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The Potency of Secondary Metabolites from *Salacca zalacca*, *Sonchus arvensis*, and *Carica papaya* against *Aedes aegypti* L.

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Abstract: Dengue infection is still as a major public health in the world including Indonesia, wherein from January to June showed about 45,387 cases and 432 deaths. There are many prevention and control activities that have been carried out but have not given contented results despite using insecticides. Plants secondary metabolites are confirmed have biological activity and can protecting the plants from an insect pest and diseases. This study proposed that secondary metabolites in several plants have the potential as biolarvicide. This study aimed to determine the potency of secondary metabolites in *Salacca zalacca, Sonchus arvensis*, and *Carica papaya* as biolarvicide. Each extract was test in five concentrations of treatment and two controls, negative control using aquadest and positive control using temephos 1%. The third instar larvae of *Ae. aegypti* mosquito were used in biolarvicide test, with 10 larvae for each treatment and 3 replications for 24 hours. This study revealed that *C. papaya* extract showed the highest potency as biolarvicide compared to *S. zalacca* and *S. arvensis*. The LC_{50} and LC_{90} for 24 hours of *C. papaya* extract were 2.62% and 5.49% respectively.

Keywords: Aedes aegypti; Biolarvicide; Carica papaya; Salacca zalacca; Sonchus arvensis

Introduction

Dengue Hemorrhagic Fever (DHF) is an infection by the dengue virus, which is spread by the biting of *Aedes aegypti* infected mosquito. It is still a significant public health issue that high cases in many areas of Indonesia. Up to June 2022, there had been 45,387 cases of dengue infection and 432 of them was deaths. Special Region of Yogyakarta is one of province with high incidence rates of dengue infection (Indonesian Ministry of Health, 2022).

To prevent dengue infection, the use of insecticide is still as choice to eliminate the vector and reduce the cases. However, resistance of *Ae. aegypti* have been reported in many areas (Yuniyanti et al., 2021). The *Ae. aegypti* resistancy with organophospate compound such as temephos have been reported from several cities in Indonesia, including Jakarta, Bali, and Bantul Yogyakarta (Adyatma et al., 2021; Prasetyowati et al., 2016; Umayana et al., 2015).

Synthetic insecticides are effective for mosquito elimination; however, it has a negative impact on the environment. It may harm to people, non-target organisms, and it will increase the environmental pollution. Natural products from plants have been test for controlling the *Aedes* population. Some of these plants, beluntas (*Pluchea indica* Less.), jarak kepyar leaves (*Ricinus communis* L.), and rhizome of *Zingiber montanum* have positive effect to the mortality of dengue vector (Ningrum et al., 2019; Rochmat et al., 2017; Utami et al., 2016).

Secondary metabolites are produced by plants to interact with their environment, defend plants against pests and disease. Alkaloids, flavonoids, saponins, tannins, and terpenoids are some of these secondary metabolites that might inhibit the insect growth (War et al., 2019). *Salacca zalacca* peel has been revealed as antibacterial and antifungus. It has examined for inhibit the growth of *Strepcoccus mutans* and *Candida albicans* (Shabir et al., 2018). *Salacca* is a tropical fruit especially in

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Indonesia, and it can be consumed directly with the peel as waste. The phytochemical screening of *Salacca* peel was found the compound of alkaloids, flavonoids, saponins, tannins, terpenoids, and phenols (Girsang et al., 2019).

Carica papaya is also a tropical fruit and it is commonly consumed in many countries. This fruit has been explored for food industry and process as jam, jelly, candy, etc. Sideline products from this fruit is the peel (Mandavgane et al., 2019). Roni et al. (2019) and Trisnawaty et al. (2021) said that this sideline products have a secondary metabolite such as alkaloids, flavonoids, saponins, tannins, steroids/triterpenoids. These compounds have positive effect to inhibit the growth of *C. albicans* and show antibacterial activities to *Escherichia coli* and *Staphylococcus aureus* (Rousdy et al., 2021; Trisnawaty et al., 2021).

Another plant that may have effects as antifungus is tempuyung leaves. This plant can growth in open land and ricefield at the 50-1650 masl. It has been reported that this plant becomes antibacterial, antiviral, diuretic, antihistamine, antihypertensive, and antihyperuricemia. The secondary metabolites of this plant are alkaloids, flavonoids, phenols, saponins, and tannins (Ashshiyami, 2019; Wulandari et al., 2021).

There was limited information of the *Salacca* peel, *Papaya* peel, and *Sonchus* leaves as botanical larvicide. This assumed that these natural products from the three plants might have potency for biolarvicide. The purpose of this research was to examine the secondary metabolites and the mortality effect of *Salacca* peel, *Papaya* peel, and *Sonchu*s leaves extracts against *Ae. aegypti* larvae.

Method

This research has been approved by the Ethics Commission by The Faculty of Medicine, Public Health, and Nursing Gadjah Mada University, within number Ref: KE/FK/0074/EC/2022.

Mosquito Rearing: *Aedes aegypti* eggs was collected from the field by using ovitrap at Prambanan village, from February-May 2022. It will rear at the Parasitology Division Laboratory of Animal Systematics. As a larva the *Aedes* was feed on pierce of dog food up to pupae and become adult. Pupae will remove to another cup of plastic and place in mosquito cages until adult. Identification of *Ae. egypti* adult has conducted with the guide book from the Indonesian Ministry of Health (2017). The nutrition for female mosquito to have good quality of eggs, it has feed on mice blood. Second ovitraps were place in the cages to collect the F2 *Aedes*. The F2 *Aedes* larvae were also feed on pierced of dog food and up to instar III stadium. These larvae were used as bioassays for biolarvicide test.

*Extraction***:** Maceration process was used for *Salacca* peel, and about 1000 gr of dried powder was added with 3000 mL ethanol 70%, and left for 24 hours. On the next day, the macerate has evaporated by using rotary evaporator on the 40°C up to get the crude extract (Girsang et al., 2019; Zhang et al., 2018). Aqueous extract of tempuyung leaves and papaya peel were each made by mashing 200 gr of sample in 2000 mL aquadest using a blender and then filtered. The result is an aqueous extract with a concentration of 10%.

Secondary Metabolites Detection for *Salacca* peel extract was done as a qualitative by phytochemical test. Moreover, for papaya peel and tempuyung leaves extract the quantitative secondary metabolites of alkaloids, flavonoids, saponins, and tannins were detected by spectrophtotometry UV-Vis. The qualitative secondary metabolites of terpenoids compound were detect by Thin Layer Chromatography (TLC) (Alen et al., 2017).

*Bioassay***:** The bioassays consist of two steps, there are preliminary test and final test. A total of 10 larvae of *Ae. aegypti* instar III was used for control and treatment tests at various concentrations for 24 hours with 3 replications. The negative control was used aquadest and the positive control was used temephos 1%, ABATE 1GR®.

Data Analysis: The results were analyzed by descriptive and statistic by using One-Way ANOVA (SPSS 27 software) and probit analysis to find out the LC_{50} and LC_{90} values.

Result and Discussion

The phytochemical test for secondary metabolites of *Salacca* peel ethanol extract was demonstrate in Table 1. It was showed that the snake fruit peel was positive for flavonoids, saponins, and tannins, but negative to alkaloids and terpenoids.

This result was difference with Girsang et al. (2019) test of *Salacca* peel extract that was positive with alkaloids and terpenoids. Environmental factors such light, temperature, groundwater, fertility, and soil salinity have a significant impact on the biosynthesis and accumulation of secondary metabolites (Yang et al., 2018). Secondary metabolites can be differed in similar plants that is grown in different environments. Environmental factors primarily influence the process of growth and development of plants, which in turn influences secondary metabolite synthesis.

Moles et al. (2019), it said that the primary and secondary metabolites are essential determinants of plants organoleptic quality. The differences of the environmental and agricultural factors will alter the accumulation of bioactive compounds (Francini et al., 2020). Toscano et al. (2019) said that the level of bioactive compounds is dependent on the plant species, cultivar/genotype, agronomic management, preharvest environmental conditions, and postharvest management practices. As Moles et al. (2019) said that in high salinity showed the reduction of the secondary metabolites, such as phenols and lycopene.

Table 1. The Phytochemical Test Result of *Salacca zalacca* Peel Ethanolic Extract

Secondary Metabolites	Result
Alkaloids	Negative
Flavonoids	Positive
Saponins	Positive
Tannins	Positive
Terpenoids	Negative

The release and accumulation of several secondary metabolites, such as phenolic compounds, triterpenoids, and flavonoids, are influenced by light radiation. Longer daylight will promote the production of flavonoids and phenolicacids, which protect plants from light exposure (Yang et al., 2018). In conditions of higher exposure, it have a positive correlation, to the increase of flavonoids and triterpens. Besides the daylight, the accumulation of the bioactive compound also affected by altitude and the temperature (Cocetta et al., 2015).

Water content may have effects to the produce and synthesis of secondary metabolite in medicinal plants. Water stress affects the growth, produce and synthesis of secondary metabolites, such as in *Bupleurum chinense* DC. There were significant effects of drought to the level of flavonoids in leaves and saikosaponin in roots (Yang et al., 2020). The affection of the synthesis was due to the changing of soil water content by altering gene transcription. These gene were synergistically respon to the soil water content and may regulate the production and concentration of flavonoids and saikosaponin (Yang et al., 2020).

Table 2. Total Secondary Metabolites Content of Tempuyung (*Sonchus arvensis*) and Papaya (*Carica papaya*) Peel Extract

Secondary	Results (Aquous Extract)	
Metabolites	Tempuyung Leaves	Papaya Peel
Alkaloids	26.72 mg/L	6.38 mg/L
Flavonoids	50.6 mg/L	23.74 mg/L
Saponins	198.7 mg/L	1 water82.11 mg/L
Tannins	0.37 % b/v	0.11% b/v

The concentration of ethanol also affects the type of secondary metabolites. Hikmawanti et al. (2021) discovered that 50% ethanol was more effective than 70% ethanol and 96% ethanol in binding secondary metabolite in katuk (*Sauropus androgynous*) leaves. Alcohols (EtOH and MeOH) are universal solvents in solvent extraction for phytochemical investigation (Zhang et al., 2018), and the high concentration of water that contained in ethanol influence its polarity.

Secondary metabolites content in tempuyung leaves and papaya peel extract showed in Table 2. Total secondary metabolites content on each extract was determined by spectrophotometry UV-Vi's method. Tempuyung leaves extract have a higher total secondary metabolite than papaya peel extract. The total saponins compound of the two extracts were not much different.

The detection of terpenoid compounds was carried out by the Thin Layer Chromatography (TLC) method using vanillin sulfuric acid reagent (Alen et al., 2017). Discoloration into purple dots on the plate give the positive results, due to the reaction of the vanillin sulfuric acid reagent with terpenoids, steroids, and volatile oil components.

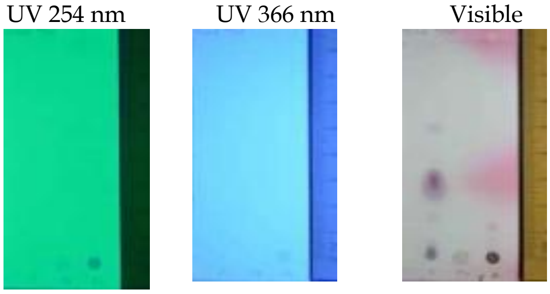

Figure 1. TLC Profile of Terpenoids Compound (1) Comparison, (2) *Papaya* Peel Extract, and (3)Tempuyung Leaves Extract; (a) UV Light 254 nm; (b) UV Light 366 nm; (c) Visible Light

Based on TLC analysis, tempuyung leaves extract was positive for terpenoids. It can see from the purple dots on the plate in Figure 1. The Rf values of tempuyung leaves extract were 0.08 and 0.14, however, the papaya peel extract showed negative for terpenoid.

The preliminary test of *Salacca* peel extract revealed that the extract has no significant effect to the mortality of larvae. At higher concentrations of the extract, it had no effect on increasing the mortality of *Ae. aegypti*, so the biolarvicide test for the *Salacca* peel extract was stopped.

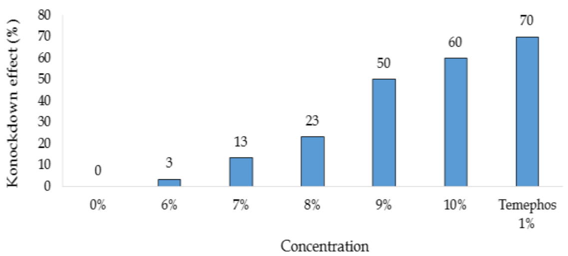

Figure 2. Knockdown effect of papaya (*Carica papaya*) peel extract in 1 hour

At preliminary test, 5% concentration of tempuyung leaves extract gives a 50% mortality. Based on the results, the concentration intervals of the tempuyung leaves extract that used in final test were 6%, 7%, 8%, 9%, and 10%. Moreover, the preliminary test of papaya peel extract revealed that at the concentration of 6% gave the 100% mortality, and the concentration intervals of papaya peel extract for the final test were 1%, 2%, 3%, 4%, and 5%.

Knockdown effect is an indicator that given by the larvae in response to the treatment. This knockdown effect may be related to the presence of reversible enzyme inhibitory activity or detoxification mechanisms, with partial paralysis which usually to the death (Athanassiou, 2021).

The tempuyung leaves extract did not give a knockdown effect on *Ae. aegypti* larvae in one hour treatment. The papaya peel extract with the lowest concentration (6%) had a knockdown effect on *Ae. aegypti* larvae (Figure 2). There was a positive correlation between the concentration and larvae mortality, in which the higher concentration papaya peel extract gave higher knockdown effect.

Table 3. Analytical Statistic of Tempuyung (*Sonchus arvensis*) Leaves Extract to the Mortality of *Aedes aegypti* Larvae for 24 Hours

Concentration (%)	Larva Mortality* (%)
0 (control -)	0
6	23.33 ± 5.774^{b}
7	33.33 ± 5.774^{bc}
8	46.67 ± 5.774^{cd}
9	73.33 ± 15.275^{e}
10	90.00 ± 10.000^{f}
Temephos 1% (control +)	100.00^{f}

Note: a number followed by a different letter indicate significant differences

The results of tempuyung leaves and papaya peel extracts revealed a positive correlation between the increasing of concentration extracts with larvae mortality. In Table 3 showed that there was a significant difference between control and treatment, as well as between all tempuyung extract tests. It was indicated that extract tempuyung have positive effects to the mortality of *Aedes* larvae. Moreover, for the papaya peel extract, similarly to the tempuyung extract, also showed the significant differences between control and treatment, however, not all test concentration showed significant differences (Table 4).

Toxicity is a substance or material possibility to give negative effects on an organism that alter its biological processes. The level of toxicity of a substance is influenced by its composition, type, concentration, number of substances, size, content, duration, frequency of exposure, and larvae stage (Rochmat et al., 2017). Differences in mortality rates of *Ae. aegypti* in each treatment may affected by the sensitivity of larvae. Higher concentration caused the viscosity of the solution increase that making the larvae difficult to breathe. As a result, the larvae's bodies run out of oxygen and eventually die (Sasmilati et al., 2017).

Table 4. Analytical Statistic Result of Papaya (*Carica papaya)* Peel Extract to the Mortality of *Aedes aegypti* Larvae for 24 Hours

Concentration (%)	Larva Mortality (%)
0 (control -)	0
1	23.33 ± 5.774^{a}
2	36.67 ± 5.774^{b}
3	53.33 ± 25.166^{b}
4	83.33 ± 15.275^{c}
5	83.33 ± 11.547^{c}
Temephos 1% (control +)	100.00^{c}

Note: a number followed by a different letter indicate significant differences

According to Table 5, papaya peel extract had lower in the value of LC_{50} and LC_{90} if compared to values of tempuyung leaves. Treatment with papaya peel extract gave 50% mortality at the concentration 2.62%, whereas the tempuyung extract showed almost three times of that. Considering to these results, papaya peel extracts have a greater potential as a biolarvicide.

Table 5. Probit Analysis of Tempuyung (*Sonchus arvensis*) Leaves and Papaya (*Carica papaya)* Peel to the Mortality of *Aedes aegypti* Larvae for 24 Hours

Extract	LC (24 hours; %)	
	50	90
Tempuyung leaves	8.33	10.26
Papaya Peel	2.62	5.49

The treatment was conducted by inserted *Ae. aegypti* larvae were into the extract solution at varying concentration. Secondary metabolite in tempuyung leaves and papaya peel extract reach the larvae body wall and mouth. The body wall is the part of the body that absorb large amounts of toxic substances. Toxic substances that enter the body through the mouth afterwards enter the cells and causing inhibited from the food consumed (Kim et al., 2017).

Alkaloids act as stomach poisons and contact poisons that destroy the membrane cell of digestive tract. Alkaloids in the larvae body will disrupt the neurological system by blocking the activity of the acetylcholinesterase enzyme, preventing the enzyme to transmit signals to the midgut and causing uncontrollable movements (Kim et al., 2017). The larvae in this research indicated more rapid movements at the beginning of the treatment, and the longer of the exposure causes the movement to slow down.

Saponins act by limit the activity of digestive enzymes, decrease the work of the digestive organs and the utilization of protein. Consequently, larvae nutrition not fulfilled and causing the larvae to die because the food absorption process is disturbed (Utami et al., 2016). The death of larvae can also cause by saponins capability to create a complex compound with sterols, which causes sterol in the larvae body unavailable. It is affecting the growth (War et al., 2019) and the synthesis of the hormone ecdysone, which plays a role in the molting process.

Tannins enter the larval body by absorption through the epidermis (Ningrum et al., 2019). Tannin will interact with midgut proteins, insect digestive enzymes and generate complex compounds with proteins that required to insects grow. Toxic substances can damage the midgut, which results in enzyme function reduction, poor digestion, and body metabolism disorder (Ahdiyah et al., 2015).

Flavonoids cause cellular damage in insects and act as respiratory inhibitors that enter the larvae body through the siphon and the disruption of the respiratory process will reduce the rate of chemical reactions in the larval body, it will reduce the ability to breathe which will be followed by a weakening of the nervous system and eventually cause death (Ningrum et al., 2019; Rodriguez-Cavallo et al., 2019).

The larvae that were test in this study demonstrate unusually rapid movements after the first hour of treatment. The larvae were anxious because the toxic substances in the extract had entered their bodies. The movement of the larvae is slower at longer treatment period. The larvae tend to be quiet and unresponsive when were given stimulus. This indicates that the larvae have been paralyzed. Some of the death's larvae were observed floating on the surface and settling at the bottom of the solution.

The difference ability between papaya peel and tempuyung leaves extracts could be affect by different compounds in each secondary metabolite group. Muñoz et al. (2020) discovered that three different types of alkaloids such as quinine, caffeine, and theophylline, had varying effects on feeding behavior, metabolism, and survival of blood-sucking insects. Quinine can affect the feeding behavior, metabolism, and survival *R. proxylus* insects at lower concentrations than caffeine or theophylline. It can be determined that the total content of each secondary metabolite has no effect on the mortality of *Ae. aegypti*.

This study indicated that secondary metabolites from the extract of *S. arvensis* leaves and *C. papaya* peel be a candidate as biolarvicide. This is because of the material is easy to obtain, cheap, and may safe for the environment.

Conclusion

The aqueous extract of papaya (*Carica papaya*) peel has the greatest potential as a biolarvicide for *Aedes aegypti* compared to ethanol extract of snake fruit (*Salacca zalacca*) peel and aqueous extract of tempuyung (*Sonchus arvensis*) leaves. The LC_{50} and LC_{90} for 24 hours of *Carica papaya* extract were 2.62% and 5.49% respectively.

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Author Contributions
Conceptualization, U.N.W.A. and A.N.I.; methodology, U.N.W.A.; software, A.N.I.; validation, U.N.W.A. and A.N.I.; formal analysis, U.N.W.A. and A.N.I.; investigation, A.N.I., W.N.S.U. and A.A.F.; resources, U.N.W.A. and A.N.I.; data curation, A.N.I. and W.N.S.U.; writing—original draft preparation, A.N.I., U.N.W.A.; writing—review and editing, U.N.W.A.; visualization, U.N.W.A., A.N.I. and W.N.S.U.; supervision, U.N.W.A..; project administration, A.N.I. and A.A.F.; funding acquisition, U.N.W.A.

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Conflicts of Interest
The authors declare, there was no conflict of interest.

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