

Larvicidal and Ovicidal Activities of Some Cinnamaldehyde Derivatives against *Anopheles Gambiae*, Malaria Vector Agent

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Abstract Main research studies have been conducted on vector control for the fight against malaria, a very devastating disease in sub-Saharan Africa. This study was designed to carry out larvicidal and ovicidal activities of some chemical constituents of essential oils. Eleven compounds including related derivatives have been either purchased or synthesized and evaluated for their activities. Larvae and eggs of anopheles have been produced. Cinnamaldehyde and *ortho*-Nitrocinnamaldehyde exhibited the highest activity with LC₅₀ = 55 mg /L against larvae. Furthermore, Citral, and Cinnamaldehyde showed the highest activity against eggs, with LC₅₀ = 0.015 and 0.020 respectively. This study revealed that the compounds were more active than their corresponding essential oils. Hence, it is important to carry out a more in-depth study of the structure activity relationship on chemical compounds was been demonstrated.

Keywords Cinnamaldehyde derivatives, Essential oil constituents, Larvicidal, Ovicidal activities

1. Introduction

Malaria remains one of the most devastating endemics in black Africa since time immemorial. It is caused by a Hemococcidae of the genus Plasmodium, transmitted to humans by a female mosquito of the genus Anopheles. The world Health Organization (WHO) statistically reported that an approximation of 627000 deaths related to malaria occurred in 2020, of which 96% were recorded in Africa. Additionally, children under 5 years and pregnant women were the most vulnerable segment of the population [1].

Several efforts have been made to combat this disease, including the use of vector control and other products such as DDT, which ended up being ban because of their detrimental effects on the environment [2,3,4,5]. However, resistance to antimalarials drugs has been observed for the past decade and we are gradually returning to vector control, with low environmental effects through intensive research on biopesticides [6,7,8]. Thus, several works investigated the activities of essential oils against *Anopheles gambiae*

[9,10,11,12,13,14,15]. Mdoe *et al.* 2014, reported that the essential oils of *Cinnamomum osmophloeum* exhibited high mortality of *A. gambiae* s.s. third instar larvae dosage and time dependant in both laboratory and semi-field trials [9]. Furthermore, several other authors including Bossou, *et al.* 2013, reported that the essential oils from *Cymbopogon. Citrates* have insecticidal properties against the vector of malaria, *Anopheles gambiae* [10].

The use of pesticides derived from plant materials may create another problem with regard to the conservation of biodiversity. Indeed, it seems impossible to reconcile the high demand for raw materials of plant origin for industry and the respect of conventions and treaties on the conservation of biodiversity [16]. The history of malaria tells us that the first natural drug was quinine, which gave rise to chloroquine [17]. Antibiotic therapy also began with molecules from biosynthesis to arrive at synthetic antibiotics [17]. Literature have showed that monoterpenes have activities against insects such as *Aedes aegypti*, *Culex pipiens* and *Anopheles gambiae* [18,19,20,21]. Newman *et al* reported on a 20, 25 and 30 years statistical studies comparing natural, hemisynthetic and synthetic products. The founding of these studies showed that industrial products are predominantly synthesis molecules [22,23,24]. The history of the evolution of antimalarial and antibiotic

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drugs has shown that the natural substance led to the synthetic product (quinine and chloroquine for example). In addition, studies by Newman *et al.* showed that a lot of drugs in the market have synthetic origin. Several studies have shown that synthetic monoterpenes are more active than the essential oils from which they come.

This research focused on the choice of synthetic molecules as chemical constituents of essential oils, and secondly on the evaluation of their larvicidal and ovicidal activities. The outcomes of this research study are directed to the finding of more bioactive compounds with significant quantity.

2. Experimental Section

Materials and methods

All chemicals and solvents were purchased from VWR-France. The melting points of synthesized compounds were determined in Kofler banc and are uncorrected. Thin layer chromatography (TLC) plate (silica gel G) were purchased from Merck and various solvents such as toluene,

acetone, ethanol were used or combined to obtained the more effective and prominent solvent systems. Finally, the UV lamp were used to visualize the TLC plate at two different wavelengths: 254 and or 365 nm. The NMR spectra were carried out on an Avance 400 MHz spectrometer (Bruker, Rheinstetten, Germany), using deuterated dimethylsulfoxide.

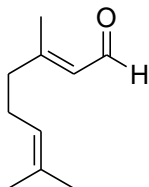
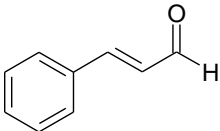
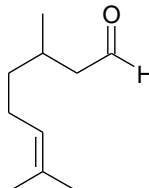
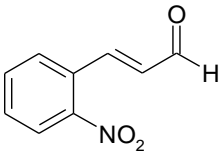
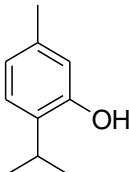
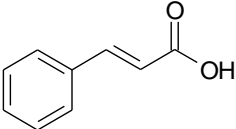
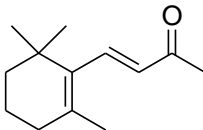
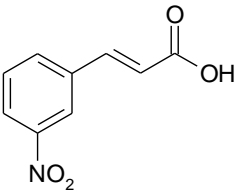
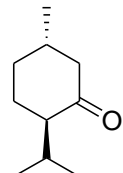
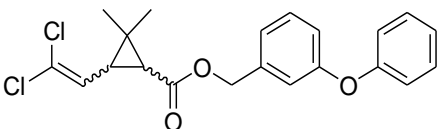
Study area

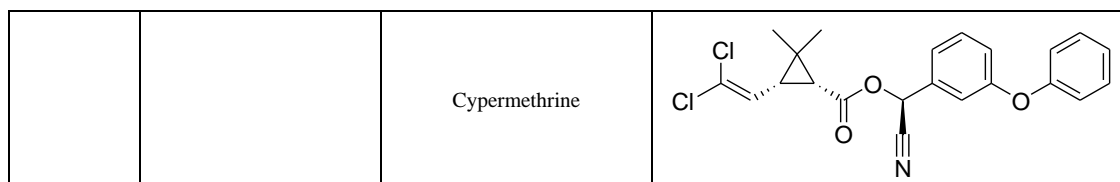
This research project was conducted in 2020 in CHIRE – CONGO at the laboratory of medicinal chemistry and pharmacotechnie of medicinal plants, B.P: 13.922 Brazzaville, Republic of Congo and at the Plant and Life Chemistry Unit, Faculty of Sciences and Techniques, Marien Ngouabi University, Brazzaville BP 69.

Chemical structures of selected compounds

Table 1 describes the molecular structures of Citral, Cinnamaldehyde, Thymol, Ionone, Menthone, Citronellal, *ortho*-Nitrocinnamaldehyde, Cinnamic acid, *meta*-Nitrocinnamic acid, Permethrin and Cypermethrin.

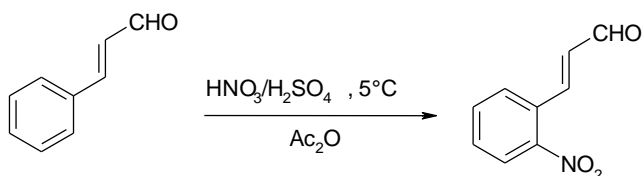
Table 1. Names and chemical structures of compounds

Name	Chemical structure	Name	Chemical structure
Citral		Cinnamaldehyde	
Citronellal		<i>Ortho</i> -Nitrocinnamaldehyde	
Thymol		Cinnamic acid	
Ionone		Nitrocinnamic acid	
Menthone		Permethrine	



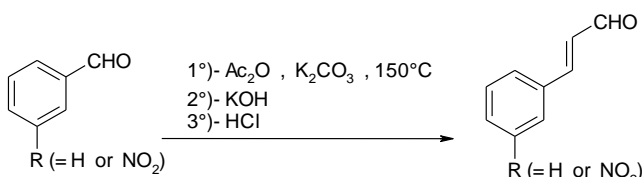
General Procedure for the Synthesis of chemical compound

Synthesis of *ortho*-Nitrocinnamaldéhyde [25]



A mass of 2.6 g (20 mmol) of cinnamaldehyde was placed in a 500 mL three necked round bottom flask. A volume 25 mL of acetic anhydride was added to the flask. The balloon was put in an ice with salt bath, and then placed on a magnetic stirrer. A volume of 1 mL of nitric acid and 2.5 mL of sulphuric acid was added and stirred for further 18 min, then for 2 hours on the ice bath. The solution was allowed to cool down for 48 hours, and, the solution of concentrated hydrochloric acid was added to the reaction medium and allow to cool down to reveal the crystals. The precipitate obtained was filtered and dried. The product was recrystallized in ethanol to obtain pure *ortho*-Nitrocinnamaldehyde.

Synthesis of cinnamic acid [26] and *meta*-Nitrocinnamic acid [27]



An amount of 3.75 g of anhydrous potassium carbonate and 12.5 mL (130 mmol) of acetic anhydride were placed in a properly equipped 250 mL three necked round bottom flask. The reaction medium was shaken, and 85 mmol of the corresponding aldehyde was added. The temperature of the mixture was increased to 150°C for 1 hour and 15 minutes while checking the foam. In a 500 mL beaker placed in an ice bath, prepare a solution of 14 g potassium hydroxide in 120 mL of water. After cooling slowly, the still warm to the reaction mixture (about 100°C) was pour into the beaker held in the ice bath. The solution was washed 2 times with 20 mL of diethyl ether. Acidify the aqueous phase with concentrated hydrochloric acid up to pH at about 1. Cool to a temperature below 10°C. The raw cinnamic acid was filtered on Buchner, then washed with cold water and recrystallized in water/ethanol mixture (2-1).

Production of *Anopheles gambiae*'s eggs

The larvae of *Anopheles gambiae* were collected at the edge of the river Tsiémé, in Ouenzé - Brazzaville. These larvae were transported to the Faculty of Sciences and Technologies, where they were fed with non-creamy cookies for 4 days, in a cubic cage, 60 cm sides, surrounded by a non-impregnated mosquito net on their face, so that adult mosquitoes from the emergence of the larvae do not escape. Several kinds of cotton soaked in glucose solution were placed in the mosquito cage so that they could feed. After 3 days of feeding, the adult mosquitoes with glucose solution, an anaesthetized rat was introduced into the mosquito cage for 48 hours, so that the fertilized females take their blood meal for the good development of their eggs. After 4 days of the blood meal, mosquito eggs were laid in small plastic tubs, then placed in the mosquito box.

Larvicidal and ovicidal activities

Larvicidal and ovicidal bioassay was carried out as described by Kende *et al.* [14,15]. Larvicid and ovicide activities have reconciled counts of dead larvae or eggs after exposure to solutions of Citral, Cinnamaldehyde, Thymol, Ionone, Menthone and Citronellal, *ortho*-Nitrocinnamaldehyde, *meta*-Nitrocinnamic acid, Cinnamic acid, Permethrin and Cypermethrin. Several 25 larvae of *Anopheles gambiae* in stage 4 or 25 eggs were introduced into a 5 cm diameter cup containing 80 mL of tested product concentration solution. The concentrations were 0 ppm (control), 12.5, 25, 50, 100, 200 and 400 ppm except for Permethrin and Cypermethrin where concentrations were 0.05 g/L; 0.025 g/L; 0.0125 g/L; 0.0062 g/L and 0.0031 g/L prepared from 10% commercial solutions. The set is incubated at room temperature for 24 hours for larvae and 72 hours for eggs. All the experiments were repeated three times. The percentage of mortality of larvae was calculated using formula 1, while the percentage of mortality of eggs was calculated using formula 2, previously described in our previous works [14,15].

$$\% \text{ larvae mortality} = \frac{\text{Number of dead larvae}}{\text{Number of exposed larvae}} \times 100 \quad (1)$$

$$\% \text{ egg mortality} = \frac{\text{Number of exposed eggs} - \text{number of larvae}}{\text{Number of exposed eggs}} \times 100 \quad (2)$$

3. Resultats et Discussion

Synthesis of *ortho*-Nitrocinnamaldéhyde

The *ortho*-Nitrocinnamaldehyde was synthesized by nitration of Cinnamaldehyde under the action of nitric-sulphuric acid mixture in acetic anhydride at 5°C. The product was obtained with a yield of 50%, purity was confirmed by CCM and the melting point was 126°C, lit. 126-127.5°C [25]. $C_9H_7O_3N$: 177,16 1H -MR (Fig. 1): 6.76 (dd, 1H, $J = 15.8$ Hz, $J = 7.6$ Hz, 1H, $-CH=CH-CHO$), 7.69

(td, 1H, $J = 7.1$ Hz, $J = 1.1$ Hz, H_5 -Ar); 7.77 (t, 1H, $J = 7.2$ Hz, 1H, H_4 -Ar), 7.90 (d, 1H, $J = 7.3$ Hz, H_6 Ar), 7.99 (d, 1H, $J = 15.8$, $-CH=CH-CHO$), 8.06 (dd, 1H, $J = 8.1$ Hz, $J = 0.9$, H_3 Ar), 9.69 (d, 1H, $J = 7.6$, $-CHO$); ^{13}C -NMR (Fig. 2): 125.25 (C_3 Ar), 129.44 (C_1 Ar), 129.76 (Ar-CH=CH), 132.10 (C_4 Ar), 132.44 (C_5 Ar), 134.50 (C_6 Ar), 147.88 (C_2-NO_2), 148.61 (Ar-CH=CH-), 195.10 ($-CHO$).

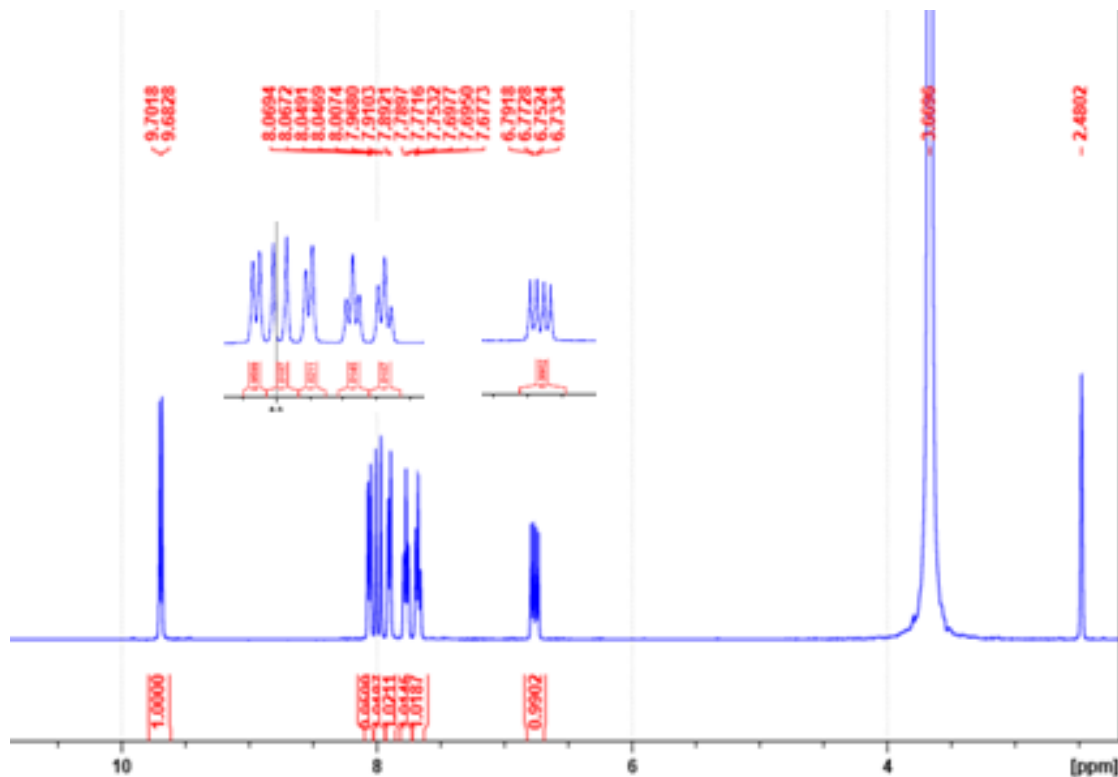


Figure 1. 1H -NMR (400 MHz, DMSO- d_6) of *ortho*-Nitrocinnamaldehyde

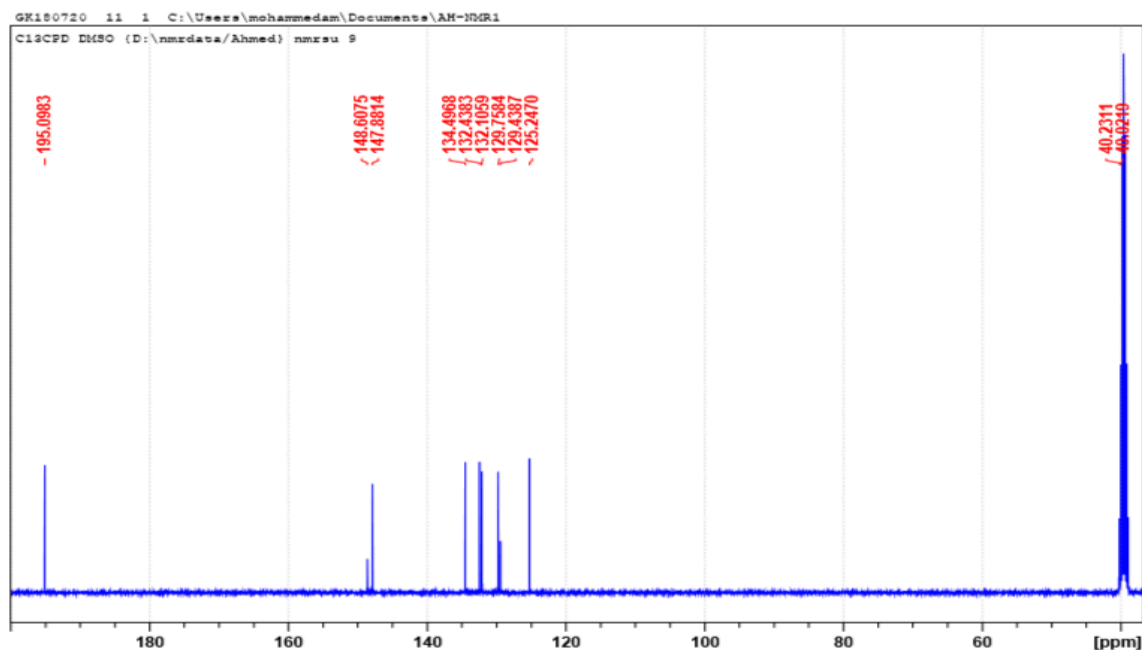


Figure 2. ^{13}C -NMR (DMSO- d_6) of *ortho*-Nitrocinnamaldehyde

Table 2. Mortality of larvae exposed to increasing concentrations of chemical compounds in percent and LC50

Name of chemical compounds	Concentrations of chemical compounds						
	0.4 g/L	0.2 g/L	0.1 g/L	0.05 g/L	0.025g/L	0 g/L	CL ₅₀ en g/L
Citral	100±0.0%	93.33±1.67%	64±0.0%	44.0±0.0%	0.0±0%	0%	0.064
Cinnamaldehyde	100±0%	100±0.0%	100±0.0%	44.0±0.0%	12.0±0.0%	0%	0.055
Thymol	100±0.0%	100±0.0%	78.67±0.88%	34.67±1.67%	0.0±0%	0%	0.067
Ionone	10±0.0%	98.67±0.0%	60.0±0.0±%	16.0±0.0%	0.0±0.0%	0%	0.090
Menthone	100±0.0%	45.33±1.77%	10.67±0.88%	0.0±0.0%	0.0±0.0	0%	0.100
Citronellal	100±0.0%	80±0.0%	50.06±1.77%	16.0±0.0%	0.0±0%	0%	0.210
<i>ortho</i> -Nitrocinnamaldehyde	100±0.0%	100±0.0%	98.68±1.77%	46.58±2.22%	12±0.0%	0%	0.055
Cinnamic acid	100±0.0%	80±0.0%	20±0.0%	0.00%	0.00%	0%	0.065
<i>meta</i> -Nitrocinnamic acid	100±0.0%	100±0.0%	70.67±1.77%	40±0.0%	00.00%	0%	0.150
Name of chemical compounds	Concentrations of chemical compounds						CL ₅₀ en g/L
	0.025g/L	0.0125g/L	0.00625g/L	0.003125g/L	0 g/L		
Permethrin	100 %	90.00 %	33.33±0.89 %	18.0±0.00%	0 %		0.011
Cypermethrin	100 %	77.33±1.77%	30.0±0.00 %	13.33±0.89%	0 %		0.012

There is a dose-dependent evolution of the larvicidal character of the tested compounds at different concentrations. In general, all these compounds prevented larval emergence into adults and caused larval death at a concentration of 0.4 g/L. This result is consistent with the reported work of Antonios *et al.*, Eliningaya *et al.* and Gad *et al.* [19-21]. Furthermore, Antonios *et al.* observed that oxygen-containing functions were important for maintaining good activity. However, our results exhibited the LC50 values for the larvicidal activity ranging from 0.055 to 0.210 g/L (Fig. 5). Cinnamaldehyde and *ortho*-Nitrocinnamaldehyde are the most toxic to *Anopheles gambiae* larvae, with the same LC50 (0.055 g/L); followed by Citral (0.064g/L), Cinnamic acid (0.065g/L) and Thymol (0.067 g/L), respectively. It is noteworthy to note that at the concentration of 0.1 g/L, Cinnamaldehyde demonstrated 100% toxicity followed by *ortho*-Nitrocinnamaldehyde (98.68%), whereas *meta*-Nitrocinnamic acid and Cinnamic acid only killed 70.67% and 20% of the larvae, respectively. It can be observed that the aldehyde function is important for this activity demonstrated because the change from aldehyde to acid causes a variation in activity of 100% to 20% with respect to observed results for the concentration of 0.1 g/L. Citral and Citronellal differed in their structure only for the conjugated double bond to aldehyde group. However, the LC50 value of Citral is 0.064 while the LC50 of Citronella is 0.210. Hence, there is a decrease in activity of a little more than three times by switching from citral to citronella. The investigation of numerous essential oils including *Zingiber officinale*, and *Cymbopogon citrates* containing Citral, Cinnamaldehyde and Thymol was carried out and the larvicide assessment of these oils showed the LC50 of 0.11 g/L and 0.19 g/L respectively (Kende G. *et al.*, 2019). It can be concluded that the activities of these essential oils are justified by the presence of these chemical compounds.

Additionally, when comparing the LC50 values of *Zingiber officinale* (0.11 g/L), and *Cymbopogon citratus* (0.19 g/L) with the LC50 of citral (0.064g/L), it was found that the activity of Citral is was approximatively twice higher than the essential oils containing them. The same finding was recorded for Cinnamaldehyde with the LC50 value of 0.055 g/L while the LC50 value of the essential oil where it is present was 0.11 g/L. Here again, the activity exhibited by Cinnamaldehyde is twice higher than the essential oil containing it. The same observation was also recorded for thymol (LC50 = 0.067 g/L), which is a compound present in *Lippia multiflora* oil (LC50 = 0.13 g/L), and the LC50 of Thymol was also twice higher than the one for *Lippia multiflora* oil.

The LC50 for Cinnamaldehyde, *ortho*-Nitrocinnamaldehyde, Cinnamic acid and *meta*-Nitrocinnamic acid are 0.055, 0.055, 0.065 and 1.150, respectively (Fig. 6). It can be observed that the introduction of a nitro substituent in position C-2 of Cinnamaldehyde does not modify the activity. However, the replacement of aldehyde function by carboxylic acid function decreases the activity. The introduction of a nitro group in the *meta* position of the acid decreases the activity three times compared to aldehyde and more than double compared to Cinnamic acid.

Based on all the observation, it can be concluded that essential oils are good sources of leading molecules for the research of biopesticides and or synthetic pesticides. This assertion is also confirmed by series of studies on the bibliography described by David J. Newman *et al.* in 2003, 2007 and 2012, over a period of 20, 25 and 30 years of research, which showed that synthetic products are essential and a safe source of raw materials for industry and trade [22,23,24]. But also, it has been established that plants, by their biodiversities, are a reliable source of molecular diversity for the research of bioactive molecules.

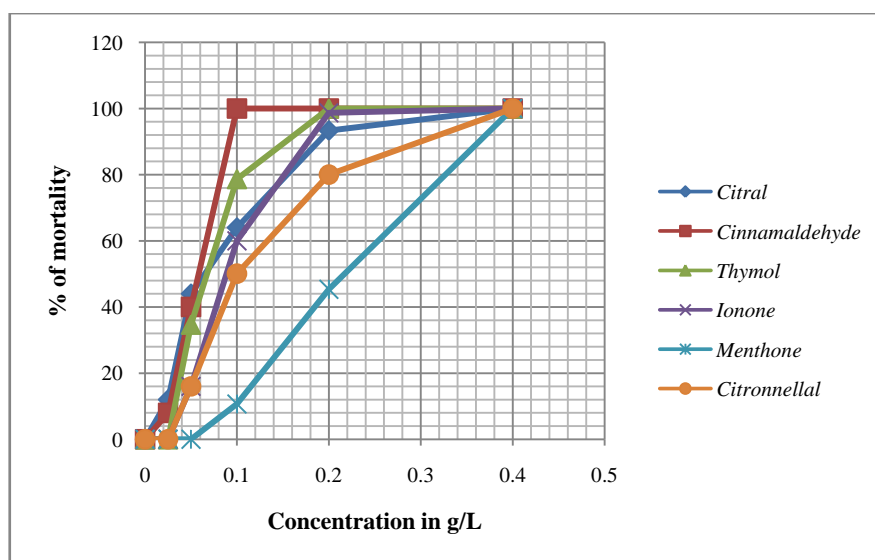


Figure 5. Evolution of *Anopheles gambiae* larvae mortality after 24 hrs of exposition to different concentrations of chemical compounds

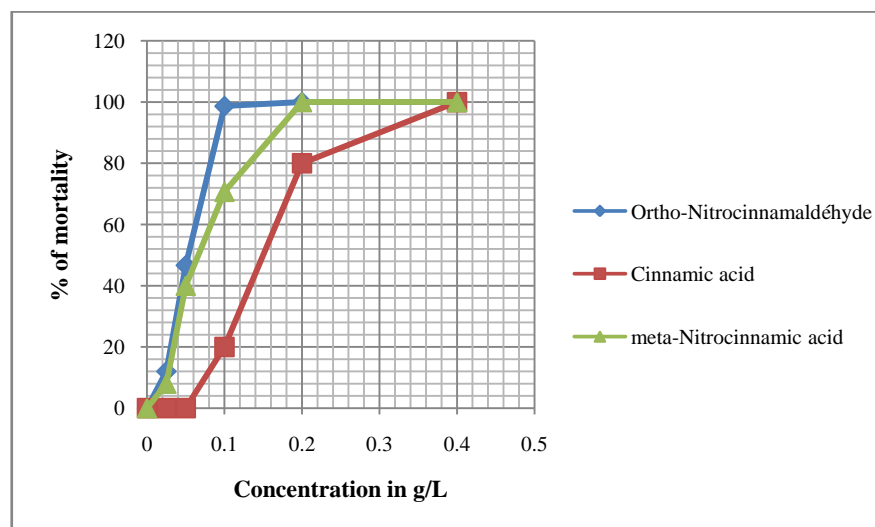


Figure 6. Evolution of *Anopheles gambiae* larvae mortality after 24 hours of exposition to different concentrations of chemical compounds

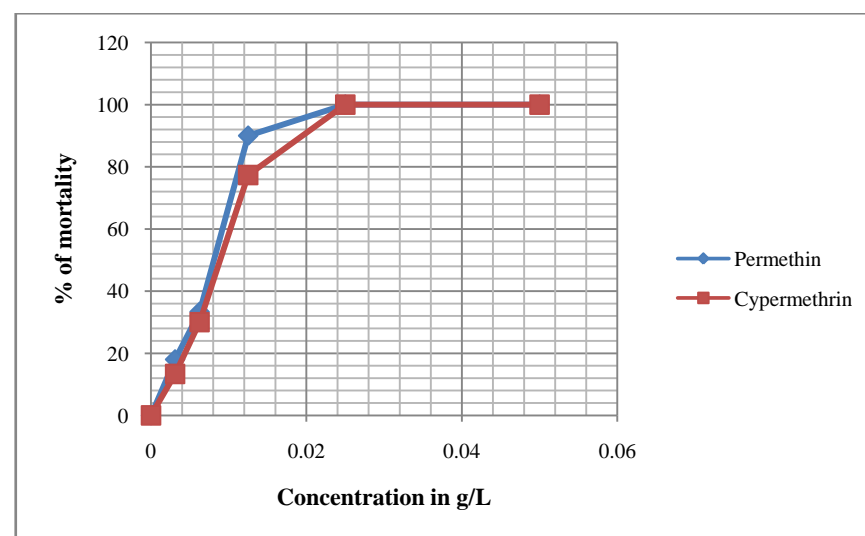


Figure 7. Evolution of *Anopheles gambiae* larvae mortality after 24 hours of exposition to different concentrations of chemical compounds Permethrin and Cypermethrin

With an LC50 value of 0.011 g/L and 0.012 g/L for permethrin and cypermethrin respectively (Fig. 7), the larvicidal activity of these reference compounds is 8 times higher than that of the essential oils, and about 5 times higher than that of other compounds present in essential oils or their derivatives.

Ovicidal activities against *Anopheles gambiae*

Table 3 shows the percentage of mortality of *Anopheles gambiae* eggs after 72 hours of exposure to different concentrations of Citral, Cinnamaldehyde, Thymol, Ionone, Menthone, Citronellal, O-Nitrocinnamaldehyde, Cinnamic acid, and m-Nitrocinnamic acid.

All these compounds inhibit the evolution of *Anopheles gambiae* eggs after 72 hours of contact. There are LC50 ranging from 0.015 to 0.16, a factor of the order of ten between the most active and the least active compound. The most active compound is Citral with a LC50 value of 0.015, followed by Cinnamaldehyde with a LC50 value of 0.020 and *ortho*-Nitrocinnamaldehyde with a LC50 value of 0.04. Intermediate-activity compounds are *ortho*-Nitrocinnamaldehyde, *meta*-Nitrocinnamic acid, β -Ionone and Thymol with LC50 value of 0.04, 0.05 0.060 and 0.075, respectively (Fig. 8). The least active compounds are in descending order such as Citronella, Cinnamic acid and Menthone with LC50 0.120, 0.15 and 0.165 respectively. Here again, the ovicidal activities evolve in the same direction as the larvicidal activities, in relation to the aldehydic function, on the one hand, and in relation to the presence or absence of the *alpha* double bound from an aldehyde, on the other. It is curious to note that at the

concentration of 0.1g/L *ortho*-Nitrocinnamaldehyde, and *meta*-Nitrocinnamic acid, the two less active compounds in terms of LC50 inhibit 100% of the evolution of eggs with a profile of activity rather comparable to that of Citral, which is the most active compound. This work does not allow to discriminate between the functions aldehyde and acid because the favorable tendency for aldehydes as more active compounds (Citral, LC50 = 0.015 and Cinnamaldehyde, LC50 = 0.020) and unfavorable for cinnamic acid (LC50 = 0.15); is annihilated by the relative equivalence between *ortho*-Nitrocinnamaldehyde and *meta*-Nitrocinnamic with LC50 values of 0.04 and 0.05 g/L. In the previously exposed, essential oil studied exhibited the LC50 values ranging from 0.088 to 0.220 g/L for larvae and from 0.040 to 0.200 g/L for *Anopheles gambiae* eggs. It can be seen that essential oils are less active than the chemical compounds studied. This study also confirms that eggs were more sensitive than larvae. What seems paradoxical is the observation of 100% toxicity on larvae but 80% on eggs at the same concentration of 0.1g/L for Cinnamaldehyde. However, the situation seems normal for *ortho*-Nitrocinnamaldehyde and *meta*-Nitrocinnamic acid, which show 100% toxicity at the concentration of 0, 1g/L on eggs but respectively 0.98 and 0.7 on larvae (Fig. 9). From all the above observation, vector control from the egg would use small amounts of products: less plant material and fewer chemicals. For development purposes, this study shows a reliable alternative for the quantitative and qualitative availability of vector control products that can reduce the exaggerated adverse effects on the environment.

Table 3. Mortality of eggs exposed to increasing concentrations of chemical compounds in percent and LC50

Name of chemical compounds	Concentrations of chemical compounds							CL ₅₀ en g/L
	0.4 g/L	0.2 g/L	0.1 g/L	0.05 g/L	0.025 g/L	0.0125 g/L	0 g/L	
<i>Citral</i>	100%	100%	100%	70.67±2.22%	49.33±0.44%	16.0±0.00%	0%	0.015
<i>Cinnamaldehyde</i>	100%	100%	80.0±0%	60±0.00%	36.0±0.00%	12±0%	0%	0.020
<i>Thymol</i>	100%	100%	80.0±0%	28.0±0.0%	0%	0.0%	0%	0.075
β - <i>Ionone</i>	100%	100%	60.0±0%	37.33±2.26%	12.0±0.0%	0.0%	0%	0.060
<i>Menthone</i>	100%	60.0±0%	32.0±0.00%	0.0%	0.0%	0.0%	0%	0.165
<i>Citronellal</i>	100%	80±0%	41.33±1.67%	12.0±0%	0.0%	0.0	0.0%	0.120
<i>Ortho-Nitrocinnamaldehyde</i>	100±0.0%	100±0.0%	100±0.0%	66.67±1.7%	32±0.0%	12.0±0%	0%	0.040
<i>Cinnamic acid</i>	100±0.0%	70.67±2.22%	28±0.0%	00±0.0%	0.00%	0.00%	0%	0.150
<i>meta-Nitrocinnamic acid</i>	100±0.0%	100±0.0%	100±0.0%	53.33±1.77%	20±0.0%	8.0±0.0%	0%	0.050

Name of chemical compounds	Concentrations of chemical compounds					CL ₅₀ en g/L
	0.0125g/L	0.00625g/L	0.003125 g/L	0.00156 g/L	0 g/L	
Permethrin	100 %	94.67±1.77%	50.66±1.77%	28.0±0.00%	0 %	0.00300
Cypermethrin	100 %	92.0 ±0.00%	40.0±0.00 %	25.33±1.77%	0 %	0.00380

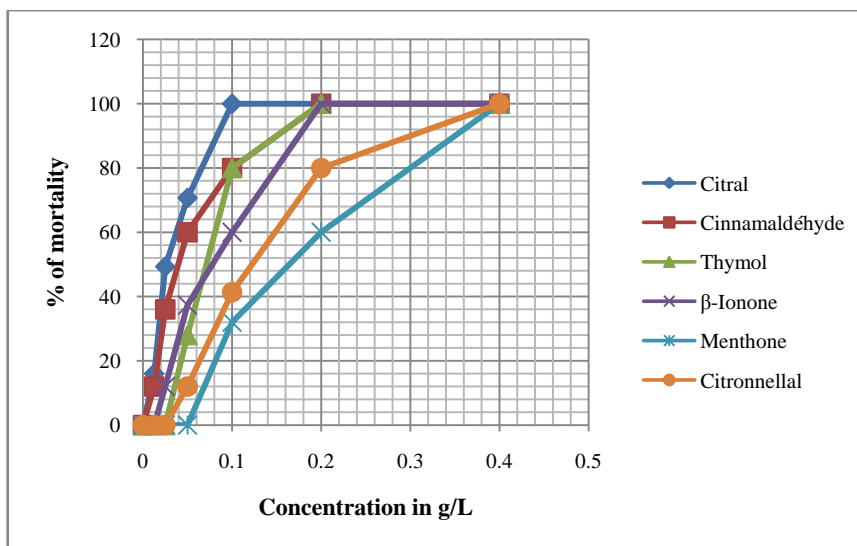


Figure 8. Evolution of *Anopheles gambiae* eggs mortality after 72 hours of exposition to different concentrations of chemical compounds

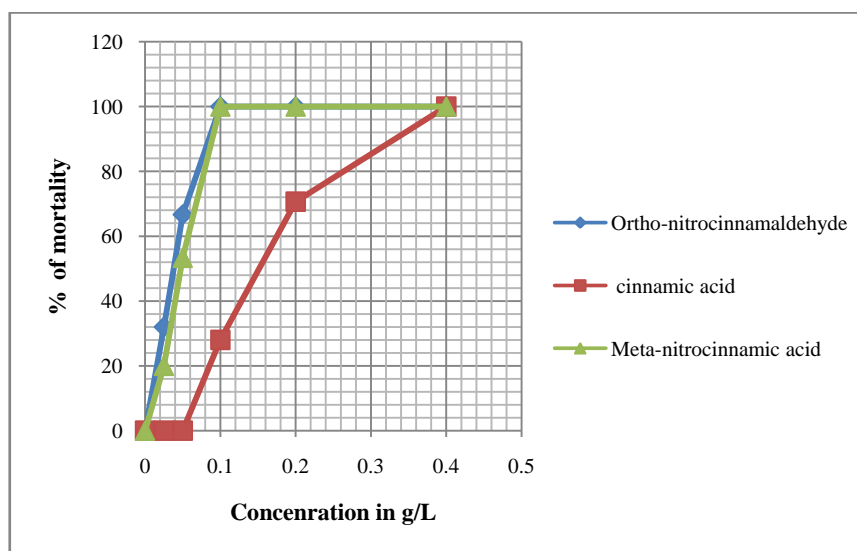


Figure 9. Evolution of *Anopheles gambiae* eggs mortality after 72 hours of exposition to different concentrations of chemical compounds

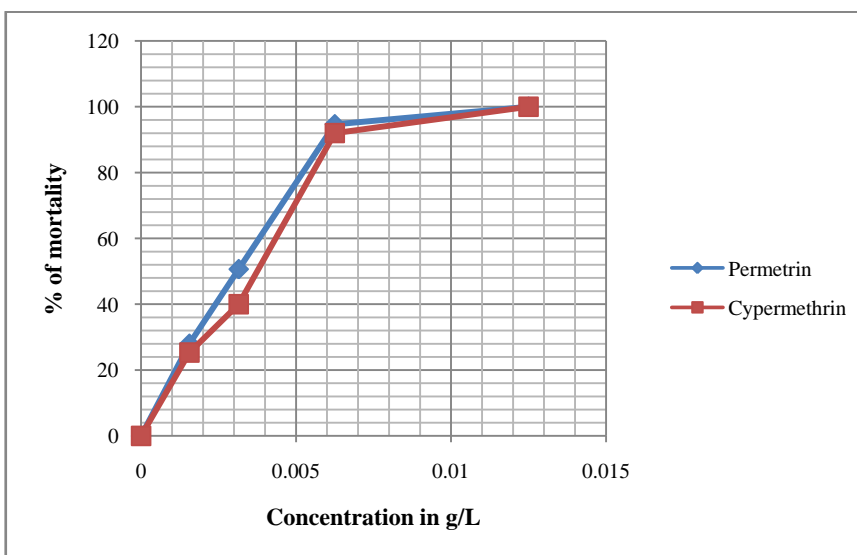


Figure 10. Evolution of *Anopheles gambiae* eggs mortality after 72 hours of exposition to different concentrations of chemical compounds

4. Conclusions

Our research focuses on vector control in the fight against malaria. After careful examination of the chemical constituents of the essential oils studied, eleven compounds were targeted based on the outcome of our previous work, done on essential oils and their larvicidal and ovicidal activities. The evaluation of the larvicidal and ovicidal activities of these compounds, synthesized in our laboratory or obtained from trade has been carried out. Further studies will be carried out on the structure activity relationship of compounds containing conjugated double bond to functional group.

The results showed that the chemical constituents of essential oils are more active than the corresponding essential oils. The activities observed corroborate with other published research works, which demonstrated that eggs were more sensitive than larvae at doses about 5 times lower. This work has shown that compounds as simple as cinnamic acid or cinnamaldehyde can also be exploited. These chemicals are industrially available and have little impact on the environment as they are potentially biodegradable.

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