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Effect of ethanol extract of Hedyotis corymbosa (L.) Lamk against parasitemia and hepatomegaly in Plasmodium berghei ANKA-infected mice

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Research Article

The differences of parasitemia in *Plasmodium berghei* infected mice treated with extract of mango parasite leaves with Artemisinin combination

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ABSTRACT

Malaria is a disease transmitted through the bite of a female *Anopheles* mosquito caused by the *Plasmodium* parasite. *Plasmodium* has been reported to become resistant to artemisinin. Thus, the study on the ethanol extract of mango parasite leaves/*Dendrophthoe pentandra* (MP) on *P. berghei*-infected BALB/c mice with and without artemisinin combination (MP+A) was conducted. This study is experimental laboratory research with a post-test only design. The percent parasitemia in mice treated with ethanol extract of MP and MP+A leaves decreased. There was no difference in the spleen index in mice given ethanol extract of MP, and MP+A leaves with p = 0.203 and the spleen weight of mice with p = 0.134 (significance: p <0.005). Pearson Correlation test showed a correlation between spleen index with parasitemia and spleen weight with parasitemia; however, there was no correlation between body weight and parasitemia. The ethanol extracts of MP and MP+A leaves had significant antimalarial activity, and the difference in the percent parasitemia between groups was significant but not so far. The spleen index value was not affected by the ethanol extract of MP and MP+A leaves, but the percent parasitemia was affected.

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INTRODUCTION

Malaria is a life-threatening disease caused by a parasite transmitted through the bite of a female Anopheles mosquito infected with the *Plasmodium* parasite. In 2016 there were 451,000 deaths caused by malaria, then in 2017, there were 435,000 deaths globally. Although there was a decrease in mortality due to malaria in 2016- 2017, it was not significant and still relatively high (World Malaria Report, 2018). However, in 2020, there was a 12% increase in cases from the previous year due to service disruptions during the COVID-19 pandemic (World Malaria Report, 2021). Malaria treatment encounters various problems, including parasite resistance to antimalarial drugs (Harijanto, 2006). In Indonesia, there has been resistance to antimalarial drugs such as chloroquine in East Kalimantan since 1973, and it is increasingly spreading to several places (Baird et al., 1996; Kemenkes, 2013). Efforts to overcome the resistance have been carried out in Indonesia by recommending drugs other than chloroquine and sulfadoxine-pyrimethamine against *Plasmodium*, namely the combination of artemisinin (Tjokroprawiro et al., 2015). WHO recommends that the use of artemisinin is not given alone but in combination with antimalarial drugs or other supportive drugs (Noedl et al., 2008).

Based on the facts explained above, alternative treatments are needed in dealing with malaria cases, for example, using plants with antimalarial properties. Mango parasite leaves/ *Dendrophthoe pentandra* (MP) contain active flavonoid compounds which are antimalarial. According to Yulianti, Dahlia, and Ahmad (2014), mango parasite leaves have a total flavonoid compound of 2.48%. The leaves of the mango parasite were extracted by maceration using 96% ethanol solvent. This study was conducted on BALB/c mice infected with *P. berghei*. Several studies on parasite leaves have revealed that parasite leaves can function as anticancer agents and antibacterial (Ikawati et al., 2008; Anita, Khotimah, and Yanti, 2014).

METHODS

Research type and design

This study is an experimental laboratory research with a post-test only design. This study was used to determine the antimalarial activity of the ethanol extract of the mango parasite (MP) leaves and MP+A (mango parasite leaves combined with artemisinin) on the percentages of parasitemia and the spleen index. The percent parasitemia in mice infected with *P. berghei* was calculated before treatment.

Sample, sample size, and sampling

The sample consisted of white male mice (*Mus musculus*) strain BALB/c. The mice were acclimatized for a week prior to the study. The mice had to meet the inclusion criteria (male white mice, weight 20-30 g, age 6-8 weeks, and in healthy condition) and did not meet the exclusion criteria (anatomical abnormalities in mice; sick or dead during research). Sampling consisted of peripheral blood smears taken on day one to day four after treatment, the spleen was taken on day four after treatment, and body weight was measured before the mice were dissected. The controls used for comparison were positive and negative controls. The positive control used artemisinin at a dose of 0.52 mg/gBW, and the negative control used 0.5% Na-CMC as much as 0.5 ml.

Research variables

The independent variables in this study were the doses of ethanol extract of MP leaves

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consisting of 10, 100, and 200 mg/kgBW/day and artemisinin with a dose of 0.52 mg/gBW/day. The control variables in this study included experimental animals (strain, age, body weight), food and drinks given to experimental animals, cages, cage sanitation for experimental animals, and tools used for conducting research in the laboratory. The dependent variables in this study were the percent parasitemia and the mean of splenomegaly of BALB/c mice treated with the ethanol extracts of MP and MP+A leaves.

RESULTS

The highest percentage of parasitemia was found in the group treated with MP leaves+A ethanol extract at a dose of 10 mg/kgBW. The lowest percentage of parasitemia was found in the group treated with MP leaves+A ethanol extract at the dose of 200 mg/kgBW. The data on the percent parasitemia of MP and MP+A leaves ethanol extracts are shown in Table 1 and Figure 1.

The analysis of parasitemia at the group level using the Anova test showed p<0,005, which means that there was a significant difference in all groups, both given the ethanol extract of MP leaves and MP leaves +A. The group of ethanol extract of MP leaves with the lowest dose showed the highest percentage of parasitemia. The higher the dose of ethanol extract of MP leaves, the lower the percentage of parasitemia. In the MP leaves+A ethanol extract group, the higher the dose, the lower the percentage of parasitemia. The percentage of parasitemia in the MP and MP+A groups with the control group also differed. The positive control group showed a lower percentage of parasitemia, while the negative control group showed a higher percentage of parasitemia compared to the MP and MP+A groups.

The highest growth percentage was found in the group treated with ethanol extract of MP leaves at a dose of 10 mg/kgBW. On the contrary, the lowest growth percentage was found in the group treated with MP +A leaves ethanol extract at a dose of 200 mg/kgBW (as shown in Figure 2).

The higher the extract dose, the higher the inhibition percentage. In contrast to the growth percentage, the higher the extract dose, the lower the growth percentage. Positive control showed a negative growth percentage, which was because artemisinin caused a decrease in parasitemia since the second day after treatment.

The highest inhibition percentage was found in the group treated with MP+A leaves ethanol extract at a dose of 200 mg/kgBW. On the other hand, the lowest inhibition percentage was found in the group treated with ethanol extract of MP leaves at a dose of 10 mg/kgBW (shown in Figure 3). The higher the dose of ethanol extract of MP leaves, the higher the inhibition percentage. Likewise, in the MP+A leaves ethanol extract group, the higher the dose, the higher the inhibition percentage.

The paired simple t-test analysis showed a significant difference between the weight of the mice before and after treatment (p<0,005). The analysis of the difference in spleen weight after the administration of MP and MP+A leaves ethanol extracts using ANOVA showed no significant difference in the spleen weight of each group (p=0.134). The results indicate that the ethanol extract of the leaves of MP and MP+A had no effect on the spleen weight of mice.

The highest spleen index was found in the group treated with MP +A leaves ethanol extract at a dose of 10 mg/kgBW, and the lowest

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Table 1. Mean of parasitemia (%) in *P. berghei* ANKA-infected mice given the ethanol extracts of MP leaves, MP leaves + A, and control.

Treatment Groups	Parasitemia (%)				Mean
	Day 1	Day 2	Day 3	Day 4	
MP10	6,9	10,7	15,4	20,3	13,3
MP100	6,9	8,9	12,2	17,4	11,4
MP200	8,3	9,7	10,4	10,4	9,7
MP10+A	9,4	12,1	14,1	17,3	13,2
MP100+A	7	9,5	9	11	9,1
MP200+A	8,4	9,4	8,7	8,2	8,7
Positive Control	6,9	7,2	5,9	5	6,3
Negative Control	9	13,8	18,5	26,7	17

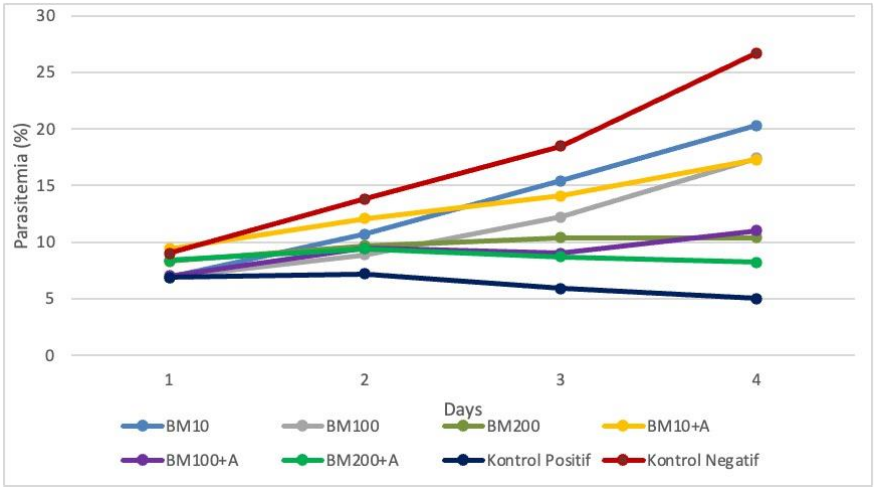

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Figure 1. Graph of the relationship between extract dose and percentage parasitemia

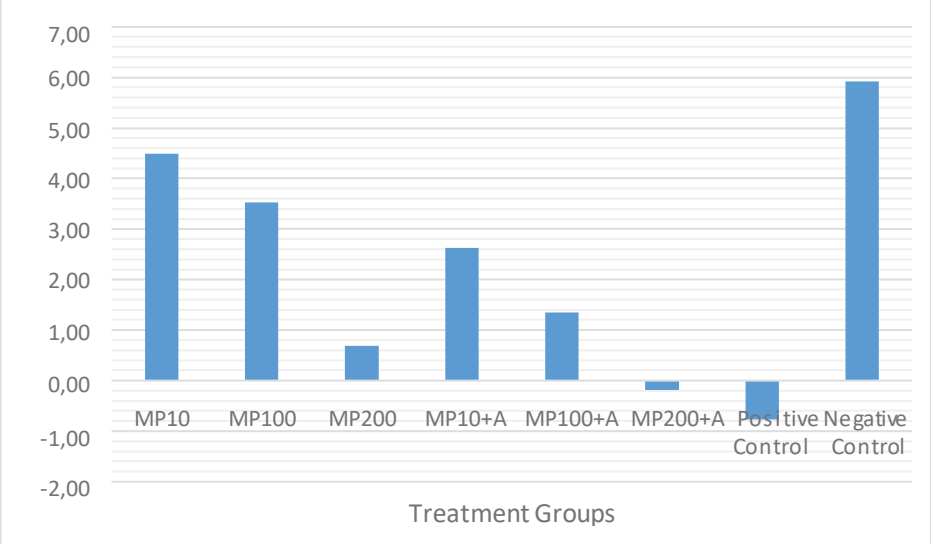

Figure 2. Diagram of the relationship between extract dose and growth percentage

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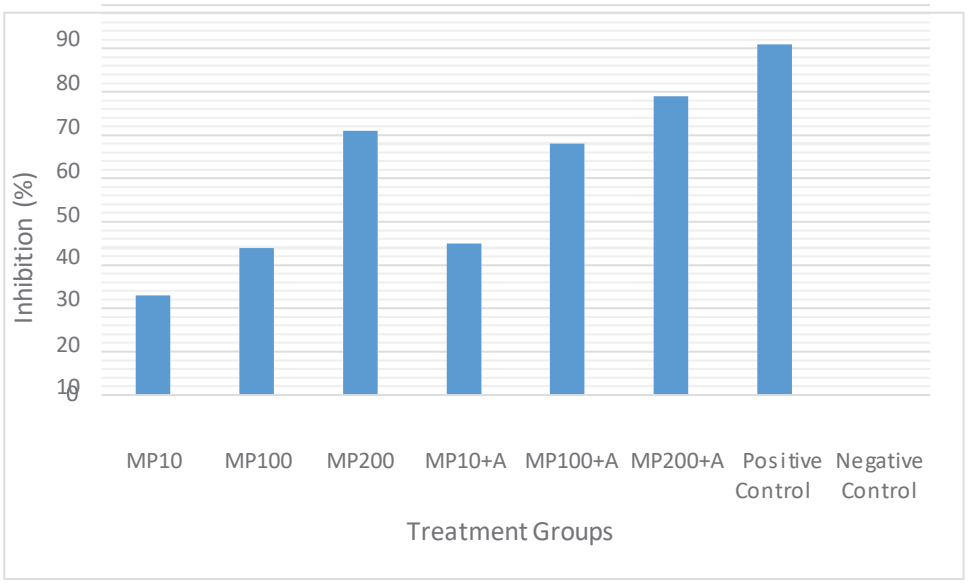

Figure 3. Diagram of the relationship between extract dose and inhibition percentage

Table 2. Mean of body weight (g), spleen weight (g), spleen index (%), and parasitemia (%) after administration of MP and MP+A leaves ethanol extracts

Treatment Groups	BW (g)	Spleen Weight (g)	Spleen Index (%)	Parasitemia
MP10	26,7	0,59	0,022	13,3
MP100	27,3	0,57	0,021	11,4
MP200	26	0,47	0,018	9,7
MP10+A	26,7	0,53	0,020	13,2
MP100+A	25	0,44	0,018	9,1
MP200+A	26,3	0,42	0,016	8,7
Positive Control	26,7	0,43	0,016	6,3
Negative Control	25,7	0,64	0,025	17

spleen index was in the group treated with MP +A leaves ethanol extract at a dose of 200 mg/ kgBW. The higher the dose of ethanol extract of MP leaves, the lower the spleen index value. Likewise, in the MP+A leaves ethanol extract group, the higher the dose, the lower the spleen.

The normality test of the spleen index using Shapiro-Wilk showed that the data were normally distributed. Analysis of the spleen index between groups using the Anova test showed p= 0.203, which means that there was no significant difference in all groups, either given MP or MP+A ethanol extract.

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DISCUSSION

Compounds contained in MP leaves, including flavonoids, are also found in several species used as antimalarial drugs, such as extracts of *Thespesia populnea* (L.) *Soland Ex Correa* leaves (Nurcahyanti et al., 2014) and *Kawista* extract (*Limonia accidisima L.*) (Tjahjandarie and Tanjung, 2015). The percentage of parasitemia in Table 1 shows that the ethanol extract of the leaves of MP and MP+A had antimalarial activity. Parasitemia in the MP+A leaves ethanol extract group showed lower parasitemia than the MP leaves ethanol extract group. It means that the ethanol extract of MP+A leaves has better antimalarial activity than the ethanol extract of MP leaves without artemisinin. The MP+A leaves ethanol extract showed lower parasitemia than the group given MP leaves ethanol extract. Tukey's test showed a significant difference in parasitemia in the two treatment groups ($p<0.05$), except for some groups. However, the difference was not significant. The flavonoid compound in the leaves is the same or lower; however, it was not measured in this study. Based on several studies, many other compounds in MP leaves and the ability to reduce parasitemia depend on the levels of flavonoids in the leaves. In addition, several studies using experimental animals also show that individual responses from experimental animals affect the test results (Gamber and Wayne, 2011).

The results of some studies on flavonoids and artemisinin show that flavonoids and artemisinin have a synergistic effect that can be seen from the interaction between flavonoids and artemisinin, showing that the combined use of flavonoids with artemisinin can increase the effectiveness of artemisinin (Ferreira et al., 2010; Wei et al., 2015; Zhou et al., 2020). Flavonoids have effective inhibitory characteristics similar to artemisinin (Wei et al., 2015) and, in total administration, provide advances in malaria therapy through dual transcriptional regulation of artemisinin (Zhou et al., 2020). The effect is shown by the dissolved flavonoids that have the same dose effectiveness as artemisinin (Suberu et al., 2014). Based on the growth percentage, it was found that the extract dose is directly proportional to the inhibition percentage and inversely proportional to the growth percentage. It is because the mice given the ethanol extract of the leaves of MP and MP+A with a higher dose had a higher inhibition percentage and a smaller growth percentage.

Spleen index is related to body weight, and spleen weight of mice after administration of ethanol extract of MP and MP+A leaves. The relationship between body weight and parasitemia analysis showed no significant relationship ($p=0.947$). This was because *P. berghei* infection reduced appetite in mice; therefore, their body weight decreased. Lack of appetite in mice resulted in weight loss. This decrease in body weight in mice is in line with the increase in red blood cells in infected mice (Syamsudin, Dewi, and Marlina, 2008). The weight loss is also in line with the increased number of red blood cells in the infected mice. Weight loss in mice is caused by organ systems damage, impaired metabolic function, and hypoglycemia disorders (Shimada et al., 2019). The impacts after *Plasmodium* infection include acute fluid and nutrient loss resulting from increased activity of the permeability of the digestive tract (Wilairatana et al., 1997). In addition, there is also a reaction to fever and decreased or reduced appetite (Karney and Tong, 1972). Thus, the weight loss of the infected mice results in increased gastrointestinal permeability and disturbances in growth and nutrition (Sowunmi et al., 2007).

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The spleen index and parasitemia showed a significant relationship with p<0,005, although weight was not associated with parasitemia. Spleen index analysis in each group using the ANOVA test showed no significant difference (p= 0.203). This result is because the ethanol extract of MP and MP+A leaves had no effect on the spleen index but did have an effect on parasitemia. It also resulted in the spleen weight between groups showing no significant difference (p= 0.134).

In this study, mice given artemisinin also showed splenomegaly, although there was a decrease in parasitemia (Table 1). This is because artemisinin is a schizonticide in the blood that acts very quickly on all malaria species and does not affect tissues such as the liver and spleen (Katzung, Masters, and Trevor, 2012). There is no effect on the spleen index on the fourth administration of the drug (Windasari, Maslachah, and Rahardjo, 2016). Spleen tissues infected by *Plasmodium* macroscopically cause spleen enlargement (Intan et al., 2017). The enlargement is caused by the immune response in the body which produces inflammatory cells and causes the size of the spleen to enlarge (Kemenkes, 2013). Splenomegaly occurred in all mice given the test extract; thus, the ethanol extract of MP leaves works the same way with artemisinin in that it affects parasites in the bloodstream but not tissues.

CONCLUSION

The percentage of parasitemia in mice given MP and MP+A leaves ethanol extracts decreased. There was no difference in the spleen index and body weight in mice given MP, and MP+A leaves ethanol extracts.

The analysis of the relationship between BW and parasitemia did not show a significant relationship. However, there was a significant relationship between spleen weight and parasitemia and spleen index with parasitemia.

Further research is needed to identify and isolate the type of active compound that acts as an antimalarial in more detail from the ethanol extract of MP leaves so that it can be developed as an antimalarial.

REFERENCES

Anita, A., Khotimah, S. and Yanti, A. (2014). Aktivitas Anti bakteri Ekstrak Daun Benalu Jambu Air (*Dendropthoe pentandra (L.) Miq*) Terhadap Pertumbuhan Salmonella typhi. Jurnal Protobiont.

Baird, J. et al. 1996. Survey of resistance to chloroquine by Plasmodium vivax in Indonesia. Transactions of the Royal Society of Tropical Medicine and Hygiene, 90(4), pp.409-411.

Ferreira, J. et al. 2010. Flavonoids from Artemisia annua L. as Antioxidants and Their Potential Synergism with Artemisinin against Malaria and Cancer. *Molecules*, 15(5), pp.3135-3170

Gamber JC, Wayne barbee. (2011). *Guide For The Care And Use Of Laboratory Animals*. 8th ed. Washington, D.C.: National Academy Press.

Harijanto, PN. (2006). Buku Ajar Ilmu Penyakit Dalam. Jakarta: PIP FKUI.

Ikawati, M., et al. (2008). Pemanfaatan Benalu Sebagai Agen Anti kanker. researchgat. net.

Intan, P., Lestari, T. and Sani, Y., 2017. Studi Histopatologi Pasca Pemberian Ekstrak Campuran Kulit Batang Pulai (*Alstonia scholaris L. R. Br.*) Dan Meniran (*Phyllanthus niruri L.*) pada mencit terinfeksi *Plasmodium berghei*.

Karney, W. W., and Tong, M. J. 1972. Malabsorption in *Plasmodium falciparum* malaria. *The American Journal of Tropical Medicine and Hygiene*. 21 :1–5

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JURNAL KEDOKTERAN FKUM SURABAYA
http://journal.um-surabaya.ac.id/index.php/qanunmedika

Katzung, B., Masters, S. and Trevor, A, (2012). Basic & clinical pharmacology. 12th ed. NewYork: McGraw-Hill Medical.

Kemenkes. (2013). Peraturan Menteri Kesehatan RI No. 5 Tahun 2013 Tentang Pedoman Tata Laksana Malaria. *Peraturan Menteri Kesehatan RI*, *128*, 5–62.

Noedl, H., et al. (2008). Evidence of Artemisinin- Resistant Malaria in Western Cambodia.New England Journal of Medicine,359(24), pp.2619-2620.

Nurcahyanti, O.,Firdaus, M. and Sundaryono, A., 2014. Uji Aktivitas Antimalaria Ekstrak Daun Baru Laut (*Thespesia Populnea (L.) Soland Ex Correa*) Pada Mus Musculus Terinfeksi *Plasmodium Berghei* dan karakterisasi hasil isolasinya. Repository.unib.ac.id.

Shimada, M., et al. 2019. Upper gastrointestinal pathophysiology due to mouse Plasmodium berghei ANKA infection. Tropical Medicine and Health. 47:18.

Sowunmi, A., et al. 2007 Effects of acute *Plasmodium falciparum* malaria on body weight in children in an endemic area. *Parasitology Research*. 101:343–349.

Suberu, J., et al. 2014. The effect of O-methylated flavonoids and other co-metabolites onthe crystallization and purification of artemisinin. *Journal of Biotechnology*, 171, pp.25-33.

Syamsudin, I., Dewi, R. and Marlina, S., 2008. Efek Anti plasmodium Ekstrak Kulit Batang asam Kandis (*Garcinia parvifolia Miq*) yang Diberikan Secara Intraperitoneal padaMencit yang Diinfeksi dengan *Plasmodium yoelii*., 8.

Tjahjandarie,, T. And Tanjung, M., 2015. Lead Compound Antimalaria Dan Antioksidan Senyawa Alkaloid, Flavonoid Dan Kumarin Dari *Limonia Accidisima L.*

Tjokroprawiro, A., et al. (2015). Buku Ajar Ilmu Penyakit Dalam. 2nd ed. Surabaya: Airlangga University Press (AUP), pp.715-720.

Wei, S., et al., 2015. Impact of chrysosplenetin on the pharmacokinetics and anti-malarial efficacy of artemisinin against *Plasmodium berghei* as well as in vitro CYP450enzymatic activities in rat liver microsome. *Malaria Journal*, 14(1).

WHO. (2018). World Malaria Report 2018. In *World Malaria report Geneva*: World Health Organization.

WHO. (2021). World Malaria Report 2021. In *World Malaria report Geneva*: World Health Organization.

Wilairatana, P., Meddings, J.B., Ho, M., Vannaphan, S., and Looareesuwan,S.1997. Increased gastrointestinal permeability in patients with Plasmodium falciparum malaria. *Clinical Infectious Diseases*. 24:430-435.

Windasari, T., Maslachah, L. and Rahardjo, A., 2016. Pengaruh paparan artemisinin berulang terhadap diameter pulpa putih dan indeks limpa pada mencit (*Mus musculus*) yang diinfeksi *plasmodium berghei*, 5(1), pp.8- 15.

Yulianti, R., Dahlia, A. and Ahmad, A. (2014). Penetapan kadar flavonoid total dari ekstrak etanolik daun benalu mangga (*Dendrophthoe pentandra L. Miq*). Jurnal. farmasi.umi.ac.

Zhou, Z., et al., 2020. Trichome And Artemisinin Regulator 2 positively regulates trichome development and artemisinin biosynthesis in Artemisia annua. *New Phytologist*,228(3),pp.932-945