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Effect of PEG and CMC on Papaya (*Carica papaya* L.) Extract Against *Aedes aegypti* Larvae

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Abstract

Dengue haemorrhagic fever (DHF) cases are still high in America and Asia region, including Indonesia. Eradication of DHF can be done by larvacide. Temephos 1%, chemical larvacide used in Indonesia for decades, can cause environment degradation and allergic reaction in human. Papaya stem extract as biolarvacide contains saponins, tannins, alkaloids, flavonoids, papain and essential oils which have larvicidal activity. It can be applicable in all over the world. This study was conducted to determine the better suspending agent between CMC or PEG of papaya stem extract to kill Aedes aegypti larvae. Objective: To determine the better suspending agent to kill *Aedes aegypti* larvae. Method: This study was true experimental study in laboratory, used post-test only controlled group design. This study used samples consist of Aedes aegypti instar III-IV larvae. There were seven experimental groups, consist of positive control group, negative control group for CMC, negative control group for PEG, extract concentration of 1.5% with CMC suspending agent, extract concentration of 1.5% with PEG suspending agent, extract concentration of 2% with CMC suspending agent, extract concentration of 2% with PEG suspending agent. Each group was repeated 4 times and counted every 6 hours (6^{th}, 12^{th}, 18^{th}, 24^{th}). Data analysis using the SPSS application ver 23. Probit test used to determine the effectiveness of the larvacide, LC50 and LT50 to determine the concentration and time to kill 50% of Aedes aegypti larvae. It used Kruskal Wallis Test to compare four dependent groups. It used Mann Whitney Test to compare the differences of each group. Result: The study showed that LC50 PEG was 0.033%, LC50 CMC was 0.321%, LT50 (PEG+1.5%) was 20.8 hours, LT50 (PEG+2%) was 30.7 hours, LT50 (CMC+1.5%) was 23.5 hours, LT50 (CMC+2%) was 40.7 hours. Based on the probit test, the LC50 and LT50 results showed that papaya stem methanol extract with PEG suspending agent was more effective than CMC suspending agent, it needed lower concentration and lower time to kill 50% of larvae. Kruskall Wallis Test result $p<0.05$, so there was significantly difference between groups. Post hoc Mann-Whitney Test result $p<0.05$ between C(-) PEG group with P1, P2, P3, P4 and between C(-) CMC group with P1, P2, P3, P4, so there was significantly difference between C(-) PEG with each group and C(-) CMC with each group. Conclusion: It can be concluded that papaya stem methanol extract with PEG suspending agent was more effective than CMC suspending agent to kill Aedes aegypti larvae.

Keywords: Papaya stem extract; CMC; PEG; Aedes aegypti larvae; Larvicide.

Abbreviations: CMC: Carboxymethyl Celulose; PEG: Polyethylene glycol

INTRODUCTION

In most regions of America and Asia including Indonesia, dengue haemorrhagic fever (DHF), brought by *Aedes aegypti* mosquito and caused by DENV types 1-4, still becomes health problem (Jatmiko et al., 2024; Yang et al., 2021). Indonesia is the 2nd country with the highest dengue cases out of 30 endemic countries (Haryanto, 2018). There were approximately 87,501 DHF cases in Indonesia (Kemenkes RI, 2022). The incidence of dengue fever increased rapidly over the past 45 years with peak incidence was in children. Incidence Rate (IR) was high (IR=78.0) and Case Fatality Rate (CFR) wa also high (Haryanto, 2018).

Control of Aedes aegypti mosquito is caried out using various methods including chemical, physical and biological control. Chemical control used larvicide namely abate, containing temephos 1% (Nurlinawati & Mulyani, 2020; Rather et al., 2017). However, the use of abate bring out resistance to Aedes aegypti, so biological larvicide need to be developed (Grisales et al., 2013; Ika Wahyu Utami, 2017; Lesmana et al., 2021; Mulyatno, Kris Cahyo; Yamanaka, Atsushi; Ngadino; Konishi, 2012; Saeung et al., 2020; Sinaga et al., 2016).

Lord, et. al. (2021) researched larvicides from the ethanol extract of papaya stem that have a larvicidal effect on Aedes aegypti. Papaya stem contains saponins, tannins, alkaloids, flavonoids, steroids, papain, and

essential oils affect larvae killing (Ayu et al., 2021; Ningrum et al., 2018; Rizki et al., 2017). Flavonoid is a phenolic component that is usually found in stems, leaves, flowers andr fruits(Purwani et al., 2024). Secondary metabolites in papaya plants are obtained through extraction.

The selection of the type of solvent used will affect the active components of the extracted material (Kafita et al., 2024). On the previous study, it was said that the extract was not dispersed perfectly (Ariesta AA; Suharyo; Kun S, n.d.; Suharyo & Susanti, 2017) and there was no study that using dispersing agent CMC and PEG. So we conduct the research by using CMC and PEG to determine the better suspending agent to kill *Aedes aegypti* larvae (Ferdiansyah, 2016; Rowe, R.C., Sheskey, P.J., Quinn, 2009; Wibowo et al., 2017).

MATERIALS AND METHODS

Research design and implementation procedures

This research is an experimental laboratory design with a post-test only controlled group design. The study was conducted for 3 months starting from September 2022 at the Pharmacology Laboratory of the Faculty of Medicine, Muhammadiyah University, Surakarta for extraction. In the Laboratory of Parasitology, Faculty of Medicine, University of Muhammadiyah Surakarta for testing with larvae.

The materials used were *Aedes aegypti* instar III - IV larvae, 90% methanol, distilled water, papaya stem (*Carica papaya* L.), abate, Polyethylene Glycol (PEG), Carboxy Methyl Cellulose (CMC). The tools used in this study included trays, black cloth, jars, blenders, filter paper, water baths, stirrers, rotary evaporators, cups, pipettes, beaker glasses, label paper, scales, analytical scales, and hand counters.

The larvae were hatched in Laboratory of Parasitology UMS. The larvae were from eggs of Loka Litbangkes Pangandaran. The determination of larvae was done from Loka Litbangkes Pangandaran and Laboratory of Parasitology UMS. The eggs were from dengue-free mosquito *Aedes aegypti*. The subject were developed in insectarium that was controlled the temperature and humidity, and given standard food. There were 175 larvae for preliminary study and 700 larvae for larvicide study, according WHO (WHO, 2005). Ethical clearance was from KEPK Medical Faculty UMS No. 4623/A.1/KEPK-FKUMS/XI/2022. The study was done by researchers.

Methanol extract of papaya stem (*Carica papaya* L.)

Methanol extract of papaya stem (*Carica papaya* L.) was prepared in the Pharmacology Laboratory of FK UMS using the maceration method. The solvent used is 90% methanol solvent. The initial process is slicing the papaya stem as much as 10 kg (*Carica papaya* L.) and then dry by cover it with a black cloth. After drying, and then crushed using a blender until it was in the form of a fine simplisia of 1.26 kg. Once smooth that given a solvent in the form of 90% methanol and then stirred. Then left for seven days with daily stirring. Then the macerate is concentrated using a Rotatory Evaporator and a water bath until a thick extract is formed but still pourable.

This study uses suspending agent as an additive, and there are few studies that focus on discussing the effect of suspending agent on larval mortality. Therefor it is necessary to carry out a stability test to determine the appropriate concentration for this study. Furthermore, stability tests were PEG and CMC.

The concentration of papaya stem (*Carica papaya* L.)

The concentration of papaya stem is as follows:

1. Papaya stem extract 1.5% + PEG
2. Papaya stem extract 2% + PEG
3. Papaya stem extract 1.5% + CMC
4. Papaya stem extract 2% + CMC

Treatment of larvae

Mosquito larvae preparation was done in the Parasitology Laboratory, Faculty of Medicine, Muhammadiyah University, Surakarta for approximately seven days from Aedes aegypti eggs to be hatched and cultured until the larvae instars III - IV.

Testing for Aedes aegypti larvae were done as follows:. There were seven groups consist of 4 treatment groups and 3 test groups, two negative controls CMC and PEG, and one positive control using abate. The four treatments consisted of 2 methanol extracts of papaya stems at a concentration of 1.5% with PEG and CMC. The other treatment group consisted of papaya stem methanol extract at a concentration of 2% with PEG and CMC as shown in Table 1.

Table 1. Variation group of the papaya stem methanol extract with CMC and PEG suspending agents against *Aedes aegypti* larvae.

Group	Concentration	Number of larvae × replication	Total Number of larvae
C(+) Abate	1%	25 × 4	100
C(-) PEG	0%	25 × 4	100
C(-) CMC	0%	25 × 4	100
P1 (1.5% + PEG)	1.5%	25 × 4	100
P2 (2% + PEG)	2%	25 × 4	100
P3 (1.5% + CMC)	1.5%	25 × 4	100
P4 (2% + PEG)	2%	25 × 4	100
Total larvae			700

Then 25 *Aedes aegypti* larvae were put into each glass containing distilled water which had been treated with abate, CMC, and PEG, and 200 ml of stock solution.

Counting larvae mortality

The death of the larvae was counted every 6 hours, 12 hours, 18 hours, and 24 hours. Counting technique was using pipet and tray, under bright lamp. Larvae considered as death when it didn't actively move and stay still. Researchers used hand counter to count death larvae.

Data analysis

The analysis was using Normality Test Shapiro-Wilk, Homogeneity Test, Kruskal Wallis, Mann-Whitney Test and Probit Test.

Ethical Approval

Ethical clearance was from KEPK Medical Faculty UMS No. 4623/A.1/KEPK-FKUMS/XI/2022. The study was done by researchers.

RESULTS AND DISCUSSION

Results

The results of the stability test presented in Table 2.

Table 2. Stability Solution test.

Indicator	PEG	CMC
Solubility	Soluble	Soluble
Direct precipitation	No precipitation	No precipitation
Precipitation in 24 hours	Low precipitation	Low precipitation
Viscosity	watery	watery

In previous the larvicidal research, a preliminary test determined whether the concentration of the extract used was effective or not. The preliminary test was in 7 groups with three control groups and four treatment groups which presented in Table 3.

Table. 3 Preliminary larvicidal test.

Group	Mortality in (hour)				Percentage mortality (%)
	6	12	18	24	
C(+) Abate	22	25	25	25	100%
C(-) PEG	0	0	0	0	0%
C(-) CMC	0	0	0	0	0%
P1 (Extract 1.5% + PEG)	3	25	25	25	100%
P2 (Extract 2% + PEG)	12	25	25	25	100%
P3 (Extract 1.5% + CMC)	20	25	25	25	100%
P4 (Extract 2% + PEG)	25	25	25	25	100%

The results of the preliminary test found that at the 12th hours the mortality of the larvae was 100%. This concentration of the extract was effective and could be continued for the larvicide test. The larvicidal Test shown at Figure 1.

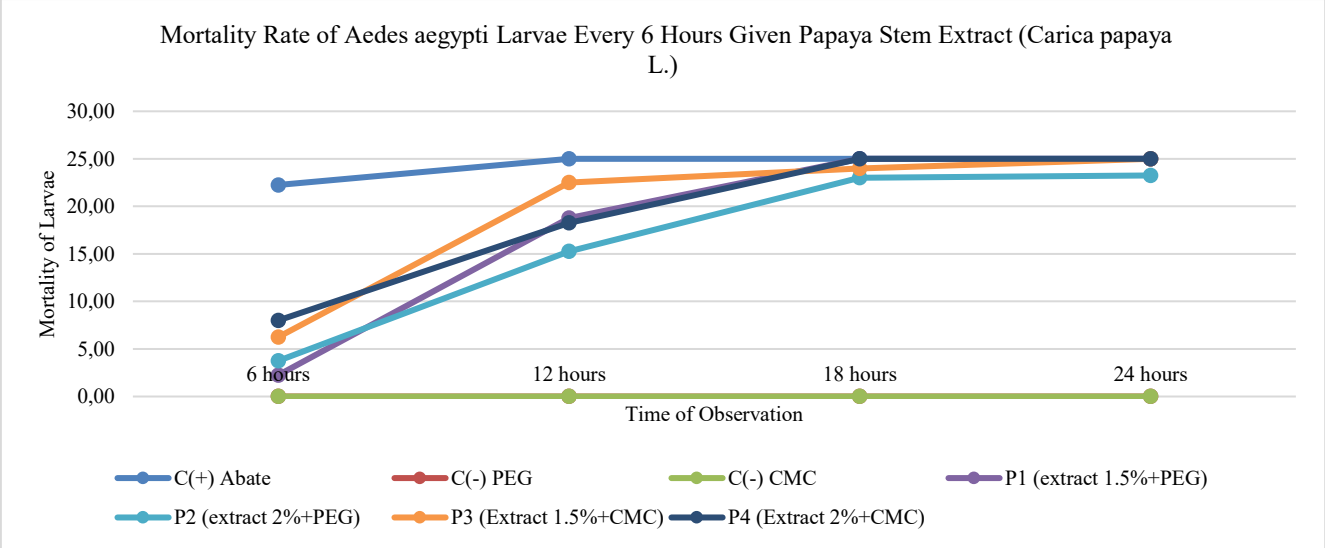

Figure 1. Mortality Rate of Aedes aegypti Larvae Every 6 Hours Given Papaya Stem Extract (*Carica papaya* L.) with 4 repetitions.

After obtaining the larval mortality results, the data obtained were analyzed. This analysis was used to determine whether there were differences or not, then different tests were conducted. Shapiro-Wilk normality test and homogeneity test revealed that from all groups, within 6, 12, 18 and 24 hour group, the results were p value < 0.000, so the data is not normally distributed and not homogeneous.

Then it proceed with the Kruskal-Wallis test to find out whether there is a significant difference between seven groups or not, shown at Table 4. The results of the non-parametric test show that p<0.05, there is a significantly difference in the data. The hypothesis null (H0) is rejected, and the alternative hypothesis is accepted.

The Post-Hoc Test was carried out because the Kruskall Wallis non-parametric test obtained meaningful group of different data. The Mann-Whitney test was performed to determine significant differences between data groups, described in Table 5 P value were taken from 24-hour larval mortality group data.

Table 4. Kruskal-Wallis Test.

Mortality	Sig.	Result
6-hour mortality	0,003	Significant difference
12-hour mortality	0,002	Significant difference
18-hour mortality	0,001	Significant difference
24-hour mortality	0,000	Significant difference

Table 5. Mann-Whitney Test.

	C(+) Abate	C(-) PEG	C(-) CMC	P1	P2	P3	P4
C(+) Abate		p : 0.008*	p : 0.008*	p : 1.000	p : 0.317	p : 1.000	p : 1.000
C(-) PEG	p : 0.008*		P : 1.000	p : 0.008*	p : 0.011*	p : 0.008*	p : 0.008*
C(-) CMC	p : 0.008*	p : 1.000		p : 0.008*	p : 0.011*	p : 0.008*	p : 0.008*
P1	p : 1.000	p : 0.008*	p : 0.008*		p : 0.317	p : 1.000	p : 1.000
P2	p : 0.317	p : 0.011*	p : 0.011*	p : 0.317		p : 0.317	p : 0.317
P3	p : 1.000	p : 0.008*	p : 0.008*	p : 1.000	p : 0.317		p : 1.000
P4	p : 1.000	p : 0.008*	p : 0.008*	p : 1.000	p : 0.317	p : 1.000	

* significantly different
P1 : PEG + methanol extract papaya stem 1.5 %
P2 : PEG + methanol extract papaya stem 2 %
P3 : CMC + methanol extract papaya stem 1.5 %
P4 : CMC + methanol extract papaya stem 2 %

LC50 probit test to find out the concentration needed to kill 50% of the larvae and LT50 lethal time which is used to determine the time needed to kill 50% of the larvae. The LC50 results in this study were used to compare which suspending agents the methanol extract of papaya stems was effective against the mortality of *Aedes aegypti* larvae. The following results of the LC50 at hour-12 and LT50 probit test are presented in Table 6.

Table 6. Probit Test.

Group	LC_{50}
PEG	0.033
CMC	0.321
Concentration	LT_{50}
PEG+1.5 %	20.804
PEG+ 2 %	30.784
CMC +1.5 %	23.508
CMC +2 %	40.718

Discussion

The study had occured on a mixture of papaya stem extract with different concentration and suspending agent. The mixture was cloudy and dispers well. The amount of death larva was good according to amount of death larva on 12 hours, almost same with abate as positive control. It can be happened because papaya stem had active material such as saponin, alkaloid, tanin, etc as larvicide.

Yield related to the number of active compounds present in a plant extract (Salim et al., 2017). The methanol extract of papaya stems, which was already viscous obtained a yield of 5.087%. When be to previous research conducted by Saputri (2021) with the same plant was found to be lower, namely 9.806%. This difference in yield can occur because influenced by several factors, namely the type of solvent, stirring time, maceration time and the origin of the plant area taken (Aprilasani & Adiwarna, 2014; Chairunnisa et al., 2019; Salim et al., 2017). In this study, maceration was carried out for six days, whereas in previous studies, the maceration time was not explained. In addition, in this study, stirring was only done once a day, whereas in the previous research it was stirred three times a day.

Results of the stability test in this study found that compound CMC and PEG could affect the solubility, precipitation, and the mixture of extracts into distilled water. Based on the stability test, it was found that the appropriate diluent concentrations were 0.01% CMC and

0.01% PEG which ordinally used 0.5% CMC and 0.1% PEG concentrations. This change in concentration was due to the acquisition of a thick solution at 0.5% CMC and 0.1% PEG, so it was worried that it would affect the death of the larvae because the thickness of the solution would interfere with the movement of the larva (Auliaputri, 2022).

In the larvicidal test, average mortality in four repetitions was obtained, larvae mortality in the treatment within 24 hours was 100% except in P2, the mortality was 93%. In previous studies, 100% of the larvae died in all treatments (Ayu et al., 2021).

The data is not normally distributed and not homogeneous which states that the mortality of larvae in each group every hour is not normal and not homogeneous. Then proceed with the Kruskal-Wallis test to find out whether there is a significant difference between groups or not. The results of the non-parametric test show that there is a significantly difference in the data. The null hypothesis is rejected, and the alternative hypothesis is accepted. It presents which groups differed significantly and which did not. There was no significant difference between the positive control with P1, P2, P3 and P4, but it was significantly different from the negative control CMC and PEG.

Based on probit analysis, it was found that the LC50 of papaya stem methanol extract with PEG suspending agent with death at 12 hours was 0.033%. LC50 papaya stem methanol extract with CMC suspending agent of 0.321%. Based on these results it can be said that papaya stem methanol extract with PEG suspending agent is more effective than CMC. When compared with previous research conducted by Ayu (2021) in the ethanol extract of papaya stems, an LC50 of 1.033 was obtained. Based on the LC50 results, papaya stem methanol extract with PEG and CMC suspending agents was more effective than papaya stem ethanol extract in previous studies. This study used CMC and PEG suspending agents, whereas in that study it was not explained which suspending agent was used to dilute the ethanol extract of papaya stems. Methanol extract of papaya stem with CMC and PEG suspending agents is included in the toxic category. The extract is said to be highly toxic if the LC50 is <1%, toxic if the LC50 is 1-10%, moderately toxic if the LC50 is 10-50%, slightly toxic LC50 is 50-100%, and if the LC50 is > 100% then it is said to be non-toxic (Ayu et al., 2021).

According to the Probit results for LT50, the LT50 at a concentration of 1.5% with PEG suspending agent was 20.804 hours and at a concentration of 2% with PEG suspending agent was 30.784 hours. The LT50 of the extract at 1.5% concentration with CMC suspending agent was 23.508 hours, and the LT50 of the extract at 2% concentration with CMC suspending agent was 40.718 hours. As a result, an extract concentration of 1.5% with PEG and CMC suspending agents can kill 50% of the larvae faster than an extract concentration of 2%. Lower concentrations kill larvae faster, possibly due to an insufficient concentration of suspending agent, which prevents the suspending agent from dissolving the extract evenly across the surface of the water.

Based on the results of LC50 and LT50, extract with a smaller concentration is more effective in killing Aedes aegypti larvae. When compared with previous studies which stated that the higher the concentration of the extract, the higher the mortality rate of larvae. So, this is contrary to the results of this study, namely the smaller the concentration, the higher the mortality. This could be due to the factor of the suspending agent. There are factors that affect the solubility of a material, namely the substance to be dissolved, temperature, PH and volume of solvent (Apsari & Chaerunisa, 2020). The two components are related because the solvent will react with the solute so that the substance can be spread evenly. The substance to be dissolved (solute) should be less and the solvent (solvent) should be more. The suspending agent must be more than the amount dissolved (Yusnidar, 2019). Whereas in this study, the suspending agent concentration was adjusted to the volume of distilled water without adjusting to the concentration of the extract.

The mortality effect of papaya stem methanol extract (*Carica papaya* L.) with CMC and PEG suspending agents, when compared to papaya stem ethanol extract (*Carica papaya* L.) conducted by Saputri et. al., (2021), is more effective when viewed based on the LC50 that has been obtained from the probit test. can be influenced by the addition of CMC and PEG which help the extract to be dispersed or dispersed evenly over the entire surface of the distilled water. The addition of CMC and PEG suspending agents did not directly affect or in other words, did not have a larvicidal effect on Aedes aegypti larvae as evidenced in the negative control, namely distilled water which was given CMC and PEG did not cause death in the larvae.

Research conducted by Baskaranatha that CMC affects mortality in larvae at a concentration of 0.5% has affected larvicidal by 8%, so the CMC concentration reduced to 0.025%. CMC with a concentration of 0.025% did not cause death in the larvae or a death percentage of 0% (Ayu et al., 2021; Baskaranatha I Made; Swastika, I Kadek, 2020; Manuahe et al., 2022). Previous research of the ethanol extract of tobacco leaves on the mortality of *Anopheles aconitus* larvae using 0.5% CMC suspending agent did not cause death in the larvae (Nurhayani et al., 2021).

Besides CMC, the suspending agent used in this study was PEG with concentrations 0.01%. Based on previous research, permot leaf extract with add of 0.1% PEG did not affect the mortality of Aedes aegypti larvae (Susilowati & Sari, 2022). This study used PEG 0.01% and did not cause death to the larvae. Therefor can be said that the concentration of PEG does not affect the mortality of the larvae. Based on this study, the CMC and PEG can increase larval mortality so that the methanol extract of papaya stem (*Carica papaya* L.) can

be dispersed evenly, and the compounds present in the methanol extract of papaya stem (*Carica papaya* L.) can cause larval death.

The death of the larvae was caused by the compounds contained in the methanol extract of papaya stem (*Carica papaya* L.), namely flavonoids, tannins, steroids, saponins, alkaloids, papain and essential oils. Saponins form complexes with protease enzymes to split the inner lining of the intestinal mucosal cells thereby disrupting the permeability of the intestinal membrane (Zaynab, 2021). Saponins interact with cholesterol which causes the attachment of food that cannot be digested by the larvae. In addition, saponins can also cause disruption of ecidsteroid synthesis, which is a hormone that helps the skin turnover cycle (Lafont et al., 2012).

Flavonoids affect mortality by inhibiting growth and interfering with the respiratory system (Krisna et al., 2022). Flavonoids inhibit energy transport and metabolism in mitochondria by inhibiting the electron transport system or the channel between ATP production and the ATP transport system so that oxygen production in mitochondria decreases (Ayu et al., 2021; Manuahe et al., 2022). In addition, flavonoids and alkaloids work by inhibiting acetyl cholinesterase by phosphorylation of the amino acid serine at the acetyl centre of the enzyme. Blocked acetyl cholinesterase causes a buildup of acetylcholine and causes poisoning larvae in the form of paralysis of the respiratory system (Ilham et al., 2019; Wahyudi et al., 2021).

Alkaloids and tannins play a role in degrading cell membranes in larvae so that the larvae cannot grow into pupae and will die (Maulana, Sidik; Musthofa, Faisal; Yamin, Ahmad; Juniarti, Neti; Putri, 2021; Wahyudi et al., 2021). Tannins react with protease enzymes which causes the larvae to lack nutrition and eventually die (Ayu et al., 2021). Papain works by breaking down protein in the proteolytic process so that the larvae will lack protein for metabolism, if metabolism continues become constructed, it will cause the larvae to die (Payangka et al., 2019). Steroids interfere with the moulting system in the larvae and interfere with the absorption of food by the larvae (Ilham et al., 2019). Essential oils damage the nervous system and change the structure of cell membranes in the larvae so that over time the larvae will die (Ilham et al., 2019).

Therefor adding CMC and PEG suspending agents can increase larval mortality so that the methanol extract of papaya stem (*Carica papaya* L.) can be dispersed evenly and the compounds present in the methanol extract of papaya stem (*Carica papaya* L.) can cause larval death.

CONCLUSIONS

Papaya stem methanol extract with PEG suspending agent was more effective than CMC suspending agent to kill Aedes aegypti larvae. It has potential to substitute abate that environmentally damaging abate, and the larvae are already resistant.

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