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CHEMICAL SCIENCES

Toxicity of copper (II) metal complexes with amino acids ligands: A study of activity in *Aedes aegypti* larvae

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Abstract: The larval control of *Aedes aegypti* has been done mainly by insecticides, which cause resistance and environmental contamination and have a high-cost development and application. The need for alternative solutions to problems caused by synthetic insecticides has led to studies to find new, active, and less toxic compounds, such as metallo-insecticides. In the present study, the toxic activity of Cu(II) - complexes with the amino acids tryptophan, histidine, methionine, and taurine in *Ae. aegypti* larvae were evaluated. The Cu(II) - histidine complex showed no toxicity. For the Cu(II) - tryptophan and Cu(II) - methionine complexes, the mortality percentages ranged from 3.16% to 46.55% and 5.46% to 12.42%, respectively. Cu(II) - taurine presented 100% mortality in 24 h at the lowest concentration tested (50 mg L^{-1}, ppm). Considering the concentration range of 50 to 1000 mg L^{-1} and 24 h of exposure of the larvae to the metal complexes, the series of decreasing toxicity is Cu(II) - taurine > Cu(II) - tryptophan > Cu(II) - methionine > Cu(II) - histidine. From these studies, the Cu (II) - taurine complex can be a candidate to be used as an alternative and less toxic insecticide, low-cost for control of *Ae. aegypti* larvae.

Key words: Alternative compounds, bioinsecticide, control, mosquito, viral disease.

INTRODUCTION

Aedes aegypti has been the subject of studies to develop control strategies due to vector competence for dengue, chikungunya, zika virus, and (urban) yellow fever (Leta et al. 2018, Marcombe et al. 2019). Prolonged use of organophosphates, among other insecticides, has led to resistant populations that, even with the intercalation of molecules, have not responded satisfactorily to the reversal and restriction of chemical control in Brazil (Valle et al. 2017, Ramos 2020, Vivekanandhan et al. 2021a).

The high cost and low procurement rate of new synthetic molecules are restrictive factors for developing insecticides (Sparks 2013, Ara et al. 2021), which signals the need to develop new control strategies, including new broad-spectrum, low-cost insecticidal molecules. That meets the environmental appeal currently in vogue.

Metal ions have been proposed as toxic bioactive compounds to insects, including *Ae. aegypti* larvae, because they cause oxidative stress with damage to the peritrophic matrix and, consequently, to the enzymatic, neurotransmitter, and digestive systems (Rayms-Keller et al. 1998, Servia et al. 2006, Ihechiluru et al. 2009, Arruda et al. 2010, Nardeli et al. 2014, Vivekanandhan et al. 2021b, 2018, Chinnasamy et al. 2023). The

bactericidal activity of copper-based metal ions (Neves et al. 2009) leads to the hypothesis of secondary activity on the microorganisms that feed the mosquito larvae, altering the microbiota and reducing the attractiveness of the females to the breeding sites.

Amino acids are constituents of the secondary metabolism of plants, sometimes used to defend themselves from herbivorous insects (Heidel-Fischer & Vogel 2015). The composition of these metabolites (amino, terpenoid, and phenolic) (Huang et al. 2011, Aljbory & Chen 2018, Rashid War et al. 2018) influences the absorption of amino acids, affecting the physiology and/or behavior of the insects (Chen et al. 2008, Aljbory & Chen 2018, Rashid War et al. 2018). Thus, amino acids can be essential tools for developing toxic complexes to control insects, as they exert the function of metal carriers to the interior of the cells, enhancing the toxicity in the target organism.

Available studies in the literature have shown that metallo-pharmaceuticals can combine characteristics of conventional non-targeted coordination molecules and organic ligands that may exhibit selectivity for biological targets. For instance, complexes with physiologically active ligands have proven to be particularly interesting. Including biologically active ligands in organometallic/metal-based insecticide complexes holds the potential for developing new drugs and even metal-based insecticides with specific activities. In this context, research on metal complexes can reveal different mechanisms of action/biological activity based on the intrinsic properties of the metal and the (bio)activity of the ligand, potentially even overcoming established pathways for drug activity. The specificity of ligands in metal complexes may allow for anchoring, permeation, and even modification of the efficacy of the diffusion process across cell membranes, with various implications, differentiated reactions with species, and intracellular content based on the ligand-metal complexation constants. It is known that complexation, coordination, or chelation can reduce the polarity of metals and increase the lipophilicity of the coordinated metal atom, which can facilitate or enhance penetration through the lipid layer of the membrane. Copper ion (Cu(II)) possesses redox properties, low cost, and intense biological activity for numerous proteins and enzymes, such as cytochrome C oxidase and Cu/Zn superoxide dismutase, which are related to respiration, energy metabolism, and DNA synthesis. Copper complexes have been considered promising in biocompatibility despite their redox nature, which can damage DNA. Published works have shown that copper has lower toxic effects than other metal ions, especially when coordinated with ligands with intense biological activity (Shivabasayya et al. 2024).

As a precursor of the present study, evaluations have shown that polar amino acids (L-aspartate and L-glutamate) form complexes with copper ions and are toxic to *Ae. aegypti* larvae (Rodrigues et al. 2017). In continuity, the present scientific research demonstrates the toxicity of the metal complexes formed by copper (II) and the amino acids histidine, methionine, taurine, and tryptophan.

MATERIALS AND METHODS

Synthesis of complexes Cu(II) - amino acids

The amino acids tryptophan, histidine, methionine, taurine, $CuCl_2.2H_2O$, and NaOH were purchased via Sigma Aldrich. The complexes were synthesized according to the following methodologies: Cu(II) - tryptophan (CuTrp) (Wagner & Baran 2004), Cu(II) - histidine (Cu-His) (Kumar 2011), Cu(II) - methionine (CuMet) (Onoa

& Moreno 1998), and Cu(II) - taurine (CuTau) (Kella et al. 2008).

In synthesizing the complex Cu-Trp, 2.00 mmol of Trp in an aqueous medium was stirred and heated to 50 °C until solubilized. Then, 1.00 mmol of $CuCl_2.2H_2O$ in an aqueous medium was added, stirred, and heated to 50 °C for 15 minutes. Subsequently, the solution was cooled to room temperature, filtered, and the precipitate was washed with water (Wagner & Baran 2004).

His (2.00 mmol) was added to methanol, followed by 1.00 mmol of $CuCl_2.2H_2O$ in an aqueous medium under stirring for 60 minutes. The CuHis complex solution was evaporated at room temperature (Kumar 2011).

The CuMet complex was synthesized according to Onoa & Moreno (1998) with modifications. Met (2.00 mmol) was added in an aqueous medium at 80 °C with constant stirring. After solubilization, 1.00 mmol of $CuCl_2.2H_2O$ was added to an aqueous medium, stirring and heating for 45 minutes. This solution was cooled to room temperature, filtered, and the precipitate obtained was washed with distilled water.

For CuTau complex, 2.0 mmol of Tau were solubilized in methanol with 2.0 mmol of NaOH. Then, was added 1.0 mmol of $CuCl_2.2H_2O$ in methanol and refluxed for 8 h. After cooling to room temperature, the solid obtained was filtered and removed with methanol. All metal complexes were obtained with the respective colors and yields: CuTrp (87%), CuMet (85%) (both violet staining), CuHis (82%), and CuTau (78%) (both with light blue) (Kella et al. 2008).

Characterization of complexes Cu(II)-amino acids

The following physicochemical parameters were analyzed to characterize the complexes. UV-Vis Absorption Spectra using Cary 50 Conc/ Varian spectrophotometer with a scanning range between 200 and 800 nm. Trp and CuTrp solutions were prepared using DMSO 100% (Sigma Aldrich®) in the concentration of 3.00 x 10^{-3} mol L^{-1}. Met and CuMet acidified aqueous solutions were prepared with 1.0 mL of 0.100 mol L^{-1} HCl (Sigma Aldrich®), in the concentration of 8.00 x 10^{-3} mol L^{-1} and for His, CuHis, Tau, and CuTau aqueous solutions at 10^{-2} mol L^{-1}. Vibrational spectra in the infrared (IR) region using an FTIR spectrophotometer (Jasco 4100) were obtained from 400 to 4000 cm^{-1} using a KBr pellet. Elemental analysis (EA) using an elemental analyzer (Perkin Elmer model 2400 CHN) and Thermogravimetric analysis (TGA) using Universal V4.1D TA Instruments. The experimental conditions were a heating range from 30 to 800 °C, a heating rate of 20 °C min^{-1}, a synthetic air atmosphere with a flow of 100 mL $min^{-1,}$ and a platinum crucible as support. The masses used for the analyses were 3.088 mg for the CuTrp complex, 3.089 mg for CuHis, 4.156 mg for CuMet, and 3.320 mg for the CuTau.

Larvae development

The larvae were from *Ae. aegypti* eggs (Rockefeller strain from Laboratory of Insect Vectors of the Federal University of Grande Dourados) were maintained in plastic trays with tap water at 25 °C. After egg hatching, the larvae were fed daily with 1 mg of fish ration (Alcon®) per larvae until reaching the third-instar larval stage (Arrivillaga & Barrera 2004).

Evaluation of toxicity in *Aedes aegypti* larvae

The toxicity of Cu(II) - amino acids complexes was evaluated by employing bioassays to determine the median lethal concentration (LC_{50}) (WHO 2005). For CuHis, CuMet, and CuTau complexes, the concentrations 50, 91, 165, 301, 546, and 998 mg L^{-1}, and for CuTrp complex, concentrations of 200, 270, 364, 492, 664, and 897 mg L^{-1} were used. The control His, Met, and Tau

were also evaluated in the larvae. The CuMet complex solutions were prepared by adding 0.1 mol L^{-1} HCl, and the Met solution was heated for solubilization. For the CuTrp complex, solutions were prepared by adding 0.40% DMSO and Trp heated in an aqueous medium to dissolve. Groups of 20 larvae of *Ae. aegypti* were kept in containers with 20 mL of solution; eight replicates were prepared for each concentration. Were used two controls: positive control (Temephos at 0.012 mg L^{-1} solubilized with 0.4% DMSO) and negative control (distilled water). The positive control was Temephos previously solubilized in 0.4% DMSO, and the negative control was distilled water. In the experiments, the positive and negative controls showed 100% and 0% mortality, respectively. After 8 and 24 hours of the application, mortality was determined, and the larvae could not remain on the water surface without reacting to a brush's physical stimulus.

Statistical analysis

The mortality data were analyzed through probit analysis using OriginPro v.9 software (OriginLab Corp.) with 95% confidence intervals (LCL: lower control limit, UCL: upper control limit), chi-square (χ^2), and degrees of freedom (*df*) were assessed.

RESULTS AND DISCUSSION

Characterization of Cu(II) metal complexes with amino acid ligands

The formation of copper complexes with the amino acids was confirmed by analyzing the absorption band shifts in UV-Vis as shown in Figure 1a-d for CuTry, CuHis, CuMet, and CuTau, respectively. The spectra have similar profiles. The complexes' UV-Vis absorption spectra are shown as dots and the copper salt as dashed. The absorption spectra of the complexes demonstrated hypsochromic displacement relative to the respective $CuCl_2.2H_2O$ spectra (Figure 1). Stanila et al. (2007) demonstrated that Cu(II)-amino acid complexes could be analyzed using spectroscopic methods. The study discusses the synthesis and characterization of copper-amino acid complexes in aqueous solution ($[Cu(L1)_2]\cdot H_2O$, where L1 = methionine; $[Cu(L2)_2]\cdot H_2O$, where L2 = phenylalanine; and $[Cu(L3)_2]$, where L3 = tryptophan), through elemental, thermal, and IR, UV-Vis, and EPR spectroscopic investigations. The IR spectra show that amino acids act as bidentate ligands with coordination involving the carboxylic oxygen and the nitrogen atom of the amino group. The ν(CO) and δ(N–H) vibrations are shifted toward higher (for $[Cu(L1)_2]\cdot H_2O$ and $[Cu(L2)_2]\cdot H_2O$) and lower-wave numbers for $[Cu(L3)_2]$. Visible electronic and powder EPR spectra at room temperature are typical for monomeric species with square-planar local symmetry around the metal ion. These displacements provide indications of complex formation by the occurrence of changes in the Cu(II) ion coordination environment since amino acids are strong field ligands. The bands in the spectra of the complexes and $CuCl_2.2H_2O$ are attributed to the electron transition in the d-d orbitals of Cu(II). The precursor salt of Cu(II) has a band with maximum intensity at 800 nm. There is a clear shift to lower wavelengths for the complexes when copper is complexed to the amino acid. For complex CuTrp (Fig. 1a) the spectrum shows a band with maximum absorption at a wavelength of around 610 nm, while for CuHis of 650 nm, CuMet at 750 nm, and CuTau at 480 nm. It is observed that the spectra present similar profiles but with the maximum absorption in different wavelengths, that is, characteristic of each compound. Thus, from these results, it is possible to suggest relatively and qualitatively that the desired materials were formed.

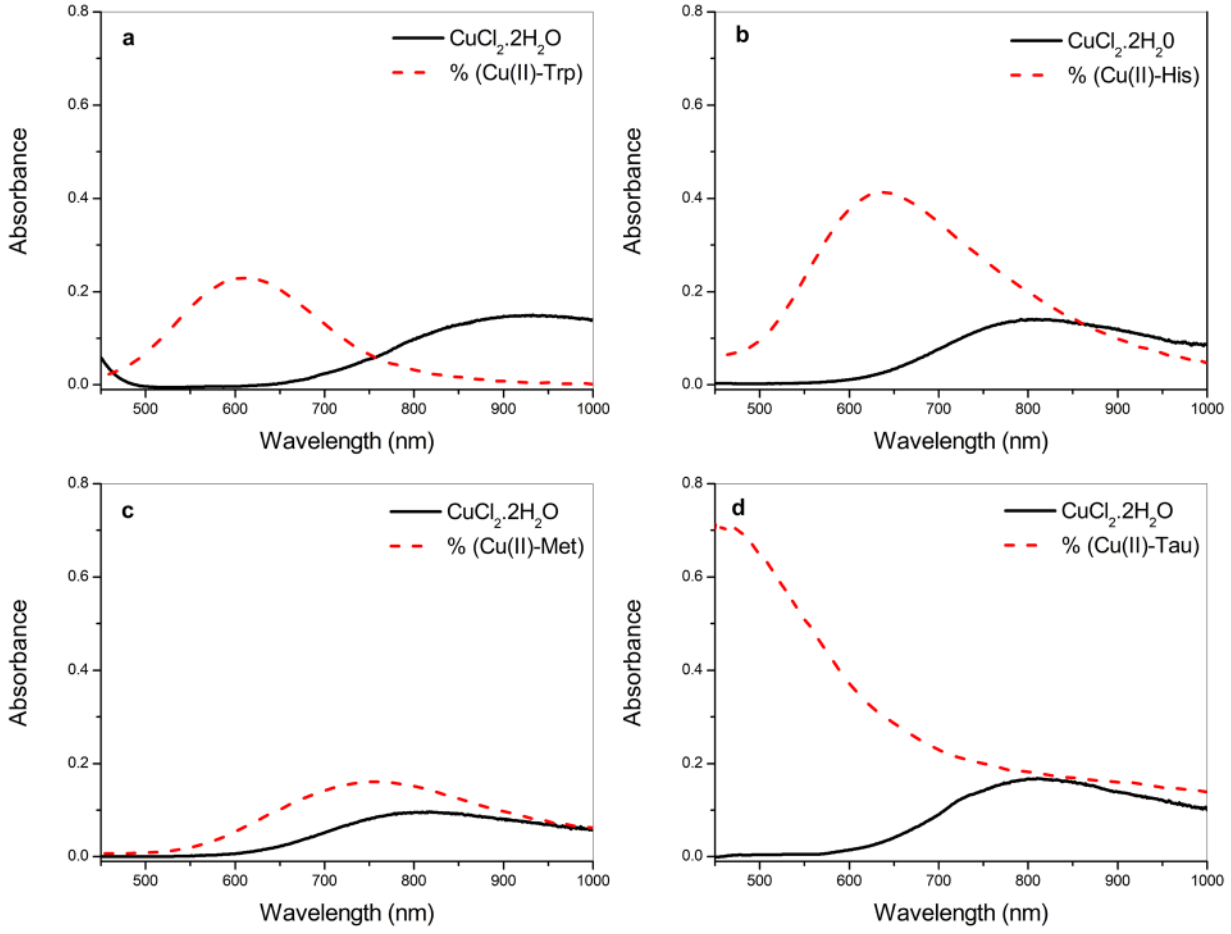

Figure 1. Absorption spectra of Cu (II) - amino acid complexes: (a) Cu(II)-Trp, (b) Cu(II)-His, (c) Cu(II)-Met, (d) Cu(II)-Tau.

The study is in agreement with Rayms-Keller et al. (1998), which serves as a motivation to investigate the toxicity and mitigation of the biological impacts of the Cu(II) ion. We consider the coordination of amino acid-Cu(II) complexes to reduce toxicity and enhance biological activity. These complexes have similar formation but different complexation constants, allowing for the transport of Cu(II) ions under experimental conditions and analysis of biological activities. In the insect's metabolism, the production of free radicals from ingestion can cause physical and metabolic damage, leading to cellular destruction in the digestive system.

FTIR

FTIR spectra of the amino acids, present as dipolar ions (zwitterions), are shown in Fig. 2. The main deformations are amine groups (NH_3^+) in the region of 3100 cm^{-1} to 2000 cm^{-1}, carboxylic group (COO^-) at 1600 cm^{-1} and 1400 cm^{-1} (Baran et al. 2002, Wagner & Baran 2004); and the sulfonic group (SO_3^-) (amino acid taurine) in the region of 1250 cm^{-1} to 1110 cm^{-1} (Kella et al. 2008) (Figure 2). For the complexes, the absence of the bands related to the NH_3^+, COO^- and SO_3^- functional groups and/or displacement or change in the spectral profile are strong indicators of coordination of the amino acids to the Cu(II)

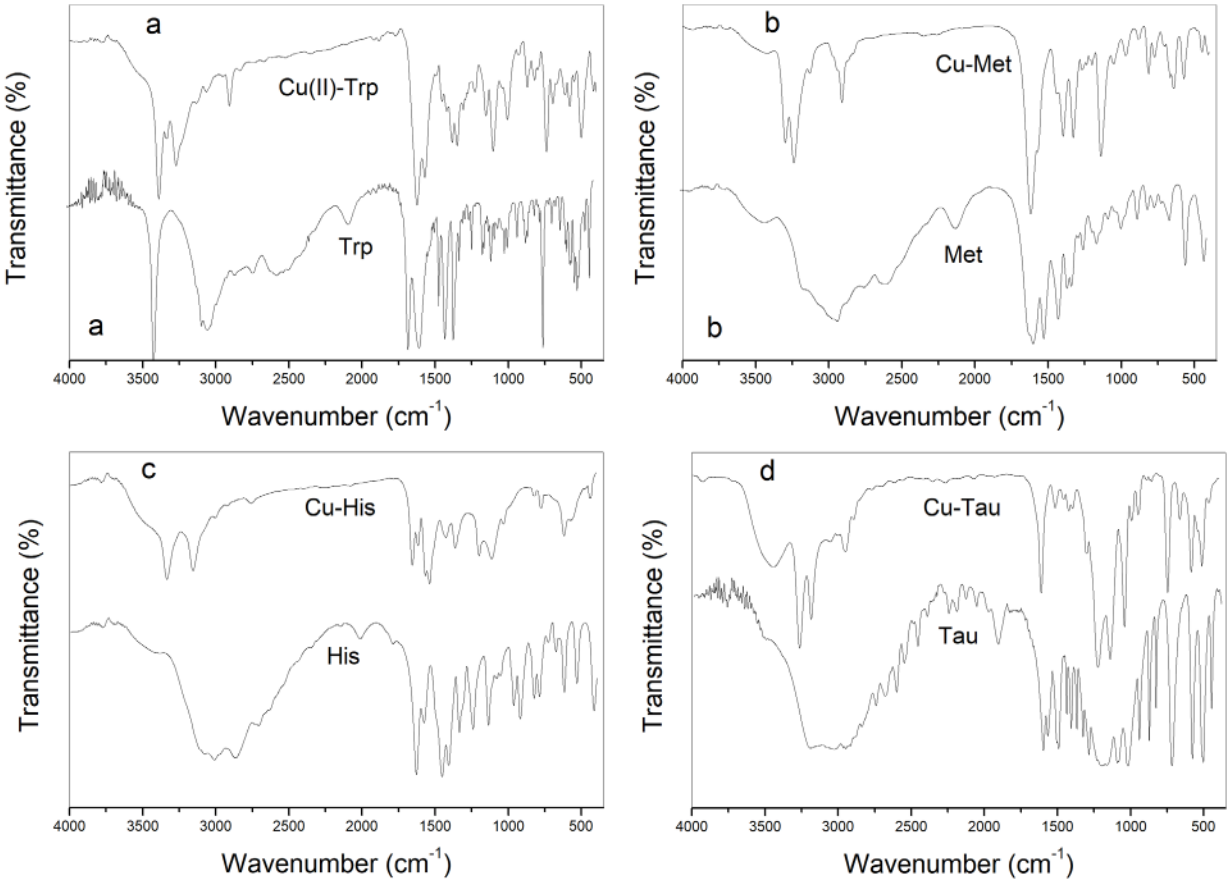

Figure 2. FTIR spectra of amino acids and their Cu(II) - amino acid complexes. (a) Cu(II)-Trp, (b) Cu(II)-Met, (c) Cu(II)-His, (d) Cu(II)-Tau.

metallic center. Another evidence of Cu - amino acids complexation is the appearance of bands attributed to the NH_2, C=O, and S=O groups since these do not exist in the free amino acids (zwitterionic form). The experimental results obtained by the FTIR spectroscopy for the CuTrp, CuHis, CuMet, and CuTau complexes are consistent with the results presented in the literature (Baran et al. 2002, Kella et al. 2008, Gao et al. 2014).

The results obtained by the elemental analysis techniques allowed us to propose the stoichiometric formula for the complexes, as shown in Table I. The molecular formulas for the CuTrp, CuMet, and CuTau complexes present metal-ligand stoichiometry 1:2. The coordination occurs by carboxyl and amino groups and with the possibility of obtaining different chemical structures. In general, in this study, all complexes were obtained in the neutral form. To corroborate the study of elemental analysis of the complexes, thermogravimetric analysis (TGA) was performed in an oxidizing atmosphere.

Thermal analysis

The thermogravimetric analysis (TGA) of the Cu(II)-amino acid complexes provided relevant information about the thermal decomposition and stoichiometry of the Cu(II)-Histidine (Cu(II)-His), Cu(II)-Methionine (Cu(II)-Met), Cu(II)-Tryptophan (Cu(II)-Trp), and Cu(II)-Taurine (Cu(II)-Tau) complexes. Based on the mass loss data observed in the TGA curves (Figure 3), it is possible to calculate the stoichiometry of the complexes,

Table I. Elemental Analysis (EA) of C, H, N, Theoretical (T) and Experimental (E), Molecular Mass (MM (g mol^{-1})) and molecular formula for Cu(II) - amino acid complexes.

Complex/ Elements	CuTrp		CuHis		CuMet		CuTau	
	T	E	T	E	T	E	T	E
C	56.22	56.34	37.01	37.05	33.37	33.44	15.41	15.77
H	4.720	4.520	5.210	5.190	5.600	5.480	3.880	3.920
N	11.92	11.93	21.60	21.590	7.780	7.590	8.980	8.930
MM	**469.98**		**389.02**		**359.96**		**311.82**	

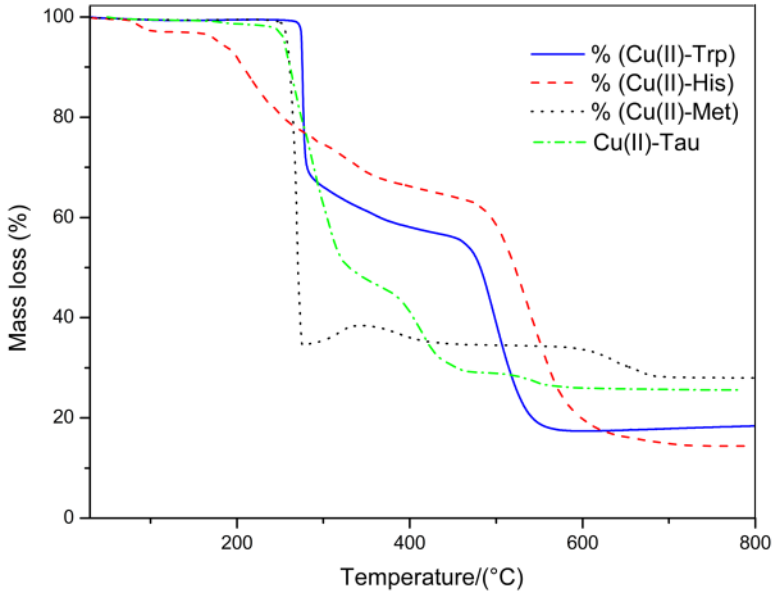

Figure 3. TG curves of Cu(II) - amino acids complexes obtained in an oxidizing atmosphere.

considering the loss of coordinated water and the decomposition of the organic ligands. These results were obtained from the complete decomposition of the ligands, which led to the formation of pure copper oxide (CuO) residues as the stable final product. The percentages of mass loss related to ligand decomposition and oxide formation are summarized in Table II. These thermoanalytical data are considered to be a comparison between theoretical and experimental mass loss (TGA). Thus, based on this information, it is possible to determine that the metal-to-ligand stoichiometric ratio is 1:2 for all the complexes studied. From the results obtained by the TGA and elemental analysis, it was possible to suggest the molecular masses as follows, 469.98 g mol^{-1} (CuTrp), 389.02 g mol^{-1} (CuHis), 359.96 g mol^{-1} (CuMet), and 311.82 g mol^{-1} (CuTau). Finally, it was possible to estimate the purity of each synthesized material, greater than 93%. This is important from the perspective of applying the compounds as an alternative and versatile product for controlling *Ae. aegypti*.

The research by Nashalian & Yaylayan (2014) sheds light on the contribution of metal complexes with amino acids to their thermal degradation. The authors demonstrated that oxidative decarboxylation can be thermally

Table II. Initial and final temperatures of the thermal decomposition steps, mass loss, and formed residues of Cu(II) - amino acids complexes.

Complex	Temperature (°C)	Mass Variation (%)	Residue (%)
CuTrp	270 - 580	81.9	18.1
CuHis	74 - 163 163 - 190 190 -750	3.0 3.0 73.5	14.0
CuMet	250 - 750	75.0	25.0
CuTau	280 - 770	75.0	25.0

induced using amino acid-Cu(II) or Fe(III) complexes, resulting in the formation of Strecker aldehydes. These synthetic pathways, typically conducted in a one-pot manner, involve a series of chemical reactions that allow for the rapid synthesis of amino acids from an aldehyde (or ketone) at low cost and high yield. The article also shows that in the Maillard reaction, the independent degradations of amino acids can play an important role in generating specific amino acid products, such as Strecker aldehydes or Schiff bases. Thus, the presence of coordinated metals can enhance oxidative decarboxylation reactions, especially in the presence of Cu(II) and Fe(III) due to their high oxidation potentials. The authors used gas chromatography/mass spectrometry studies to demonstrate that alanine and glycine-copper complexes served as critical intermediates in the oxidative degradation by free radicals, resulting in the loss of CO_2 and the formation of Strecker aldehydes, which were detected as stable Schiff base adducts or incorporated as pyridine or pyrazine derivatives.

Evaluation of toxicity in *Ae. aegypti* larvae

For controls using 0.4% DMSO, there was no mortality of the larvae nor for the CuHis complex concentrations. The insecticide temephos caused 100% mortality.

The toxic activity of CuTrp and CuMet occurred only after 24 h of exposure. Nonetheless, CuTau at 8 h, caused a high mortality of larvae (Table III). CuMet and CuTrp required 1000 mg L^{-1} and 998 mg L^{-1} to cause mortality of 12.42% and 46.55% of larvae, respectively.

CuTau, at the lowest concentration (50 mg L^{-1}), caused mortality of 74% of the larvae, reaching more than 90% with 301 mg L^{-1} in 8 h. At 24 h, there was 100% mortality at all concentrations. Compared to other Cu(II) - amino acid complexes, CuTau showed a more pronounced toxic effect.

The different toxicities of amino acid-Cu(II) complexes can be explained by the ligands, metal coordination, and experimental results showing that there is no toxicity for the ligand amino acids up to 1000 ppm (mg L^{-1}). After coordination, the toxicity of the Cu(II)-Tau complex is greater than other complexes in the toxicity sequence: tryptophan-Cu(II) > methionine-Cu(II) >>> histidine-Cu(II). The hypotheses suggest that, from a chemical, molecular, and biological perspective, the activity of the complexes in the insect metabolism is related to the availability of the Cu(II) ion and/or complementary activities of the coordinated ligand, since it is an essential amino acid for the organism and can be used for coordination and transport of the toxic metal ion, i.e., Cu(II). The taurine ligand in the formation of the Tau-Cu(II) complex has greater insecticidal activity for immature forms

Table III. Mean percentage of mortality ± standard deviation of *Aedes aegypti* larvae exposed to Cu(II) – amino acid complexes at different concentrations (mg L^{-1}) and periods (hours).

	Concentrations (mg L^{-1})	Hour	
		8	24
CuTrp	200	0	3.16 ± 2.62
	276	0	8.18 ± 4.33
	381	0	8.06 ± 4.55
	526	0	10.18 ± 8.94
	725	0	25.35 ± 6.70
	1000	0	46.55 ± 8.81
CuMet	50	0	0
	91	0	0
	165	0	0
	301	0	5.54 ± 4.02
	549	0	5.45 ± 4.78
	998	0	12.42 ± 6.65
CuTau	50	74.04 ± 5.14	100
	91	80.10 ± 5.76	100
	165	85.35 ± 9.54	100
	301	91.51 ± 6.28	100
	549	94.35 ± 7.32	100
	998	96.36 ± 4.26	100

of the insect; the toxicity may be related to the activity of taurine in the digestive system and central nervous system (CNS), primarily due to the concentration and availability of Cu(II) in the metabolism of *Ae. aegypti* larvae, inducing oxidative stress.

Meleshkevitch et al. (2013) showed that L-methionine and L-cysteine are proteinogenic amino acids with sulfur that can form portions of disulfide bridge in peptides and proteins and serve as precursors to taurine and glutathione, being fundamental for a series of metabolic processes (methylation, glutathione-coupled antioxidant defense, biosynthesis of cysteamine and polyamines, and production of coenzyme-A and iron-sulfur clusters). Kouřimská et al. (2023) indicated that taurine (2-aminoethanesulfonic acid) (Tau) is an important amino acid that living organisms cannot synthesize metabolically, requiring dietary supplementation for normal physiological processes. Taurine can coordinate the Cu(II) ion, which is essential for insect metabolism and allows for more efficient cellular permeation; it is a biologically active molecule that transports the metal and can more effectively provide Cu(II) ions in cells and the intracellular environment, inducing *in situ* production of free radicals and enhancing the toxic effect of the metal.

The mortality results made it possible to calculate the LC_{50} for the CuTau complex after 8 hours of application (Table IV). The lower LC_{50} and shorter time to reach 50% mortality demonstrate the high toxicity of the CuTau complex. The confidence intervals of the CuTrp and CuMet complexes are not superimposed on CuTau complexes.

For the Cu(II)-Tau complex, no larval mortality was observed at 2, 4, and 6 hours of exposure; however, at 8 hours, the average mortality percentage varied from 74.04% to 96.36%. After 24 hours of exposure, all evaluated concentrations' mortality rates reached 100% (50-998 ppm). Thus, it was considered that the Cu(II)-Tau complex has larvicidal potential. The Polo-PC software was used to determine the lethal concentrations for 10% (LC_{10}), 50% (LC_{50}), and 90% (LC_{90}) mortality based on the average mortality values obtained at 8 hours of exposure due to the high mortality rates (74.04-96.36%). After 24 hours, obtaining these values would not have been possible, as 100% mortality occurred at all tested concentrations (50-998 ppm). The lethal concentration values determined by the Polo-PC software are shown in Table V.

The retrieved experimental results showed that the LC_{50} was 9.516 ppm, with lower and upper limits of 3.026 ppm and 18.428 ppm, respectively, for 8 hours of exposure of the larvae to the Cu(II)-Tau complex. The Polo-PC software provided the values for the chi-square (χ^2) parameter, the T parameter, and the angular coefficient (b). The chi-square (χ^2) value corresponded to the fit of the data to the Probit model; for fitting, the χ^2 value must be less than the tabled value (p=0.05). The T parameter value confirms linear regression if it is greater than 1.96, and the angular coefficient (b) corresponds to the homogeneity or heterogeneity of the obtained results. The value for the angular coefficient was 0.8888, indicating heterogeneity in the mortality of the larvae. The T parameter value was equal to 6.94, confirming linear regression. The obtained chi-square was 45.5678 for 46 degrees of freedom; comparing this with the tabled value of 67.5048 (for a 95% confidence

Table IV. Median Lethal Concentration (LC_{50}) (95% CI) of Cu(II) - amino acid complexes for *Aedes aegypti* larvae.

Hour	Complex	LC_{50} ($CI_{0.05}$)	b ± SE	χ^2	*df*
8	CuTau	9.52 (3.03 - 18.43)	0.89 ± 0.13	45.57	46
24	CuTrp	1263.48 (1083.64 - 1563.58)	2.49 ± 0.24	41.94	46
24	CuMet	4979.43 (2741.46 - 16350.10)	1.59 ± 0.28	28.04	46

CI – Confidence Interval; b – slope; SE – standard error; *df* – degrees of freedom.

Table V. Experimental values of Lethal Concentration (LC_{10}, LC_{50}, and LC_{90}) for *Ae. aegypti* (Rockefeller) larvae exposed to the Cu(II)-Tau complex for 8 hours.

Lethal concentration (ppm)	Value (ppm)	Lower limit (ppm)	Upper limit (ppm)
LC_{10}	0.344	0.030	1.351
LC_{50}	9.516	3.026	18.428
LC_{90}	263.143	199.088	380.834

limit (p=0.05)), it can be inferred that the data fit the Probit model.

The analysis of the parameters mainly showed that based on the value of b obtained for the Cu(II)-Tau complex, larvae mortality did not occur homogeneously. Considering that the larvae must ingest the complex e in the aquatic environment for toxicity to occur, that is, it must act in the digestive system (DS) and possibly alter the insect's metabolism and even cause changes in the central nervous system (CNS) and/or peripheral nervous system (PNS) of the insect. It can still be inferred that there is heterogeneity in the *Ae. aegypti* larvae, and likely, the complex was not ingested homogeneously and, therefore, mortality was not homogeneous.

Taurine is a β-amino acid not used for protein synthesis, found freely in the intracellular fluid, and one of the most abundant free amino acids in leukocytes, the brain, skeletal muscle, retina, and heart, having an essential role in several biological processes.

The effect of amino acids on the nervous system of insects is related to proteins of the plasma membrane. The excitatory amino acids (AE) mediate Na^+/K^+ absorption of L-glutamate and DL-aspartate. In the nervous system, these proteins contribute to the withdrawal of glutamate from the synaptic cleft and maintain excitatory concentrations of amino acids below the excitotoxic levels. In *Drosophila melanogaster*, two homologs (dAE1 and dAE2) are specifically expressed in nerve tissue. The dAE2 can also carry the amino acid taurine with high affinity, a characteristic not shared by two other transporters of the same family, dAE1 and human hAE2. The transport of taurine by dAE2 is efficiently blocked by an AE antagonist but not by inhibitors of the structurally unrelated mammalian taurine transporters. Taurine and Aspartate (Asp) are transported with similar efficacy and behave as mutually competitive inhibitors. The dAE2 can mediate the uptake and exchange of its two substrates, dependent on the presence of Na^+ ions in the external environment. The exchange occurs only in a certain orientation, with taurine being transported inward and aspartate outwards, suggesting an intracellular trans-inhibition mechanism of aspartate uptake by taurine. Therefore, dAE2 is an aspartate/taurine transporter. Taurine is believed to act as a neuromodulator and cellular survival factor in the *Drosophila melanogaster* nervous system (Besson et al. 2005).

The effect of taurine on the release of acetylcholine (ACh) and acid-γ-aminobutyric acid (GABA) from locust synaptosomes was studied. Veratridine (100 μM) and K^+ (100 mM) caused the release of ACh, and this is reduced by taurine in a concentration-dependent manner (5, 10, and 20 mM). In contrast, veratridine does not induce any observable release of GABA, and the response to K^+ ends rapidly. However, a concentration-dependent increase in GABA release was observed in the presence of taurine. Since nipecotic acid (1 mM), an inhibitor of neuronal GABA uptake has also demonstrated the release of GABA induced by veratridine, it is suggested that both this effect and that of taurine are due to the prevention of GABA reuptake. These results suggest that taurine can act as an insect's neuromodulator (Besson et al. 2005).

The distribution of immunoreactivity caused by taurine has been demonstrated in compound eyes and *Drosophila* and *Locusta ocelli*. A comparison with the immunoreactivity caused by taurine, described in bees' brains, has shown that the photoreceptor cells of these insect species are immunoreactive. Immunoreactive Kenyon cells were found in both species, with the graded immunoreactivity intensity. Although most Kenyon cells were stained in *Apis* and *Drosophila*, locust immunoreactivity was

confined mainly to neurons originating from the accessory calyx (Bicker 1991, Sinakevitch et al. 2017, Scheffer et al. 2020).

Tian et al. (2009) showed that taurine plays an important role in human metabolism: cytoprotection, antioxidant, anti-inflammatory, and anti-apoptosis. Copper is important in wound healing processes, including induction of endothelial growth factor, angiogenesis, antimicrobial potency, and extracellular matrix expression and stabilization. The formation of copper-taurine complexes can wound healing by improving both compounds' bioavailability (Tian et al. 2009).

Other studies have shown that taurine has antioxidant properties against reactive oxygen and nitrogen species, and there is no reaction between taurine and hydrogen peroxide. On the other hand, taurine reacts significantly with nitric oxide and superoxide. It can act by removing peroxyl radicals and decrease the *ex-vivo* damage caused by tert-butyl hydroperoxide in slices of rat liver. Taurine, at physiological concentrations, may be efficient in removing different reactive oxygen and nitrogen species, suggesting a possible role in cellular functions and mitochondria (Oliveira et al. 2010).

Transition metals such as copper can induce oxidative stress in insects that produce reactive oxygen species (ROS), undesirable aerobic life products continuously produced and eliminated by living organisms for maintenance at certain steady-state levels that do not damage the body. In some circumstances, the balance between ROS production and elimination is disrupted, leading to an increase in the ROS level called oxidative stress. The altered dynamic balance and the increased concentration of ROS species can cause damage to the cell and cellular constituents.

The LC_{50} obtained by Rodrigues et al. (2017) is also higher than that obtained for CuTau, being L-glutamine-Cu(II) - 53.401 mg L^{-1} (ppm) and L-aspartate-Cu(II) – 108.647 mg L^{-1} (ppm). Since taurine is an organic acid containing sulfur, it is understood that amino acids in the acid form (aspartic acid, glutamic acid, and taurine) associated with Cu(II) are more toxic to *Ae. aegypti* larvae than those in the non-acid form (Rodrigues et al. 2017).

The complexation of Cu(II) with taurine increased the toxic effect, probably by better bioavailability for the Cu(II) loading by the amino acid through the plasma membrane of the cells of the larvae digestive system. The high concentration of taurine by itself must have caused some toxicity due to its neurotransmitter activity, and when associated with Cu(II), there was an increase in toxicity. The Cu(II) salts that have some LC_{50} values for *Ae. aegypti* larvae reported in the literature show that, despite the varied contribution of counterions, these values are within the average range of 32-33 ppm (Rayms-Keller et al. 1998) and 1-182.05 ppm (Arruda et al. 2010) for metal, associations, and complexes, respectively.

The amino acids glutamate (Glu) and aspartate (Asp) provided a complementary or additive toxic effect as ligands, but in a differentiated manner, as the LC_{50} values varied. The ligands Tau, Glu, and Asp, in relation to Cu(II), exhibited lower LCs; that is, these ligands can enhance toxicity, induce a metabolic state of oxidative stress, and/or more efficiently transport the metal to exert cellular toxicity, consequently leading to mortality and reducing the LC values. Among all the amino acid ligands, taurine (Tau) resulted in the greatest increase in the toxic effect of Cu(II) on *Ae. aegypti* larvae (L3).

The amino acid ligands Trp, His, Met, Tau, and the Cu(II)-His complex showed no toxic activity for *Ae. aegypti* larvae at concentrations tested up to 1000 ppm; no mortality was observed in

larvae exposed to the control solution. For the Cu(II)-Tau complex, no mortality was observed in larvae at 2, 4, and 6 hours of exposure; however, at 8 hours, used for calculating the LC_{50}, the average mortality percentage varied from 74.04% to 96.36%, and after 24 hours of exposure, the mortality value reached 100% for all tested concentrations. The Cu(II)-Tau complex has larvicidal potential. The Polo-PC software was used to determine the lethal concentrations for 10% (LC_{10}), 50% (LC_{50}), and 90% (LC_{90}) mortality, using the corresponding average mortality values obtained after 8 hours of exposure, as 24 hours would not be possible due to the occurrence of 100% mortality at all concentrations. The lethal concentration values determined by the Polo-PC software are presented in Table V.

Essential and non-essential amino acids are metabolically important and are utilized in the synthesis of neurotransmitters and hormones. They serve as energy sources and components for metabolic functions in organisms. These amino acids can act as ligands and be used to coordinate metals with biological activity in insects and animals.

Cappelaere et al. (2021) demonstrated that in animal production, diets with low protein content can be supplemented with amino acids to mitigate environmental impacts from animal feed and emissions from animal waste. They showed that amino acids are vital for living beings through nutrition and the maintenance of animal health and can also reduce greenhouse gases and lessen environmental impacts. Biologically, amino acids perform metabolic functions in plants, are signaling molecules, regulators, and architecture of roots, shoots, flowering, and defense against environmental stress. Nitrogen is transported in the form of amino acids, and its availability in the soil can reduce the need for fertilizers from organic nitrogen. It can be considered that nitrogen is transported in the form of amino acids, and its availability in the soil may reduce the need for fertilizers derived from organic nitrogen. Based on their functionalities, amino acids are proposed as active metal carriers, as ligands for the coordination of bioactive metals. Metallo-insecticides are biodegradable, recyclable, and reabsorbable from their residues. The advantages of metal coordination, metabolic transport, and toxicity in insects, parasites, and other organisms, along with environmental recycling, justify their use despite economic costs. Meleshkevitch et al. (2013) demonstrated that amino acids are micronutrients and selective transporters; for example, methionine was cited as a transporter that can act through the digestive system and via food intake pathway in larvae, even contributing to biological mechanisms and mosquito development in neural tissues. The authors demonstrated indicated that experimental data partially corroborate the toxic effects of amino acid-Cu(II) complexes with taurine, tryptophan, methionine, and histidine on *Ae. aegypti* larvae, which could be used and, perhaps, favored as part of the population control strategy of Culicidae. The experimental results showed that the taurine-Cu(II) complex exhibited the highest toxic activity against *Ae. aegypti* larvae, achieving 100% mortality within 24 hours at the lowest concentration tested (50 mg L^{-1}; ppm). Conversely, the histidine-Cu(II) complex showed no larvicidal activity at concentrations up to 1000 ppm. The larval mortality rates for tryptophan-Cu(II) and methionine-Cu(II) complexes varied between 3.16% to 46.55% and 5.46% to 12.42%, respectively. Thus, considering concentrations of 1000 mg L^{-1} for 24 hours of exposure of larvae to amino acid-Cu(II) complexes, a series of toxicities can be established: taurine-Cu(II) >> tryptophan-Cu(II) > methionine-Cu(II) >>> histidine-Cu(II). Female *Ae. aegypti* mosquitoes require blood from vertebrates (hematophagy)

to produce viable eggs and continue their reproductive process, thereby becoming vectors for viral human diseases. The amino acids and nutrients derived from the blood meal activate vitellogenesis and support embryonic development in anautogenous mosquitoes. Thus, insulin-like peptides (ILPs) are essential for the reproduction of female mosquitoes, regulating glycogen and lipid metabolism, and other essential functions that are still understudied. Ling & Raikhel (2023) showed that amino acids/TOR signaling controls the ILP pathway in modulating the metabolic requirements of female mosquitoes during the reproductive process.

Biologically active ligands coordinated with metal have the potential to produce organometallic complexes for various applications, such as drugs with different mechanisms—conjugated or complementary—based on the properties of the metal and the bioactivity of the ligand. It can be observed that these complexes with transition metals in 1:1 and 1:2 ratios can be produced with Schiff base ligands in bi-, tri-, and tetradentate forms using donor atoms of oxygen and nitrogen, serving as metallo-pharmaceuticals and even metal-based insecticides.

Lin et al. (2021) demonstrated that amino acid-Cu(II) complexes (CuL; alanine, valine, leucine, isoleucine, phenylalanine, glycine, methionine, and proline) can undergo photochemical reactions, primarily from nonpolar chains under irradiation at 313 nm, with the intramolecular carboxylate capable of transferring charge from carboxylate-Cu(II) to form Cu(I) and decompose the amino acid into ammonia and aldehydes, except for proline. The studies indicated that photo-transformation can occur directly from the amino acid-Cu(II) complexes, providing nitrogen to aquatic microorganisms and inducing *in situ* production of free radicals through insect metabolism and/or stimulated by radiation, to be used as an insecticidal species produced *in situ* in the metabolism of *Ae. aegypti* larvae, causing extensive cellular and/or tissue damage in these aquatic organisms in breeding sites. Additionally, there is potential for stimulation under direct solar irradiation and/or stimulated conditions for the degradation of the amino acid-Cu(II) complex, promoting biosafety and reducing environmental impacts and/or effects on non-target organisms.

Marinova & Tamahkyarova (2024) demonstrated that amino acids, peptides, and both natural and synthetic proteins can enable applications across various fields of knowledge, including therapeutic and health areas. Metals, such as Cu(II), are bioactive and micronutrients essential for life; despite their narrow benefit/toxicity range, they can help in understanding the biological role and interaction of metals with proteins, peptides, and amino acids for scientific and technological studies with numerous applications. The authors utilized analytical techniques such as UV-Vis, IR, EPR, NMR spectroscopy, and X-ray for characterizations; thus, products and strategies can be proposed through studies of transition metals complexed with amino acids, peptides, and proteins for various applications of metallo-pharmaceuticals/organometallics, including therapies for cancers.

Most published studies on toxic metals have shown that free ions can be toxic to larvae of other species, particularly culicids. However, despite their bioactivity being concentration-dependent and not significantly affecting flora or fauna, they are essential micronutrients. Therefore, the authors do not believe there is an environmental imbalance, as there is a diversity of target and non-target species, and factors such as reactivity/interactions, concentration, environmental conditions, pollution, and

other factors can be deleterious to humans, biodiversity, and the environment due to bioaccumulation and the potential to enhance biological activity with environmental elements (water, soil, and air), humans, and other living organisms through the food chain. However, the ecotoxicological studies conducted by the group with other organisms have shown a range of concentration-dependent biological effects. It is important to consider that these residues can be diluted in wastewater, biodegraded, contained on surfaces, and recycled during disposal. Therefore, significant environmental impacts with compounds and/or associations involving Cu(II) are not expected. On the other hand, anthropogenic sources such as mining and copper processing can severely harm biodiversity and human health, including air pollution, soil contamination, water contamination, damage to crops and buildings, and the release of hazardous chemicals. However, copper is a micronutrient that can be recycled and phytoabsorbed and is necessary for human health and biodiversity. Nonetheless, the range of benefits and harms from Cu(II) is narrow, and caution should be exercised regarding its uses and applications. Published studies in the literature have shown through integrated research that these are related to short- and long-term pathways and interactions with substances and chemical mixtures in environmental systems and subsystems, but they can be toxic based on their bioavailability, circulation, and assimilation in target and non-target organisms. Metals can exist in ionic form (more toxic and reactive) and even as nanoparticles, which have differentiated effects, depending on bioavailability and/or absorption by organisms, as shown by Mitra et al. (2022).

The study by Rayms-Keller et al. (1998), which motivated this research, demonstrated that exposure to toxic metals at concentrations of 3 to 35 ppm (mg L^{-1}) (Hg, Cd, and Cu) during the early developmental stages of *Ae. aegypti* can have harmful effects on larvae, including fertilization (exposure to metals during fertilization may block fertilization), development (exposure to metals can lead to disrupted development and morphological abnormalities), as well as hatching issues. Conversely, the authors showed that toxic metals can cause fish larvae to hatch late, induce deformities in fish larvae, including spinal deformities and mortality, and impact the reproductive performance of fish - reducing fecundity, hatching rates, and fertilization success, as well as bioaccumulating in organisms and concentrating through the food chain. The biomagnification of toxic metals can cause environmental pollution and affect humans and biodiversity. The studies were conducted to determine the biological effects of heavy metals (toxic metals) on the development of *Ae. aegypti*; specifically, embryos immersed in 32 ppm of Cu or 5 ppm of Cd were affected. The disruption of hatching was partially reversible upon removal of the heavy metals. The mortality rate of 3rd instar larvae (3L) exposed to heavy metals for 24 hours was dependent on the metal and the dose; the lethal concentration 50% (LC_{50}) values were 3.1, 16.5, and 33 ppm for Hg, Cd, and Cu, respectively. It was observed that a proportion of 3rd instar larvae (3L) of *Ae. aegypti* exposed to Cu or Cd for 24 hours failed to produce a dissectible peritrophic matrix, indicating that the digestive system is an important target for these metal ions. This failure to produce a dissectible peritrophic matrix depended on the metal and concentration. The results were discussed in the context of *Ae. aegypti* as a model system for investigating the biological and/or molecular effects of toxic metals in aquatic insects. In this regard, the studies showed that *Ae. aegypti* is sensitive to the chronic or short-term effects of toxic metals (Cd, Cu, Hg), confirming that *Ae.*

aegypti serves as a biological model due to its anatomy, physiology, molecular biology, and biochemistry, along with a short life cycle (up to 2 months in the environment), and its ease of breeding and manipulation under laboratory conditions, making it suitable for investigating the biological and/or molecular effects of toxic metals in aquatic insects.

One aspect of the study can be used to discuss toxicity and the prevention of toxic effects related to the Cu(II) ion. This aspect involves its immobilization and recycling through adsorption, phytoaccumulation, and even the reduction of the Cu(II) ion from wastewater. Typically, it can be observed that the reduction of the Cu(II) ion to Cu(0) (the reduction of Cu(II) ions to metallic copper) in the form of nanoparticles can be achieved through galvanic replacement. This phenomenon can occur due to the higher oxidation potential of Cu, which can lead to the deposition of the Cu(II) ion as metallic copper nanoparticles. If this condition exists, for example, with organic and/or decomposing material, one could consider another discussion regarding the biological activity of a metal nanoparticle.

Khalaj et al. (2018) demonstrated that the properties of Cu nanoparticles can affect reactivity, *in vivo* and *in vitro* toxicity, and can even be evaluated and discussed in terms of doping for high reactivity and low toxicity in environmental cleanup processes. They consider that synthesizing nanomaterials may have diverse applications, particularly copper-based nanomaterials for treating persistent effluents. Copper-based nanomaterials can provide an efficient and cost-effective method for treating persistent wastewater. The present study aimed to investigate various parameters that may involve the overall performance of copper-based nanomaterials for environmental cleanup purposes. To this end, characteristics related to copper-based nanomaterials and their effects on the reactivity of the nanomaterials, as well as environmental and operational parameters, were critically reviewed. The toxicological study of copper-based nanomaterials was also considered a highly important factor in selecting a typical nanomaterial with optimal performance and minimal subsequent environmental and health effects.

CONCLUSIONS

The results revealed the formation of CuTrp, CuHis, CuMet, and CuTau complexes. Among these, Cu(II)-amino acid complexes exhibited toxicity to *Ae. aegypti* larvae, with the toxic effect intensifying as Cu(II) was associated with taurine. The CuTau complex, in particular, emerges as a promising candidate for developing new insecticides derived from neurotransmitters. These insecticides could induce either excitatory or non-excitatory states in target insects, thereby increasing metabolic activity and inducing oxidative stress. The order of toxicity for *Ae. aegypti* larvae was as follows: CuTau >> CuTrp >> CuMet >> CuHis.

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