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Potential Use of Papaya Flower Extract (*Carica papaya Linn*) for *Aedes Aegypti* Larvicide

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Abstract

Introduction: Temefos as larvicide to prevent dengue hemorrhagic fever is known to be resistant to *Aedes aegypti* larvae in several regions in Indonesia. Therefore, alternative larvicides are needed. Papaya plants are one of the alternative solutions as papaya flowers contain secondary metabolite compounds that can kill *Aedes aegypti* larvae. This study aimed to determine the potential of papaya flower extract to be an *Aedes aegypti* larvicide.

Methods : This study was a *true experimental study* with *posttest only control group design*, with 6 treatment groups namely 1%, 5%, 10%, 15%, and 20% extract concentrations (Experimental Group) and distilled water (Control Group). The experiment was repeated 4 times with testing time of 24 hours. A total 600 *Aedes aegypti* instar larvae III/IV were used. Larvae toxicity was analyzed using *Probit* Analysis to determine the value of *Lethal Concentration* (LC) and *Lethal Time* (LT) and *Kruskall-Wallis* test to determine the differences of larval deaths in each experimental group.

Results: Results showed that the highest and the lowest average larval mortality was at 20% concentration (25 larvae) and 1% concentration (14.75 larvae), respectively. LC_{95} and LC_{99} values were 4.84% and 10.39%, while LT_{95} values of five concentrations were 115.74, 24.24, 23.41, 25.24, and 16.55 hours and LT_{99} values of five concentrations were 241.95, 29.42, 26.20, 32.24, and 24.48 hours. There was a difference in the number of larval deaths after 24 hours treatment in the experimental group (*p-value* = 0.011).

Conclusion: Papaya flower extract has the potential to be an *Aedes aegypti* larvicide with 20% concentration as the optimum dose. However, phytochemical screening needs to be done to determine the dominant papaya flower compounds act as *Aedes aegypti* larvicides.

Keywords: Aedes aegypti, Papaya Flower extract, Larvicide, Lethal concentration, Lethal time.

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Introduction

Dengue hemorrhagic fever is one of public health problems in Indonesia. Dengue hemorrhagic fever is caused by the dengue virus and is transmitted through the bite of female *Aedes sp.* mosquitoes, with the *Aedes aegypti* mosquito as the main responsible vector.[1] The *A aegypti* mosquito as the main vector of dengue hemorrhagic fever transmission can be controlled in several ways, one of which is preventing mosquito breeding.[2] Prevention of mosquito breeding can be done in several ways, one of which is by chemical

means, which in Indonesia generally uses temefos (abate) as a larvicide.

The use of temefos in preventing mosquito breeding is indeed very beneficial if it used in the right way, dose, and frequency. Otherwise, if it is not used properly, larval resistance can be increased. Previous studies have shown that *Aedes aegypti* larvae have been resistant to temefos. A study by Mulyatno et al showed that *A aegypti* larvae from 12 sub-districts in Surabaya were resistant to temefos with a mortality rate within 24 hours from 22% to 60%.[3] Ikawati et al study also showed that *A aegypti* larvae from Demak, Klaten, and Banjarnegara districts were resistant to temefos with a mortality rate within 24 hours of 57.22% to 74.58%.[4] Hasmiwati et al research also showed that *A aegypti* larvae from Gunung Pangilundan and Jati villages were resistant to temefos with a mortality rate within 24 hours of 50% to 71.30%.[5] Thus, alternative larvicides are needed to replace the use of chemical larvicides (temefos). Alternative larvicides can be made by utilising natural materials such as plants to become natural larvicides. Papaya plant is a common plant that thrive in a tropical environment. Papaya plants are known to have several medicinal properties and based on several previous studies it is known that papaya plants, in this case papaya leaves, can be used as a natural larvicide for *A aegypti* larvae. Papaya leaves are known to contain secondary metabolite compounds such as: alkaloids, papain, tannins, saponins, and flavonoids, which with their respective roles can cause the death of *A aegypti* larvae.[6]

Research by Dhenge et al showed that papaya leaf extract in various doses or concentrations (5%, 10%, 15%, 20% and 25%) is effective larvicide for *A aegypti* instar larvae III/IV ($p<0.05$), where the dose or concentration of 25% is the most effective dose or concentration to kill larvae.[7] Payangka et al research also showed that papaya leaf extract in various doses or concentrations (0.5%, 1%, 1.5%, 2% and 2.5%) had an effect on the death of *A aegypti* instar larvae III, where the lowest effect was at a dose or concentration of 0.5%, namely 4% and the highest effect was at a dose or concentration of 2.5%, namely 85%.[8] Ramayanti and Febriani research also showed that papaya leaf extract in various doses or concentrations (0.25%, 0.5%, 0.75%, 1%, 1.25%, and 4%) had a larvicidal effect on *Aedes aegypti* larvae, where the dose or concentration of 4% was the dose or concentration that most effectively killed the larvae.[9]

According to research by Yogiraj et al and Ukpabi et al in Mukhaimin et al, it is known that papaya flowers also contain secondary metabolite compounds that are almost the same as papaya leaves, namely: alkaloids, flavonoids, saponins, and tannins.[10.11] Based on previous studies on the use of papaya leaves as *A aegypti* larvicides and supported by the results of Kumara literature review which showed that the secondary metabolite compounds with their respective roles can cause the death of *A aegypti* larvae leading to research in the use of papaya flowers as a natural larvicide for *A aegypti* larvae.[12] The selection of papaya flowers as the object of research is because papaya plants in the province of East Nusa Tenggara (NTT) are thriving, but in the community papaya flowers are not in use as much as other parts of papaya, because of its taste.

Methods

This study used a type of *true experimental* research with a *posttest only control group design*, using 6 treatment groups (distilled water as a control group, concentration of papaya flower extract of 1%, 5%, 10%, 15%, 20% as an experimental group) where each treatment underwent 4 replications with a testing time of 24 hours. This research was conducted at the Entomology Laboratory of the Sanitation Study Program, Polytechnic of the Ministry of Health Kupang. The experiments were conducted to investigate the function of papaya flower extract in various doses or concentrations, the optimum dose of, *Lethal Concentration* (LC), *Lethal Time* (LT) of deaths of *A aegypti* instar larvae III/IV.[13] The population in this study was *A aegypti* larvae instar III/IV obtained from the Entomology Laboratory of the Sanitation Study Program, Polytechnic of the Ministry of Health Kupang, while the sample in this

study were 600 *A aegypti* instar larvae III/IV. Data were collected through observation using observation sheet instrument. The data were analyzed using *Probit Analysis* to determine the value of *Lethal Concentration* (LC) and *Lethal Time* (LT) and *Kruskall-Wallis* test to determine the differences in the number of larval deaths in the experimental group with a significance level of $\alpha < 0.05$.

Results

Results of Papaya Flower Extract Preparation

Papaya flower extract in this study was made from papaya flowers obtained from the Kupang City area. A total of 1,200 grams of papaya flowers were used. The papaya flowers were then separated from the stalks and washed thoroughly, then dried in the sun and after drying it was mashed into papaya flower powder. The total of 140 grams papaya flower powder was obtained from 1,200 grams flowers. The papaya flower powder was then macerated with 70% ethanol with a ratio of papaya flower powder and 70% ethanol solution of 1: 10, with the maceration process lasting for 3x24 hours, where at every 1x24 hours the remaceration and filtration of the filtrate was carried out into a bottle, with a filtrate of 3,600 liters. The filtrate was then evaporated to obtain papaya flower extract which was then put into a bottle, with the result of 250 grams extract.

Mortality Results of A aegypti Instar Larvae III/IV After 24 Hours of Treatment

The results of the death of *Aedes aegypti* instar III/IV larvae after 24 hours of treatment using papaya flower extract with a dose or concentration of 1%, 5%, 10%, 15%, and 20% can be seen Table 1.

Table 1. Mortality Results of *A aegypti* Larvae After 24 Hours of Treatment Using Papaya Flower Extract in Various Doses

Doses or Concentrations	Number of Larvae per Replicate (Tails)	Number of Larval Deaths per Replicate (Tails)				Total Larval Mortality (Tails)	Average Larval Mortality (Tails)	Percentage of Larval Mortality (%)
		1	2	3	4			
Control (Aquades 100 ml)	25	0	0	0	0	0	0	0%
1%	25	18	15	10	16	59	14.75	59%
5%	25	25	25	22	24	96	24	96%
10%	25	25	25	25	24	99	24.75	99%
15%	25	25	25	25	24	99	24.75	99%
20%	25	25	25	25	25	100	25	100%

Table 1 shows that the dose or concentration with the highest number of deaths of *A aegypti* instar larvae III/IV after 24 hours of treatment is a dose or concentration of papaya flower extract 20% with a total death of 100 larvae with an average death of 25 larvae and a percentage of larval mortality of 100%. Meanwhile the dose or concentration with the lowest number of deaths of *A aegypti* larvae after 24 hours of treatment was a dose or concentration of control using 100 ml of distilled water with a total death of 0 larvae with an average death of 0 larvae and a percentage of larval mortality of 0%.

Table 1 shows that papaya flower extract has the potential as an *A aegypti* larvicide, especially at doses or concentrations of 5%, 10%, 15%, and 20% because the percentage value of larval mortality at the four doses or concentrations is ≥ 95%, then it is also known that a dose or concentration of 20% is the optimum dose or concentration of papaya flower extract as an *Aedes aegypti* larvicide in this study because a dose or concentration of 20% has the highest total larval mortality after 24 hours of treatment, namely 100 larvae with an average larval mortality of 25 larvae and a larval mortality percentage of 100%.

LC_{95}, LC_{99}, LT_{95}, and LT_{99} Values of Papaya Flower Extract as A aegypti Larvicide

The determination of the *Lethal Concentration* value in this case the LC_{95} and LC_{99} values and the determination of

the *Lethal Time* value in this case the LT_{95} and LT_{99} values were carried out using *Probit analysis*, with the results of the analysis which can be seen Table 2.**Table 2** shows that the LC_{95} value of 4.84 which can be interpreted that at a dose or concentration of 4.84% papaya flower extract within 24 hours of treatment can kill 95% of *A aegypti* larvae. Thus, it is also known that LC_{99} value of 10.39 can be interpreted at a dose or concentration of 10.39% papaya flower extract within 24 hours of treatment can kill 99% of *A aegypti* larvae.

Table 2. LC_{95} and LC_{99} values of Papaya flowers extracts as the larvaside of *A aegypti*

Lethal Concentration **(LC)**	**Estimated Concentration (%)**	**Lower Limit Concentration (%)**	**Upper Limit Concentration (%)**
LC_{95}	4.84	0.00	11.88
LC_{99}	10.39	0.28	20.50

Table 3 shows the LT_{95} and LT_{99} values of the 1%, 5%, 10%, 15%, and 20% doses or concentrations of papaya flower extract. The LT_{95} and LT_{99} values shown in the estimated time (hours) column can be interpreted as the time required for each dose or concentration of papaya flower extract to kill 95% and 99% of the larvae. **Table 3** shows that the dose or concentration of papaya flower extract at 20% has the lowest LT_{95} and LT_{99} values compared to other doses or concentrations of papaya flower extract, with an LT_{95} value of 16.55 which means that to kill 95% of *Aedes aegypti* instar III/IV larvae using papaya flower extract at a dose or concentration of 20% takes 16.55 hours, and the LT_{99} value of 24.48 which means that to kill 99% of *Aedes aegypti* instar III/IV larvae using papaya flower extract dose or concentration of 20% takes 24.48 hours.

Table 3. LT_{95} and LT_{99} Values of Papaya Flower Extract as *Aedes aegypti* Larvicide

Doses or Concentrations	**Estimated Time (Hours)**		**Lower Limit Time (Hours)**		**Upper Limit Time (Hours)**	
	LT_{95}	**LT_{99}**	**LT_{95}**	**LT_{99}**	**LT_{95}**	**LT_{99}**
1%	115.74	241.95	62.58	94.25	517.883.73	160.188.838.33
5%	24.24	29.42	21.81	25.54	28.93	38.41
10%	23.41	26.20	21.30	23.03	35.63	52.84
15%	25.24	32.24	20.46	24.60	6567	184.96
20%	16.55	24.48	-	-	-	-

Differences in the Number of Deaths of Aedes aegypti Larvae in the Experimental Group

Determination of the difference in the number of deaths of *Aedes aegypti* instar III/IV larvae after 24 hours of treatment in the experimental group or group treated using papaya flower extract in various doses or concentrations, namely doses or concentrations of 1%, 5%, 10%, 15%, and 20% was carried out using statistical tests, namely the *Kruskall-Wallis* test, with the results of the analysis which can be seen in **Table 4**.

Table 4. Differential Test Results of the Number of Deaths of *A aegypti* Larvae After 24 Hours of Treatment Using Papaya Flower Extract in Various Doses

Doses or Concentrations	***p-value***
1%	
5%	
10%	0.011
15%	
20%	

Table 4 shows that the *p-value* of the *Kruskal-Wallis* test is 0.011, the value of 0.011 <0.05 means that there is a difference in the number of deaths of *Aedes aegypti* instar III/IV larvae after 24 hours of treatment in the experimental

group or group treated using papaya flower extract in various doses or concentrations, namely doses or concentrations of 1%, 5%, 10%, 15%, and 20%.

As differences between concentration was observed, the differences between the number of deaths of *A aegypti* larvae after 24 hours of treatment in certain doses or concentrations was performed using the *Kruskal-Wallis* test, with the results of the analysis that can be seen in **Table 5**.

Table 5. Differential Test Results Between The Number of Deaths of *A aegypti* Larvae After 24 Hours of Treatment Using Papaya Flower Extract in Various Doses

Doses or Concentrations		*p-value*				
		1%	**5%**	**10%**	**15%**	**20%**
p-value	**1%**	**-**	0.020	0.018	0.018	0.014
	5%		**-**	0.405	0.405	0.131
	10%			**-**	1	0.317
	15%				**-**	0.317
	20%					**-**

Table 5 shows that there is a significant difference between the number of deaths of *A aegypti* larvae after 24 hours at a dose or concentration of 1% papaya flower extract with a dose or concentration of 5%, 10%, 15%, and 20% papaya flower extract due to the *p-value* obtained from the *Kruskal-Wallis* test < 0.05, which is 0.020, 0.018, 0.018, and 0.014 respectively.

Discussion

The results of the potential use of papaya flower extract for *A aegypti* larvicide showed that 4 out of 5 doses or concentrations of papaya flower extract had larvicidal effects. Based on the average percentage of mortality of *A aegypti* instar larvae III/IV during 24 hours of treatment at 4 doses or concentrations, 5%, 10%, 15%, and 20%, shows that the administration of papaya flower extract has the potential as a natural larvicide. This is because the average percentage of larval mortality at 4 doses or concentrations is at 96%, 99%, 99%, and 100%, respectively.[13] Previous research conducted by Dhenge et al using papaya leaves as a plant-based larvicide showed that papaya leaf extract was effective as a plant-based larvicide for *A aegypti* instar larvae III/IV.[7] Dhenge et al study used 5 doses or concentrations of papaya leaf extract, namely doses or concentrations of 5%, 10%, 15%, 20%, and 25%, with the results of the average percentage of mortality of *A aegypti* larvae during 24 hours of treatment of 38%, 47%, 51%, 59%, and 78%, respectively.[7] The doses or concentrations of extracts used in the study of Dhenge et al and this study are similar, with the doses or centration used in this study, 5%, 10%, 15%, and 20%. Although using the same dose or concentration, the average percentage of larval mortality in this study was greater than the study of Dhenge et al. The difference is thought to be due to differences in the amount of secondary metabolite content in papaya leaves and flowers, where differences in the amount of secondary metabolite content depend on environmental factors and internal factors of the plant itself. According to Febrianasari in Siregar, differences in the amount of secondary metabolite content are strongly influenced by environmental factors, plant age at harvest, and harvest time.[14] According to Siregar, temperature, light, and drought factors are environmental factors that can affect the amount of secondary metabolite content.[14] For example, according to Nur et al in Siregar, adequate sun exposure can increase the process of making secondary metabolites, but if excessed sun exposure can cause a reduction in the process of making secondary metabolites in plants.[14] The difference in the amount of secondary metabolite content can also be influenced by differences in extraction methods, where in this study maceration and remaceration were used as extraction methods, while in Dhenge et al research only maceration was used as an extraction method. According to Nurhasnawati et al in Ningsih et al, the remaceration method has more power to attract secondary metabolite compounds in plants optimally due to the process of changing solvents in the extraction stage,

while in the maceration method the power to attract secondary metabolite compounds in plants is much smaller so that it is less optimal due to the absence of the process of changing solvents in the extraction stage.[15]

According to research by Yogiraj et al and Ukpabi et al in Mukhaimin et al, it is known that papaya flowers contain secondary metabolite compounds such as: alkaloids, flavonoids, saponins, and tannins.[10,11] Based on the results of Kumara literature review which shows the results that the secondary metabolite compounds mentioned above with their respective roles can cause death in *A aegypti* larvae.[12] The first secondary metabolite compound that acts as a larvicide is alkaloid, according to Kurniawan et al in Kumara alkaloid compounds have a mechanism of action that can prevent the ability of *Aedes aegypti* larvae to eat and to act as a stomach poison Whilst, alkaloid compounds as larvicides are thought to work by inhibiting the activity of the acetylcholine enzyme, causing the accumulation of acetylcholine which then damages the impulse distribution system to muscle cells, which results in *A aegypti* larvae experiencing convulsions, then paralysis and death.[12] The second secondary metabolite compound that acts as a larvicide is flavonoids, where flavonoid compounds have a mechanism of action that can inhibit breathing or strong respiratory toxins, so that they can block the respiratory tract of *A aegypti* larvae, flavonoid compounds as larvicides work by entering the respiratory tract of *A aegypti* larvae, then causing the nerves and respiratory muscles of *A aegypti* larvae to wither, causing *A aegypti* larvae failed to breathe and die.[12] The third secondary metabolite compound that acts as a larvicide is saponin. According to Minarni et al in Kumara, saponin compounds have a mechanism of action that can irritate the mucous membranes of the digestive tract of *A aegypti* larvae, besides that saponins also have a bitter effect on *A aegypti* larvae so that they can reduce the appetite of *A aegypti* larvae and cause death. Saponin compounds also have a mechanism of action that can damage the protective wax layer of the outer skin of *A aegypti* larvae, causing *A aegypti* larvae to lose a lot of body fluids and die.[12] The fourth and last secondary metabolite compound that acts as a larvicide is tannin, where tannin compounds have a mechanism of action that disrupts the digestion of *A aegypti* larvae, because tannin compounds result in the binding of proteins needed for the growth of *A aegypti* larvae in the digestive tract, which results in the absorption of proteins in the digestive system being disrupted and if it continues can cause the death of *A aegypti* larvae.[14] According to Tandi in Kumara, tannin compounds also have a mechanism of action that can reduce the activity of protease enzymes in converting amino acids, which causes the metabolic process of *A aegypti* larvae cells to be disrupted, making the larvae lack of nutrients.[12]

The results of statistical tests, namely *Probit analysis* of *Lethal Concentration* (LC) values in **Table 2** show that at a dose or concentration of 4.84% papaya flower extract within 24 hours of treatment can kill 95% of larvae (LC_{95}) and at a dose or concentration of 10.39% papaya flower extract within 24 hours of treatment can kill 99% of larvae (LC_{99}). According to Haditomo in Siregar, the lower the Lethal Concentration of a substance, the greater the activity of the substance in killing test animals, because the substance requires a lower concentration to kill test animals.[14] Research by Dhenge et al showed an LC_{99} value of 55.03% which can be interpreted that at a dose or concentration of 55.03% papaya leaf extract within 24 hours of treatment can kill 99% of larvae.[7] Based on the LC_{99} value of this study and Dhenge et al research, it is known that there is a significant difference, where in this study the LC_{99} value is lower than that of Dhenge et al research. According to Wulan in Siregar, differences in LC values can be caused by differences in doses or concentrations used in each study.[14] This is evidenced by the slight difference in doses or concentrations used where in this study which used doses or concentrations of 1%, 5%, 10%, 15%, and 20% and in the Dhenge et al study which used doses or concentrations of 5%, 10%, 15%, 20%, and 25%. According to the Ministry of Health of the Republic of Indonesia in Siregar, differences in LC values can be caused by

biological factors such as the selection and use of plant parts that can affect secondary metabolite levels.[14] This can be proven by the different selection of papaya plant parts used for making extracts, where in this study using flowers while in Dhenge et al research using leaves. The results of statistical tests, namely Probit analysis of Lethal Time (LT) values in **Table 3** show that each dose or concentration of papaya flower extract has different LT_{95} and LT_{99} values. The LT_{95} and LT_{99} values can be interpreted as the time required for each dose or concentration of papaya flower extract to kill 95% and 99% of the larvae. **Table 3** shows that a dose or concentration of 20% papaya flower extract has the lowest LT_{95} and LT_{99} values compared to other doses or concentrations of papaya flower extract, with an LT_{95} value of 16.55 and an LT_{99} value of 24.48.

The results of the statistical test, the *Kruskal Wallis* test in **Table 4** show that there is a difference in the number of deaths of *A aegypti* instar larvae III/IV after 24 hours of treatment in the experimental group (*p-value* = 0.011). These results are in line with Siregar's research which shows that there is a difference in the number of deaths of *A aegypti* instar III larvae after 24 hours of treatment in the experimental group (*p-value* = 0.001).[14] This study also found that there is a significant difference between the number of deaths of *A aegypti* instar larvae III/IV after 24 hours of treatment at a dose or concentration of 1% with a dose or concentration of 5%, 10%, 15%, and 20%.

Based on this study, the researcher believed that papaya flower extract had the potential to be developed into an alternative larvicide for the prevention of dengue hemorrhagic fever (*A aegypti* larvicide), therefore further research is needed to prove the safety of papaya flower extract as *A aegypti* larvicide so that it can be applied as an alternative natural larvicide in the community.

The limitation in this study is that the evaporation process or filtrate evaporation was not done with a rotatory evaporator. The evaporation process or filtrate evaporation was carried out using simple tools on the stove. In addition, this study did not conduct phytochemical screening, so it is not known which secondary metabolite compounds in papaya flowers dominantly act as natural larvicides for *A aegypti*. Recommendations for future researchers to conduct similar research but in the process of evaporation or evaporation of filtrate for making extracts can use rotatory evaporator tools, besides that for future researchers to carry out phytochemical screening, so that secondary metabolite compounds in papaya flowers that dominantly act as natural larvicides of *Aedes aegypti* can be known.

Conclusion

Papaya flower extract has potential as *A aegypti* larvicide with a optimum dose or concentration of 20%. The *Lethal Concentration* (LC) value of papaya flower extract as *A aegypti* larvicide is 4.84 and 10.39 for LC_{95}, LC_{99} , respectively. The *Lethal Time* (LT) value of papaya flower extract at doses or concentrations of 1%, 5%, 10%, 15%, and 20% is 115.74, 24.24, 23.41, 25.24, and 16.55 for LT_{95}, respectively and 241.95, 29.42, 26.20, 32.24, and 24.48 for LT_{99} respectively. There is a difference in the number of deaths of *A aegypti* instar larvae III/IV after 24 hours of treatment in the experimental group or group treated using papaya flower extract in various doses or concentrations, 1%, 5%, 10%, 15%, and 20% (*p-value* 0.011<0.05). Therefore, this study may suggest that health agencies can conduct further research to prove the safety of papaya flower extract as an *A aegypti* larvicide to be applied as an alternative natural larvicide in the community. The phytochemical screening may be required to determine the secondary metabolite compounds in papaya flowers that dominantly act as natural larvicides of *A aegypti*.

Ethics approval

This study has received ethical approval from the Health Research Ethics Commission, Faculty of Public Health, Nusa Cendana University with number: 2023134-KEPK.

Availability of data and materials

Available

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Author Contribution

SCMP conducted tests on the potential of papaya flower extract as an *Aedes aegypti* larvicide and then analyzed and interpreted the results. All authors read and approved the final manuscript.

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