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ORIGINAL RESEARCH ARTICLE

Efficacy of porous silica nanostructure as an insecticide against filarial vector *Culex pipiens* (Diptera: Culicidae)

Mohamed M. Baz[1] · Nehad M. El-Barkey[1] · Aida S. Kamel[1] · Aya H. El-Khawaga[1] · Mostafa Y. Nassar[2]

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Abstract

There is a need to formulate new insecticides against insect-borne diseases. Silica nanoparticles (SNPs) prepared by sol–gel (A_{800}) and sol–gel/combustion (B_{800}) methods were tested at different concentrations of 5, 25, 50, 100, and 200 ppm after 24 and 48 h on *Culex pipiens* larvae. The synthesized SiO_2 was characterized by using different spectroscopic techniques. Our data revealed that silica nanoparticles (B_{800}) showed high larvicidal activity as the LC_{50} values were 19.7, 37.4, 61.1, and 85.2 for the 1st, 2nd, 3rd, and 4th larval instar and 234.8 ppm for the pupal stage at 24 h, respectively. A higher mortality percentage was observed in the 1st larval instar than in all the other immature life stages treated with silica nanoparticles. At 200 ppm, the mortality reached 100% and 90% on treating mosquitoes with B_{800} and A_{800} silica nanoparticles, respectively for the1st larval instar compared to 81.7% and 63.3% for the 4th larval instar at 24 h. On treatment with an LC_{50} concentration of the B_{800} and A_{800} silica nanoparticles, the larvae took 22.7 and 18.4 days respectively, compared to 13.3 days for the control, to reach the pupal stage. Glutathione-S-transferase and α-esterase activities increased significantly after treatment with the LC_{50} concentration of SNPs (A_{800} &B_{800}). Conversely, alkaline/acid phosphatase enzyme activity and total protein were reduced. We suggest the use of silica nanoparticles in mosquito control as an eco-friendly approach.

Keywords Porous silica nanoparticles · *Culex pipiens* · Insecticidal efficacy · Bioassay activity · Combustion synthesis

Introduction

Arthropods can be vectors for many significant pathogens and parasites, which may cause epidemics or pandemics among humans and animals as well (Gubler 2009). Among them, mosquitoes (Diptera: Culicidae) threaten millions of organisms around the world because they can transmit many diseases, in addition to being nuisance pests (Mehlhorn et al. 2012; Sivapriyajothi et al. 2014; Murugan et al. 2015).

Culicidae is a common mosquito family with more than 3200 species divided into three subfamilies: Anophelinae, Culicidae, and Toxorhynchitinae; these can be classified into 40 genera spread out in almost every location around the world (Das et al. 2018; Shaukat et al. 2019). The *Culex* mosquito is the most common and is present in every continent except Antarctica; it thrives mostly in tropical regions and as well as temperate areas (Ressiguier 2011; Ruybal et al. 2016). In Egypt *Culex pipiens* is widely distributed in rural as well as urban areas, and transmits terrible diseases that cause severe morbidity and death in humans and animals, as well as dermatitis in people, especially children (Abdel-Shafi et al. 2016; Selim et al. 2020).

Current studies have clarified that traditional pesticides are no longer the best way to control insects for several reasons (Sarkar et al. 2021), such as negative impacts on human health, non-target organisms, air, water, and soil, and high costs (Aktar et al. 2009; Kaur et al. 2019; Gupta and Gupta 2020). Furthermore, the insects have developed a resistance to all classes of insecticides (Zettler and Cuperus 1990) including organophosphates, organochlorines, carbamates, and even pyrethroids (Naik 2018), insect growth regulators, and microbial agents (Sawicki and Denholm 1984; Brogdon and McAllister 1998; Liu et al. 2006). Therefore, it is necessary to search for an effective alternative to synthetic chemical pesticides.

✉ Mohamed M. Baz
mohamed.albaz@fsc.bu.edu.eg

✉ Mostafa Y. Nassar
m_y_nassar@fsc.bu.edu.eg

[1] Entomology Department, Faculty of Science, Benha University, Benha 13518, Egypt

[2] Chemistry Department, Faculty of Science, Benha University, Benha 13518, Egypt

Today, nanotechnology is a promising field of interdisciplinary research; it is used in several fields like agriculture, pharmaceuticals, industry, medicine, and insecticides (Park et al. 2006; Jo et al. 2015). Therefore, nanomaterials-based insecticides could act as efficient and green alternatives for pest management without harming nature (Bhan et al. 2018). The atom by atom arrangement allows the processing of nanoparticles and thus affects their size, shape, and direction in terms of how they interact with the target tissue (Bhattacharyya et al. 2010; Ragaei and Sabry 2014). Silver, gold, carbon, polystyrene, silica, alumina, titanic, and zinc oxide nanoparticles have been demonstrated to have different insecticidal effects against insects (Rouhani et al. 2012; Duhan et al. 2017; Benelli 2018).

Furthermore, silica nanoparticles have been tested against the *Cx. quinquefasciatus, Ae. aegypti* and *An. stephens* mosquito species (Harve and Kamath 2004; Barik et al. 2012). Additionally, silica nanoparticles are applicable in various fields including pesticides for plant protection against agricultural pests (Drum and Gordon 2003; Ulrichs et al. 2006; Barik et al. 2008; Benelli 2018; Thabet et al. 2021). Newly-used nanoparticle materials being used as pesticides are expected to reduce the volume of application and energy consumption because the matter structure would be expected to change (in terms of size, shape, and disparity) (Niemeyer and Doz 2001; Elibol et al. 2003; Kumar and Yadav 2009). Various preparation methods for silica nanoparticles have been reported (Mao et al. 2018; Nassar et al. 2019; Imoisili et al. 2020). However, developing new methods for the synthesis of silica nanoparticles using a facile approach and inexpensive materials is challenging. Furthermore, merging both natural products and nanotechnology opens up a very promising field for integrated control programs (El Wakeil et al. 2017). Several natural product-based nanoformulations were reported as potential larvicidal agents (Angajala et al. 2014) including nanoparticles and nanoemulsions (Ghosh et al. 2013). Therefore, we assume that the preparation of silica nanoparticles is effective against mosquito larvae as an alternative to the use of synthetic insecticides, to avoid harming the environment. The objective of this study is to fabricate silica nanoparticles via a facile auto-combustion method and investigate the toxicity of the as-prepared silica nanoparticles against *Cx. pipiens* mosquito larvae and pupae as well as the alteration of some biological aspects following treatment with sub-lethal concentrations of the tested silica nanoparticles.

Materials and methods

Materials

Silica-gel, sodium hydroxide, starch, sucrose, and nitric acid (98%, density of 1.5 g/cm^3) were supplied by El-Nasr Pharmaceutical Chemicals Company, Egypt. Bovine albumin standard was purchased from the Stanbio laboratory (Texas, USA). Coomassie's brilliant blue G-250 was supplied by Sigma-Aldrich Company. P-nitro anisole (purity 97%) was obtained from Ubichem Ltd. (Hampshire) the UK, while nicotinamide adenine dinucleotide phosphate (reduced form, NADPH) was supplied by BDH Chemicals Ltd. (Poole, England). The rest of the chemicals were of high quality and were purchased from local commercial companies.

Synthesis of silica nanoparticles

Silica nanoparticles were prepared using two different methods; the sol–gel method (A_{800}) and the sol–gel/combustion method (B_{800}). Four grams of silica gel were dissolved in 50 mL of 3 M sodium hydroxide aqueous solution and subject to continuous magnetic stirring at 80 °C. To this solution, a nitric acid aqueous solution (5.8 M) was added dropwise until the gel was formed. Afterward, the generated gel was subsequently separated, washed three times with nitric acid solution (5.8 M), and then separated by centrifugation at 2500 rpm for 5 min. The washed gel was dried at 100 ºC for 4 h and divided into two samples; one of them ignited at 600 ºC and the other at 800 ºC for 2 h. The produced SiO_2 samples were referred to as A_{600} and A_{800}. The aforementioned steps were repeated until the obtained gel form was washed and centrifuged. After that, 50 mL of nitric acid solution (5.8 M) was added to the separated gel. A starch aqueous solution (2 g in 10 mL distilled water) as fuel was added to the reaction blend and magnetically stirred for 5 min. The stir bar was removed, then the reaction mixture was subjected to combustion at about 300 °C for 10 min. After the combustion process, the sample was washed three times in warm distilled water, centrifuged, dried at 100 ºC for 4 h and divided into two samples; one of them calcined at 600 ºC and the other at 800 ºC for 2 h, producing SiO_2 nanoparticles referred to as B_{600} and B_{800}.

Laboratory rearing of *Culex pipiens*

Culex pipiens were obtained from the Medical and Molecular Entomology Section, Entomology Department, Faculty of Science, Benha University. They were maintained at 27 ± 2 °C, 75 ± 5% RH for a photoperiod of 14:10 h (light/dark) in the insectary. The larvae were fed fish food (Tetramin) with ground bread at a ratio of 3:1. The pupae were then transferred from the enamel pans to a cup containing de-chlorinated tap water and placed in screened cages (35 × 35 × 40 cm dimension) where the adults emerged. The adult colony was provided with a 10% sucrose solution and female mosquitoes obtained blood meals through a hamster rat, periodically. Two developmental stages, larvae, and

pupae were continuously available for the experiments and were maintained in the same laboratory conditions (Baz 2013).

Larvicidal and pupicidal bioassay activity

The two samples of silica nanoparticles (A_{800} and B_{800}) were tested on the 1st, 2nd, 3rd, and 4th larval instars and pupal stage of *Cx. pipiens* under laboratory conditions. One gram of silica nanoparticles was suspended in 1000 mL of distilled water using an ultrasonicator so that it was equally distributed in distilled water in order to prepare various concentrations. The toxicity of the silica nanoparticles was tested against larvae and pupae at 5, 25, 50, 100, and 200 ppm concentrations. Twenty larvae per concentration were transferred to a glass beaker containing 250 mL of distilled water used for all experiments. It is worth mentioning that silica nanoparticles were suspended in the water to make a suspension. The experiment was replicated three times with an untreated group. Mortality % was recorded 24 and 48 h after first exposure (WHO 1981). The larval-adult developmental period of *Culex pippins* was calculated at sublethal concentrations (LC_{50}) of silica nanoparticles.

Preparation of samples for biochemical analysis

To perform the biochemical analysis to determine the detoxifying enzymes and total protein in the larval body of a mosquito, 0.5 to 1 g (equivalent to the weight of a hundred 4th larval instar) were taken from the treated larvae at a LC_{50} concentration of the tested nanoparticles and kept in the freezer device (–25 °C) for a period of not more than a week. Untreated larvae were also kept in the same conditions. All samples were transferred to the Central laboratory of the Faculty of Veterinary Medicine in iceboxes (-20 °C) for biochemical analysis. Insect bodies were homogenized using a treatment buffer (1 g insect body / 1 mL) in a chilled glass Teflon tissue (ST-2 Mechanic-Preczyina, Poland) grinder for 3 min according to a modified method (Laemmli 1970). Homogenates were centrifuged at 14,000 rpm for 15 min at –2 ºC in a refrigerated centrifuge. The supernatant was stored at –5 ºC until used for biochemical determination (2 weeks). α-esterases and β-esterases were determined using α-naphthyl acetate or β-naphthyl acetate as substrates, respectively (Asperen 1962). The reaction mixture consisted of 5 ml of substrate solution (3×10^{-4} M α or β-naphthyl acetate, 1% acetone, and 0.1 M phosphate buffer, pH 7) and 20 µl of larval homogenate. The mixture was incubated (27 °C) for 15 min. The color which developed was read at 600 or 555 nm for α- and β-naphthol resulting from the hydrolysis of the substrate, respectively. Standard curves for α- and β-naphthol were prepared by dissolving 20 mg of α or β-naphthol in a 100 ml phosphate solution, pH 7 (stock solution). The total proteins were determined by the method (Bradford 1976). Protein reagent was prepared by dissolving 100 mg of Coomassie Brilliant Blue G-250 in 50 ml 95% ethanol (Bradford 1976), and phosphoric acid (100 ml, 85% W/V) was added to this solution. A standard curve (50 µl) of serial concentrations containing 10 to 100 µg of bovine serum albumin was pipetted into test tubes. The absorbance (595 nm) was measured after 2 min and before 1 h against a blank prepared from 1 ml of phosphate buffer and 5 ml of protein reagent. Glutathione S-transferase (GST) catalyzes the conjugation of reduced glutathione (GSH) with 1-chloro 2,4-dinitrobenzene (CDNB) via the -SH group of glutathione (Habig et al. 1974). 1 ml of the potassium phosphate buffer (pH 6.5), 100 µl of GSH, along 200 µl of 4th larval were homogenized. The concentrations of both GSH and CDNB were adjusted so that they were 5 mM and 1 mM, respectively. Enzyme and reagents were incubated (30 ˚C) for 5 min. Acid and alkaline phosphatases were determined according to Powell and Smith (1954). In this method, the phenol released by enzymatic hydrolysis of disodium phenyl phosphate reacts with 4-amino antipyrine, and by the addition of potassium ferricyanide, a characteristic brown color is produced. Three replicates were carried out for each determination test. Total protein, α-/β-esterases, Glutathione S-transferase (GST), acid phosphatase, and alkaline phosphatases were determined in treated and untreated larvae.

Characterization

The as-prepared products were characterized by using an 18 kW diffractometer (Bruker; model D8 Advance) with monochromated Cu-Kα radiation (λ = 1.54178 Å) to collect the XRD patterns to study their composition, the crystallinity, and the phase purity. FT-IR spectra of the as-synthesized samples were measured in the range of 4000–400 cm^{-1} using an FT-IR spectrometer (Thermo Scientific; model Nicolet iS10) using KBr pellets, at the Faculty of Science, Benha University. A field-emission scanning electron microscope (SEM; JEOL JSM 6510 lv) and high-resolution transmission electron microscope (TEM; JEOL JEM-2100) at Mansoura University were used to collect FE-SEM and TEM images of the as-prepared nanoparticles.

Statistical analysis

The statistical analysis was subjected to one-way ANOVA with five factors at a significance level of 0.05 for all the results using SPSS (ver. 22). Data were treated according to a completely randomized design according to Stell et al. (1997). Multiple comparisons were made, applying LSD. Statistical data analysis of LC_{50} was carried out using Finney (1971). Probit analysis software was used.

Results

Synthesis and characterization of silica nanoparticles

The phase composition of the as-prepared SiO_2 nanoparticles was investigated utilizing the XRD technique. XRD patterns of the products (prepared without and with starch fuel; A and B, respectively) calcined at 600 and 800 ºC are illustrated in Fig. 1. This figure reveals that the SiO_2 products were compatible with the tetragonal phase of the SiO_2 nanoparticles [No. 01-082-1410; space group: P41212]. Moreover, no other peaks for impurities can be observed which confirms the pure phase of SiO_2 (Parise et al. 1994). It is worthy of note that the calculated crystallite size (D, nm) for SiO_2 products calcined at 800 ºC; A_{800} and B_{800} were found to be 11.2 and 3 nm, respectively, using the Debye–Scherrer equation (Jenkins and Snyder 1996). However, SiO_2 products ignited at 600 ºC; A_{600} and B_{600} were almost amorphous and the crystallite size was smaller than 3 nm.

$$D = 0.9\lambda/\beta\cos\theta_B$$

where λ (nm) is the X-ray radiation wavelength, β is the full width of the diffraction peak at half maximum (FWHM), and θ_B is the Bragg diffraction angle.

In addition, the chemical composition of the calcined samples was further identified using the Fourier transform infrared (FT-IR) spectra and the results are displayed in Fig. 2. The band appearing at ca. 467 cm^{-1} may refer to a siloxane bond (Si-O-Si) bending vibration. The bands appearing at ca. 807 cm^{-1} may be due to symmetric stretching vibrations of the Si-O-Si bond. The band appearing at ca. 1099 cm^{-1} may be assigned to asymmetric stretching vibrations of the Si-O-Si bond. Eventually, the band appearing at ca. 1635 and 3450 cm^{-1} may be attributed to hydroxyl groups of the adsorbed surface water molecules and the band appearing at ca. 2927 and 1635 cm^{-1} may be attributable to the vibrational frequencies of the hydroxyl groups of silanols (-Si-OH) (Liou and Yang 2011).

Furthermore, the surface morphology of the as-prepared SiO_2 nanoparticles calcined at 800 ºC, prepared without starch and with starch fuel, was investigated employing a scanning electron microscope (SEM), as shown in Fig. 3A, B, respectively. The microstructure of the products was also examined using a transmission electron microscope (TEM) and the results are presented in Fig. 3C, D, respectively. The SEM micrograph of the SiO_2 demonstrates that the product can be considered to be made up of irregular agglomerates composed of spherical-shaped particles. Besides, the TEM images of the as-synthesized silica NPs clarified that the product was composed of spherical and irregular-shaped particles. Moreover, the TEM image (Fig. 3D) of the nano-silica product B_{800} exhibited that this product is porous compared to the silica product A_{800} prepared in the absence of starch fuel (Fig. 3C).

Larvicidal and pupicidal bioassay activity

The larvicidal and pupicidal activity of the as-synthesized SiO_2 nanoparticles were evaluated and are presented in Tables 1 and 2. Treatments with two different SiO_2 nanoparticles recorded a high mortality % in all of the mosquito development stages compared to the untreated groups. On the one hand, the obtained results indicated that the highest mortality % was observed in the 1st larval instar compared to almost all other immature life stages at the highest

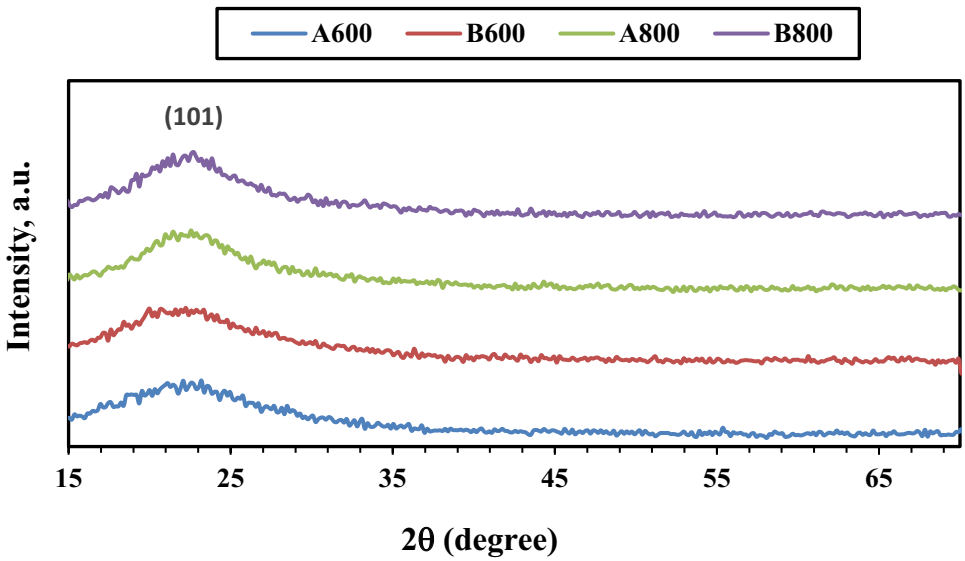

Fig. 1 XRD patterns of silica nanoparticles were calcined at 600 ºC (A_{600} and B_{600}) and 800 ºC (A_{800} and B_{800})

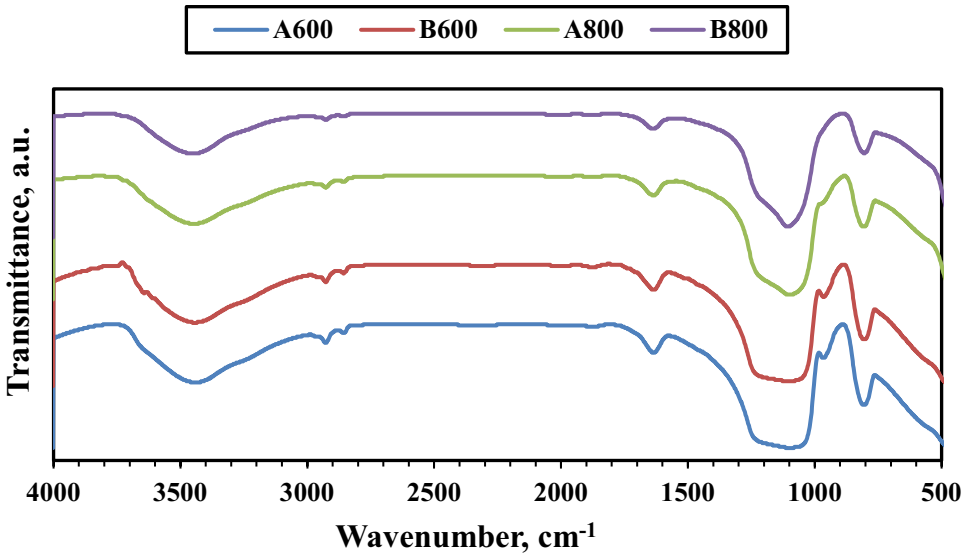

Fig. 2 Fourier transform infrared (FT-IR) spectra of silica nanoparticles calcined at 600 ºC (A_{600} and B_{600}) and 800 ºC (A_{800} and B_{800})

concentration (200 ppm) of silica nanoparticles; mortality reached 100% and 90% for the B_{800} and A_{800} silica nanoparticles at 24 h exposure compared to 0.0% mortality for the control. On the other hand, the lowest mortality was recorded in the pupal stage (36.6% and 46.6%) for A_{800} and B_{800}, respectively, followed by the 4th larval instar (63.3% and 81.6%) at 24 h exposure to 200 ppm, respectively. Moreover, 100% mortality in the 1st larval instar was observed at 48 h exposure to both samples of silica nanoparticles (B_{800} & A_{800}); likewise, 100% mortality in the 2nd larval instar was recorded for B_{800} silica nanoparticles at 48 h (200 ppm). Furthermore, the data presented in Tables 1 and 2 show significant differences ($P \leq 0.05$) between the susceptibilities of *Cx. pipiens* mosquitoes. Mosquito larvae

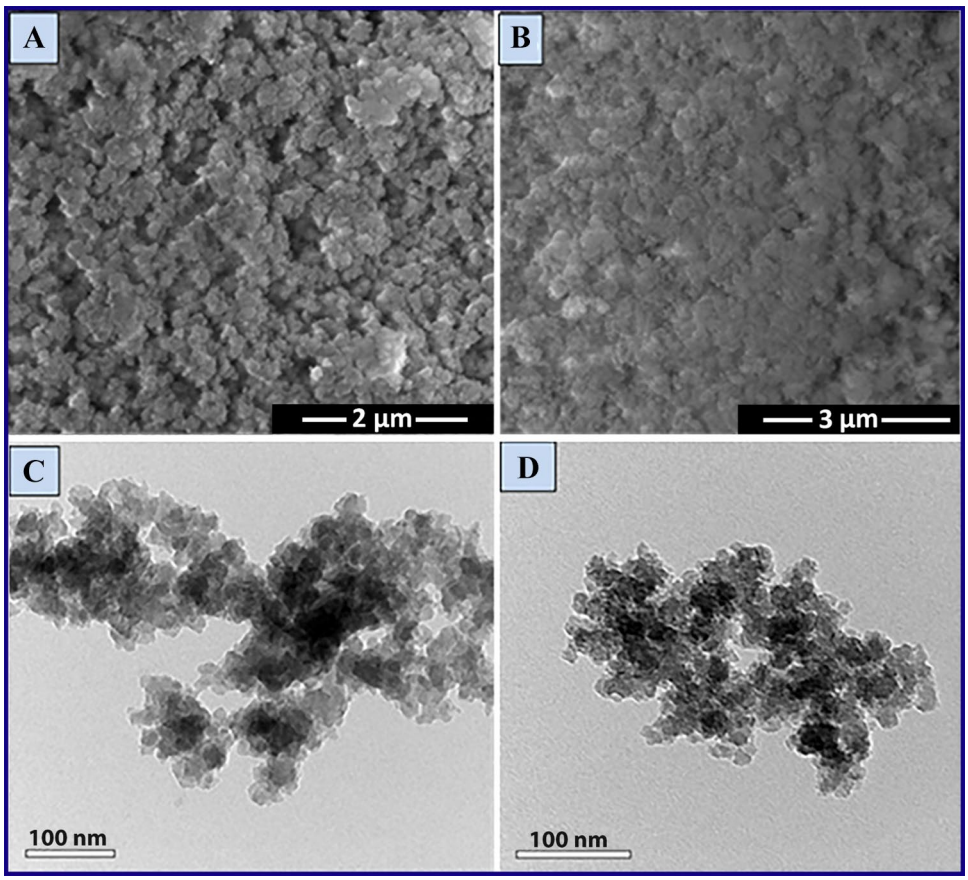

Fig. 3 FE-SEM and TEM images of calcined silica nanoparticles prepared without fuel; A_{800} (**A**, **C**), and with starch fuel; B_{800} (**B**, **D**), respectively

Table 1 Toxicity of silica nanoparticles (A_{800}) in larvae and pupae of *Culex pipiens* mosquitoes at different concentrations and time intervals

Time (h)	Concentration (ppm)	Means of mortality % of *Culex pipiens* larval and pupal stages					Total mean (%)
		1st mean ± SD	2nd mean ± SD	3rd mean ± SD	4th mean ± SD	Pupa mean ± SD	
24	Control	0 ± 0^{fA}	0 ± 0^{fA}	0 ± 0^{fA}	0 ± 0^{fA}	0 ± 0^{eA}	0 ± 0^{f}
	5	15.0 ± 2.9^{eA}	13.3 ± 1.7^{eB}	8.3 ± 1.6^{eC}	5.0 ± 0.0^{eD}	0 ± 0^{eE}	8.3 ± 1.6^{e}
	25	31.6 ± 4.4^{dA}	28.3 ± 1.6^{dB}	18.3 ± 3.3^{dC}	13.3 ± 1.6^{dD}	5.0 ± 2.9^{dE}	19.3 ± 2.8^{d}
	50	53.3 ± 4.4^{cA}	41.8 ± 1.6^{cB}	30.0 ± 2.8^{cC}	25.0 ± 5.0^{cD}	11.6 ± 4.4^{cE}	32.3 ± 4.1^{c}
	100	70.0 ± 5.7^{bA}	61.7 ± 4.41^{bB}	45.0 ± 2.8^{bC}	33.3 ± 4.4^{bD}	23.3 ± 1.6^{bE}	46.6 ± 4.8^{b}
	200	90.0 ± 2.8^{aA}	80.0 ± 2.8^{aB}	75.0 ± 2.9^{aC}	63.3 ± 1.6^{aD}	36.6 ± 4.4^{aE}	69.0 ± 5.0^{a}
48	Control	0 ± 0^{fA}	0 ± 0^{fA}	1.6 ± 1.6^{fA}	0 ± 0^{fA}	1.6 ± 1.6^{fA}	0.6 ± 0.4^{f}
	5	25.0 ± 2.9^{eA}	23.3 ± 4.4^{eA}	16.6 ± 1.6^{eB}	13.3 ± 1.6^{eC}	3.3 ± 1.6^{eD}	16.3 ± 2.3^{e}
	25	48.3 ± 3.3^{dA}	45.0 ± 2.8^{dB}	28.3 ± 3.3^{dC}	25.0 ± 5.7^{dD}	8.3 ± 1.6^{dE}	31.0 ± 4.1^{d}
	50	68.3 ± 6.6^{cA}	63.3 ± 6.0^{cB}	45.0 ± 5.0^{cC}	36.6 ± 1.6^{cD}	21.6 ± 3.3^{cE}	47.0 ± 4.9^{c}
	100	86.6 ± 3.3^{bA}	81.6 ± 3.3^{bB}	63.3 ± 4.4^{bC}	50.0 ± 2.9^{bD}	36.6 ± 1.6^{bE}	63.6 ± 5.1^{b}
	200	100.0 ± 0.0^{aA}	93.3 ± 4.4^{aB}	83.3 ± 6.0^{aC}	76.7 ± 4.4^{aD}	55.0 ± 5.0^{aE}	81.6 ± 4.5^{a}

Where, a, b, and c symbols mean that there is no significant difference ($P > 0.05$) between any two means, within the same column having the same superscript letter. Likewise, A, B, and C symbols mean that there is no significant difference ($P > 0.05$) between any two means for the same attribute, within the same row having the same superscript letter

were more susceptible to B_{800} silica nanoparticles than A_{800}; the mean of the highest potential larval mortality was 82.3% and 91.6% for B_{800} compared to 69% and 81.6% for A_{800} silica nanoparticles, at 24 and 48 h, respectively. Both silica nanoparticle products had the highest mortality at 200 ppm.

The LC_{50} values for the larval and pupal stages of *Culex pipiens* after being treated with silica nanoparticles at 24 and 48 h are displayed in Fig. 4. The depicted data in Fig. 4 reveal that LC_{50} values for B_{800} silica nanoparticles were 19.76 and 85.24 ppm at 24 h (*P*-value = 0.2 & 0.26) for the 1st and 4th larvae instar compared to 39.03 and 155.17 ppm (*P*-value = 0.3 & 0.45) for the A_{800} silica nanoparticles for the 1st and 4th larvae instar, respectively.

Furthermore, the presence of SiO_2 nanoparticles affected larval and pupal development as well as survival (Table 3). The results show that development was faster in the untreated groups (control) than in mosquito larvae and pupae treated with silica nanoparticles. The total duration of larval-adult development was 18.4 and 22.7 days for A_{800} and B_{800} silica nanoparticles respectively compared with

Table 2 Toxicity of silica nanoparticles (B_{800}) in larvae and pupae of *Culex pipiens* mosquitoes at different concentrations and time intervals

Time (h)	Concentration (ppm)	Means of mortality % of *Culex pipiens* larval and pupal stages					Mean (%)
		1st mean ± SD	2nd mean ± SD	3rd mean ± SD	4th mean ± SD	Pupa mean ± SD	
24	Control	0 ± 0^{fA}	0 ± 0^{fA}	0 ± 0^{fA}	0 ± 0^{fA}	0 ± 0^{eA}	0 ± 0^{f}
	5	25.0 ± 2.8^{eA}	16.6 ± 2.8^{eB}	10.0 ± 2.9^{eC}	5.0 ± 2.8^{eD}	1.6 ± 1.6^{eE}	11.7 ± 2.4^{e}
	25	48.3 ± 4.4^{dA}	35.0 ± 5.0^{dB}	25.0 ± 2.8^{dC}	16.6 ± 4.4^{dD}	8.3 ± 1.6^{dE}	26.6 ± 3.9^{d}
	50	68.3 ± 4.4^{cA}	45.0 ± 13.2^{cB}	36.6 ± 4.4^{cC}	28.3 ± 3.3^{cD}	16.6 ± 4.4^{cE}	39.0 ± 5.0^{c}
	100	81.6 ± 1.6^{bA}	71.6 ± 2.9^{bB}	58.3 ± 4.4^{bC}	50.0 ± 5.7^{bD}	31.6 ± 1.6^{bE}	58.6 ± 4.8^{b}
	200	100.0 ± 0.0^{aA}	95.0 ± 5.0^{aB}	88.3 ± 7.3^{aC}	81.6 ± 4.41^{aD}	46.6 ± 4.4^{aE}	82.3 ± 5.3^{a}
48	Control	0 ± 0^{fA}	0 ± 0^{fA}	1.6 ± 1.6^{fA}	0 ± 0^{fA}	1.6 ± 1.6^{fA}	0.6 ± 0.4^{f}
	5	41.6 ± 1.6^{dA}	26.6 ± 2.8^{dB}	18.3 ± 1.6^{eC}	15.0 ± 2.8^{eD}	6.6 ± 1.6^{eE}	21.6 ± 3.3
	25	70.0 ± 2.8^{cA}	51.6 ± 5.7^{cB}	38.3 ± 3.3^{dC}	30.0 ± 2.8^{dD}	13.3 ± 4.4^{dE}	40.6 ± 5.3^{d}
	50	91.6 ± 4.4^{bA}	76.6 ± 7.6^{bB}	66.6 ± 4.4^{cC}	50.0 ± 7.6^{cD}	$31.6 \pm 4.4cE$	63.3 ± 5.9^{c}
	100	100.0 ± 0.0^{aA}	98.3 ± 2.8^{aA}	93.3 ± 1.6^{bB}	81.6 ± 4.4^{bC}	46.6 ± 7.3^{bD}	84.0 ± 5.5^{b}
	200	100.0 ± 0.0^{aA}	100.0 ± 0.0^{aA}	100.0 ± 0.0^{aA}	95.0 ± 2.8^{aB}	63.3 ± 4.4^{aC}	91.6 ± 3.9^{a}

Where, a, b, and c symbols mean that there is no significant difference ($P > 0.05$) between any two means, within the same column having the same superscript letter. Likewise, A, B, and C symbols mean that there is no significant difference ($P > 0.05$) between any two means for the same attribute, within the same row having the same superscript letter

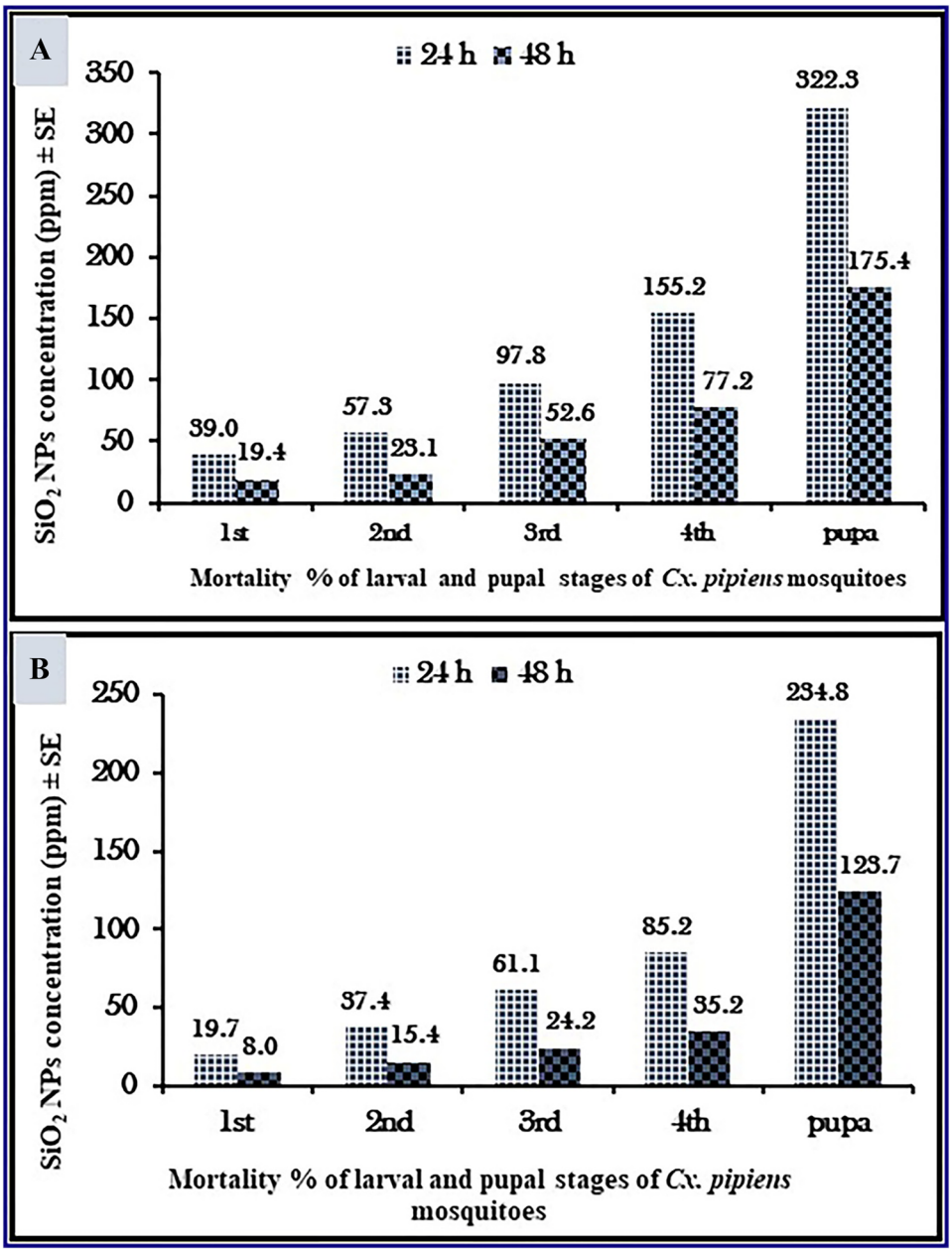

Fig. 4 LC_{50} values for silica nanoparticles; A_{800} (**A**) and (**B**) B_{800} in larvae and pupae of *Culex pipiens* mosquitoes at 24 and 48 h

13.3 days for the control. The survival of larvae to adult mosquito was reduced after treatment with A_{800} and B_{800} silica nanoparticles reaching 79.2% and 64.5% compared to 94.4% in the control groups.

The effect of a sub-lethal concentration (LC_{50}) of the tested nanoparticles on total protein, and the amount of developmental and detoxification enzymes in 4th instar larvae *Cx. pipiens* are recorded in Table 4. The data show that total protein decreased after treatment with LC_{50} of SNPs, while there was a significant decrease in alkaline phosphatase and acid phosphatase enzyme activity in treated larvae (developmental enzymes). The activity of detoxification enzymes, such as glutathione transferase (GSTs) and α-esterases, increased significantly after treatment compared with the control groups.

Discussion

Medical insect control includes mosquito vectors based on chemical insecticide, where it is the key component of various strategies to stop the transmission of mosquito-borne diseases. However, the advent of insect resistance has necessitated the development and use of alternative control tools and methods (Barik et al. 2012). The hope is that nanoparticles represent a new scientific technology

Table 3 Means of larval and pupal duration (days) and survival (%) (±S.D) of *Culex pipiens* larvae and pupae at LC_{50} of silica nanoparticles

Sample	***Culex pipiens* larval instars and pupal stage (LC_{50})**											
	1st		2nd		3rd		4th		Pupal stage		Larval-adult period	
	D	S	D	S	D	S	D	S	D	S	D	S
Control	2.0 ± 0.0^{bC}	93.3 ± 1.3^{aA}	2.53 ± 0.29^{cB}	96.0 ± 2.3^{aA}	2.9 ± 0.15^{cAB}	93.3 ± 2.7^{aA}	3.2 ± 0.2^{cA}	93.3 ± 1.3^{aA}	2.6 ± 0.3^{cB}	96.0 ± 2.3^{aA}	13.3 ± 0.7^{c}	94.4 ± 0.8^{a}
A_{800}	2.73 ± 0.1^{aD}	62.6 ± 3.5^{bD}	3.20 ± 0.42^{bC}	69.3 ± 3.5^{bC}	3.83 ± 0.3^{bB}	86.6 ± 3.5^{bB}	5.20 ± 0.7^{bA}	86.6 ± 3.5^{bB}	3.4 ± 0.3^{bB}	90.6 ± 1.3^{bA}	18.4 ± 1.3^{b}	79.2 ± 3.2^{b}
B_{800}	3.0 ± 0.0^{aC}	48.0 ± 0.0^{cE}	4.33 ± 0.3^{aB}	53.3 ± 2.6^{cD}	4.70 ± 0.3^{aB}	64.0 ± 2.3^{cC}	6.43 ± 0.3^{aA}	72.0 ± 2.3^{cB}	4.3 ± 0.4^{aB}	85.3 ± 3.5^{cA}	22.7 ± 1.6^{a}	64.5 ± 3.7^{c}

Where, a, b, and c symbols mean that there is no significant difference ($P > 0.05$) between any two means, within the same column having the same superscript letter. Likewise, A, B, and C symbols mean that there is no significant difference ($P > 0.05$) between any two means for the same attribute, within the same row having the same superscript letter. Moreover, D refers to Duration (days) and S to Survival (%)

that could provide a cost-effective solution to some of the most challenging environmental problems. They are already applied in other fields such as industry, biomedicine, and in agriculture (Kitherian 2017; Jeelani et al. 2019), where they have recently been used as pesticides against insects either in medical or agricultural settings (Rouhani et al. 2013).

Metal oxide nanoparticles have received much attention and have been produced widely over the past years due to their broad application in many fields (Aitken 2006; Rizwan et al. 2017). These metal oxides include silica (SiO_2), zinc oxide (ZnO), titanium dioxide (TiO_2), copper oxide (CuO), chromium dioxide (CrO_2), barium titanate ($BaTiO_3$), and lithium cobalt dioxide ($LiCoO_2$) (Lead et al. 2018; Chang et al. 2020). Researchers have shed light on the general advantages of nanomaterials recommending their safe application in agriculture and pesticide production as nanotechnology will be useful to meet targeted delivery of pesticides and for the control of harmful pests that destroy crops and their products (Kitherian 2017). Silica is one of the most abundant materials on the earth and it has been introduced in many applications including as a pesticide against insects in agricultural and medical fields (Gordon et al. 2009; Priya and Santhi 2014; Ramanibai and Velayutham 2016; Vignesh and Moorthi 2017). Amorphous silica has been considered a safe insecticide and it has been classified as a non-carcinogenic material by the United States Department of Agriculture (USDA) and International Agency for the Research of Cancer (IARC) (Mucha-Pelzer et al. 2008; Liu and Sun 2010) and due to the fact that nano-materials are more effective than their bulk counterparts (Emami-Karvani and Cehrazi 2011), silica nanoparticles were employed in this study.

In the present work, synthesized silica nanoparticles were produced using a combustion method with and without starch fuel. The products were calcined at different temperatures and the results revealed that 800 ºC was a sufficient temperature to obtain pure nanosilica products. Calcination of the samples at lower temperatures produced silica products contaminated with carbon residues, as was obvious from the grey color of the products and their FT-IR spectra. Additionally, the FT-IR spectra of the silica samples calcinated at 600 ºC revealed vibrational bands at ca. 974 and 1860 cm-1 due to the carbon residue contaminants in the silica samples (Nassar et al. 2017).

Our data indicated that this carbon residue hindered SiO_2 nanoparticles from growth during the combustion and calcination processes. Therefore, the silica nanoparticles (B_{800}) produced using starch fuel have a smaller crystallite size than those of the silica nanoparticles (A_{800}) due to the action of the fuel during the combustion and calcination process. This was supported by the obtained XRD and TEM results. Besides, the TEM images revealed that silica nanoparticles (B_{800}) produced by using starch fuel are more porous than

Table 4 Determination of total protein, alkaline phosphatase, acid phosphatase, beta esterases, GST, and alpha esterases of 4th instar larvae of *Cx. pipiens* treated with LC_{50} of tested silica nanoparticles

Sample	**Enzyme activities (U × 103 /g.b.wt) ± SD**					
	Total protein	Alkaline phosphatase	Acid phosphatase	α-esterase	β-esterase	GST
Control	49.6 ± 1.2^{a}	3807.0 ± 96.6^{a}	497.3 ± 13.9^{a}	763.6 ± 8.1^{b}	455.3 ± 11.3^{a}	132.6 ± 5.9^{b}
A_{800}	47.5 ± 0.8^{a}	1767.0 ± 61.7^{b}	165.3 ± 4.8^{c}	835.3 ± 11.8^{a}	258.0 ± 7.5^{c}	141.3 ± 5.9^{b}
B_{800}	44.8 ± 1.2^{b}	1527.0 ± 66.1^{c}	213.6 ± 5.8^{b}	857.3 ± 9.8^{a}	309.6 ± 5.1^{b}	169.0 ± 7.8^{a}

Where, a, b, and c symbols mean that there is no significant difference ($P > 0.05$) between any two means, within the same column having the same superscript letter. Likewise, A, B, and C symbols mean that there is no significant difference ($P > 0.05$) between any two means for the same attribute, within the same row having the same superscript letter

the A_{800} silica product generated without starch fuel. This is probably due to the fact that the combustion reaction is an exothermic process and it gives off CO_2, N_2, and H_2O gases during the combustion process which results in the generation of products with high porosity (Nassar et al. 2017). Therefore, this kind of porous silica product has higher activity and is more applicable in various fields. However, we examined both SiO_2 nanostructures (A_{800} and B_{800}) in our subsequent investigation to explore their toxicity on *Culex pipiens* larvae and pupae, their impact upon the development, and consequently, their effect on enzymatic activity.

It is interesting to mention that the obtained results indicated that the mortality % of *Culex pipiens* increased gradually when increasing the concentration and time-exposure, with high scores for mortality in the 1st, 2nd, 3rd, and 4th larval instars and the pupal stage that reached 90%, 80%, 75%, 63.3%, and 36.6% respectively for the larvae treated with SiO_2 nanoparticles (A_{800}) of 200 ppm concentration. Besides, the mortality reached 100%, 95%, 88.3%, 81.6%, and 46.6% respectively at 24 h for the nanosilica product (B_{800}) of 200 ppm concentration. However, silica nanoparticles (B_{800}) were more effective on the mosquitos' immature stages than silica nanoparticles (A_{800}) generated in the absence of starch fuel and this may be attributable to the small crystallite size of silica nanoparticles (B_{800}) and accordingly their high surface area.

These results are in accordance with Santo-Orihuela et al. (2016) and Barik et al. (2012), which indicated that silica nanoparticles can be used as a larvicidal and pupicidal on mosquito species including *Anopheles stephensi*, *Aedes aegypti*, and *Culex quinquefasciatus* with high toxicity at low doses (112.5 and 225 ppm). The obtained results were also compatible with that data published earlier by Ziaee and Ganji (2016) which assessed the effects of two silicon dioxide nanoparticles of Aerosil® and Nanosav on adults of *Rhyzopertha dominica* and *Tribolium confusum* at 50, 100, 200, and 300 ppm after 7 days of exposure; the data showed that the mortality % for both species increased by increasing the concentration and time-exposure to each concentration and that the Aerosil® silicon dioxide nanoparticles were more effective than Nanosav silicon dioxide. Debnath et al. (2011) evaluated the effect of silica nanoparticles on *Sitophilus oryzae* and found that hydrophilic nanoparticles were more effective than Malathion at concentrations of 1 g kg-1 and 2 g kg-1. The authors explained that the deaths may be due to the nano-sized silica itself or due to losing water through damage in the water barrier that includes desiccation. The authors explained that the deaths may be due to the nano-sized silica itself or due to the loss of water from the insect cells, which resulted in dehydration and death.

As the study results indicated, a higher mortality % was observed in the 1st larval instar than in other immature life stages treated with silica nanoparticles A_{800} and B_{800}. At a 200 ppm silica concentration, the mortality rate was 100% and 90% in silica nanoparticles B_{800} and A_{800}, respectively. This finding was completely in line with the data obtained by Patil et al. (2012) that reported that the LC_{50} values increased as the developmental stage of the *Ae. aegypti* mosquito increased on treatment with silver nanoparticles at concentrations of 4.39, 5.12, 5.66, and 6.18 ppm for the 1st, 2nd, 3rd, and 4th instar larvae, respectively. Moreover, ZnO nanoparticles induced 100% mortality in *Ae. aegypti* when tested at 100 mg/L, where the LC_{50} was low; 1.57 mg/L (Banumathi et al. 2017). Interestingly, this high mortality % in the 1st larval instar may be due to their susceptibility as a result of a declined rate of detoxification enzymes (Bouvier et al. 2002).

Besides experiments in toxicity and development, the detoxifying enzymes of mosquito larvae, *Cx. pipiens* were estimated with Glutathione transferase (GSTs), α-/β-esterases, alkaline/acid phosphatases, and total protein. Glutathione transferase (GSTs) and α-/β-esterases are defensive enzymes that cause the elimination and/or transformation of endogenous and exogenous compounds through numerous metabolic pathways in insects (Intirach et al. 2019).

Evaluation of these defensive enzymes at 24 h of exposure showed that the activities of these enzymes were, to some extent, different in treated samples. Accordingly, glutathione transferase (GSTs) and α-esterase enzymes were significantly increased in treated samples in comparison with

the untreated ones and this result demonstrated that GSTs and α-esterase of *Cx. pipiens* mosquito larvae are involved in the detoxification of SiO_2 nanoparticles. This result agreed with the data recorded by Muthusamy et al. (2014). It is worth pointing out that β-esterase activity decreased as it is often opposite to α-esterase (Hafez et al. 2014). This may be attributed to esterases' proteins that do not share the same degree of similarity in their primary DNA sequences and differ widely in terms of substrate specificities. Therefore, the catalytic site and binding site that together comprise the enzyme's active site are different in both α-/β-esterases (Montella et al. 2012). On the other hand, Hamadah (2019) noted that, in the treatment of red palm weevil larvae with Pyriproxyfen, Neemazal, and Spinetoram (LC_{50} 1067.5, 14,600 and 18.37 ppm), respectively, the phosphatases (acid phosphatase; ACP, alkaline phosphatase; ALP) and transaminases (glutamic oxaloacetic transaminase; GOT, glutamine pyruvic transaminase; GPT) led to inhibited and altered enzyme activities in the hemolymph and fat body of larvae.

Similar to the results reported by Durairaj et al. (2014), alkaline/acid phosphatases were significantly reduced in treated samples in comparison with the control samples. Notably, this reduction in acid phosphatase lysosomal enzyme could be due to ingestion of any xenobiotic or toxic substances which may affect the lysosome's activity (Shaurub and El-Aziz 2015). As for alkaline phosphatase, its reduction could be attributed to the binding of SiO_2 nanoparticles at the active site of enzymes in the gut or/and the reduced synthesis of enzymes (Shakoori et al. 1994). The prolonged larval-adult development that takes 18.4 and 22.7 days when treated with A_{800} and B_{800} silica nanoparticles respectively compared with 13.3 days in the control was in conformity with previously-published results by López-Muñoz et al. (2019). This delay may be owing to the remarkable reduction in alkaline/acid phosphatases as they play a prominent role in metabolism, cell signaling, and other physiological processes (Torres and Forman 2006).

The present results revealed that the total protein content decreased after treatment with LC_{50} and this result was in line with data cited by Koodalingam et al. (2012). Under insecticidal stress, it's likely that total protein decreases as a result of the reduction in RNA and the breakdown of protein into free amino acids as well (Ali et al. 2014). Furthermore, a potential decrease in the hemolymph volume due to insecticidal stress may reduce the total protein content (Sugumaran 2010). Protein depletion may involve a physiological mechanism as it might play a role in the compensation of cells and tissues under insecticidal stress (Khosravi and Sendi 2013).

To sum up, the theory of nanoparticle toxicity has been varied, and some of it is thought to be due to the cause of oxidative stress in arthropods (Imoisili et al. 2020). Interestingly, toxicity can be due to the penetration of nanoparticles through the exoskeleton (Rai et al. 2014). It was reported that surface-charged modified nanoparticles caused dehydration in insects by absorption in the insect cuticular lipids that lead to insect death (Benelli 2018). Amorphous silica nanoparticles were absorbed in the midgut cells of *Drosophila* through endocytic vesicles and by direct membrane penetration (Pandey et al. 2013). Furthermore, nanoscale material binds to sulfur from DNA proteins in the intracellular space, leading to the rapid denaturation of organelles and enzymes. Accordingly, nanoparticles maybe affect membrane permeability resulting in a loss of cellular function and cell death.

Conclusions

This study contributes to increasing the understanding of the mechanism of silica nanoparticles and the extent of their influence on the physiological aspects of mosquito larvae. Actually, silica nanoparticles lead to some developmental and enzymatic alterations in *Culex pipiens* larvae, proving their insecticidal activity. The physiological changes in the larvae may be due to the accumulation and localization of nanoparticles in the larva's body. Moreover, this type of formulation may contribute to reducing the usage of chemical pesticides, which is a major cause of environmental pollution and to which insects are developing resistance. In anticipation of the upcoming need for effective integrated pest management strategies, nano-based insecticides may be involved in the fight against different insects which cause medical problems and economic pests without disturbing the environmental balance.

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Declarations

Conflict of interest The authors declare that there is no conflict of interest.

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