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Influence of temperature combined with photodynamic inactivation on the development of *Aedes aegypti*

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ABSTRACT

To reduce the speed of selection of populations resistant to chemical insecticides, photodynamic inactivation (PDI) against *Aedes aegypti* is a hot-topic and promising alternative technique to vector control. Temperature is an important factor in the survival of *Ae. aegypti* larvae and mosquitoes as it influences physiology, behavior, and ecology. This work aimed to evaluate parameters of the biological cycle of *Ae. aegypti* such as: hatching rate, larval development, adult mosquito longevity, sex ratio, weight, and lethal concentration of larval mortality (LC) through the combination of PDI with different temperatures. The number of larvae found after 48 h suggests that temperature affects hatching rate. Additionally, results showed a delay in development of surviving larvae after PDI when compared to control groups, and there was a reduction in the longevity of mosquitoes that undertook photodynamic action. PDI also led to a predominance of male insects, and observed weight indicates that the inactivation method may have also interfered in mosquito size. The results point to a satisfactory performance of PDI at all tested temperatures. Experimental conditions that were not lethal to all larvae implied that PDI impacts the mosquitoes' biological cycle. Though metabolism and development are improved at higher temperatures, so is PDI action, thus maintaining the net benefit. Therefore, it is assumed that the proposed photolarvicide can be useful in reducing arbovirus transmission, and results invite for future research in different abiotic conditions.

1. Introduction

Aedes aegypti acts as a vector responsible for the transmission of several viruses that can cause human diseases, including dengue, chikungunya, and Zika, which is listed as a neglected tropical disease and a major public health issue (NTD) [1–4]. The spread of these arboviruses present a multivariable character, but urbanization has favored a scenario with different conditions, such as microhabitats for the immature stages and the growth of the human population, possibilities of virus transmission [5,6].

One the most used approaches to eliminate *Ae. aegypti* depends usually on chemical control (insecticides) and their action varies depending on the active substance affecting both the immature and adult stages. Application for long periods has been causing a selection of resistant populations [7–9]. It is therefore important to seek alternative methods for vector control, relying on different mechanisms, to avoid the resistance process.

In this regard, photodynamic inactivation (PDI) shows as a promising and alternative in the control of vector-borne diseases [10] particularly against *Ae. aegypti* [11–13]. The process consists of combination of light with specific wavelength, a photosensitive compound (PS) and cellular oxygen triggering the formation of reactive oxygen species (ROS) capable of destroying a biological target. The potential of using PSs under visible light for controlling larvae population has been demonstrated by previous research [14,15] on curcumin, a dye extracted from the roots of *Curcuma longa*, commonly known as Turmeric.

Environmental applications must consider variables that extrapolate controlled settings. In this concern, temperature is one of the most important abiotic factors for insect survival as it influences physiology, behavior, ecology, and distribution. Mosquitoes are ectotherm organisms, i.e., they have internal temperatures that depend on external conditions [16,17]. Due to seasonal changes and thermal variations,

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mosquitoes can face desiccation, metabolic alterations, and even impaired mobility. However, over evolutionary time, these insects have developed strategies to deal with thermal variations and avoid heat stress. Whether they synthesize heat shock proteins, thermoregulate or adjust their behavioral activity, mosquitoes are able to maintain cellular integrity to optimize their fitness and survival [17,18]. Despite these mechanisms, temperature influences parameters such as exposure time and resultant efficiency in the application of conventional chemical treatments in general, and insecticides [19,20]. Given that temperature is a key abiotic factor for insect survival and development, it is important to evaluate whether it affects the performance of PDI.

The aim of the work was therefore to evaluate the impacts of different temperatures in PDI carried out in sublethal doses of curcumin and visible light. We have also evaluated the damage caused by PDI in the life cycle of *Ae. aegypti*, considering larval development, sex ratio, adult longevity, and weight.

2. Experimental

Fig. 1 displays a simplified diagram of the experimental scheme carried out in the present study. Details are given further for bioassays and each of the parameters analyzed through larval and mosquito development.

2.1. Chemicals and PS formulation

D-mannitol was obtained from Sigma-Aldrich. Curcumin was synthesized in accordance with literature [21], supplied to the Laboratory or Bioorganic Chemistry – Federal University of São Carlos – UFSCar (São Carlos, SP – Brazil).

Formulations with d-mannitol and curcumin (50:50 w/w) were prepared according to peer protocol [15]. Curcumin and ethanol were kept under magnetic stirring at 80 °C. Then, d-mannitol in water was added and maintained under stirring at 100 °C for 1 h. After evaporating the solvents, the solid obtained was vacuum dried.

2.2. Target-organism, hatching and development

Mosquitoes of the Rockefeller strain, an insecticide-susceptible reference strain, were used in all tests. They were hatched in dechlorinated water and kept in an incubator under controlled conditions for each experimental group (20, 25, 30 and 35 °C) under a photoperiod of 12:12 h light:dark with 60.0 ± 5%. Egg viability was calculated by the percentage ratio of eggs (previously preserved on dry filter paper) hatched after their immersion in dechlorinated water. Calculations were performed considering 500 eggs for each experimental condition.

Following previous research [22], total development time was checked for each individual, accounting for the number of days between egg immersion in water and emergence of the adult. Note that, as shown by Fig. 1, it was divided into a block that comprised the first (L1), second (L2), and third stage (L3), as well as fourth stage (L4) and pupal stage (P). That is because when larvae reached L3, they were subjected to PDI under different temperatures, so some of the development parameters referred to surviving organisms, as further described.

2.3. Bioassays

Larvicidal activity was assessed according to the adapted World Health Organization [23] standard protocols. Tests were carried out on groups of 20 to 25 larvae each, in 150 mL of distilled water (control group) and containing curcumin formulations (PDI group). They were evaluated at different PS concentrations (0.00156, 0.00313, 0.00625, 0.0125, 0.025, 0.05, 0.1, 0.2, 0.4 and 0.8 mg/L) according to Garbuio [15], exposed to fluorescent light (0.83 mW/cm^2), dose of light 35.86 J/cm^2 (Fig. 2).

Larval mortality (%) was recorded after 12 h after PDI (12 h light, 12 h dark totalized 24 h) (three genuine replicates for each experimental group (carried out on different occasions) and triplicates for each

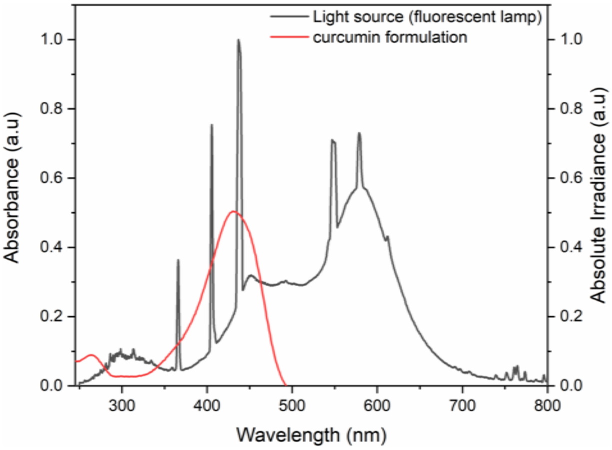

Fig. 2. Normalized absorption spectrum of the light source used in the bioassays (black line) and absorbance spectrum of the curcumin formulation (red line).

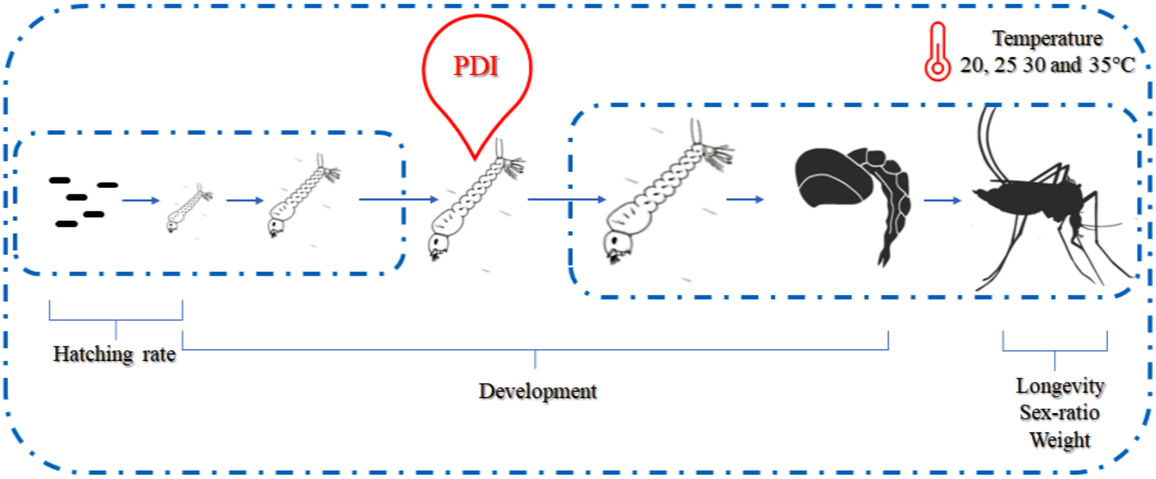

Fig. 1. Experimental scheme during all biological development *Ae. aegypti* and photodynamic inactivation against of *Ae. aegypti* under four temperatures (20, 25, 30 and 35 °C).

concentration).

After the photolarvicidal assays, the surviving larvae were returned to clean trays with dechlorinated water divided into two groups: control and PDI to continue their development. In the pupal stage, they were placed in plastic cages measuring 30×30×30 cm for the mosquitoes to emerge. Adults were maintained at 20, 25, 30, and 35 °C and 60.0 ± 5% relative humidity under a 12:12 h photoperiod.

2.4. Development parameters of surviving individuals

The sex of each individual was determined after emergence of the adults in the rearing cages. The number of males and females at different temperatures was evaluated leading to the sex ratio. Individual's weight considered 40 individuals (20 males and 20 females) of each experimental group. This analysis relied on direct weighting on an analytical scale. Nutrition was provided by honey as a source of carbohydrate, as ingestion is the main nutritional source (energy metabolism) and its accumulation (glycogen and triglycerides) can determine a potential in the activity and longevity of mosquitoes [24,25].

Adult survival was measured as the number of days between adult emergence and death. The longevity of adults was evaluated and compared based on sex and temperatures. Adults found dead in breeding cups were excluded from the analysis.

2.5. Statistical analysis

Lethal concentrations ($LC_{25;50;90}$) values were obtained using a dose-response by non-linear regression, calculated using Origin 2018 software. For group comparisons (hatching rate and longevity of adults), one-way ANOVA, with a post-hoc Tukey test. T-student test was used with two groups in comparison (development time, sex-ratio and weight). All statistical tests were applied considering a 95% confidence interval.

3. Results and discussion

3.1. Hatching rate

After 48 h of immersing the eggs in dechlorinated water, the viability percentage was calculated. There was significant difference ($p < 0.05$) in the viability of *Ae. aegypti* eggs hatched in different temperature, as shown by Fig. 3.

In this study, we showed that the highest egg hatching rate for *Ae. aegypti* was obtained at 30 °C (~78 %) in the range of temperatures evaluated, which is consistent with the information that this species is more adapted and has a life cycle present between temperatures of 26 – 30 °C. This result is in agreement with the report for the species, which is adapted to tropical and subtropical climates [17].

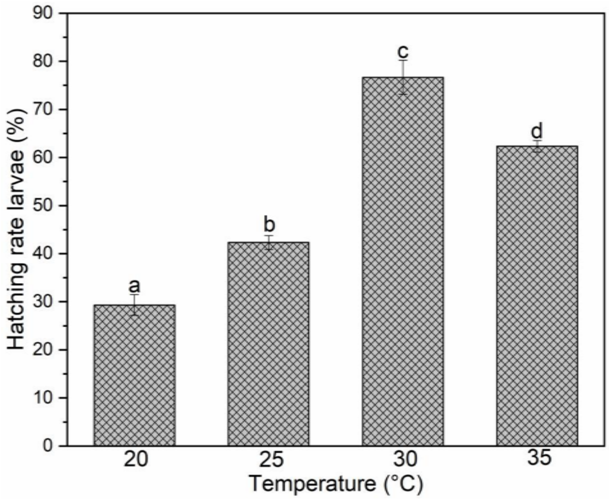

Fig. 3. Average percentage of larvae hatching at temperatures 20, 25, 30 e 35 °C. Different letters indicate significant differences ($p < 0.05$).

Temperature can affect population dynamics such as: the development, density and dispersal of mosquitoes, in addition to embryogenesis and egg diapause [17,26]. According to scientific literature [27], using strains of *Ae. albopictus*, a species of mosquito that has the same genus as *Ae. aegypti*, similarities in morphology and evolutionary cycle, egg viability was higher at lower temperatures (15–25℃) (regions with a temperate, subtropical climate), as the species has capacity for development in these conditions. Löwenberg Neto and Navarro-Silva discovered that when females are raised under a thermal regime of 20 – 27 °C they have better gonadotrophic cycles, increasing their egg laying and viable eggs [17,28].

Farnesi varied the temperature between 12 and 36 °C and evaluated the hatching of *Ae. aegypti* larvae and the viability of the eggs, resulting in a maximum temperature limit of 35 °C and a lower minimum temperature of 12 °C [16]. Edilo demonstrated that the location of the eggs with different latitudes, amplitudes and climate influenced the egg hatching rate [29] as well, Beserra, the temperature range between 22 °C and 30 °C is more favorable for the fecundity of adult mosquitoes, consequently adults, consequently the viability of eggs [30].

3.2. Development time

Larval development was evaluated from L1 to the pupal stage, with growth identified by the presence of the exoskeleton in the hatching containers. PDI assays were performed when larvae reached the L3 stage. The survivors returned to development, as shown in Fig. 1. The results indicated a delay in development for larvae that survived after PDI (**Figure 4**) when compared to larval in control groups.

Fig. 4**A** shows the development of larvae subjected to a constant temperature of 20 °C. The results showed larvae development in 21.3 ± 1.3 days for control and 24 ± 1.15 days for PDI. At 25 °C 10 ± 2 days for control and 14.3 ± 1.45 days for PDI (Fig. 4**B**). In Fig. 4**C** (temperature of 30 °C) the results show a development of 9 ± 1.15 days for the control and 11.33 ± 0.85 for PDI. And for the highest temperature (35 °C), 10 ± 1.15 days (control) and 12.3 ± 0.88 (PDI) (Fig. 4**D**). All temperatures evaluated showed a significant difference in relation to the control group after PDI ($p < 0.05$).

The developmental consequences may lie in the damage caused by curcumin, as after PDI, it generates oxidative stress, damaging the epithelial cells of the midgut of larvae [9,14]. Furthermore, these damages suggest a decrease in the ability to absorb nutrients from the midgut, which is the main organ of larvae for digestion and absorption of nutrients [31]. This delay makes the next stage of metamorphosis difficult, a fact that is corroborated by results found in similar PDI research [32,33].

3.3. Larvicidal assays

The results of larval mortality, after 24 h of exposure, and the lethal concentration (LCs) values are shown in Table 1.

Table 1 was structured with the aim of contributing to future studies with the values of LC_{25}–24 h for sublethal dose studies, LC_{50}–24 h for comparisons and LC_{90}–24 h for semi-field or simulated field tests. According to the results, following an ascending order, the LC_{50}–24 h was 0.044 (20 °C), 0.027 (25 °C), 0.019 (30 °C) and 0.013 (35 °C), respectively.

The increase in temperature impacted the PDI process. We hypothesized that temperature may have influenced the solubility of curcumin and availability of PS to the environment, as suggested by larval lethality results. According to Jagannathan [34], as the temperature increases between 25 and 95 °C, intramolecular hydrogen bonds become freer, exposing the polar regions, leading to the dissolution and

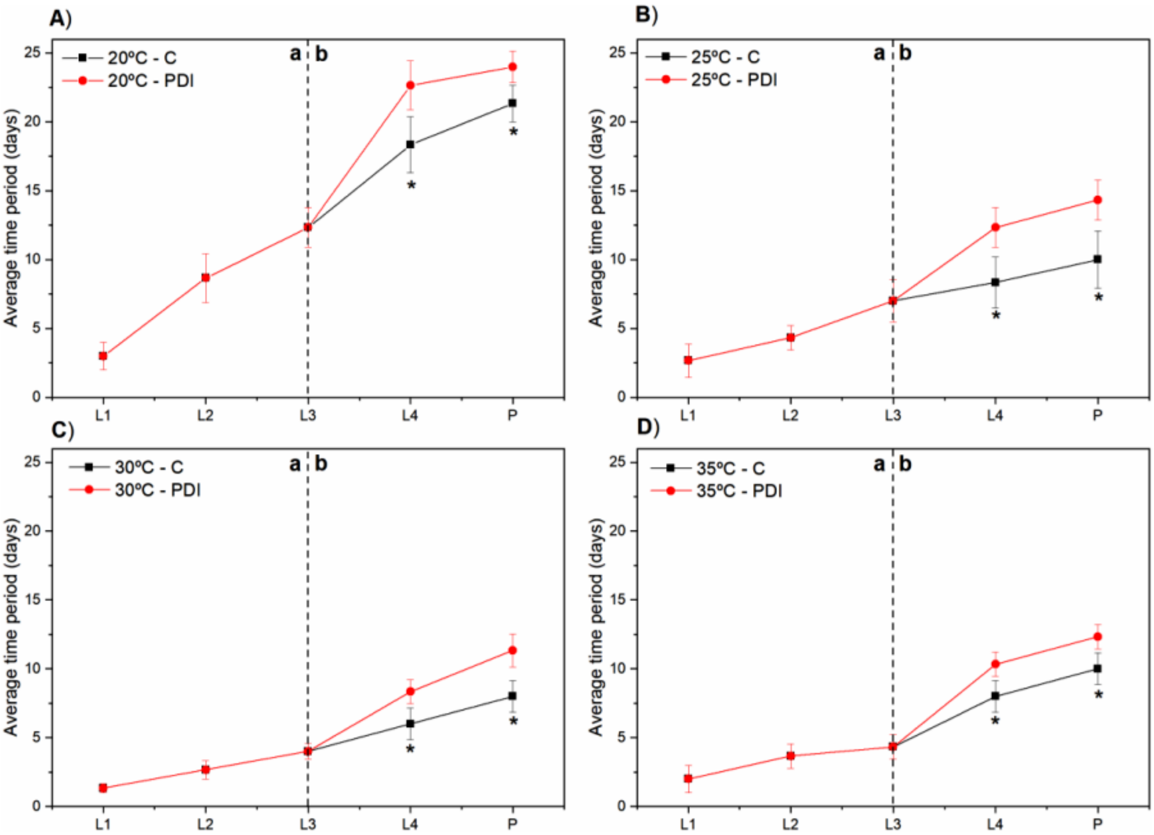

Fig. 4. The average period of development from L1 to the pupal stage (P) at different temperatures: (A) 20 °C, (B) 25 °C, (C) 30 °C and (D) 35 °C in two groups: control and PDI. Side (**a)** of the figure represents larval development before PDI, side (**b)** after the PDI and the dashed line at the time when the PDI occurred. The symbol (*) indicates statistical difference in means ($p < 0.05$).

Table 1
Lethal concentration (LC$_{25;50;90}$) of the curcumin formulation in *Aedes aegypti* larvae exposed for 24 h at different temperatures.

Temperature (°C)	LC$_{25}$–24 h (mg/L) (LCL-UCL)	LC$_{50}$–24 h (mg/L) (LCL-UCL)	LC$_{90}$–24 h (mg/L) (LCL-UCL)
20	0.008 (0.007–0.009)	0.044 (0.017–0.112)	0.720 (0.647–0.905)
25	0.006 (0.004–0.007)	0.027 (0.021–0.035)	0.431 (0.322–0.653)
30	0.005 (0.004–0.006)	0.019 (0.016–0.023)	0.224 (0.173–0.318)
35	0.004 (0.003–0.006)	0.013 (0.010–0.016)	0.099 (0.074–0.140)

LC, Lethal concentration; LCL, 95% Lower Confidence Limit; UCL, 95% Upper Confidence Limit.

availability of curcumin in the medium.

Another factor that must be taken into account is the metabolism of the larvae, in which lower temperatures below 22 °C can lead to diapause and consequently less mobility and search for food [17]. These factors corroborate the results found in the present study, where lower temperatures presented higher concentrations of LC$_{50}$. As for higher temperatures, it should be noted that maximum transmission of dengue, chikungunya, and Zika ranges from 26 to 29ºC, based on reported mechanistic models [35]. This brings attention to PDI action within this interval, showing a promising perspective, to scenarios in which changes in temperature may favor arboviruses transmission [36]. PDI improved efficiency at 30 °C is a method that could perhaps be compensatory in such a scenario.

3.4. Sex-ratio

The results Fig. 5 shows sex ratio between mosquitoes in two groups: control and PDI.

This may be associated with environmental changes, such as nutritional or heat stress. In Fig. 5A, the sex ratio for the control as a function of temperature is shown. The proportion of females is between 22 and 34% for temperatures of 20 and 25 °C, respectively. For temperatures of 30 and 35 °C there was an increase in the ratio of females varying between 47 and 68%, respectively. High temperatures (26–35 °C) favor larvae feeding [17]. According to Steinwascher, larvae are always competing for food and females are generally dominant over males [37].

Fig. 5B, combining PDI and temperature, the sex ratio was inversely proportional to the control group. The *Ae. aegypti* larvae that received this photolarvicidal treatment and temperature showed a higher proportion of males, gradually increasing by 38, 41, 51 and 78% as a function of the temperature increase of 20, 25, 30 and 35 °C, respectively. We suggest that with the dominance of females in the diet, curcumin particles were retained in greater quantities in their cellular tissue and midgut, possibly for longer compared to males, and consequently females are more susceptible to damage caused by the PDI process. Other studies also observed that in the L3 phase, applying the PDI technique to control larvae, females retain an amount of food for development and complete metamorphosis [33,37].

3.5. Longevity of adults

Fig. 6 shows the profile of the longevity rate of male and female mosquitoes divided into a control group and which underwent PDI at four different temperatures (20, 25, 30 and 35 °C). Dead adults were excluded from the analysis because they represent between 1 and 2% of

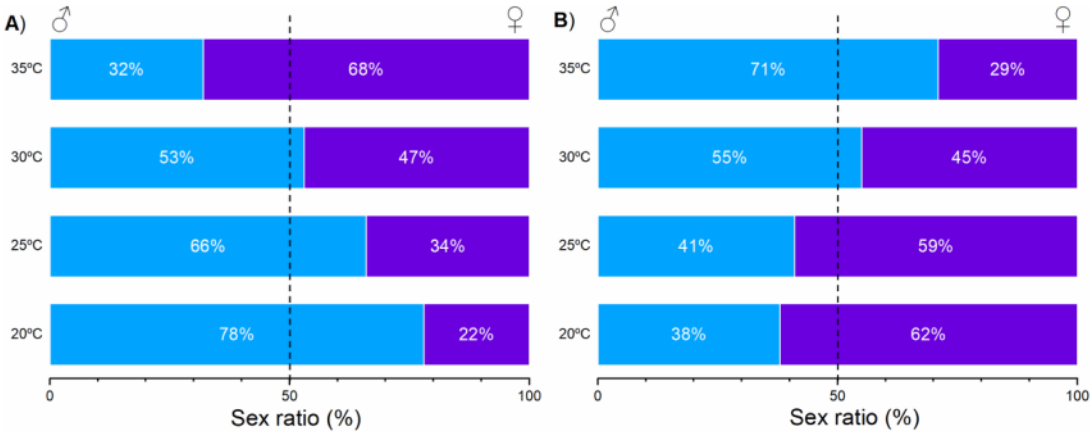

Fig. 5. Sex ratio of adults emerged after exposure to different temperatures (20, 25, 30 and 35 °C), (A) control and (B) PDI.

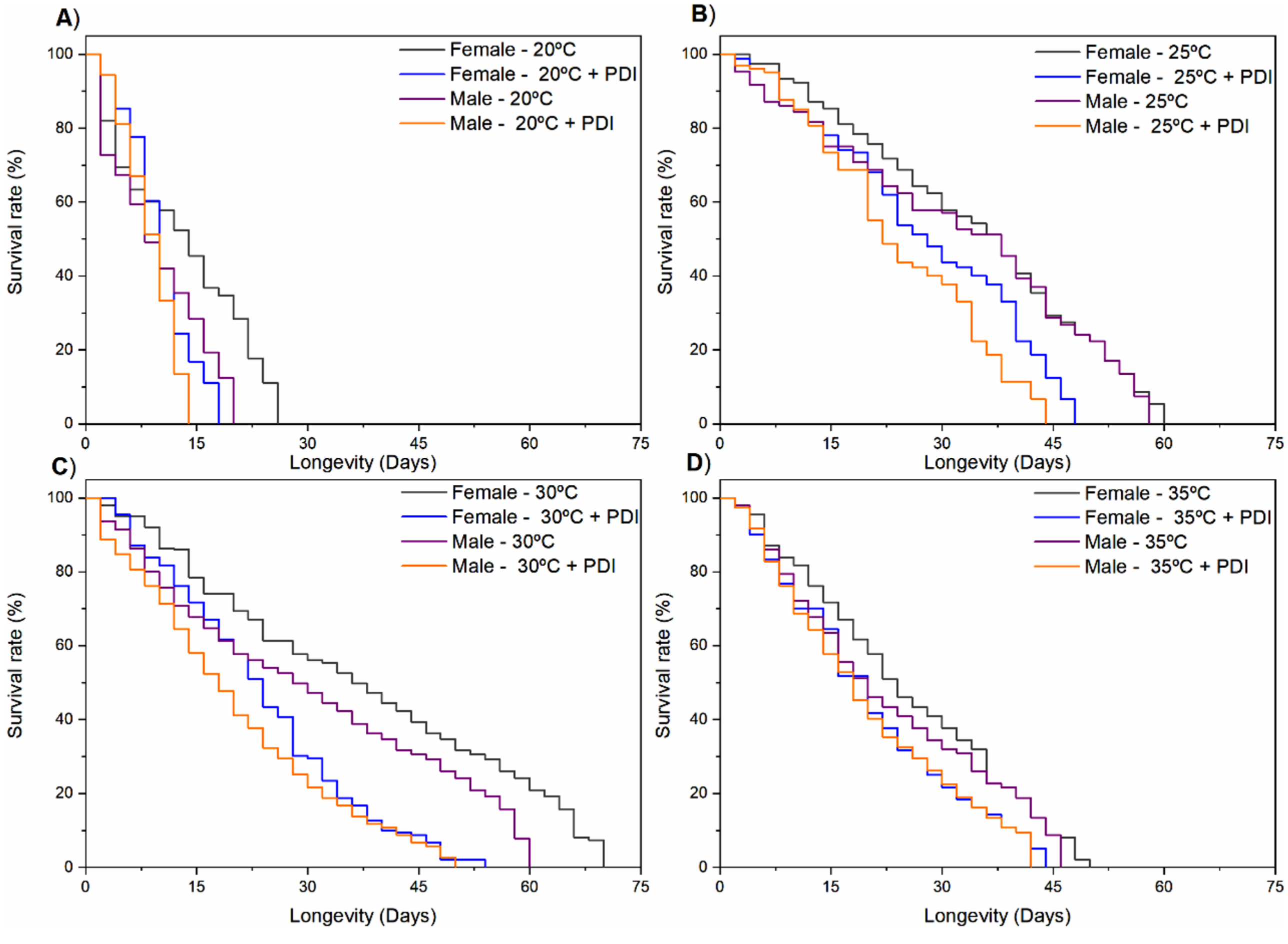

Fig. 6. Survival rate of adults exposed to different temperatures: 20 °C (A), 25 °C (B), 30 °C (C) and 35 °C (D), divided into two groups, control (temperature only) and PDI plus temperature.

the total population.

At 20 °C, female mosquitoes survived for 26 days in the control and 18 in the PDI group, males only survived 20 days in the control and 14 PDI (Fig. 6A). In Fig. 6B 60 and 48 days for females at 25 °C in the control and PDI groups, respectively, and males 58 days (control) and 44 (PDI). 30 °C was the temperature at which mosquitoes showed greater survival compared to other temperatures (Fig. 6C), females survived 70 days in the control group and 54 in the PDI group and males 60 days (control) and 50 (PDI). And in Fig. 6D, representing the highest temperature of the present work, the survival of mosquitoes was shown in 50 (control) and 44 days (PDI) for females and for males, 46 and 42 days for the control and PDI groups respectively.

Considering only temperature, the data indicate a significant difference ($p < 0.05$) for the longevity profile rate of individuals kept at 20 °C. This temperature was not favorable for the development of the vector, as *Ae. aegypti* are mostly found in subtropical and tropical climates (26–30 °C), as describes [17]. Furthermore, a greater physiological cost, such as changes in metabolism and energy expenditure, may reflect on longevity, previously also observed by Guitiérrez and collaborators [38].

When comparing the survival of male and female mosquitoes from the two groups (control and PDI), there was evidence that females had greater survival than males in all experimental conditions ($p < 0.05$), except at 25 °C (there was no difference significant). This is because, under natural conditions, females have a longer life expectancy than male, each sex plays a specific role in the survival and reproduction of the species [25,39,40]. While male mosquitoes are related to the possibility of mating (territorial competitions or disputes for mates), females are directly linked to their gonadotrophic cycles, such as blood feeding, oviposition of offspring and subsequently vectorial action [17,25,40].

Mosquitoes (males and females) who survived PDI showed significant differences ($p < 0.05$) compared to the control group, showing a reduction in longevity. This result may also indicate a reduction in the transmission of arboviruses, through a reduction in the lifespan of mosquitoes. Some authors, such as Belinni and collaborators [41], showed reduced longevity in *Ae. aegypti* larvae exposed to diflubenzuron, and so did others with diflubenzuron and methoprene [42,43]. Other results using growth regulators showed similarity, such as: triflumuron [44] and spinosad [45]. And more recently, Mezzacappo, using a curcumin formulation showed similarities in results [33].

Unlike other insecticides, curcumin is a natural compound that, as a photolarvicide, presents multi-sites of activity through the oxidative processes of PDI mechanisms. The concentrations (LC_{50}) used in larvicidal activity in *Ae. aegypti* in these studies with curcumin [15,46] are lower compared to studies with essential oils: values of 2 to 10 mg/L [47] and essential oil from *Pimenta dioica Lindl.* (26.91 mg/L) [48]. They are also lower when compared to other plant extracts: Coelho and collaborators [49] obtained 197 mg/L with *Moringa oleifera lectin*, extracts from *Syzigium aromaticum, Lippia medoides* and *Hyptis martiusii*, with values of 18.5, 19.5 and 21.4 mg/L, respectively [50].

Furthermore, Venturini [51] and Garbuio [15] demonstrated that in curcumin ecotoxicity tests (acute tests), up to 100 mg/L can be used following the OECD protocol [52], which does not present toxicity in some non-target organisms such as Denio rerio. And according to Lima and collaborators, the photoproduct tests did not present a prediction of toxicity [53].

3.6. Weight

Fig. 7 shows the body weight results of male and female mosquitoes (control and PDI).

Male and female mosquitoes from the two groups (control and PDI) showed a significant difference between them ($p < 0.005$). This result corroborates the results of Section 3.4 also show that males and females play different roles in reproduction and feeding. Females tend to be heavier due to the need for energy and nutrients for egg maturation and oviposition [28,54].

Male mosquitoes showed no significant difference ($p > 0.05$) when compared between the control and PDI groups. However, there was a significant difference ($p < 0.05$) between females in the control group with PDI at all temperatures. This means, that there was a decrease in body weight in the PDI group when compared to the control group.

The body size of mosquitoes may be correlated with the total reserves of proteins, lipids and carbohydrates acquired during larval development. After the PDI test with curcumin, Venturini [52] analyzed changes in the digestive system of *Ae. aegypti* larvae, such as: folds in the peritrophic membrane (protective layer of the intestinal epithelium), constrictions in some regions of the intestine, formation of apical vesicles and cytoplasmic vacuolation. These morphological lesions caused in the intestine may have hindered the absorption of nutrients and the increase in ROS may trigger cellular damage, repressing development. However, smaller females have a shorter life expectancy, often not taking their first blood meal, reducing their vector capacity compared to larger females. These factors corroborate studies found in the scientific literature by Briegel [55], Alto [56] and Juliano et al. [54].

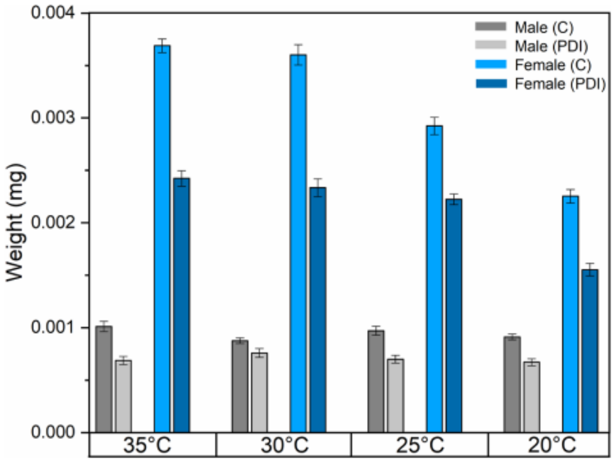

Fig. 7. Weight (mg) of adult female *Ae. aegypti* males (control and PDI (not fed with blood)).

4. Conclusions

This study showed that PDI, when not fully lethal, alters the life cycle of *Ae. aegypti* by a delay in larvae development as well as early death and a difference in sex ratio of emerged mosquitos' adults. This was observed in different temperatures associated with PDI. Thermal effect was also perceived in lethality presenting those higher temperatures required lower LCs. In this regard, PDI in higher temperatures may be contributed to the PS solubility increase, along with higher larval activity in higher temperatures. These may have contributed to curcumin uptake by larvae *Ae. aegypti*. This work maps out temperature impact in egg hatching, PDI performance, and physiological effects of surviving larvae and adults. Overall, PDI may be considered an effective measure for control of *Ae. aegypti* larval population even at different temperature settings between the optimal disease transmission interval. The efficiency found in different temperatures encourages future work considering extreme scenarios. Temperature directly influences the life cycle of the *Ae. aegypti* and in the action of PDI, demonstrating that in tropical countries, where they have the highest incidence of the mosquito *Ae. aegypti*, can amplify the effectiveness of the technique and vector control.

CRediT authorship contribution statement

Matheus Garbuio: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Alessandra Ramos Lima:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Formal analysis, Data curation, Conceptualization. **Kamila Jessie Sammarro Silva:** Writing – review & editing, Writing – original draft, Visualization, Formal analysis. **Mariana De Souza:** Writing – review & editing, Methodology. **Natalia Mayumi Inada:** Writing – review & editing. **Lucas Danilo Dias:** Writing – review & editing, Methodology. **Vanderlei Salvador Bagnato:** Visualization, Supervision, Resources, Project administration, Funding acquisition, Conceptualization.

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