Comparative biochemical effects of seeds extract Cerbera manghas and leaves Carica papaya the vector of Aedes aegypti mosquitos

by Alkausyari Aziz

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Comparative biochemical effects of seeds extract *Cerbera manghas* and leaves *Carica papaya* the vector of *Aedes aegypti* mosquitos

Alkausyari Aziz*, R. Sahknan, Khayan Khayan*** and Slamet Wradoyo*****

Poltekkes Kemenkes Riau, Pekanbaru, Indonesia

ABSTRACT

The research aims to determine the toxicity of sea mango *(Cerbera mangas)* seeds extract and Papaya (*Carica papaya)* leaves in controlling the vector of *Aedes aegypti* mosquitos. The experiment was conducted with 600 adult *Aedes aegypti* mosquitos being 3-5 days old. Mortality was recorded 24 h post-treatment, while spray effect toxicity of adult mosquitoes was recorded at 3 min intervals for 20 min. The value of LC_{50} sea mango seeds extract got 1.995% (19.950 ppm) and LC_{95} of 23.659 (236.590 ppm), while that of the papaya leaves was 3.168% (31.680 ppm) in 100 ml of distilled water and 122.202% (1222.020 ppm) in 100 ml distilled water, respectively. The sea mango seeds extract showed a significant value of 0.001 ($p < 0.05$). Amongst two groups substantial differences in toxicity were observed besides there were significantly differences between each concentration of sea mango seeds extract toward *Aedes aegypti* mosquitos' death.

Key words : *Aedes aegypti*, biochemical insecticides, *Carica papaya*, *Cerbera manghas*.

INTRODUCTION

Mosquitoes are vectors of many tropical and subtropical pathogens that may cause severe health problems in countries where they are endemic. The mosquito, *Aedes* (Stegomyia) *aegypti* (Linnaeus, 1762), is an essential vector for transmitting life-threatening human diseases like dengue, chikungunya, Zika, and yellow fever in tropical and subtropical regions worldwide (Knudsen and Slooff, 1992; Intirach *et al*., 2019). In several parts of the world, it has been reported that *Aedes aegypti* has been resistant toward several classes of insecticide. In 2001, Brazil said that *Aedes aegypti* had been resistant toward Temephos (Braga *et al*., 2004). The same thing happens in Thailand who reported that *Aedes aegypti* have been resistant toward Permethrin and Temephos. However, they are still susceptible toward Malathion (Brengues *et al*., 2003) report that *Aedes aegypti* from Semarang has been resistant 296 times toward Permethrin. Resistance cases of *Aedes aegypti* toward Pyrethroid, and the resistance mechanism that occurred are also reported by stating that *Aedes aegypti* from Bandung has been resistant 79.3 times toward Permethrin and that from Palembang have been resistant 23.7 times toward Deltamethrin (Ahmad *et al*., 2007). A concern that Aedes aegypti in Indonesia has been resistant toward Malathion and Temephos is an entirely reasonable thing because those two insecticides have been used in many places in Indonesia for more than 32 years.

Mosquitoes represent a huge threat for lives and livelihoods of millions of people worldwide (Jensen and Mehlhorn, 2009) since they act as vectors for important pathogens, including malaria, yellow fever, dengue and West Nile (Benedict *et al*., 2007; Paupy *et al*., 2009). In this scenario, vector control is a crucial prevention tool. Culicidae larvae are usually targeted using organophosphates and insect growth regulators. Indoor residual spraying and insecticide-treated bed nets are also employed for reducing transmission of malaria in tropical countries. However, these chemicals have negative effects on human health and/or the environment and induce resistance in many mosquito species (Hemingway and Ranson, 2000; Lees *et al*., 2014).

Classic control strategies have traditionally focused on killing mosquitoes using a variety of chemical (i.e., organophosphates, carbamates, pyrethroids, and insect growth regulators) and microbial (i.e., mainly an endotoxin from *Bacillus thuringiensis* var. *israelensis*, which is currently the most used product in European countries) pesticides (Benelli, 2015). This has been often coupled with

*Corresponding author's E-mail : alkausyari@pkr.ac.id
**Department of Nursing, Poltekkes Kemenkes Riau, Pekanbaru, Indonesia
***Poltekkes Kemenkes Banten, Serang, Indonesia

the reduction or removal of mosquito breeding sites, even on large-scale, as well as to with the employ of personal mosquito repellents (Amer and Mehlhorn, 2006a, 2006b). However, the overuse of chemical pesticides, targeting both mosquito adults and young instars, has led to important detrimental consequences on human health and the environment, as well as to the development of pesticide resistance in targeted species (Hemingway and Ranson, 2000; Naqqash *et al.*, 2016).

Management of mosquito vectors by applying appropriate chemical compounds such as larvicides, adulticides, attractants, deterrents, and repellents is an essential element to minimize disease transmission (Badolo *et al.*, 2004; Intirach *et al.*, 2019). At least four main classes of synthetic insecticides; namely organochlorines (exclusively DDT), organophosphates, carbamates, and pyrethroids have been in use over decades in vector control programs. In addition to low mammalian toxicity, synthetic pyrethroids have become the most popular and prevalent active ingredients in public health vector control programs, due to their high invertebrate potency at low levels, resulting in rapid immobilization ('knockdown') and killing of mosquitoes (Zaim *et al.*, 2000; Chareonviriyaphap *et al.*, 2013).

Female mosquitoes are the major vector to transmit diseases causing serious health problems among people living in developing countries of the tropical and subtropical zones (Dharmagadda *et al.*, 2005). The most common approach to vector-borne disease is by chemical control, mostly through the use of insecticides (Nyamador *et al.*, 2010). Larviciding is an effective tool to decrease mosquito populations before they emerge as adults (Govindarajan and Karuppannan, 2011). The chemical method is an effective weapon for quick and easy use because such chemicals, even in smaller quantities, are sufficient for the control of a large population of mosquitoes. Although synthetic organic insecticides are very effective, they are ecologically unsound and have many bad impacts, resulting in ecological hazards (Marimuthu, 2010). This would be highly dangerous for the environment and there are higher chances of developing resistance in insects and affecting the non target organisms (Kweka *et al.*, 2011; Phasomkusolsil and Soonwera, 2011).

Although synthetic substances that dramatically reduce the risk of vector-borne diseases have been documented, the overuse and misuse of conventional chemicals, for example, pyrethroids and other insecticides, have led to mosquito resistance, which threatens the potentiality of vector control (Grieco *et al.*, 2007). A recommended approach for monitoring and managing insecticide resistance in mosquito populations is to search for alternative interventions to restrain or reduce the evolution of further resistance as well as preserve the efficiency of existing insecticides (Intirach *et al.*, 2019). The use of biopesticides is encouraged as a promising economic and eco-friendly strategy for fighting the resistance problem(Chansang *et al.*, 2018; Tong and Bloomquist, 2013).

Various types of herbs have been known potentially as pesticide plants because they contain bioactive compounds include saponins, tannins, alkaloids, alkenyl phenols, flavonoids, and terpenoids. Bintaro (Cerbera mangas) was one of them that proposed in this research. Cerbera mangas extract feed inhibited the growth and development of *Spodoptera litura* F at a concentration of 2%. While concentration of 0.5%, 1%, 1.5% and 2% might also inhibit the formation of the cocoon (Purwani *et al.*, 2017). The chemical substances are as follows: steroid, triterpenoid, saponin, and alkaloid. Alkaloid consists of cerberin (0.6%), cerebroside, neerifolin, and the vain. The alkaloid compound has toxic, repellent, and antifeedant properties on insects, while saponin has the property like dissolved soap in the water leading to the decline of digestive enzymes and the inhibition of food absorption (Utami, n.d.).

Carica papaya belongs to the family of Caricaceae, and several species of Caricaceae have been used as a remedy against a variety of diseases (Mello *et al.*, 2008; Munoz *et al.*, 2000). Originally derived from the southern part of Mexico, Carica. Papaya is a perennial plant, and it is presently distributed over the whole tropical area. In particular, Carica papaya fruit circulates widely, and it is accepted as food or as a quasi drug. Many scientific investigations have been conducted to evaluate the biological activities of various parts of Carica papaya, including fruits, shoots, leaves, rinds, seeds, roots, or latex. The leaves of papaya have been shown to contain many active components that can increase the total antioxidant power in the blood and reduce lipid peroxidation level, such as papain, chymopapain, cystatin, à-tocopherol, ascorbic acid, flavonoids, cyanogenic glucosides, and glucosinolates (Seigler *et al.*, 2002). Many researchers have reported on the effectiveness of plant extracts or essential oils against mosquito larvae (Govindarajan, 2009; Rawani *et al.*, 2009; Mehlhorn *et al.*, 2005) reported that the leaf methanol, benzene, and acetone extracts of Cassia fistula were studied for the larvicidal, ovicidal, and repellent activities against *Aedes aegypti*. Daniella Oliveri is traditionally used to reduce the number of mosquitoes indoors at night.

So far, the influence of sea mango seeds (Cerbera mangas) and papaya leaves (Carica papaya) extracted with ethanol solvent for adult *Aedes aegypti* mosquitoes have not been conducted. Therefore, it is necessary to conduct further research on the toxicity of sea mango seeds and papaya leaves extracted with ethanol toward *Aedes aegypti* mosquitoes on a laboratory scale.

MATERIALS AND METHODS

Research design : The type of this research is the post-test only controlled group design with 2 controls. This research used concentration of sea mango seeds (Cerbera manghas) and papaya leaves (Carica papaya) in 4 levels (2.5%, 5%, 10% and 20%). Preliminary tests were conducted with 6 treatments and 2 controls in 3 repetitions. Further test were conducted with 8 treatments and 2 controls in 3 repetitions. The subjects used in this research were 3-5 days old female/male adult mosquitoes which live and actively move obtained from the Entomology Laboratory of Health Research and Development Center of Disease Vector and Reservoir in Salatiga, Central Java. The research method of insecticides was done by spraying the extracts of sea mango seeds (Cerbera manghas) and papaya leaves (Carica papaya) toward *Aedes aegypti* mosquitoes.

Data collection technique : The tools used in this study were square Glass Chamber in size of 70 √ 70 √ 70 cm^3, stopwatch, measuring cylinder, sprayer (mini compressor with a particle size of 0.3 MM), aspirator, pipette, indoor thermometer, and hygrometer. Cerbera manghas (Fig. 1a) and leaves Carica papaya (Fig. 1b) plant were collected from the Riau province. Specimens were deposited in the laboratory Riau Health Polytechnic.

The materials used in this study were the extracts of sea mango seeds (Cerbera manghas) and papaya leaves (Carica papaya) in 4 levels (2.5%, 5%, 10% and 20%), the solvent ingredient namely ethanol 96%, sterile aqua des, adult *Aedes aegypti* mosquitoes which were alive and actively moving. Glass chamber was cleaned in order not to be contaminated by other insecticides, by (1) the inside of the glass chamber was washed thoroughly with a wet rag containing detergent liquid, (2) glass chamber was rinsed with wet rag without detergent, and (3) glass chamber was dried with wet rag without detergent then it was stretched for one hour.

Fig. 1. (a) Cerbera manghas, (b) Carica papaya.

20 *Aedes aegypti* mosquitoes were released in the glass chamber, and the room temperature of the glass chamber was recorded. The extract of sea mango seeds (Cerbera mangas) and papaya leaves (Carica papaya) was sprayed at a determined concentration in which the amount of spray was suitable with the application result of spray levels (Y times of rush). The control was sprayed with the solvent (aqua des) as much as Y times of rush. The sprayer, which had been filled with the extracts of sea mango seeds (Cerbera mangas) and papaya leaves (Carica papaya), is weighed; for example, is A gram. Sprayed the sprayer maximally ten times. The sprayer and the extracts of sea mango seeds (Cerbera mangas) and papaya leaves (Carica papaya) were re-weighed (B gram). The spraying was conducted and repeated three times (C gram and D gram), then the weight difference for each repetition was averaged. It was observed for 20 min, the number of fainting or dying mosquitoes every specified period of time were counted and recorded. All the mosquitoes were transferred with an aspirator into a paper cup and stored in a holding for 24 h. The mortality rate of the mosquitoes was calculated after 24 h. The calculation results were inserted in the table. If the mosquitoes' mortality rate in the negative control group were less than 5%, it would be ignored. Still, if the mosquitoes' mortality rate in the negative control group was more than 20%, the test must be repeated. Whereas, if the mortality rate of the mosquitoes in the negative control group was 5-20%, so the Abot formula was conducted to calculate the percentage of mosquitoes' mortality rate in each concentration as follows:

RESULTS AND DISCUSSION

The effect of insecticides on the mortality of mosquitoes was determined by the 24 h of mortality rate after contacting to the walls sprayed with insecticides based on the standard testing carried out by World Health Organization (Organization

2006). The result of the analysis probit LC_{50} and LC_{95} showed that the mortality could reach 50%, 90%, and 95% in *Aedes aegypti* mosquitos which was on the concentration of 3.168% (31.680 ppm) in distilled water, 54.540% (545.400 ppm) in 100 ml distilled water, and 122.202% (1222.020 ppm) in 100 ml distilled water at the 24th h after the treatment (Tables 1-2). The measurement of room temperature at the beginning and the end of the research on average was 270C. The air humidity at the beginning and the end of research showed the average number of 80%.

Based on the one way ANOVA test result on sea mango seeds, it was discovered that the existence of meaningful differences. Therefore, the Least Significance Difference (LSD) test was done. Based on the result of the LSD test, it could be found that the two groups had significant differences, namely between the group with a concentration of 2.5% and 10% and the group with a concentration of 2.5% and 20%. On the other groups, between 2.5% and 5%, the difference was not significant because of the value of $p > 0.05$ (Fig. 2). The biological activity of the natural ingredients could influence the behavior of insect-like feeding inhibitor, feeding refusal, or spawn activity inhibitor. Besides that, it also could influence the physiological activity of insects such as the inhibitor of growth, ovicidal,

Table 1. Knockdown (fainted) of *Aedes aegypti* mosquito in the treatment of bintaro fruit seed extract and papaya leaves.

Ingredient	Concentration (%)	Total	*Knockdown* (minute)						Mortality (hour)		
			1	3	8	10	15	20	24	Average	%
Sea mango seeds	2,5	60	0	0	0	0	0	0	35	11.67	58.33
	5	60	0	0	0	0	0	0	42	14.00	70.00
	10	60	0	0	0	0	0	0	51	17.00	85.00
	20	60	0	0	0	0	0	0	57	19.00	95.00
Papaya leaves	2,5	60	0	0	0	0	0	0	27	9.00	45.00
	5	60	0	0	0	0	0	0	36	12.00	60.00
	10	60	0	0	0	0	0	0	41	13.67	68.33
	20	60	0	0	0	0	0	0	48	16.00	80.00
Control (-)		60	0	0	0	0	0	0	0	0.00	0.00
Control (+)		60	40	60	60	60	60	60	60	20.00	100

The test results in table 1 showed that sea mango seeds seed extract spray, papaya leaves, and on negative control (distilled water) the number of mosquitoes that knockdown from minute 1 to minute 20 were not found.

Table 2. Mortality of mosquito *Aedes aegypti* in the extract treatment of sea mango seeds and papaya leaves.

Material	Concentration (%)	Total	Number of dead mosquitoes in replication						Mortality (hour)		
			1	%	2	%	3	%	24	Average	%
Sea mango seeds	2.5	20	10	50	12	60	13	65	35	11.67	58.33
	5	20	13	65	14	70	15	75	42	14,00	70.00
	10	20	17	85	16	80	18	90	51	17.00	85.00
	20	20	20	100	17	85	20	100	57	19.00	95.00
Papaya leaves	2.5	20	7	35	9	45	11	55	27	9.00	45.00
	5	20	7	35	15	75	14	70	36	12.00	60.00
	10	20	9	45	17	85	15	75	41	13.67	68.33
	20	20	17	85	16	80	15	75	48	16.00	80.00
Control (-)		20	0	0	0	0	0	0	0	0.00	0.00
Control (+)		20	20	100	20	100	20	100	60	20.00	100

In every increase of concentration (2.5%, 5%, 10% and 20%), it would be followed by an increase in average mortality from both extracts. The death of mosquitoes on the negative control treatment did not occur, whereas in the positive control the death of *Aedes aegypti* mosquitos was always 100%.

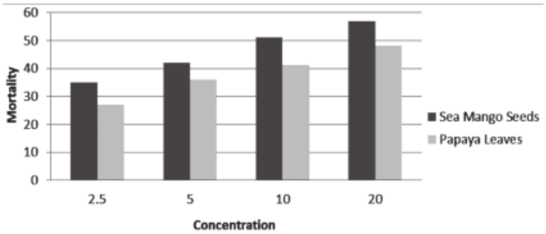

Fig. 2. The mortility of mosquito toward both sea mango seeds and carica papaya leaf.

The extract with different concentrations would have a different effect on the death of the mosquitoes. The higher concentration of the extract was, the higher number of death on the mosquito would be. The data was presented in Fig 2.

larvicidal, or death. The effect of insecticide on the death of *Aedes aegypti* mosquitos was determined by the mortality rate of 24 hours after the exposure following the standardized test done by the World Health Organization (Organization, 2006) (Tables 3-5).

The temperature and humidity were important factors in the survival of mosquitos. According to the research (Simoy *et al.*, 2015), studying the temperature condition toward population dynamics of *Aedes aegypti* in every growth phase, adult mosquitos phase could live at the temperature between 110C and 350C. Under the temperature of 110C, the activity of mosquitos would be lowered. If it was over 350C, the lifetime of mosquitos would be shorter. While the optimal humidity required for the growth of mosquitos was between 60% and 80%. The temperature and humidity in the research were still in optimum condition, which supported the survival of mosquitos, so the occurrence of mosquitos' death was caused by the existence of insecticide exposure toward the mosquitos. The concentration enhancement of sea mango seeds extract and papaya leaves caused the increase of death from the 1st hour until the 24th hours. The contents of the secondary metabolite compound existing in sea mango seeds extract and papaya leaves could cause an increase in the number of mosquitos' death in 24 hours observation.

Based on the result of the study, sea mango seed extract and papaya leaves have a different level of insecticide activity. Sea mango seed extract has more potential to kill mosquitoes compared to papaya leaves extract. The different ability in insecticide activity is probably due to the difference in the concentration of metabolic compound as well as the presence of other compounds contained in sea mango seeds causing the death of mosquitoes. Sea mango also contained steroids (Kuddus *et al.*, 2011). The ripe and fresh core of sea mango contains cerberin alkaloids, a substance that tastes bitter and poisonous. Sea mango bark also contains alkaloid compounds that function as antifungal

Table 3. Lethal concentration and confidence limits value of sea mango seeds extract against *Aedes aegypti* after 24 hours.

LC	Concentration	95% confidence limits for concentration	
		Lower	Upper
LC_{50}	1.995	0.953	2.906
LC_{90}	13.701	9.646	26.759
LC_{95}	23.659	14.784	63.152

The obtained lethal concentration value in sea mango seed LC_{50} was 1.995% (19.950 ppm) in 100 ml of distilled water, LC_{90} 13.701% (137.010 ppm) in 100 ml of distilled water and LC_{95} 23 659% (236, 590 ppm) in 100 ml of distilled water.

Table 4. Lethal concentration and confidence limits value of papaya leaf extract against *Aedes aegypti* after 24 hours.

LC	Concentration	95% confidence limits for concentration	
		Lower	Upper
LC_{50}	3.168	1.356	4.733
LC_{90}	54.540	25.680	420.312
LC_{95}	122.202	45.010	1969.337

Table 5: Test result one way ANOVA sea mango seeds and carica papaya leaves.

Extract		Sum of squares	df	Mean square	F	Sig.
Sea mango seeds	Between groups	94.250	3	31.417	17.136	0.001
	Within groups	14.667	8	1.833		
	Total	108.917	11			
Carica papaya leaves	Between groups	78.000	3	26.000	2.516	0.132
	Within groups	82.667	8	10.333		
	Total	160.667	11			

(Singh, Alsamarai and Syarhabil, 2012). In the sea mango seeds, six new types of cardenolide glycoside had been isolated, namely, 3β-O-(2'-O-acetyl-α-L-thevetosyl)-14β-hydroxy-7-en-5β-card-20(22)-genocide, (7,8-dehydrocereberin), 17β-neriifolin, deasil tahnginin, tanghinin, cerebral, and 2'-O-acetyl-cerleaside. Among those six substances, cerberin had the cardioxity potential (Cheenpracha *et al*., 2004).

Catherine was a monoacetyneriifolin compound (Gaillard *et al*., 2004; Chang *et al*., 2000). Cerberin also had toxic nature, so that it could cause anorexia in larvae (Dono *et al*., 2008; Intirach *et al*., 2019). Several substances were also found in sea mango, namely alkaloids, tannins, and saponins having antibacterial, cytotoxic nature and as central nervous system depressants because of the presence of two alkaloids and saponins (Ahmed *et al*., 2008). The data from the research result showed that the ethanol extract of sea mango seeds (Cerbera mangas) and papaya leaves (Carica papaya) had an insecticidal effect that could kill *Aedes aegypti* mosquitoes. The higher the concentration of ethanol extract of sea mango seeds and papaya leaves were, the higher the presentation of mosquito death would be.

The effect was caused by the components of the active compounds contained in papaya leaves, namely alkaloids, saponin, flavonoids, and the enzyme papain. The alkaloid compounds found in papaya leaves were campaign alkaloids. Alkaloid compounds worked by inhibiting the activity of the enzyme acetylcholinesterase, which affected the transmission of nerve impulses, causing the enzyme to undergo phosphorylation and became inactive. This would result in the inhibition of the degradation process of acetylcholine, so that acetylcholine accumulation occurred in the synaptic cleft. This condition caused transmission problems that could lead to impaired muscle coordination, convulsions, respiratory failure, and death (Chidozie and Adoga, 2014). The Papain enzyme was a proteolytic enzyme that plays a role in breaking down connective tissue and had a high capacity to hydrolyze exoskeleton proteins by breaking peptide bonds in proteins so that the protein would be broken off (Junkum *et al*., 2004).

Carica papaya contained bioactive compounds, namely alkaloids, saponin, phenolic, flavonoid, and tannin (Baskaran *et al*., 2012). Papaya leaves also had proteolytic activity because of the content of the enzyme papain they have. Alkaloids, terpenoids, phenolic, flavonoid, and tannin had the ability to inhibit microbes through various mechanisms. Based on the research conducted by (Vuong *et al*., 2015), it was shown that saponin was a bioactive compound mostly contained in papaya leaves extract. Other compounds such as tannin and steroid became the synergistic compounds in the larvicidal activity. Tannin was known to inhibit bacterial growth by damaging bacterial cells (Sulaiman *et al*., 2011). The secondary metabolite compound in the alkaloid group found in sea mango seed extract was cerberin. Cerberin was a toxic and repellent substance, and it causes anorexia in larvae (Dono *et al*., 2008).

Flavonoid acts as antimicrobial and antifungal, and it has cytotoxic effects on larvae (Andersen and Markham, 2005; Das and Das 2011). Saponin, as detergent-like materials, had the ability to damage cell membranes (Mert-Türk, 2006). Saponin could inhibit the action of the acetylcholinesterase enzyme so that there was an accumulation of acetylcholine, which caused damage to the delivery system of impulses to muscles leading to seizures and paralysis of the muscles. It also ended in death. Saponin also had the function of antifungal, antibacterial, antiviral, and antiprotozoal (Francis *et al*., 2002; Mert-Türk, 2006).

Tannin could suppress the feed consumption, body growth, and the survival abilities of insects. The component of tannin prevented insects from digesting the food since it bounded protein in digestive tracts, which were required by insects for growing. Therefore, the absorption of protein in the digestive tract was disturbed (Yunita *et al*., 2009). The clinical symptoms for individuals who tannin-poisoned including anorexia, depression, ulcer in the digestive tract. It depended on how much tannin entering the body (Frutos *et al*., 2004). The research result of (Utami, n.d.), mortality was a direct effect of plant bioactive substance in insects. Rapid mortality effects could be observed in insects with exposure to vegetal insecticide working as a nerve poison.

Plant-based phytochemicals and plant products are increasingly being used for their efficacy as biocontrol agents for the control of insecticide-resistant mosquitoes (Nathan *et al*., 2005). Biopesticides from plant origin are more effective on agricultural and medical pests (Nathan *et al*., 2005; Senthil *et al*., 2004). Nowadays, plant and microbial sources are increasingly used for vector control programs because they have been shown to have the potential to be effective, more target-specific than chemical insecticides, and ecofriendly (Nathan *et al*., 2006; Imelouane *et al*., 2009; Nathan *et al*., 2005).

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