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Anthelmintic Activity of Methanol Extract of *Bischofia javanica* (Euphorbiaceae) Leaves against *Hymenolepis diminuta* (Cestode) Infection in Rats

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Abstract

Bischofia javanica has been used in traditional medicine for the people of Napu, Central Sulawesi, Indonesia, to treat intestinal worm infections. This study investigates the activities of anthelmintic methanol extract of B. javanica (MEBJ) against H. diminuta worm infection in rats. Six groups of experimental animals (n=4) were infected with five cysticercoids each by oral inoculation. MEBJ was given in doses of 25, 50, 100, and 200 mg/kg for groups 2-5, while Mebendazole was given in doses of 5 mg/kg for group 6 (positive control). Group 1 was a negative control infected with H. diminuta but not treated. Activity anthelmintic MEBJ was determined by monitoring the number of eggs per gram (EPG) of H. diminuta worms in each group of experimental rats. The results showed that MEBJ had efficacy as an anthelmintic against H. diminuta worms. Experimental evidence obtained in animal models given MEBJ at various doses showed the number of eggs per gram (EPG) of H. diminuta worms was significantly reduced. The results of the Paired Sample T-Test showed that the pretreatment and posttreatment EPGs were significantly different. Thus, the results of this study provide a rationale that B. javanica has activity as an anthelmintic agent for H. diminuta.

Keywords: *Bischofia Javanica*, Anthelmintic Activity, Herbal Medicine, Soil-Transmitted Helminths

1. Introduction

Hymenolepis diminuta is a rodent parasite, and its distribution is found throughout the world (Weisse and Raszka, 1996). Infection in humans is relatively rare but can still occur through an intermediate host in the form of an arthropod that carries the cysticercoid worm (Safar, 2010) [29]. This is the reason why *H. diminuta* infection is rare in humans, and only some cases have been reported globally (Patamia *et al*, 2010) [25].

Arthropod groups, including rat fleas, mealybugs, cockroaches, and caterpillars, can serve as intermediate hosts suitable for developing cysticercoid larvae (Andreassen *et al*, 1999) [3]. Human infection is possible due to accidental ingestion of stored grain beetles (Tribolium spp.). It is estimated that more than 20 million people are infected with this tapeworm disease; the infection mainly attacks children under 15 years. This happens because of bad habits in hygiene (Brown, 1979) [6]. Transmission to humans will increase in communities in close contact with rats. H. diminuta infection in humans has a broad spectrum of symptoms, ranging from asymptomatic abdominal pain, irritability, pruritus, and eosinophilia (Ahmad *et al*, 2014) [1]. In children, it causes abdominal pain and defecation (Thakur, 2009) [31]. The treatment of H. diminuta infection in humans uses Praziquantel (PZQ), but drug resistance and side effects of synthetic drugs have attracted the focus of modern research on natural remedies and the increasing demand worldwide for drugs from natural sources (Kundu *et al*, 2012) [20].

According to the World Health Organization (WHO), more than 80% of the world's population depends on traditional medicine for their primary health care needs (Betge *et al.* 1997) [5], and WHO also states that people can use natural plant materials as alternative treatments for specific diseases on a local or regional scale (Tilburt and Kaptchuk, 2008) [32]. Various parts of medicinal plants such as seeds, roots, bark, fruits, leaves, flowers, or even whole plants are used as sources of traditional medicine (Chy *et al*, 2020) [10]. Some of the main phytochemical compounds found in plants can provide intrinsic defense benefits against pathogens (Mwonga *et al*, 2015) [23]. These phytochemicals have several direct or indirect therapeutic potentials and can be used to synthesize and develop modern drugs (Hasan and Hasan, 2012) [14].

Bischofia javanica is a kind of tree from the family Euphorbiaceae, large, deciduous, up to 35 m high, with the highest diameter up to 80 cm (Plaza *et al*, 2014) [26]. This plant is widely distributed in Bangladesh, India, Indonesia, China, the Philippines, and Vietnam (Chowdhury *et al*, 2020) [9]. In England, it is known as bishop wood, Java cedar Hindi (Bhillar, paniala, kotsemla), Japanese (Akagi), and Vietnam (nhoi)(Chowdhury *et al*, 2020) [9], and in Indonesia, this plant is known as

pepolo. There have been many studies on the benefits of the *B. javanica* plant; among others, it can be used as an antileukemic, anti-inflammatory, antimicrobial, anti-allergic, anthelmintic, treat burns, relieve diarrhea, and is beneficial for hair growth (Seed leaflet, 2012) [30]. In addition, the results of other studies show that *B. javanica* has intense antiparasitic activity (Alen *et al*, 2000) [2] and has antimicrobial activity (Khan *et al*, 2001) [19].

The main ingredients in *B. javanica* are tannins, amyrins, betulinic acid, friedelan-3α-ol, epifriedelinol, friedelin, luteolin, and glucosides, quercetin, beta-sitosterol, stigmasterol, ursolic acid (Gupta *et al*, 1988; Whistler, 1991) [13, 35]. In addition, *B. javanica* leaves contain compounds, among others, flavonoids, phenolics, saponins, steroids, alkaloids, and tannins. Ihwan *et al*, 2018) [17]. and contains protein (18.69%), carbohydrates (18.91%), stearic acid (3.89%), linoleic acid (56.76%), palmitic acid (12.28%), fiber (5.32 %), calcium, potassium, sodium, magnesium, vitamin C, elagic acid (8-10%) (Rajbongshi *et al*, 2014) [27]. Considering the use of *B. javanica* as an anthelmintic agent in traditional medicine systems in the Napu community, Central Sulawesi, Indonesia, this study was conducted to investigate the anthelmintic activity of the methanol extract of *Bischofia javanica* (Euphorbiaceae) leaves against infection with *Hymenolepis diminuta* (cestodes) in rats.

2. Method

Preparation of plant materials and manufacture of extracts

B. javanica leaves were collected from the village of Napu, Poso Regency, Central Sulawesi, Indonesia, and identified by plant taxonomists at the Biology Laboratory of the Faculty of Teacher Training and Education at Tadulako University. The leaves that have been cleaned of dirt are air-dried and then powdered for extraction using methanol in a Soxhlet extractor at 40°C. The resulting suspension was poured into removing the remainder, and the filtrate was further concentrated in a rotary evaporator at reduced temperature and pressure to remove the solvent. The percentage yield (w/w) of crude extract was 7.056%. Extracts were stored in plastic bottles at 8°C until use (Yadav and Tangpu, 2009) [36].

Experimental Animals

The animals used were male and female rats (*Rattus norvegicus*) Wistar strain aged 10-12 weeks with a 200-250grams bodyweight, bred in the Biology Laboratory of the Faculty of Education Tadulako University. All animals were acclimatized for two weeks under laboratory conditions and given food and drinking water according to standards on an ad libitum basis. Stool samples of the experimental animals were checked daily to ensure that they were not infected with intestinal worms. All experimental animal protocols in this study were approved by the Committee Experimental Animal Ethics, Tadulako University.

Administration of Standard Drugs to Experimental Animals

The standard drug used in this study was Mebendazole 500 (Vermox), Taisho Pharmaceutical Manufacturing. The plant extract and mebendazole solution were prepared in 0.9% phosphate buffer salt solution at pH 7.3 before being administered to experimental animals (Yadav and Tangpu, 2009) [36].

How to Infect Rats with *H. diminuta* worms and Administration of MEBJ

Six groups of animals (n = 4) were used in this experiment. Each animal was infected by oral inoculation with five cysticercoids obtained from the flour beetle (*Tribolium confusum*) as an intermediate host. The infection in flour beetles was carried out by means of a gravid tapeworm segment being lightly scratched on filter paper in a petri dish, and the beetles were allowed to eat the flour for 72 hours. These beetles were then reared at room temperature for 12-14 days to develop cysticercoid larvae (Yadav & Tangpu, 2011). Cysticercoid was collected by dissecting the beetle and inoculated into uninfected mice to initiate infection. Mice that had been inoculated with *H. diminuta* were kept in separate cages. MEBJ was given in 25, 50, 100, and 200 mg/kg doses for groups 2-5, while Mebendazole was given in 5 mg/kg doses for group 6 (positive control). Group 1 was a negative control infected with H. diminuta but not treated. All MEBJ and Mebendazole treatments were administered on day 12 postinoculation of the cysticercoids. On the 20th day post-infection, 1g of fresh feces was collected from each rat cage in control and treated groups to determine the number of eggs per gram (EPG).

How to Calculate the Number of Eggs of Hymenolepis diminuta

Counting worm eggs using the Modified Mc Master Technique (Chandrawathani *et al*, 2015) [7] was carried out before and after treatment of *H. diminuta*-infected rats with different MEBJ doses. To get the EPG value, eggs of H. diminuta worms were calculated using the following formula: EPG = number of eggs counted × 100 (Chandrawathani *et al*, 2015) [7].

Statistic analysis

Data on the number of worm eggs were expressed as the mean (Mean ± SEM) of the experiments and analyzed using IBM SPSS version 25. The effect of MEBJ on experimental rats infected with *H. diminuta* was statistically analyzed using ANOVA with One Way ANOVA (Analysis of Variance) with a 95% confidence level and comparing the treatment group and the control group followed by Duncan's Post Hoc test. To determine the EPG before administering MEBJ (Pretreatment) and after giving MEBJ (Posttreatment), a Paired Sample T-Test was performed.

3. Results

Table 1: The number of eggs per gram (EPG) of *H. diminuta* in mice (n = 4 in each group) on day 11 postinoculation of cysticercoids.

Group	EPG (Mean±SEM) Day 11
Group 1	3925.00 ± 85.391
Group 2	3825.00 ± 170.171
Group 3	4125.00 ± 85.391
Group 4	3950.00 ± 119,024
Group 5	4025.00 ± 165.202
Group 6	3875.00 ± 125.000

Data on postinoculation of cysticercoids on day 11 (Pretreatment) showed the number of worm eggs per gram

(EPG) was relatively high (Table 1). Based on these data, the group of rats divided into six groups (n=4) had an EPG range of 3500-4400 and an average EPG of 3954.17.

Table 2: MEBJ anthelmintic activity on number of eggs per gram (EPG) of *H. diminuta* in rats (n = 4 in each group) at day 20 postinoculation of cysticercoids

Group	EPG (Mean±SEM) Days 20	Percentage reduction in EPG count
negative control	5000.00 ± 219.848a	-
MEBJ 25 mg/kg	3875.00 ± 213.600b	-22.50
MEBJ 50 mg/kg	3600.00 ± 108.012b	-28.00
MEBJ 100 mg/kg	1900.00 ± 108.012c	-62.00
MEBJ 200 mg/kg	1125.00 ± 85.391d	-77.50
Positive Control (Mebendazole)	425.00 ± 47.871d	-91.50

a, b, c, d Post Hoc Duncan test(P<0.05). The same letter in one column between groups shows no significant difference.

In this study, the effect of MEBJ on *H. diminuta* infection was obtained that the extract had a relatively high level of efficacy (p<0.05) against the Number of EPG *H. diminuta* worms, MEBJ at a dose of 200 mg/kg, given for nine days, showed a 77.50% reduction in the amount of EPG, compared to the control group. In comparison, the reference drug mebendazole, administered at a dose of 5 mg/kg for the same duration, showed a 91.50% reduction in the amount of EPG (Table 2). The results of statistical tests (ANOVA) showed the effect of MEBJ on *H. diminuta* infection in rats monitored from the amount of EPG (Table 2). The EPG value of the group of animals treated with MEBJ was significantly reduced as the dose was increased.

The results of Duncan's Post-Hoc test showed that the administration of MEBJ at a dose of 25 mg/kg to a dose of 200 mg/kg and positive control (Mebendazole) for nine days could significantly reduce the number of eggs per gram (EPG) of *H. diminuta* (p<0.05). When compared with negative controls. Doses of 25 and 50 mg/kg had the same efficacy, but MEBJ at doses of 100 mg/kg and 200 mg/kg differed significantly from MEBJ at 25 mg/kg and 50 mg/kg doses. There was a significant difference between the 100 mg/kg dose and the 200 mg/kg dose, but the MEBJ dose of 200 mg/kg with the positive control was not significantly different (Table 2). The decrease in EPG H diminuta in the group of rats given MEBJ at a dose of 200 mg/kg showed a reasonably high decrease in EPG compared to negative control and other doses, which reached 77.84 percent (Fig 1). In comparison, the reference drug Mebendazole, which was given at a dose of 5 mg/kg with the exact duration of administration as other treatments, showed a significant decrease in EPG amount (p<0.05). The reduction in the amount of EPG reached 91.63%.

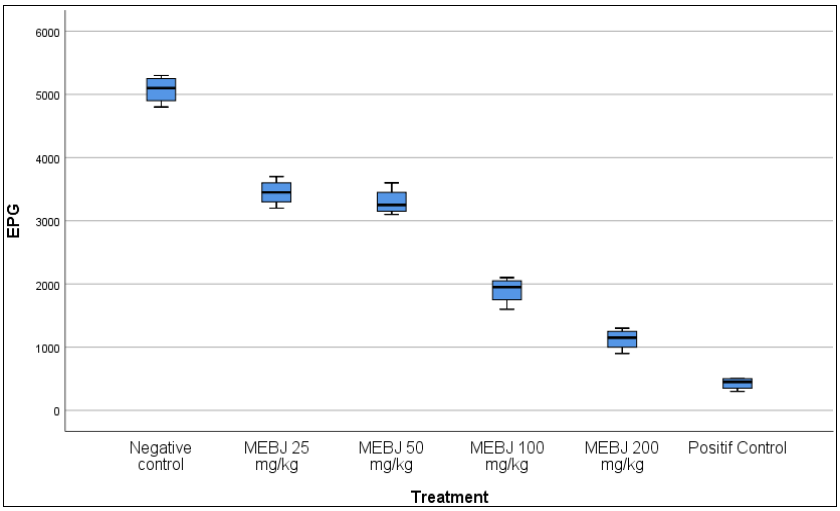

Fig 1: Decrease number of eggs per gram (EPG) of *H. diminuta* in rats (n = 4 in each group) on day 20 after administration of MEBJ and Mebendazole

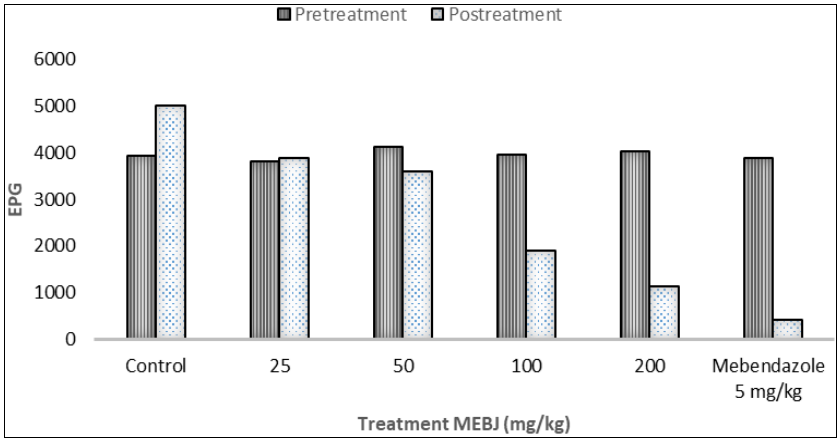

Fig 2: Comparison of MEBJ pretreatment and posttreatment EPG

Based on the results of the Paired Sample T-Test before and after administration of MEBJ and Mebendazole, it showed a sig value (2-tailed) of 0.001 < 0.05 thus, it can be concluded that there is a difference in the average EPG of pretreatment and posttreatment, which means that after administration of MEBJ the amount of EPG *H. diminuta* decreased significantly (Fig 2).

4. Discussion

This study was conducted to determine the anthelmintic efficacy of MEBJ using an experimental model of *H. diminuta*, which was infected in white rats. The use of animals as models in this study has been widely carried out to evaluate the efficacy of several anticestodal agents (Ghaffar, 2011 [12]; Yadaf and Tangfu, 2012). One of the criteria used to assess the anthelmintic efficacy of plants is reducing the amount of EPG (Lateef *et al*, 2003 [22]; Yadaf and Tangfu, 2012). The results obtained showed that MEBJ with various tested doses had efficacy ($p<0.05$) against EPG *H. diminuta* (Table 2).

MEBJ administration from day 11 to day 20 showed a significant decrease in the amount of EPG at all doses compared to a negative control. The group of mice given MEBJ 200 mg/kg showed a minimum reduction in the number of eggs per gram (EPG) of H. diminuta worms compared to the other treatment groups. However, MEBJ 200 mg/kg activity was still lower than the group of rats given Mebendazole. This difference can be explained that plant extracts have active ingredients with small concentrations while synthetic anthelmintics are chemical compounds that have been isolated in pure form (Rates, 2001) [28]. Lacey (1990) [21] explained that Mebendazole acts by inhibiting the production of microtubules by binding to the colchicine binding site of -tubulin and thereby blocking the polymerization of tubulin dimers in parasitic intestinal cells. As a result, glucose uptake and the digestive and reproductive abilities of the parasite are impaired, resulting in immobilization, inhibition of egg production, and death of the worm.

Researchers speculated that the anthelmintic efficacy of MEBJ in reducing the number of eggs per gram (EPG) of H. diminuta was caused by the presence of secondary metabolites, namely ethanol, flavonoids, phenolics, saponins, steroids, alkaloids, and tannins (Ihwan *et al*, 2018) [17] and also some triterpenoids and phenolics such as betulinic acid, ursonic acid, -amyrine, chrysoeriol, quercetin (Wada and Tanaka, 2005; Gupta, 1988) [33, 13]. Chhetri *et al*. (2017) [8] reported that the main chemical component found in *B. javanica* is tannin. The tannin content in *B. javanica* leaf extract is very high, namely 22.36 mg/100g dry, and it is known that this component has anthelmintic activity because it can bind free protein in the digestive tract of the host animal and cause death in worms (Jain *et al*, 2001; Chhetri *et al*, 2017 [8]) and interfere with energy formation in worm parasites by releasing oxidative phosphorylation (Athanasiadou *et al*, 2001). The experiments conducted by Novobilsky *et al*. (2011) [24] showed that the tannins contained in plants could also control gastrointestinal nematodes. Enwerem *et al*. (2001) [11] investigated the anthelmintic activity of methanol, hexane, and ethyl acetate extracts from the bark of *Berlina grandiflora*. The ethyl acetate extract was found to be the most active. Betulinic acid isolated from the ethyl acetate fraction at 100 and 500 ppm showed stronger anthelmintic activity than piperazine.

Besides having anthelminthic properties, bioactive compounds found in plants also have beneficial effects on animal health and production (Hoste *et al*, 2006) [15] and reduced host infection rates (Hoste *et al*, 2012) [16]. Medicinal plants have a promising future because they are considered a rich source of materials used in the development and synthesis of drugs. For this reason, it seems that further research is needed to evaluate the various ingredients found in the *B. javanica* plant for their efficacy as anthelmintics.

5. Conclusion

In conclusion, our study showed that MEBJ had significant anthelmintic efficacy on the EGP count of *H. diminuta* worms. Experimental evidence obtained in animal models showed the Number of eggs per gram (EPG) *H. diminuta* decreased significantly with increasing dose. Thus, this can provide a rationale for using *B. javanica* plants as anthelmintic *H. diminuta*.

6. Conflict of Interests

In this study, the authors state that they do not have a conflict of interest with the writing team or other parties.

7. Acknowledgments

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