important alkaloid content is xeronine as much as 1339.254 (one unripe noni fruit) and 893.960 (one ripe noni fruit). Xeronine content on unripe noni fruit is more than the ripe one; this suggests that the efficacy of unripe noni needs to be studied further. This finding is reinforced by the studies conducted by Anon [12] and Peter, PI [3] which suggests that noni fruit contains an alkaloid compound to and its derivatives, which are called xeronine and proxeronin, as well as the research by Solomon [13] which says that xeronine is useful for relieving headaches and muscle nerves.

The limitation of this study is that the the researchers did not isolate the active ingredient in the xeronine compound of noni fruit juice so it is likely there are other compounds that affect the employment effects of noni juice.

Frequency of Writhing Mice Test between treatment groups (Noni Fruit Juice) with Negative Control group (distilled water) and Positive Control (asetosal)

Examination on guinea pigs writhing test in response to pain showed that the average expression of guinea pigs writhing frequency in the treatment group (noni juice) was reduced when compared to control group (distilled water and asetosal) and the difference between the treatment and control groups was significant ($p = 0.000$). This study has shown that noni juice can reduce the pain response of guinea pigs as indicated by a decrease in the frequency of writhing, thus giving noni juice to guinea pigs led to a significant difference to the control group. This is due to its content of phytochemical compounds including terpenes, acubin, lasperuloside, alizarin, anthraquinone substances, ascorbic acid, caproic acid, caprylic acid, scopoletin substances, damnakantal, and alkaloids [12]. Anthraquinone derivatives in noni fruit include Morindin, morindon and alizarin, while its alkaloid are Xeronine and proxeronin (xeronin precursor).Xeronine is an alkaloid that human body needs to activate enzymes and regulate and establish the structure of proteins [3] Xeronine and proxeronin has the main function to regulate the form and rigidity of specific proteins present in the cell, so that the proteins can normalize the abnormal body cells, therefore if these proteins function abnormally, then the body will experience health problems. This was confirmed by Dr. Ralph Heinicke (a famous biochemist from the U.S.) theories, who give or take that xeronine is one substance functions as an agent in relieving pain. This is attributed to the ability of the protein to normalize xeronine on abnormal cells, including cells of the brain tissue, where the pain comes from.

Noni can also inhibit the secretion of prostaglandins that can cause pain. World Noni Reseach Foundation (WNRF) explains that noni fruit inhibits the action of Cyclooxygenase (COX) enzyme. COX enzyme is composed of two types of COX type 1 and COX type 2. Noni fruit has the ability to selectively inhibit COX2 enzyme activity so that prostaglandins are not formed. The excretion of prostaglandins can cause pain and inflammation.

These findings reinforce previous research studies conducted by Dyatmiko W *et al* [5] about the effect of anti inflammation of dried Morinda citrifolia Linn fruit juice administered orally to guinea pigs. The dosage given to group I was the control group dosage, group II was the group given a dose of the test material with the dosage of 1500 mg/kg body weight of guinea pigs or 2100 mg/kg body weight of m guinea pigs and group III was the group function as comparison fed with Indomethacin at a dose of 10 mg/kg body weight of guinea pigs or asetosal at a dose of 190 mg/kg body weight of guinea pigs. The results show no significant difference to the amount of writhing of the 3 groups. Asetosal can lower overall pain by 64.79%, while the test group which were given experiment material can lower the pain by 59.41%.

In this study, the average writhing frequency of the group which was given distilled water was higher when compared with the treatment group that was given noni juice. This is possible because this group was given the solution that did not contain any analgesic, only water, so the manifestation of pain was due to administration of pain stimulant chemicals of acetic acid intraperitonium will cause a writhing reflex response in the form of pulling foot to the back, retraction, tetanus seizures by bending the head and back legs would be bigger. Likewise, to the treatment group that was given noni juice, the average writhing frequency is lower when compared with the positive control group (asetosal), especially to the group given unripe noni fruit juice. The decrease of writhing frequency of guinea pigs in this group is more than 75%. This new finding proves that the analgesic effects of unripe noni are similar with analgesic drugs even better.

Frequency of guinea pigs Writhing Test between treatment groups (Noni Fruit Juice)

Writhing frequency of test mice was not significantly different between treatment groups that were given ripe noni fruit juice of 2 ml, 4 ml and 6 ml with $p = 0.882$, $p = 0.170$ and $p = 0.130$. This may be due to the small difference in the dose of noni juice so that it does not give a significant difference in reduction of writhing frequency between the groups of guinea pigs. Writhing frequency decreases along with the increasing dose of noni juice. This suggests that the three kinds of doses can reduce the frequency of guinea pigs writhing, but the increase in dosage does not always provide a significant reduction in the writhing frequency.

Writhing frequencies differ significantly in the groups of guinea pigs given unripe noni fruit juice at 4 ml of dose when compared with the group given ripe noni fruit juice, with a significantt value of p = 0.000, except in the group with the provision of ripe noni fruit juice with the dose of 6 ml were not significantly different (p = 0.098). The results of this study indicate that the analgesic effects of noni juice at a light dose of 4 ml are of the same effect with ripe noni fruit juice in the maximum dose of 6 ml. This is possible because the content of Xeronine on unripe noni fruit (1339.254 ppm/mg/kg) is more than the ripe noni fruit (893.960 ppm/mg/kg). The more active substances in a material the greater effect it will make.

Another thing that might explain the condition that noni fruit also contains several other anti-inflammatory compounds such as scopoletin, which probably will work synergistically in the body, as discovered by Dyatmiko W *et al* [5] research on the effects of anti inflammation of dried Morinda citrifolia Linn fruit juice given orally to guinea pigs, which showed no significant difference to the amount of writhing of the 3 groups of guinea pigs.24

Thus, the administration of unripe noni fruit juice at a dose of 4 ml/100 grBW is quite an effective dose and provides excellent analgesic effect, so it can be used as one alternative for the treatment of pain. But, other important contents of unripe noni fruit still need to be studied further.

Decreased Pain after Treatment

The results of the study demonstrate that administration of noni fruit juice can decrease the pain response of guinea pigs more than 50% after being induced with 1.5% of acetic ASAT intraperitoneally. For the ripe noni fruit juice given at a dose of 2 ml, 4 ml, and 6 ml, it showed a good reduction in pain response, that is more than 60%. Meanwhile, giving unripe noni fruit juice can decrease the pain response to more than 75%. This suggests that noni juice has a good analgesic effect to reduce pain, then it can be concluded that this finding supports previous studies.

The benefits of Noni as an efficacious analgesic substance have been demonstrated by several previous studies. Younos *et al*.[14], concluded that noni extract has analgesic and sedative effects. Results show that guinea pigs which were given noni juice with concentrations of 10% and 20% have a pain tolerance to 162% and 212% when compared to the placebo group/control. In animal experiments, it was proven that noni juice can make the guinea pigs more tolerant to pain.

It can be explained that noni fruit contains Xeronine and proxeronin that play a role in pain relief, and inhibits the secretion of prostaglandins, this is line with the theory from Dr. Ralph Heinicke (a famous biochemist from the U.S.) which states that xeronine has analgesic effects that can relieve pain.

CONCLUSION

The conclusion of this study are (1) the frequency of guinea pigs writhing in the treatment group (noni juice) is lower if compared to the control group (distilled water), (2) There are significant differences of writhing frequency between the control groups (distilled water and asetosal) and the treatment group (morinda citrifolia fruit juice).

SUGGESTION

1. A similar study must be conducted to determine the toxicity effects of noni fruit
2. The result of this research can be used as a reference in pharmacological studies on the use of appropriate dose for noni fruit juice
3. The result of this research can be used as an input in the health field that unripe noni fruit can be used as an alternative to herbal therapy against pain.

RECOMMENDATION

Based on the research findings on the effects of noni juice to decrease pain and its toxic effects, the following suggestions can be recommended: (1) There needs to be more research on the effects of noni juice to menstrual pain that must also be clinically tested, (2) it is recommended to use unripe noni fruit for further research related to pain decrease.

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PAGE 2

PAGE 3

PAGE 4

PAGE 5

PAGE 6

PAGE 7

PAGE 8

PAGE 9