The synthesis of nanosilver and carbamat to control of *Anopheles* in malaria endemic areas

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ABSTRACT

Malaria is a national and global problem that really needs attention and Indonesia is the second highest country with the highest number of cases 304,607 in 2021. The use of insecticides at inappropriate doses causes resistance to targets. The aim of this study was to analyze the toxicity of silver nanoparticles to adult Anopheles mosquitoes in malaria endemic areas as well as to determine the lethal concentration (LC50) and to project effectiveness in the lifetime. This research is experimental and uses a post-treatment with control design which was carried out in 4 stages from 2019-2022, which includes laboratory scale tests (2019), field laboratory scale tests (2020), ecological endemic area scale tests (2021), and lifetime tests (2022). Calculation of LC50 in nanosilver toxicity 5965 mg/l and Calculation of life time projections produces the formula Y=(-) 0.012Ln(X)+0.6933. Absorption of silver nanoparticles into the bodies of Anopheles sp. occurs through the spiracles and attacks the Ache enzyme in the central nervous system thereby stopping the working system of the mosquito which will then die. Nanosilver is a very effective herbal insecticide used as an effort to control malaria cases in endemic areas with the right dose and method. For life time, a dose of 1500 mg/l nanosilver effectively kills 74% of adult Anopheles sp mosquitoes on day 32 and it is projected that on 1 year the efficacy of nanomaterials still has an efficacy of 62%).

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1. INTRODUCTION

Malaria is a disease transmitted by the bite of a female *Anopheles* mosquito that contains plasmodium. Globally, malaria is still a problem, malaria threatens children and pregnant women. The highest rate of exposure to malaria infection during pregnancy 35% occurred in 2018. In 2018, an estimated 872,000 low birth weight children were born to 11 million pregnant mothers who had been exposed to malaria. Delivery to malaria sufferers also raises cases of anemia, babies born prematurely, low birth weight babies (LBW) and interferes with growth, so there is the potential for stunting sin children [1]. It was recorded that in 2019 there were 227 million cases worldwide, and in 2020 it increased to 241 million. In Southeast Asia, Indonesia has the highest percentage of confirmed malaria cases at 49.6% [2].

Indonesia is a country that is very at risk of malaria. In 2020, 254,050 cases of malaria occurred. Malaria morbidity is determined by annual parasite incidence (API) per year. API in Indonesia in the three years (2018-2020) again experienced an increase of 0.83, 0.93, 0.94 per 1,000 population, respectively [3]. One of the government programs to overcome malaria is the elimination of malaria, as stated in the Decree of the Minister of Health Republic of Indonesia no 293 of 2019 concerning malaria elimination. The stages of malaria elimination start from the district/city, provincial, regional and national levels. The target for malaria elimination in Central Java Province was initially set in 2019. However, this target failed and was extended in 2023. This is because Central Java still has areas that must meet the established elimination targets, namely malaria-free regions. Currently, out of 35 districts/cities, there is still 1 district that has yet to be declared malaria elimination, namely Purworejo District. Purworejo's achievements in reducing cases of high malaria of 1,411 issues in 2015, 58 cases in 2018, 25 cases in 2019, to 5 points in 2020 put This district in the maintenance phase of malaria [4]. Re-emerging disease of malaria in July 2021 failed Purworejo to get a malaria-free certificate. Malaria cases again soared, with 584 cases occurring in the year 2021. The increase in cases continues into 2022. Within four months (January-April), malaria cases reached 135 cases [4].

Various biological, sociological, and chemical approaches have also been made to combat Malaria. Although this substance is toxic in vector control, it also causes mosquitos to develop tolerance to new mosquito vectors [5]. According to the findings, *Anopheles* gambiae type M resistance to treatment with the long-lasting insecticide net (LLIN) approach in mosquito nets ranged from 32% to 58%. In 2010, protection for indoor residual spraying (IRS), which involves applying pesticides to inside walls of homes in malaria-affected areas, was 5%. By 2018, that protection had dropped to 2%. As pyrethroid resistance has increased, more expensive pesticides may have been substituted, which may be the cause of the fall in IRS coverage [3]. Increasing resistance to the use of insecticides necessitates increasing doses that harm non-target organisms. So, it is urgent to break through materials that are more effective and environmentally friendly.

The results of previous studies showed better benefits, especially the silver nitrate (Ag_2NO_3) against *Anopheles* mosquitoes compared to other insecticides. Silver nitrate (Ag_2NO_3) is more friendly to the environment. Silver nitrate (Ag_2NO_3) has not affected non-target aquatic organisms [6]. The results of basic research by researchers from the Directorate of Research and Community Service (DRPM) funding sources in 2019 and 2020, show that silver nitrate (Ag_2NO_3) can kill 100% at a concentration of 1; 1.5; and 2 mg/lt; Carbamate, 80% mortality, at a concentration of 0.1; 0.5; 1; 1.5; and 2 mg/lt. Organophosphate (C10H19O6PS2) 80% mortality, at concentrations of 1.5 and 2 mg/lt. The calculation results of lethal concentration 50 (LC50) with concentration to eradicate *Anopheles* mosquitoes, namely silver nitrate 2.22 mg/lt; Organophosphate 3.15 mg/lt; Carbamate 5.59 mg/lt; Synthesis of silver nitrate with Carbamate 4.78 mg/lt; and synthesis of silver nitrate with organophosphate 5.71 mg/l [7].

Carbamate (CO_2NH_3 derivates) is a carbon compound containing carbamic acid, which leaves little residue. Based on the best quantitative structure-activity relationship (HKSA) equation model, A new carbamate derivatives compound, 3-ethyl-2-isopropoxyphenyl methylcarbamate, was discovered that demonstrated superior predicted insecticidal performance to the previous carbamate insecticide molecule. The results showed that the synthesis between carbamate and nanosilver increased the effectiveness of using carbamate from a concentration of mg/lt with the addition of nanosilver nitrate of mg/lt. The efficiency increases twice (200%) when using only a single carbamate compound. This research shows that the results of the synthesis form new compounds. A previous study by Agus using silica ions produced 3-ethyl-2-isopropoxyphenyl methylcarbamate. By substituting silica with silver nitrate, it is suspected to have combinations with the same properties [8]. The ability of nanosilver and its synthesis still requires trials in demonstration areas. This study aimed to analyze the effect of nanosilver and carbamate synthesis on the control of *Anopheles* vectors in malaria-endemic regions.

2. METHOD

2.1. Vector collection and maintenance

The test animal to be used is the adult *Anopheles* mosquito. We obtained the test animals from laboratory breeding results at the laboratory and field laboratory scale. In contrast, on the endemic area scale and lifetime, The Purworejo District Health Office trained malaria cadres to catch mosquitoes in malaria-endemic regions of Purworejo Regency. The mosquitoes were then gathered in maintenance kits and fed sugar water to keep them alive while being used for testing.

2.2. Study design

This research is experimental and uses a post-treatment with control design which was carried out in 4 stages from 2019-2022, which includes laboratory scale tests (2019), field laboratory scale tests (2020), ecological endemic area scale tests (2021), and lifetime tests (2022). In the first and second years, techniques were used using insecticide-treated net (ITN), and in the third and fourth years, IRS. The number of samples was determined through an experimental process employing factorial or random groupings. The research's registration number is 386/EA/KEPK-FKM/2021, and it was authorized by the Faculty of Public Health's Health Ethics Commission.

2.3. Tools and materials

In this study, adult *Anopheles* mosquitoes, carbamate (furan), silver nitrate, and mosquito netting were used. Aspirator, maintenance kit, water quality kit, air quality kit, LLIN, nanoconverter, paper cup, rearing cage, sprayer, and overhead stirrer for converting silver nitrate to nanosilver particles are among the tools utilized.

2.4. Preparation of nanosilver and carbamat solutions

The Diponegoro University Integrated Bio-Nano Laboratory provided the silver nitrate. Wet chemical synthesis of nanosilver colloids was carried out in distilled water and polyvinyl alcohol (PVA) medium. In 50 ml of distilled water, 1.5 grams of PVA were dissolved while being stirred at 70 °C until the mixture was uniform and the color became translucent. A different container was used to dissolve 1.5 grams of silver nitrate ($AgNO_3$) in 5 ml of distilled water while stirring to create a homogenous solution. The silver nitrate ($AgNO_3$) solution was then gradually added to the homogenous PVA solution while being stirred continuously at 70 °C at a rate of one drop per second. Aqua dest is then used to dilute the primary solution according to the total dissolved solid content that was established. In order to lessen the chance of buildup, the produced nanosilver solution was also kept in a dark glass container at a temperature of 2-4 °C. Make a carbamate solution by pulverizing furan and then weighing it according to the desired weight. Furthermore, the carbamate powder was stirred with distilled water until the solution was homogeneous and the colour changed to purple [8].

2.5. Preparation of insecticide solution

The insecticide-infused mosquito nets are made in accordance with the locations where adult mosquitoes breed. Each mosquito net is supplied with an insecticide solution that is tested in laboratories at concentrations of 0.001-0.2 mg/l carbamate with 2.5 mg/l nanosilver, in fields at concentrations of 0.01-2 mg/l carbamate with 0.5 mg/l nanosilver, in ecological areas at concentrations of 100-1,000 mg/l carbamate with 750 mg/l nanosilver with IRS, and over the course of a lifetime at The mosquito nets are constructed from synthetic fabrics that are frequently used by the general public to keep mosquitoes at bay.

2.6. Statistic analysys

Utilizing a graph and the study data for each concentration, the LC50 calculation was performed. The charting outcomes will yield the equation y=Ax+B. This formula can be used to calculate the LC50 concentration by entering 50% of y. To calculate lifetime exposure logarithms, use the equation y=A ln (x)+B. Enter the x variable with days and the y variable with efficacy into this formula to find the logarithm's result for estimating lifetime exposure. Data are entered into Microsoft Excel tables for this study's observational analysis, and they are then presented graphically and table.

3. RESULTS AND DISCUSSION

Toxicity testing of carbamate and nanosilver synthesis on adult *Anopheles* sp. mosquitoes was carried out in 4 scale stages: laboratory scale, field laboratory scale, ecological endemic scale, and lifetime scale. In each test scale, some characteristics differ from one another. Techniques were carried out using insecticide treated net (ITN) on the laboratory and field laboratory scales and IRS on the ecological endemic and lifetime scales

3.1. Laboratory scale test

On a laboratory scale, tests were carried out using a nanosilver solution of 2.5 mg/l and a carbamate concentration of 0.001; 0.005; 0.01; 0.05; 0.1; 0.15; and 0.2 mg/l. The method used at this scale includes ITN or the immersion technique, namely by using a mosquito net formed in a square box as a test site with a total of 5 adult *Anopheles* sp. mosquitoes which are products of laboratory breeding. The advantage of employing ITN is that they are particularly effective in preventing mosquito bites at a relatively low cost and require no specific tools or knowledge to immerse [9].

In this laboratory scale test, along with the addition of carbamate concentration, the percentage of mosquito mortality increased. It can be seen from Figure 1 the results of synthesis tests between nanosilver and carbamate where carbamate concentrations of 0.005-0.5 mg/l can kill test animals by up to 60% and increase to 100% at concentrations of added carbamate of 0.1-0.2 mg/l. This is because carbamate acts on insects by inhibiting the nervous system, namely the enzyme acetylcholinesterase (AChE). This enzyme receives impulses, which will then be forwarded to the brain's nervous system. If the performance of this enzyme is disrupted, gradually, the test animal will not receive a response and will die. This inhibition is reversible. This means that the enzyme inhibitor will not last long and, at one time, will reproduce the cholinesterase enzyme.

This is also related to nanoparticle compounds where the properties of nanoparticles can also inhibit the action of enzymes, so this is a good combination of carbamate and nanosilver. Nanosilver technology can be developed, especially in the health sector, which is currently widely used with Nano-TiO2, Silica, and herbal ingredients [10]. A study conducted by Aviitabile found that nanosilver particles have the potential to act as anti-malaria in the *Artemisia* parasite species, where human erythrocytes come into contact with nanosilver particles, making them sensitive and, after 24 hours of incubation, there is no rise in hemolytic activity, preventing malaria cases. The antibacterial properties of silver nanoparticles (AgNPs) reveal various aspects that are pertinent to the formation of reacrive oxygen species as promoters of cell death mechanisms, primarily through the mitochondrial apoptotic pathway, along with severe cell membrane damage and enzyme inactivation through silver binding, which can impair the function of plasmodium cells [11]. Spherical AgNPs with diameters of 20-50 nm were synthesised in a single pot using biomass from *Nocardiopsis* sp. GRG1 (KT235640). At 5-60 g/mL, the synthesised AgNPs demonstrated antibacterial and antibiofilm properties against a clinical isolate Staphylococci [12].

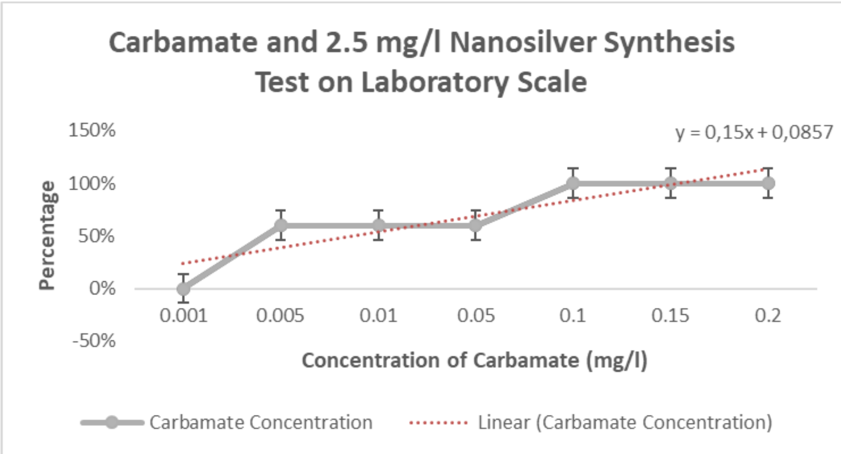

Figure 1. Carbamate and 2.5 mg/l nanaosilver synthesis test on laboratory scale

3.2. Field laboratory scale test

The compound synthesis could kill adult mosquitoes by up to 20% at a concentration of 0.01 mg/l carbamate, and increased to the highest peak mortality reaching 60% at a concentration of 0.1 mg/l carbamate, according to a field laboratory scale toxicology test of 0.5 mg/l nanosilver and carbamate synthesis on *Anopheles* sp. mosquitoes in Figure 2. At a carbamate concentration of 0.5-1.5 mg/l, mortality was reduced by up to 40%; at a carbamate concentration of 2 mg/l, mortality was again reduced by 20%.

The research was conducted on a field laboratory scale test to synthesize carbamate and nanoparticles of 0.5 mg/l using insecticide-treated nets (ITN). The concentration of carbamate used is 0.01; 0.05; 0.1; 0.5; 1; 1.5; and two mg/l. The test animals used were 5, with breeding results at the study site. On this scale, the highest number of deaths reached 60% with a carbamate concentration of 0.1 mg/l, which then decreased and stagnated at a concentration of 0.5-1.5 mg/l with a mortality of 40% and decreased again to the lowest number of deaths of 20% with a concentration carbamate of 2 mg/l.

Field laboratory-scale tests showed that the adult *Anopheles* sp. experienced a level of resistance, so the addition of carbamate concentrations did not make the mosquito population die more. Still, fluctuations occurred at a concentration of 0.1 mg/l, and then these mosquitoes experienced adjustment and resistance so that at a concentration of 2 mg/l, the number of mosquito deaths was low. Continuous exposure to carbamate can be resistant. Studies in southern Zambia showed that the subspecies of *Anopheles* group funestus showed evidence of resistance to deltamethrin (a pyrethroid) and bendiocarb (a carbamate) with a resistance rate of 40.9% [13]. If most of the vector mosquito population is resistant to insecticides, then using insecticides will be ineffective for controlling vectors. Other research has demonstrated that *Anopheles* in Sri Lanka may be susceptible to malathion resistance because of the high metabolic activity of the esterase enzyme [14]. The HKSA equation model was used to create a novel carbamate derivative, 3-ethyl-2-isopropoxy phenyl methylcarbamate, which outperformed existing carbamate insecticides in terms of predicting insecticidal performance.

The existence of a new carbamate derivative which is then synthesized with 0.5 mg/l nanosilver, is expected to cause mosquitoes to become weak. The toxic effectiveness of nanoparticles on the physiology of the *Anopheles* stephensi vector, namely in nanomaterial compounds (Ag, Au, ZnO, Polystyrene, SiO_2), can cause physiological effects in the form of epithelial damage, loss of hair, damage to the midgut and cortex, abuse of body structure in *Anopheles* mosquito larvae [15]–[17]. It turns out that when this synthesis was carried out, it did not produce 100% effectiveness of dead mosquitoes, but this has been effectively applied in small-scale field laboratories so that it can become the basis for endemic area scale with a more significant number of test mosquitoes and direct application in endemic areas.

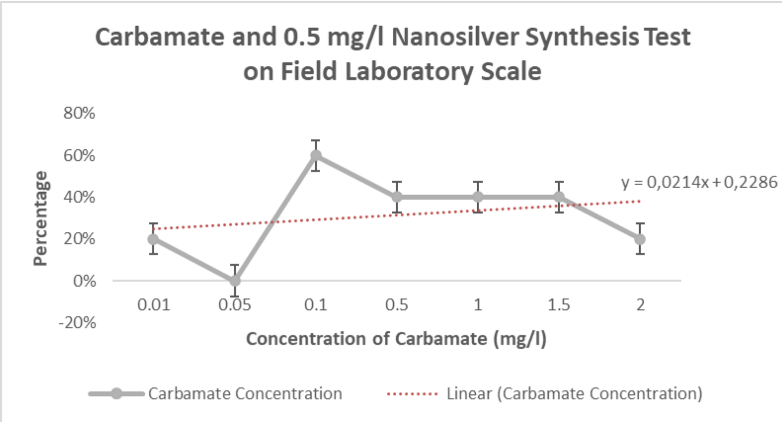

Figure 2. Carbamate and 0.5 mg/l nanosilver synthesis test on field laboratory scale

3.2.1. Endemic ecological test

The compound synthesis could kill adult mosquitoes up to 40% at a dosage of 300 mg/l carbamate, according to a toxicology test using 750 mg/l nanosilver and carbamate on *Anopheles* sp. mosquitoes in the ecological region in Figure 3. Adult mosquito mortality increased until the maximum mortality reached 76% at a concentration of 900 mg/l carbamate, and subsequently reduced to 64% at a concentration of 1,000 mg/l carbamate.

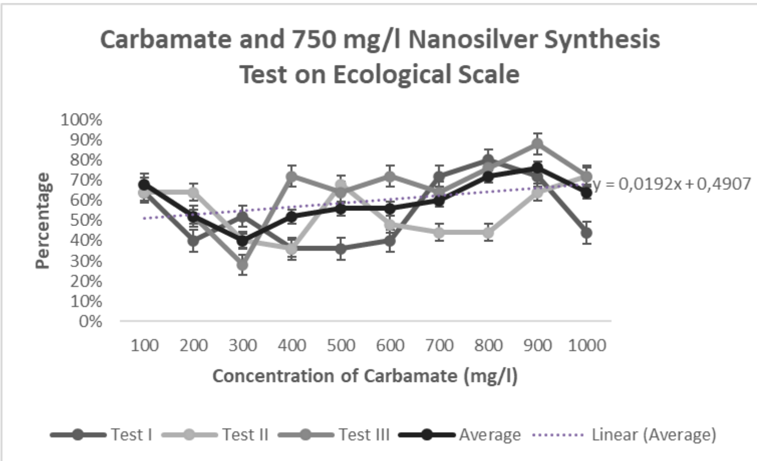

Figure 3. Carbamate and 750 mg/l nanosilver synthesis test on ecological scale

The endemic area scale was carried out using a method different from the two previous test scales, namely the IRS method, where an effective vector control tool currently includes IRS [18]. IRS, is a vector control effort to reduce the spread of malaria and reduce malaria morbidity by sticking certain insect poisons in a predetermined amount (dose) evenly on the surface of the sprayed house wall. This scale test synthesizes 750 mg/l nanosilver and 100-1,000 mg/l carbamate concentrations. The test animals used were adult *Anopheles* sp. mosquitoes weighing 25. These mosquitoes were obtained from the environment around endemic areas near cattle pens, bushes, plantations, and rivers. The synthesis test with the lowest mortality was at a carbamate concentration of 300 mg/l with a mortality percentage of 40%, while the highest mortality reached 76% at 900 mg/l carbamate concentration.

This was done in research into endemic ecological areas showing that the synthesis of nanosilver and carbamate was dosed correctly, especially at a fixed concentration of 750 mg/l nanosilver. This is because, as the concentration of carbamate increases, the number of deaths increases, with the highest peak concentration at 900 mg/l carbamate. The synthesis of carbamate and nanosilver encourages a more effective reaction to react with the enzyme AChE. The AgNP mechanism can kill anopheles' mosquitoes because Ag^+ can seep into the bacteria through the cell wall, which causes the bacterial cell wall to break, causing protein denaturation and death. Formation of positively charged Ag^+ free radicals and negatively charged prak nanoparticles so that antimicrobials can be bound and effective in inhibiting microbial growth in the body of anopheles mosquitoes [19]. The size of nanoparticles is 1-100 nm which can enter the mosquito's body through digestion and pores so that it can efficiently inhibit the performance of the brain's nerves to doing an activity [20]. Nosilver materials have the features of being biodegradable, biocompatible, and versatile in their use because they are made of synthetic and semi-synthetic polymers as well as naturally occurring active medicinal compounds [21], [22].

3.2.2. Life time scale test

Toxicity test of nanosilver and carbamate synthesis on adult Anopheles sp mosquitoes on a lifetime scale in Table 1 showed indicated the synthetic substances were capable of killing up to 97% of people on day 1, 84% on day 2, and 96% on day 1 with the highest death peak. The lowest number of mosquito deaths was on the last day, namely day 32, at 51%.

The research scale test in a lifetime takes a continuation of the scale test in endemic ecological areas where took the fixed concentration of nanosilver and took carbamate synthesis was carried from the highest percentage of mortality with fixed attention of 900 mg/l carbamate and 750 mg/l nanosilver. This makes the concentration tested again to determine effectiveness in the lifetime. On the lifetime scale, the test is carried out by calculating the sample based on the day of death, where the determination of the day has six stages, namely days 1;2;4;8;16; and 32, which can project the results for the lifetime. The method used on this scale is using IRS or indoor residual spraying with 25 samples of test animals. Test animals were obtained from environmental areas around endemic areas, namely livestock pens, plantations, rice fields, and rivers.

Table 1. Synthesis test results of 900 mg/l carbamate and 750 mg/l nanosilver lifetime scale

Day	Observation of *Anopheles* mosquito death (24 hours)							
	I	%	II	%	III	%	Average	%
1x24 hour	24	96%	24	96%	25	100%	24	97%
2x24 hour	22	88%	20	80%	20	80%	21	84%
4x24 hour	22	88%	25	100%	25	100%	24	96%
8x24 hour	10	40%	17	58%	24	96%	17	68%
16x24 hour	20	80%	21	84%	21	84%	21	83%
32x24 hour	17	58%	11	44%	10	40%	13	51%

By displaying the outcomes of toxicity experiments in Figure 4, the LC50 for carbamate and nanosilver production was calculated using a linear prediction approach. Figure 4 shows the variation of carbamate and nanosilver concentrations at fixed concentrations of 900 mg/l carbamate and 750 mg/l nanosilver. Results of a linear prediction using the equation $Y=(-)0.0746x+1.0593$ were obtained. By entering a Y value of 0.5, the concentration value produced is 7.497 mg/l, which is the LC50.

Shanmugasundaran's research stated that the biosynthesis of AgNP and $AgNo_3$ Nanosilver showed significant larvicidal activity against malaria vectors where this approach was a fast, cost-effective, environmentally friendly step to inhibit the growth of malaria vectors with an LC50 of 51.34 mg/l and an X_2 value of 8.228) [23]. The formula for trend analysis is displayed in the logarithmic chart in Figure 5, $Y=(-)0.108Ln(X)+0.9822$. The prediction results using this formula show that on the 60th day (two months after spraying), the effectiveness of carbamate utilization is 54%. This effectiveness decreased by 42% six months after the IRS (180 days) and by one year after the IRS (360 days) to 35%.

The lifetime efficacy test showed that the highest number of deaths was on the first day, with a percentage of 97% which then fluctuated, and the lowest decrease in the number of deaths was on the last day, namely day 32, with a portion of 52%. This shows that the synthesis of 900 mg/l carbamate and 750 mg/l nanosilver is still adequate for the future. Where the use of nanosilver has the potential to be used on mosquitoes, green fabricated nanoparticles can be applied as a toxic agent against young instar mosquitoes and as an adult ovipositor. The efficiency of an enzyme affects how well an insecticide is absorbed by target mosquitoes. Typically, specific target sites are proteins or enzymes that function as insecticide effectors [24].

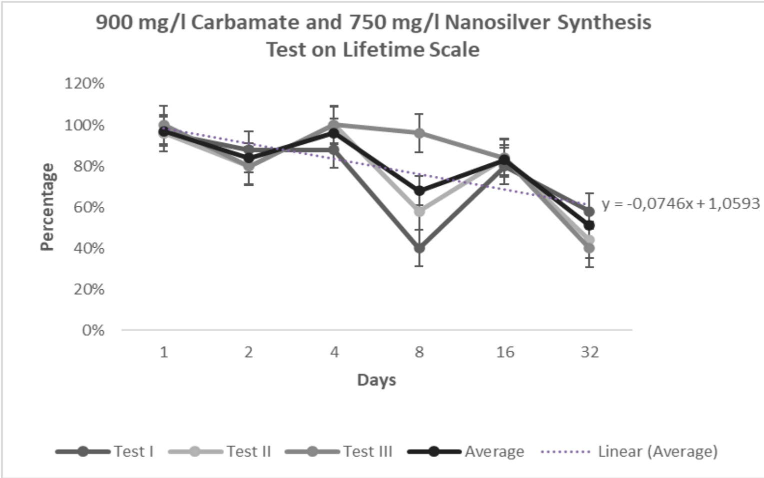

Figure 4. The 900 mg/l carbamate and 750 mg/l nanosilver synthesis test on lifetime scale

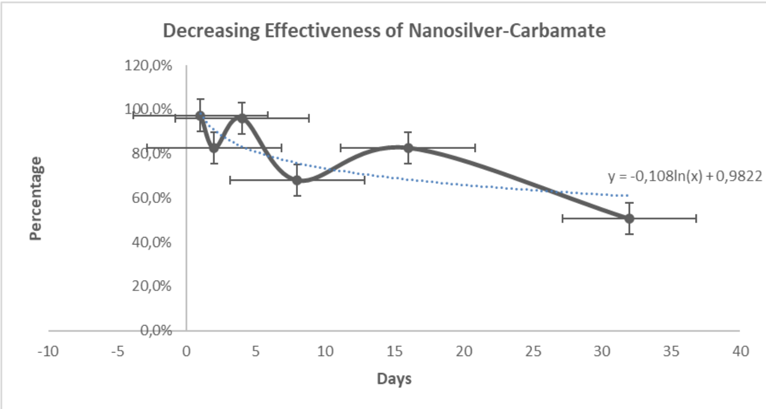

Figure 5. Decreasing effectiveness of nanosilver-carbamate

Overall, carbamate is a pesticide that can inhibit the breeding of *Anopheles* sp. mosquito vectors so that it can reduce mortality from malaria. However, as time passes, these mosquitoes are increasingly resistant to chemical insecticides, one of which is carbamate. This is also due to the length of exposure and incorrect doses. In addition, chemicals can also harm the surrounding environment. It is known, Resistance causes an increase in the quantity of insecticide use, and an increase in the dose threatens non-target organisms and endangers the environment [25]. This was proven in Pwalia's research, which stated that anopheles' mosquitoes experienced resistance to carbamate pesticides where concentrations of 0.99 and 0.76 mg/l carbamate caused high resistance with 10x survival and 16.2% mortality. So it is necessary to synthesize with other environmentally friendly materials to not cause environmental pollution from the high concentrations and doses of carbamate pesticides [26].

WHO classifies the types of carbofuran, butocarboxim, and butoxycarboxim carbamates to class 1b (very dangerous) [27]. Therefore, a breakthrough used is the herbal insecticide in nanosilver. Nanosilver is a breakthrough technology that can operate in various fields. The synthesis used was a mixture of carbamate and nanosilver, so I found the proper dose to kill *Anopheles* sp. Nano-based insecticide formulations in India show many benefits over conventional formulations, as applying nano pesticides with eco-friendly organic ingredients has demonstrated toxicity against ticks and mosquitoes, and can control a variety of insects and pests [28].

Nanoparticles containing silver and minocycline. Minocycline and silver were both quite effective when taken alone, but the combination outperformed the individual agents, allowing for lower doses of both treatments to achieve comparable antibacterial efficacy [29]. The individual nanoparticles interact with each other through chemical bonds and physical interfacial attractions, resulting in accumulation. Must maintain this enormous surface energy arising from the individual nanostructures to obtain a stable dispersion of nanoparticles. The concept of stabilizers can be carried out by synthesis with organophosphates or carbamates [30].

The biomechanical principle of nanosilver and carbamate synthesis where nanosilver particles can penetrate the mosquito's stomach, thereby accelerating the biochemical reaction with AChE, making it more effective and having a lower dose. The synthesis of nanosilver and carbamate works because it inhibits the AChe enzyme as a nervous response to the central system. If the AChe enzyme is blocked, the central nervous system cannot receive impulses, so there is no response. The rate at which the enzymes esterases, monooxygenases, glutathione S-transferase (GST), and AChE are metabolized during the pesticide detoxification process determines these features [25]. The presence of herbal insecticides can lower carbamate concentrations, and the level of exposure efficacy to mosquitoes remains optimal by adding herbal substances in nanosilver.

4. CONCLUSION

The synthetic concentration between nanosilver and carbamate (CO_2NH_3 derivative) is very appropriate to use to control anopheles at a dose of 7,497 mg/lt. The synthesis of this material is effective for controlling Anopheles using the material diffusion method in captivity with indoor spraying (IRS). Findings from the Synthesis of Nanosilver and Carbamate, are alternative insecticides that are more environmentally friendly and have the potential to be developed in further research.

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