Goitrogenic Study of *Katuk* and Moringa Leaf Boiling on TSH, Free T4 Levels, Physical Growth, and Memory in Normal and Hypothyroid Rats

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Abstract. The aim of this study was to determine and assess the effect of giving katuk or moringa leaf decoction to mother rats during lactation on TSH and fT4 levels, spatial memory and anxiety levels in congenitally hypothyroid rat offspring. This is an experimental post test and controlled group design. The research subjects were normal and congenitally hypothyroid rat offspring obtained from mother Sprague Dawley rats whose drinks were mixed with 0.0015% PTU from the 6th day of pregnancy until weaning. Subjects were divided into 4 groups for the cough test and 4 groups for the moringa test, namely the normal group, normal with cough or moringa, congenital hypothyroidism, and congenital hypothyroidism with cough or moringa. Each group consisted of 8 mice. Giving 40 g% katuk or moringa leaf decoction to the mother at a dose of 430 mg/KgBW per day starting on the 4th day after giving birth until weaning. The Open Field Test was carried out at the age of 33 days and the Morris Water Maze test was started when the mice were 35 days old. Measurement of TSH and fT4 levels using the Elisa method was carried out at the end of the study. Data analysis uses one-way anova or Kruskal-Walli. Giving boiled katuk leaves had no effect on TSH and fT4 levels in normal or congenital hypothyroid rats ($p<0.05$). In the Morris Water Maze, giving katuk leaves significantly worsened latency time, latency distance, and retention time when combined with giving PTU ($p<0.05$). Open Field Test, time in the middle box and number of passes by normal rats given katuk increased significant ($p<0.05$). Administration of Moringa leaf decoction significantly reduced fT4 levels in normal rat pups ($p<0.05$), the percentage of memory retention time in congenitally hypothyroid rat pups with Moringa increased significantly ($p<0.05$) in the Morris Water Maze test, the number of stands and passes in the litter. Normal mice with Moringa increased significantly ($p<0.05$) in the Open Field Test. PTU 15 ppm causes hypothyroidism in mother and child. Consuming boiled katuk leaves had no effect on TSH and fT4 levels in normal or congenitally hypothyroid mother rats or pups. The combination of katuk leaves and PTU in the parent reduces the child's learning ability and spatial memory. Hypothyroid conditions and giving decoction of katuk leaves increases courage. Consuming katuk leaf decoction increases exploration behavior and reduces anxiety. The effect of giving Moringa leaf decoction reduced the fT4 levels of normal rat pups but did not worsen the fT4 levels of congenital hypothyroid rat pups, increased the percentage of spatial memory retention time of congenital hypothyroid rat pups, and increased the explorative behavior and boldness of normal rat pups.

INTRODUCTION

Success in forming superior quality human resources starts from the beginning of fetal growth up to the first 1000 days (1). Especially the first 2 years of life is a critical period for child development, where brain development occurs very rapidly. This time is also the right time for recovery if a disruption occurs (1). One of the causes of growth and development disorders in babies is congenital disorders and poor nutrition. The incidence of under-five children with malnutrition and malnutrition in Indonesia is still 17.7% (Riskesdas 2018). This certainly requires all of our attention to provide highly nutritious food that is safe for children's health. On the other hand, impaired thyroid function in the mother causes congenital disorders in the child and will interfere with the child's subsequent growth and development (2,3). Highly nutritious food ingredients that still need to be researched are katuk leaves (Sauropus androgynus) and moringa (Moringa oleifera). Consuming katuk leaves has been proven to increase baby weight significantly (Yuliastuti, 2019). Katuk leaves also have anti-oxidant effects ((4), and are good for use as food coloring (5). Apart from containing high nutrition, katuk leaves also contain chemical compounds including tannins (catechin), flavonoids, saponins (Juana, 2008) which apparently It is a goitrogen (inhibitor of thyroid hormone synthesis). Likewise with Moringa leaves (6). Therefore, it is necessary to study the goitrogenic effects of katuk and Moringa leaves for safety if consumed by mothers during pregnancy and breastfeeding, both in euthyroid and hypothyroid conditions. Research This study chose a basic research scheme considering that the results to be obtained are the theory or knowledge needed as a scientific basis for supporting a healthy lifestyle. The aim of this research is to examine the goitrogen effect of katuk leaves and Moringa leaves on normal and hypothyroid mice, as well as monitor the outcome of the goitrogenic effect of katuk and moringa on physical growth and memory.

Hypothyroidism and its effects Children's growth and development are formed from the results of a balanced interaction between genetic, hereditary, constitutional and environmental factors. Genetic factors and the environment of the fetus in the womb are the initial determinants which can be said to be the program for postnatal life. Environmental factors in the form of nutrition and socio-economics are strongly correlated with children's level of cognition (7). Other studies have found that environmental factors such as place of residence, physical activity, family income, parental education, and father's occupation have an impact on children's IQ (8). Optimal environmental factors are needed to support the development of a child's genetic potential. The growth and development of children in mountainous environments is threatened with disruption due to low soil iodine content due to glaciation, flooding, and deforestation (9). . Iodine is a micronutrient needed at every stage of development and growth. Childhood, even starting in the womb, is the phase that most requires adequate iodine intake (10,11). Iodine deficiency causes broad spectrum disorders in children's physical and mental growth and development (12) because iodine is needed for the formation of thyroid hormones, namely T4 (tetraiodothyronine) and T3 (triiodothyronine). Thyroid hormones play an important role in physical and neurological growth and development (13). Brain growth and development is strongly correlated with thyroid hormone adequacy (14). The highland area of Samigaluh Kulonprogo Yogyakarta is a GAKI replate area (15). Measurement of TSH and fT4 levels in elementary school children showed that 42.1% of children had subclinical hypothyroidism (16). Cases of thyroid disorders found in children in this area are subclinical hypothyroidism. An increase in serum TSH, except in very rare pathological circumstances, indicates insufficiency of T3 receptor saturation in the brain and a decrease in serum thyroid hormone levels. So an increase in serum TSH indicates a risk or potential for thyroxine deficiency due to various causes or prematurity (17). Serum T3 and T4 levels are less specific indicators as indicators of deficiency due to changes in levels influenced by age and gender (18).

Adequate thyroid hormone levels are very important for the development of the nervous system of the fetus and child during growth. Thyroid function disorders due to various antithyroid substances consumed for therapy or from food require greater caution. The use of antithyroid drugs has been supervised by a doctor (19). However, the presence of antithyroid substances or goitrogens in food and drink is often not realized and interferes with thyroid function. Consumption of grains containing maximum concentration of glycosylflavones exhibited maximum anti-thyroid effect and significant increase in thyroid weight along with maximum inhibition of thyroid peroxidase activity of TPO (20). The presence of perchlorate as a food contaminant interferes with iodine absorption (21), reduces thyroid hormone levels and increases thyroid size (22,23). Consumption of foods containing goitrogens by school age children is quite high, such as processed soybeans (tempeh, tofu, milk, soy sauce), onions, tomatoes, cassava leaves, cassava, cabbage, broccoli, turnips, mustard greens, radishes, bamboo shoots, legumes (22, 24,25). Green tea is said to be a strong goitrogen (26,27) and is now widely consumed as a drink and as a food flavoring. Moringa leaves have a stronger goitrogen effect than spinach leaves (6). *Katuk* leaves contain many nutrients, anti-oxidants, hormones and also contain chemical compounds which are thought to be goitrogens (28).

METHODS

This was experimental posttest and controlled group design. The research subjects were normal and congenitally hypothyroid rat offspring obtained from mother Sprague Dawley rats whose drinks were mixed with 0.0015% PTU from the 6th day of pregnancy until weaning. Subjects were divided into 4 groups for the cough test and 4 groups for the moringa test, namely the normal group, normal with cough or moringa, congenital hypothyroidism, and congenital hypothyroidism with cough or moringa. Each group consisted of 8 mice. Giving 40 g% katuk or moringa leaf decoction to the mother at a dose of 430 mg/KgBW per day starting on the 4th day after giving birth until weaning. The Open Field Test was carried out at the age of 33 days and the Morris Water Maze test was started when the mice were 35 days old. Measurement of TSH and fT4 levels using the Elisa method was carried out at the end of the study. Data analysis used one way anova or Kruskal-Wallis.

RESULTS

Research was carried out using 64 rat pups which were divided into 2 research sets of 4 groups each consisting of normal rats, normal rats given *katuk* or moringa leaves, congenital hypothyroid rats and congenital hypothyroid rats given *katuk* or moringa leaves. Rat maintenance is carried out by providing standard rat cages, ad libitum feed which has a protein composition of 19%, water content 14%, crude fat 3%, crude fiber 18%, calcium 0.9-1.2%, total phosphorus 0 .6-1%, total aflatoxin 50 ppb and amino acids, drink ad libitum clean water and PTU. Bedding is changed every 3 days. The appropriate room temperature is 25-280C, humidity 70-80%, adequate ventilation and sufficient lighting, namely 12 hours of darkness and 12 hours of light.

Measurement of anxiety behavior in rat pups using the Open Field Test at 33 days of age. Morris Water Maze probe test on 43 day old rat pups. At the end of the study, blood was taken from the orbits of rat offspring for measurement of TSH and fT4. The research data obtained was tested for normality of the data with Shapiro-Wilk because the total sample was less than 50. It was found that some of the data had a normal and non-normal distribution. Normal distribution data was subjected to the One-Way ANOVA statistical test and non-normal distribution data was subjected to the Kruskal Wallis statistical test. Then a test was carried out to assess significant differences between groups, namely Post Hoc and Mann Whitney.

The effect of moringa leaves

Table 1. TSH and fT4 mother rat

No	Group	Amount	Mean TSH ± SD (IU/mL)	Mean fT4 ± SD (ng/Dl)
1.	Normal	2	4.68 ± 1.00	0.71 ± 0.16
2.	Normal given moringa	2	3.10 ± 0.05	0.82 ± 0.47
3.	PTU	2	3.91 ± 0.10	0.44 ± 0.06
4.	PTU given moringa	2	3.44 ± 0.14	0.69 ± 0.02
Kruskal-Wallis Test			p= 0.104	p= 0.332

Note: unequal letter ranks indicate there is a significant difference p≤0.05

Table 1 shows that the highest average fT4 level was in the normal group, namely 0.82 + 0.47 ng/dL. Meanwhile, the lowest average fT4 level was in the group of parent mice given PTU, namely 0.44 + 0.06 ng/dL. However, no differences were found between the average TSH and fT4 levels in the four groups (p>0.05).

No	Group	Amount	Mean TSH ± SD (IU/mL)	Mean fT4 ± SD (ng/Dl)
1.	Normal	2	3.68 ± 0.30	0.98 ± 0.47[a]
2.	Normal given moringa	2	3.95 ± 0.62	0.82 ± 0.53[ac]
3.	Congenital hypothyroidism	2	5.33 ± 3.45	0.44 ± 0.06[b]
4.	Congenital hypothyroidism given moringa	2	6.29 ± 5.06	0.69 ± 0.02[bc]
Kruskal-Wallis Test			p= 0.479	p= 0.013

Note: unequal letter ranks indicate there is a significant difference p≤0.05

Table 2 shows that the highest average fT4 level was in the congenital hypothyroid group given catuk, namely 0.98 ± 0.47[a] ng/dL. Meanwhile, the lowest average fT4 was in the congenital hypothyroid group only, namely 0.42 ± 0.20[b] ng/dL. There was a significant difference in the average fT4 of the normal group with congenital hypothyroidism and also the normal group with congenital hypothyroidism given cath (p<0.05). However, in the mean TSH levels there were no differences between groups (p>0.05).

Spatial memory measurements in mice were carried out using the Morriz Water Maze method. Data obtained from measurements included changes in learning latency time, differences in latency distance traveled by each group of mice, and the percentage of memory retention time for mice.

Table 3. Average Change in Latency Time

No	Group	Amount	Average Change in Latency Time ± SD (sec)
1.	Normal	8	-28,12 ± 7,68[a]
2.	Normal given moringa	8	-17,56 ± 19,69[ac]
3.	Congenital hypothyroidism	8	-11,34 ± 14,05[bc]
4.	Congenital hypothyroidism given moringa	8	-5,84 ± 11,26[bc]
One-Way Anova			p = 0.023

Table 3 shows that the largest average change in latency time was in the normal group, namely - 28.12 + 7.68a seconds, and the smallest was in the congenital hypothyroid group given catuk, namely -5.84 + 11.26bc seconds. A significant difference was found between the average change in latency time of the normal group and the congenital hypothyroid group (p<0.05). Likewise, the normal group with congenital hypothyroidism were given cath (p<0.05).

Table 4. Average Latency Distance Change

No	Group	Amount	Rata-rata perubahan jarak latensi pembelajaran + SD (cm)
1	Normal	8	-452,34 + 266,92[a]
2	Normal given moringa	8	-359,37 + 536,07[ac]
3	Congenital hypothyroidism	8	78,12 + 513,30[bc]
4	Congenital hypothyroidism given moringa	8	106,34 ± 420,38[b]
	One-way ANOVA		*p = 0,032*

Note: unequal letter ranks indicate there is a significant difference p≤0.05

Table 5. Average Memory Retention Time

No.	Group	Amount	Average Memory Retention Time ± SD (sec)	Retention time percentage memory
1	Normal	8	27,12 ± 8,18[a]	45,20%
2	Normal given moringa	8	29,37 ± 6,56[a]	48,95%
3	Congenital hypothyroidism	8	17,12 ± 3,31[b]	28,54%

4	Congenital hypothyroidism given moringa	8	15,12 ± 3,09[b]	25,20%
	One-way Anova		*p = 0,001*	

Note: unequal letter ranks indicate there is a significant difference p≤0.05

Table 5 shows that the highest average retention time was the normal group given moringa, namely 29.37 + 6.56a seconds, and the lowest was the congenital hypothyroid group given moringa, namely 15.12 + 3.09b seconds. A significant difference was found between the normal group and the congenital hypothyroid group without and given a moringa; The normal group was given a moringa and the congenital hypothyroid group without and given a moringa (p<0.05).

Furthermore, the measurement of mouse anxiety was carried out using the Open Field Test method in the form of the average time in the middle box, the number of times standing (rearing), cleaning (grooming), passing (crossing), and the number of mouse feces.

Table 6. Average Time in the Middle Box

No	Group	Amount	Average Time in the Middle Box ± SD (sec)	Percentage time in the middle box
1	Normal	8	3 ± 5.65[a]	1%
2	Normal given moringa	8	14,50 ± 19,75[acd]	4,83%
3	Congenital hypothyroidism	8	21,62 ± 10,75[bc]	7,20%
4	Congenital hypothyroidism given moringa	8	21,62 ± 28,72[bd]	7,20%
	Kruskal-Wallis Test		*p = 0,017*	

Note: unequal letter ranks indicate there is a significant difference p<0.05

Table 6 shows that the average time in the middle box was the highest in 2 groups with the same results, namely the group with congenital hypothyroidism only and those given moringa, namely 21.62 + 10.75bc seconds and 21.62 + 28.72bc seconds. The lowest average time in the middle box is the normal group, namely 3 + 5.65a seconds.

There was a significant difference between the normal group and the congenital hypothyroid group without and with moringa (p<0.05). The congenital hypothyroid group that was given a moringa was the same as the congenital hypothyroid group without the moringa.

Table 7. Average Rearing, Grooming, Crossing and Number of Feces

No	Group	Amount	*Rearing*	*Grooming*	*Crossing*	Feces
1.	Normal	8	13,00 ±4,34	2,25 ± 0,88	0,50 ± 0,92[a]	1,75 ± 0,46
2.	Normal given moringa	8	18,62 ±8,29	2,25 ± 1,16	2,50 ± 1,41[b]	1,37 ± 1,18
3.	Congenital hypothyroidism	8	11,37 ±5,85	2,62 ± 1,30	3,50 ±2,44[bc]	2,75 ± 1,03
4.	Congenital hypothyroidism given moringa	8	9,50 ±2,92	1,75 ± 0,88	2,62 ±2,13[bc]	2,25 ± 0,88
	Kruskal-Wallis Test		*p =0,070*	*p = 0,597*	*p = 0,010*	*p = 0,059*

Note: unequal letter ranks indicate there is a significant difference p<0.05

Table 7 shows that the highest average rearing was the normal group given catapults, namely 18.62 + 8.29 times, and the lowest was the congenital hypothyroid group given moringa, namely 9.50 + 2.92 times, no difference was found in the average rearing. four groups. The mean grooming for the congenital hypothyroid group was the highest among the four groups, namely 2.62 + 1.30 times, while the lowest was for the congenital hypothyroid group, namely 1.75 + 0.88 times. However, the same as rearing, there was no difference in grooming mice. The highest crossing mean was 3.50 + 2.44bc times in the congenital hypothyroid group, and the lowest was 0.50 + 0.92bc times in the normal group. It was found that there was a significant difference in the normal group with the normal group given moringa, the normal group with congenital hypothyroidism given moringa (p < 0.05). The congenital hypothyroid group had the highest average number of feces, namely 2.75 + 1.03 times, and the lowest for the normal group given moringa namely 1.37 + 1.18 times. However, there were no differences between the four groups (p > 0.05)

Testing mouse serum using the ELISA method to obtain TSH and fT4 levels. Measurements were carried out on mother and child mice. In terms of the average fT4 levels of mother mice, the highest results were obtained in the normal group given katuk. Meanwhile, the lowest average fT4 levels were in the group of parent mice given PTU. The mean TSH and fT4 levels used the Kruskall Wallis Test with p values respectively of 0.104 and 0.332. Thus, no differences were found between the average TSH and fT4 levels in the four groups (p>0.05). Although no differences were found, the mean value of fT4 levels was lowest in the hypothyroid group. Normal TSH levels are 0.3–4.0 µIU/ml and normal fT4 levels are 0.8–2.0 ng/dl. Hypothyroidism is a condition where TSH levels in the blood are high (>4 mIU/L) and low fT4 levels (fT4 <0.8ng/dl or <10pmol/L) (Nurcahyani et al., 2017). The absence of differences in mean fT4 levels may be due to the absence of T3

measurements in this study. T3 measurements may be able to show if there is a decrease so that rat offspring are still born congenitally hypothyroid. Induction of 15 ppm Propylthiouracil (PTU) in pregnant rat mothers will inhibit thyroxine synthesis and peripheral conversion of throxine to tri-iodothyronine which causes hypothyroid rat mothers and pups. PTU is preferred over methimazole because the protein binding is stronger and is considered good for breastfeeding mothers because it does not accumulate and has low secretion in breast milk. PTU administration blocks iodine organification as the main mechanism of action, and prevents thyroid hormone synthesis by inhibiting the thyroid peroxidase catalyzed reaction, as well as blocking iodotyrosine coupling in the peripheral deiodination process (deiodinase D1) from T4 to T3. So PTU can cross the placental barrier and cause congenital hypothyroidism (Noor et al., 2015).

The TSH and fT4 levels of rat pups were also tested using the ELISA method. The highest mean fT4 level was in the normal group. Meanwhile, the lowest average fT4 levels were in the congenital hypothyroid group only. This is in accordance with fT4 levels in congenital hypothyroid conditions, namely <0.8 ng/dL (Nurcahyani et al., 2017). The statistical test used Kruskall Wallis with a p value = 0.479 on the mean TSH so there was no difference ($p>0.05$) and the mean fT4 level had a p value = 0.013 so there was a difference between groups. Significant differences were noted in the mean fT4 levels of the normal group with congenital hypothyroidism; also the normal group with congenital hypothyroidism was given moring ($p<0.05$). This shows that giving PTU at a dose of 15 ppm to mother rats can make rat offspring congenitally hypothyroid.

A decrease in fT4 levels stimulates the pituitary gland through a negative feedback mechanism thereby increasing the production and secretion of TSH into the peripheral circulation under the positive control of the hypothalamus by thyrotropin releasing hormone (TRH) (Hidayat and Susbiantonny, 2018). The congenital hypothyroid group given a cath had higher fT4 levels than the congenital hypothyroid group alone. This indicates that the content in katuk leaves can improve the condition of hypothyroid mice. However, in contrast to the normal group, the catuk was actually lower than the normal group, although there was no significant difference. This explains that the content of katuk leaves, namely goitrogens in flavonoids, can inhibit the synthesis of thyroid hormones in the organification phase (Dewi, 2015).

The largest mean change in latency time was in the normal group and the smallest in the congenital hypothyroid group given cath. In the mean latency time using the One-way ANOVA statistical test, the p value = 0.023 so there are differences between the four groups. A significant difference was found between the average change in latency time of the normal group and the group with congenital hypothyroidism alone and those given catukuk ($p<0.05$). This shows that there is a bad influence on giving katuk leaves. The antioxidant compounds in katuk leaves can reduce memory because they have a neuroprotective effect on the brain due to oxidative stress. Oxidative stress is a state of imbalance between the production of reactive oxygen species (ROS) and the body's antioxidant defense system (Sari, 2018). Disruption of memory processes is related to the process of neurofibrillary degeneration. This type of degeneration disrupts mild memory (mild cognitive impairment) (Illiandri et al., 2010).

The largest mean change in latency distance was in the congenital hypothyroid group given moringa, while the lowest was in the normal group. Statistical tests were carried out using One-way ANOVA, p value = 0.032. There was a significant difference in the average change in latency distance between the normal group and the congenital hypothyroid group alone or those given moringa, and the normal group given moringa and the congenital hypothyroid group given moringa ($p<0.05$). This can happen because the stored memory is a neuronal response due to physiological experience. The activity of neurons in forming new synaptic pathways or modifications of existing ones is called memory traces. Changes related to experience are called plasticity (Sitepu and Saputra, 2016).

The highest mean memory retention time was in the normal group given cath, while the lowest was in the congenital hypothyroid group given cath. The statistical test used was One-way ANOVA with p value = 0.001. A significant difference was found between the normal group and the congenital hypothyroid group without and given a moringa; The normal group was given a moringa and the congenital hypothyroid group without and given a moringa ($p<0.05$). Rat pups that lack the hormone thyroxine (T4) will experience brain damage and reduced cognitive abilities. This can occur because there is an increase in cell proliferation, cell migration, cell differentiation, formation and decline of synapses, neurite growth, neurotransmitter formation, myelin formation and increased cell death and astrocyte proliferation which results in imperfect connections between nerve cells.

The highest average time in the middle box was found in 2 groups with the same results, namely the congenital hypothyroid group only and those given cath. Meanwhile, the lowest mean was in the normal group. Kruskal-Wallis Test statistical test with p value = 0.017. There is a significant difference between the normal group and the congenital hypothyroid group without and with a cough ($p <0.05$). The congenital hypothyroid group that was given a cath was the same as the congenital hypothyroid group without the cath. The low presence in the middle box indicates that the rat feels anxious so it tends to spend more time near the wall (thigmotaxis) than in the middle box (Ramadhayani, 2021).

The highest rearing average was in the normal group given moringa, while the lowest was in the congenital hypothyroid group given moringa. The statistical test used was the Kruskal-Wallis Test with a p value = 0.070 so that no differences were found between the four groups. Rearing behavior is the behavior of standing on the 2 back legs, whether supported or not. Rearing frequency shows high exploration properties and low anxiety status in mice (Ardianty and Manurung, 2020). Both types of rearing are caused by two different factors. The mouse leaning against

the wall only contains movement/activity factors, while sitting contains emotional behavioral factors and is inversely correlated with defecation, as a marker of stress and anxiety (Sturman et al., 2018).

The grooming mean for the congenital hypothyroid group was the highest among the four groups, while the lowest was for the congenital hypothyroid group given catching. The statistical test used was the Kruskal-Wallis Test with p value = 0.597. So there were no differences between groups. Grooming behavior shows concern for personal hygiene. Rats lick almost their entire body in a semi-upright position resting on their hind legs (Anggara et al., 2015). However, the highest mean for grooming belonged to the congenital hypothyroid group, indicating a sense of comfort. Rearing and grooming will be opposites because the less frequently rearing is done, the greater the potential for grooming (Sturman et al., 2018).

The crossing mean was highest in the congenital hypothyroid group, and lowest in the normal group. The statistical test used was the Kruskal-Wallis Test, p value = 0.010, meaning that there was a significant difference between the normal group and the normal group given moringa ($p < 0.05$). It was found that there was a significant difference in the normal group with the normal group given moringa, the normal group with congenital hypothyroidism given moringa ($p<0.05$). The congenital hypothyroid group had the highest crossing rate, probably due to confused rat pups being placed in a new place. Congenital hypothyroidism can cause rat offspring to experience confusion, paranoia or manic behavior (Anwar, 2005). Crossing behavior is used to measure animal locomotor activity (Nordquist, 2017). If locomotor activity is high, it indicates a low level of anxiety (Zimcikova et al., 2017).

The highest average number of feces was in the congenital hypothyroid group and the lowest was in the normal group given moringa. The statistical test used was the Kruskal-Wallis Test, p value = 0.059, meaning there was no difference between the four groups ($p > 0.05$). The amount of feces itself has an influence on the rat's anxiety. The activities in the Open Field Test can measure anxiety because they cause stress and emotionality in rats when they are separated from their group mates or cage (Valvassori et al., 2019).

Based on the average fT4 of the rat mothers, it shows that the congenital hypothyroid group had the lowest ft4 value. Low fT4 levels (fT4 <0.8 ng/dL) indicate hypothyroidism (Nurcahyani et al., 2017). However, based on the results of the Kruskal-Wallis statistical test, it was found that the p value = 0.321 ($p>0.05$) for TSH indicated that there was no difference in TSH values in the group of mice studied and the p value = 0.212 ($p>0.05$) for fT4 also shows that there is no difference in fT4 values in the groups of mice studied. This may be due to a lack of T3 thyroid status examination so it is incomplete. Research shows that giving 15 ppm PTU to mother rats starting from the 6th day of pregnancy until weaning, namely when the rat pups are 28 days old, makes the rat mothers experience hypothyroidism and the rat pups experience congenital hypothyroidism (Dong et al., 2009).

Based on the average fT4 of rat pups, it shows that the group of congenital hypothyroid mice experienced a decrease in fT4 values compared to normal mice. However, in the normal group with moringa there was a decrease in fT4 compared to the normal group. Based on the results of the Kruskal-Wallis statistical test, the p value = 0.315 ($p>0.05$) for TSH means that no differences in TSH values in the groups of mice studied. Meanwhile, the p value = 0.016 ($p<0.05$) for fT4 shows that there are differences in fT4 values in the groups of mice studied. Hypothyroidism is indicated by low fT4 levels (fT4 <0.8 ng/dL) (Nurcahyani et al., 2017). Administration of PTU reduces fT4 levels because the mechanism of action of PTU inhibits iodine organification to prevent thyroid hormone synthesis (Sukandar et al., 2014). Apart from that, Moringa leaves contain active flavonoid compounds (Kristina et al., 2014). The high content of flavonoid active compounds is goitrogenic or can affect thyroid hormone synthesis and reduce thyroid hormone activity (Dewi, 2015).

The change in learning latency time shows the difference in the average time for mice to get to the platform on the eighth and first day. The largest average change in learning latency time was the normal group with Moringa. So it's quicker to learn to find platforms. The smallest average change in learning latency time was in the congenital hypothyroid group. Based on the results of the One-Way Anova statistical test, the p value = 0.008 ($p<0.05$), which means that there is a difference in the average change in learning latency time in the group of mice studied. There was a significant difference between the normal group and the normal group with moringa and the congenital hypothyroid group and the congenital hypothyroid group with moringa. Decreased spatial memory in congenital hypothyroid mice was caused by giving PTU to the mother mice. The mechanism of action of PTU is to inhibit iodine organification to prevent thyroid hormone synthesis (Sukandar et al., 2014). In fact, thyroid hormone plays a role in increasing the body's metabolism for the growth and development of neurons in the brain so that it can be used for thinking and learning (Simic et al., 2013).

Changes in distance learning latency show the difference in the average distance traveled by mice on the eighth and first days. The largest average change in learning latency distance was the normal group with Moringa. So it's quicker to learn to find platforms. The smallest average change in learning latency distance was in the group of congenital hypothyroid mice. In addition, groups of congenital hypothyroid mice often did not encounter platforms. Based on the results of the Kruskal-Wallis statistical test, the p value = 0.016 ($p<0.05$), which means that there is a difference in the average change in learning latency distance in the group of mice studied. The group of normal and normal mice with Moringa had a larger and more significant average change in learning latency distance so they learned more quickly to find the platform and the distance traveled was less compared to the group of congenital hypothyroid and congenital hypothyroid mice with Moringa. Moringa leaves can improve spatial memory. This happens because Moringa leaves contain high

flavonoids which play a role in increasing brain blood flow. This is an important factor in synapse plasticity and neurogeneration. Apart from that, increasing cerebral blood flow can prevent neurodegeneration (Saputra & Sitepu, 2016). In addition, research shows that the antioxidant content of Moringa leaves can improve memory disorders (Illiandri et al., 2010).

Memory retention time shows the length of time the mouse is in the platform quadrant. The largest average memory retention time was found in the group of normal mice with Moringa. Meanwhile, the smallest average retention time was found in the group of congenital hypothyroid mice. Average memory retention time of a group of congenitally hypothyroid rats with moringa. Based on the results of the Kruskal-Wallis statistical test, the p value = 0.01 ($p<0.05$), which means that there is a difference in the average memory retention time in the group of mice studied. The average memory retention time of the congenital hypothyroid rat group had a significant difference compared to the congenital hypothyroid rat group. This shows that there was an increase in spatial memory in congenital hypothyroid mice who were given Moringa leaf decoction. Moringa leaves have a high flavonoid content which plays a role in perfusion, especially by increasing the bioavailability of nitric oxide in endothelial cells. Apart from that, nitric oxide also functions to regulate protein transcripts / CREB (cAMP response element-binding protein). Nitric oxide synthesis in the endothelium plays a role in regulating the expression of BDNF (Brain Derived Neurotrophic Factor). BDNF has a role in regulating long-term and short-term memory. Through roles in facilitating long-term potentiation or LTP (Long Term Potency) and increasing BDNF is responsible for episodic memory (Saputra & Sitepu, 2016). In addition, research shows that Moringa leaves can stimulate nerve development. Moringa leaf extract can increase the number and length of dendrites and axonal branches, axon length and facilitate synaptogenesis. Research shows that Moringa leaf extract can improve spatial memory and prevent neurodegeneration in the cornu ammonis, namely CA1, CA2 and CA3 (Kou et al., 2018).

Anxiety behavior in mice was measured using the Open Field Test. The largest average time for mice in the middle box was the group of congenital hypothyroid mice and the smallest was the group of normal mice. Based on the results of the Kruskal-Wallis statistical test, the p value = 0.007 ($p<0.05$), which means that there is a difference in the average time the mice were in the middle box between groups. There was a significant difference between the congenital hypothyroid group and Moringa compared with the congenital hypothyroid rat group. The length of time the mice spent in the middle box showed that the mice had low anxiety behavior. The long-term congenital hypothyroidism of mice in the middle box can be attributed to the presence of thyroid hormone insufficiency since the early stages of life development. Thyroid hormone insufficiency can cause a decrease in the hormone dopamine, causing hyperactive and impulsive behavior (Umezu et al., 2019).

The largest average standing (rearing) mice was the group of normal mice with moringa and the smallest was the group of congenital hypothyroid mice. Based on the results of the One-way Anova statistical test, the p value = 0.001 ($p<0.05$), which means that there is a difference in the average standing (rearing) of rats. The group of normal mice with Moringa had a significantly greater average standing (rearing) than the other groups. This shows explorative behavior or curious behavior towards a new, higher level environment. Research shows that flavonoid content can improve cognitive function, including exploration behavior (Bakoyiannis et al., 2019). Moringa leaves contain a high flavonoid content.

The largest average of mice cleaning themselves (grooming) was in the group of congenital hypothyroid mice and the smallest was in the normal group with moringa. However, based on the results of the Kruskal-Wallis Test statistical test, the p value = 0.655 ($p>0.05$) shows that there is no difference in the average rate of grooming for mice. Research shows that rat grooming behavior is related to emotional behavior (Rojas-Carvajal & Brenes, 2020).

The largest average crossing rate for mice was the group of normal mice with Moringa and the smallest was the group of normal mice. Based on the results of the Kruskal-Wallis Test statistical test, it was found that the p value = 0.001 ($p<0.05$), so it can be interpreted that there is a difference in the average rate of mice crossing. The group of normal mice with moringa and congenital hypothyroidism had a significantly greater crossing rate. A lot of crossing behavior shows courage in mice (Noor et al., 2021).

The congenital hypothyroid group had the highest average number of stools. However, based on the results of the Kruskal-Wallis Test statistical test, the p value = 0.140 ($p>0.05$), which means that there is no difference in the average number of rat feces between groups. The amount of feces indicates the stress level of the rat (Clinton et al., 2014). This shows that the stress level in all groups is the same.

CONCLUSION

1. The effect of giving katuk leaf decoction did not worsen thyroid function in normal mice or those given PTU.
2. The effect of giving katuk leaf decoction tends to worsen spatial memory in congenital hypothyroid rats.
3. The effect of giving katuk leaf decoction tends to increase courage in congenital hypothyroid mice.
4. The effect of giving Moringa leaf decoction on fT4 levels is that it significantly reduces fT4 levels in normal rat pups, but does not worsen fT4 levels in congenitally hypothyroid rat pups.
5. The effect of giving Moringa leaf decoction on spatial memory is that it significantly increases the

percentage of memory retention time in congenitally hypothyroid rats.

6. The effect of giving Moringa leaf decoction on anxiety is that it significantly increases exploratory behavior and courage in normal rat pups.
7. The effect of giving Moringa leaf decoction significantly reduced fT4 levels in normal rat pups, but did not worsen fT4 levels in congenitally hypothyroid rat pups.
8. Administration of Moringa leaf decoction significantly increased the percentage of memory retention time in congenitally hypothyroid rats.
9. Administration of Moringa leaf decoction significantly increased exploratory behavior and courage in normal rat pups.

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