Effect of glutamine, glucose unhidrate and *Moringa oleifera* on blood lymphocytes in white mice (*Rattus Novergicus*) Wistar strain, following induction of a protein-energy-deficient diet

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Abstract

The aim of this research was studied the influence of giving Glutamine, Glucose Unhydrate and *Moringa oleifera* the blood lymphocyte of white rat (*Rattus novergicus*) Strain Wistar that was induced with protein energy malnutrtion (PEM). This was an experimental study with Completely Random Design, sample was white rats in PEM induced with parched rice for 15 days and those with normal diet with total 30 sample. The concluded is that there was a significant difference in the blood lymphocytes of white rats (*Rattus novergicus*) Strain Wistar gived glumorry with sig. (0.000) and glutamin + glucose unhydrate with sig. (0.001), while in the group gived *Moringa oleifera* there was no significant difference with sig. (0.076). Glumorry intervention has the highest level of significance by 19,2382 × 103/mm3 compared to all treatment groups. This suggests that the glumorry (Glucose Unhydrate, Glutamine, and *Moringa oleifera*) intervention successfully increased the lymphocyte count higher in the study sample with PEM condition compared to the group that was only given Glucose Unhidrat + Glutamine and the group that was only given Moringa Oleifera.

Introduction

In Indonesia there are various kinds of nutritional problems less, one of the nutritional problems that need attention is Less Energy Protein. According to Treating, PEM or Protein Energy Malnutrition is a general shortage of food sources of energy, in the form of carbohydrates, fats and proteins over a long period of time continuously accompanied by infection resulting in deficiency disease. The prevalence of undernutrients in toddlers (BB/U<-2SD) provides a fluctuating picture from 18.4 percent (2007) decreasing to 17.9 percent (2010) then increasing again to 19.6 percent (in 2013). Some provinces, such as Bangka Belitung, East Kalimantan, Central Kalimantan, Central Sulawesi show a downward trend. Two provinces with a very high prevalence (>30%) are NTT followed by West Papua, and two provinces whose prevalence <15% occurs in Bali, and DKI.[1] According to the Total Diet Survey (SDT) in 2014, most of the population in Indonesia has a very less and less energy adequacy rate of 79.6%, consisting of 45.7% of the population with a very less / minimal energy adequacy and 33.9% of the population with less energy adequacy.[2]

Protein energy malnutrition (PEM) might stifle a student's ability to learn. According to Yahaya's 2009 research, various factors influence student achievement in school, including consuming behaviors and food intake. Furthermore, according to Grebneva's research from 2021, pre-school nutrition fulfillment determines achievement when the child enters school age. Moreover, healthy diet and adequate exercise, offers lower-cost options for preventing and managing long-term illness in adolescents.[3] Therefore, it is important to introduce health education from an early age. Glutamine has the ability to increase and change immunity in the body. Glutamine deficiency has a negative effect on the functional integrity of the intestines and leads to weakening of the immune system leading to a decreased ability to fight infections and Lymphocytes, macrophages and neutrophils play an important role in the immune and inflammatory response. According to Hasdianah, B lymphocytes produce and secrete antibodies in response to stimulating antigens while T lymphocytes have a role in helping B cells in producing antibodies, activating macrophages in phagocytosis, and later T cells will produce a wide variety of cells namely CD4+, CD8+, and Ts (Th3) cells.[4] According to Wasinski *et al*. glucose and glutamine are essential for energetic and nutritional biosynthesis for T and B lymphocytes.[5]

Every cell and tissue in the body of living things needs glucose as the body's fuel in every process. Glucose is an important substance and is needed for the body's defense, size, cell activation and also for the production of cytokines. Glucose provides the energy needed for T-lymphocytes for the metabolic process of producing ATP

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Key words: Glucose unhydrate, Glutamine, Lymphocyte, Moringa oleifera, Protein Energy malnutrition.

Contributions: Design the work: SK, MY, AWK, AS, RF, SS, DAC. Data analysis: SK, DAS, OSW, AGA. Interpretation of data: SK, MY, AWK, AS, RF, SS, DAC. Drafting: SK, MY, AWK, AS, RF, SS, DAC, DAS, OSW, AGA. Review & editing: SK.

Conflict of interest: The authors declare no potential conflict of interest.

Acknowledgments: Appreciation and sincere gratitude to Faculty of Sports Science, Universitas Negeri Malang that given support, information and suggestions to authors so that this article would be finished.

Conference presentation: This article was presented at the 4th International Scientific Meeting on Public Health and Sports (ISMOPHS 2022).

Received for publication: 24 October 2022.
Accepted for publication: 17 November 2022.

Journal of Public Health in Africa 2022; 13(s2):2418
doi:10.4081/jphia.2022.2418

Research conducted by Katmawanti *et al*. showed that the combined formula of glutamine and unhydrous glucose given to PEM-model mice for 10 days significantly increased the number of blood lymphocyte levels.[6] In addition to glutamine and glucose, amino acids are very important for people with PEM. One of the plants that have a high amino acid content is moringa leaves. Moringa oleifera is one type of tropical plant that has a variety of benefits, one of which is as an alternative food to overcome nutritional problems. The results showed that giving moringa leaf extract in addition to increasing the number of CD4+ T cells has also been shown to increase the relative number of CD8+ T cell as well as moringa leaves have a role as immunostimulatants because it can increase macrophage activity. Research conducted by Sari *et al*. showed that a single dose of 500 mg/kgBB dose of moringa leaf ethanol extract had an activity as an immunostimulator against CD3+ and CD8+ which was more effective when compared to a single dose of 750 mg/kgBB dose of ethanol extract.[7] Research conducted by Rizqiyah, the administration of moringa flour can increase the number of lymphocytes of wistar rats that experience a condition of significantly less protein energy, said so because moringa has a high protein content and complete amino acid composition.[8] This study was conducted by examining the administration of Glumorry in white mouse lymphocytes (Rattus novergicus) Wistar strain that has been induced with the PEM diet.

Materials and Methods

This study proved the effect of glutamine, glucose and *moringa oleifera* (moringa leaf extract) on changes in the number of blood lymphocytes as a result of PEM (Lack of Protein Energy). This type of research is experimental research *with control design* because it meets 3 experimental research principles namely treatment, control and randomization. The sample in the study was a white mouse *(Rattus novergicus)* Wistar strain taken randomly with the following criteria: (1) Male sex; (2) Age 7-8 weeks; (3) Weight 160-180 grams; (4) Adapted for 3 days in a laboratory environment. The provision of rat rations based on the amount of rat feed needs per day is 30 grams per day, using BR-1 feed, while the PEM diet used is karak (rice aking) with a daily giving of 30 grams. Calculation of diet at the time of treatment using the principles of isokalori and isoprotein dietary. Dieting was based on the protein needs of mice and adapted to the ability of mice to spend the diet. It is estimated that in a day the capacity to eat rats is as much as ±30 g, then the diet is given with an amount of approximately ±30 g. The provision of glutamine and glucose unhydrate supplements is adjusted to the study Katmawanti *et al.* which states that rats given glutamine and glucose unhydrate as much as 2 grams within 10 days can increase the number of lymphocytes, so this study the amount of glutamine and glucose unhydrate per day is 2 grams.[6] The addition of glucose according to the study Curi *et al.,* it shows that the ratio of glutamine and glucose given to the animals is compared to 1:1, resulting in the addition of 2 grams of glucose.[8] In the study of Michael, the dilution that should be done for combined glutamine and glucose is 10 cc. According to Sari *et al.,* it was stated that mice given ethanol extract and moringa leaves of 500 mg/kgBB within 7 consecutive days had effective immunostimulatory activity against CD3+ and CD8+.[7] Therefore, the proportion of moringa leaves given according to the weight of mice is 500 mg/1000 gr = 1:2, 80 mg/160 gr = 1: 2. 80 mg = 0.08 gr. So the proportion of moringa leaf extract is 0.08 gr.

The data collected includes: (1) Weight data obtained from the results of weighing the weight of rats using the brand *Sartorius Melter* with a precision of 0.1 Kg every week; (2) Daily food intake data is calculated by weighing the rest of the food given to animals try every day using *Sartorius Melter* brand scales with a precision of 0.1 Kg; (3) Number of T-lymphocyte cells. The technique of measuring the number of lymphocytes by taking blood with a syringe (disposable syringe*)* through the heart of themouse. After that, calculations were carried out at the Clinical Pathology Laboratory of Universitas Brawijaya.

The results of the assessment of the number of lymphocytes obtained from the average number of animal blood lymphocytes tried in each treatment group, in addition to analyzing clinical physical data in the form of body weight and daily food intake, to find out whether the distribution of variables above normal distribution then conducted a normality test using the *Saphiro-wilk* test. The analysis that will be used is the One *Way* ANOVA test.This test is a type of parametric statistical test that aims to find out if there is an average difference between more than two sample groups. If there is a difference continued with the *Post Hoc Tukey Test* to see the difference between each treatment group. Testing all data using computer programs through the operational Application *Statistics Packet for Social Science* (SPSS) 22.

Results

Based on the results of the analysis of data on the average lymphocyte levels can be seen in Table 1.

Based on Table 1, it is seen that the highest number of blood lymphocyte levels occurred in group A (Normal diet + glumorry) (19.2382×10^3)·while the lowest amount was found in group D (positive control)

Table 1. Average lymphocyte levels in each group.

Group	N	Mean (cells)	Std. Deviation	Std. Error
A	6	19.2382	1.63461	0.66733
B	6	18.6717	2.92635	1.19468
C	6	16.3600	2.10695	0.86016
D	6	12.7150	2.91894	1.19165
E	6	14.5641	1.54409	0.63037
Total	30	16.3098	2.226188	0.908838

Group A: D N+ Glucose unhydrate + Glutamine + Moringa oleifera. Group B: DN+ Glucose unhydrate + Glutamine. Group C: DN+ Moringa *oleifera.* Group D: Positive control. Group E: Negative control.

Table 2. Test normality of lymphocyte levels in each group.

Group	Shapiro-Wilk		
	Statistics	Df	Itself
A	0.832	6	0.112*
B	0.899	6	0.366*
C	0.897	6	0.357*
D	0.880	6	0.267*
E	0.889	6	0.315*

Group A: D N+ Glucose unhydrate + Glutamine + Moringa oleifera. Group B: DN+ Glucose unhydrate + Glutamine. Group C: DN+ Moringa *oleifera*. Group D: Positive control. Group E: Negative control. Sign (*): Indicates normal data or (p>0.05).

only the treatment of PEM diet (12.7150 × 10^3). Therefore, to see the significant or not the comparison of each group, it is necessary to test different ANOVA, but before the test is done different ANOVA first conducted a prerequisite test that is a test of normality and homogeneity with the following stage.

Based on Table 2 of the normality test, showing the distribution of lymphocyte levels is normal (p>0.05), the analysis continued with the homogeneity test.

Based on Table 3 homogeneity tests, showing the distribution of lymphocyte level data is homogeneous (p>0.05), followed by different ANOVA

Based on a Table 4 different tests Anova showed that there was a significant difference in lymphocyte levels with a value of p = 0.000 (p>0.05), to find out the differences between groups then the test continued with different tests. Tukey HSD is like Table 5 following.

Based on the different Tukey HSD tests in Tables 4 and 5 showed a significant difference between group A and group D (Sig. 0.000 or p<0.05), group A with group E (Sig. 0.001 or p<0.05) group B with group D (Sig. 0.001 or p<0.05), group B with group E (Sig. 0.00E or p<0.05), While the other group did not have a significant difference (p > 0.05).

Discussion

The results of the analysis of the number of lymphocytes after the intervention showed that lymphocyte levels were different in all treatments. Glumorry intervention showed the highest number of lymphocytes in all treatment groups with an average number of lymphocytes at 19.2382 × 103/mm^3. The results of statistical analysis of the ratio of lymphocytes in the glumorrry administration group and the positive control group showed significant differences. This suggests that glumorry-giving interventions successfully increased the number of lymphocytes of study samples experiencing PEM conditions.The formation of lymphocytes begins from the differentiation of stem cells in the spine, lymphocytes then differentiate into 2 types, namely B lymphocytes and T lymphocytes. B lymphocytes then go to the lymph, while T lymphocytes go to the thymus gland. T lymphocytes undergo maturation in the thymus gland which will then be released into the blood vessels.[6] The results of the calculation of the average nutrients in each treatment obtained that the normal dietary treatment group with the addition of glutamine, unhidric glucose and *Moringa oleifera* had the highest energy intake levels compared to the other four treatments. The treatment group added glutamine and unhydrous glucose also increased the number of lymphocytes but not as high as the treatment group of glutamine addition, unhydrate glucose and *Moringa oleifera.*

Low-protein dieting results in a state of lack of protein in the blood. The body balances so that there are no abnormal changes in circumstances. When the body can no longer protect against starvation, there is a state of PEM. Clinical physical changes are abnormal weight. Serum biochemical changes that occur are decreased lymphocytes. Decreased blood lymphocyte levels are caused by the availability of amino acids, glutamine and glucose in the liver decreases. Lack of amino acids, glutamine and glucose can cause the immune system to decline. Moreover, glutamine supplementation in animal studies was also proven to be useful in gut associated lymphoid tissue (GALT). It prevents the decrase of immunoglobulin A (IgA) producing plasma cells, increases levels of secretory fecal IgA (sIgA), and also prevents adherence and bacterial translocation from the gut.[10] Other research states that the utilization of glutamine by cells of the immune system such as lymphocytes, neutrophils, and macrophages is fourfold greater than that of glucose as indicated by the production of glutamate, aspartate, lactate, and ammonia.[11] Similiarly, dietary supplementation with glutamine or glycyl-Gln dipeptide improves growth performance, small intestinal morphology and immunity response in endotoxin-challenged weaning piglets, enhance intestinal and whole-body growth, to promote enterocyte proliferation and survival, and to regulate intestinal barrier function in injury, infection, weaning stress, and other catabolic conditions.[12] Lymphocyte levels describe the size of the body's immune system in fighting all kinds

Table 3. Test homogeneity of lymphocyte levels.

Levene Statistic	df1	df2	Itself
1.006	4	25	0.423

Group A: D N+ Glucose unhydrate + Glutamine + Moringa oleifera. Group B: DN+ Glucose unhydrate + Glutamine. Group C: DN+ Moringa *oleifera*. Group D: Positive control. Group E: Negative control. Sign (*): Indicates normal data or (p>0.05).

Table 4. Different ANOVA test results of lymphocyte levels.

	Sun of Squares	df	Mean Square	F	Itself
Between Groups	224.853	4	56.213	10.575	0.000
Within Groups	132.896	25	5.316		
Total	357.749	29			

Table 5. Results of different tests Tukey HSD lymphocyte levels.

Group	N	Mean (cells)	Std. Deviation	Std. Error
A	6	19.2382	1.63461	0.66733
B	6	18.6717	2.92635	1.19468
C	6	16.3600	2.10695	0.86016
D	6	12.7150	2.91894	1.19165
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of foreign bodies that enter the body. When lymphocyte levels are abnormal or decrease, it will result in the body easily exposed to various infectious diseases and cell activity in the immune system is inhibited. One of the main functions of proteins is as a defense function. In addition to being the basic complement of the immune system itself, protein also has an important role to change the immune system. Research conducted by Katmawanti *et al*. states that White Rats Wistar Strains that have intervened with the PEM diet cause a decrease in the number of lymphocytes.[6] Some research suggests that PEM conditions can cause a decrease in the number of lymphocytes and the first immune response delivered by *cell mediated immunoity. Cell Mediated Immunity* depends on the function of lymphocytes T. Cell *Mediated Immunity* suppression is something typical found in almost all people with general energy protein malnutrition. This is because the formation of various components of the immune system in the body depends on the body's ability to synthesize.

Glutamine is a non-essential amino acid and a major part of the de novo synthesis that occurs in the human body, especially in skeletal muscles because the body has the ability to synthesize amino acids through glutamine synthase reactions, but glutamine becomes an essential nutrient during which the body suffers from pain. Glutamine is the most abundant amino acid in the body because it is used in central metabolic processes by acting as an energy substrate for the tricarboxylic acid cycle and nitrogen donor in several pathways including purine/pyrimidine synthesis, nicotinamide adenine dinucleotide metabolism, and the urea cycle.[13] According to Darwin *et al*. glutamine is an amino acid found in the body that has the function of improving the body's immunity.[14] Glutamine plays an important role in the interorgan spinning of nitrogen and carbon and has been seen as the primary oxidative energy for cell division such as enterocytes and lymphocytes. Glutamine is an important substrate for producing ammonia by the kidneys, which is a precursor to the formation of purines and pyrimidines, and plays an important role in the regulation of protein synthesis. Glutamine has been shown to have an important function to the function of various organ systems, including the intestinal, immune system, and for maintaining acid-base.[6] Glutamine is a nitrogen donor needed for de novo synthesis of both purines and pyrimidines, therefore essential for the production of net nucleotides during cell proliferation.[12] Decreased concentration of glutamine in the blood can cause impaired immune function that can lead to immunodepression. Decreased glutamine in the blood is related to strenuous physical exercise, although weak evidence suggests a link between strenuous physical exercise and decreased glutamine.[14] The low glutamine concentration in humas tissues affects the whole body since the amino acid provides nitrogen atoms to the synthesis of purines, pyrimidines, and amino sugars.[15] According to Fan *et al.,* his research showed that the administration of glutamine nutritionally emeral increases the amount of lymphocyte, serum Ig and CD4 and CD8 ratios.[16] In research conducted by Katmawanti *et al*. showed that after intervention with the administration of glutamine and glucose unhydrate in mice the PEM model experienced a significant increase in the number of lymphocytes.[6] Moreover, glutamine mitigates numerous risk factors for cardiovascular disease, such as hypertension, hyperlipidemia, glucose intolerance, obesity, and diabetes.[17]

In addition to glutamine and glucose there is also moringa *oleifera* (moringa leaves). PEM causes disruption to the immune system, if a person with PEM then the immune system decreases. The immune system, especially CD4+ T cells and CD8+ T cells, can be improved, one of which is by using immunomodulatory agents derived from natural materials such as plants. One of the plants that is thought to function as an immunomodulator is *Moringa oleifera* (moringa leaves). Moringa leaves contain several active compounds, including arginine, leusine and methionine. Arginine content in fresh moringa leaves reaches 406.6 mg; While in dried leaves 1,325 mg, arginine plays a role in improving immunity or immunity herbal supplements can come from fruits, vegetables, or plants that have content as immunomodulators.[18] One plant that has immunomodulatory content is Moringa *oleifera.* Extracts of moringa leaves, seeds and flowers with several solvents contain proteins, carbohydrates, tannins, steroids, carotene, protein, vitamin C, calcium, potassium, amino acids, and various phenolics. According to research conducted by Rizqiyah, the administration of moringa flour can increase the number of whistar mouse lymphocytes that experience a condition of significantly lacking protein energy, it is said that because moringa has a high protein content and complete amino acid composition.[9] Research conducted by Sari *et al*. showed that a single dose of 500 mg/kgBB dose of moringa leaf ethanol extract had more effective activity as an immunostimulator against CD3+ and CD8+ when compared to a single dose of ethanol extract of 750 mg/kgBB, suggesting that ethanol extract groups and moringa leaves had a more effective ability to boost the immune system.[7] And research conducted by Fathir *et al.* (2014:114-120) showed that giving moringa leaf extract can increase the number of CD4+ T cells and CD8+ T cells in all mice infected with *salmonella thypi* and the administration of high doses of moringa leaf extract causes immunosuppression and can also serve as immunostimulated and immunosuppression in CD4+ T cells and CD8+ mice, this is due to an increase in the number of CD8+ T cells affected by the presence of active substances in moringa leaf extracts. Saponins and flavonoids that can stimulate increased IL-2 in CD4+ T cells and increased IL-2 also allow for an increase in the number of CD8+ T cells.

Conclusions

Based on the results of the above research and analysis can be concluded: 1) There is a difference in the number of white mouse blood lymphocytes (*Rattus novergicus*) Wistar strains given Glumorry to a positive control group; 2) There was a difference in the number of white mouse blood lymphocytes (*Rattus novergicus*) Wistar strains given glutamine and glucose unhydrate to the positive control group; 3) There was no difference in the number of white rat blood lymphocytes (*Rattus novergicus*) Wistar strain in the moringa oleifera administration group against the positive control group; 4) The results showed that blood lymphocytes in white mice (*Rattus novergicus*) Wistar strain in the Glumorry (Glucose Unhydrate, Glutamine, and Moringa Oleifera) administration group had the highest degree of significance compared to the group that was only given Glucose Unhidrat + Glutamine and the group that was only given Moringa Oleifera.

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