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# Evaluation of the redox state of *Swiss* mice treated with *Cnidoscolus urens* and scopolamine

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**ABSTRACT:** The antioxidant activity of a promising plant species, *Cnidoscolus urens* (CU), can be investigated through its effects on the redox state of an organism exposed to scopolamine (SCO), an inducer of oxidative stress. In this study, the impact of the ethanolic extract of CU on the redox state of *Swiss* mice treated with SCO was evaluated. The animals were divided into three groups: control (C; physiological solution), SCO (0.8 mg $kg^{-1}$), and SCO+CU (0.8 mg $kg^{-1}$ + 150 mg $kg^{-1}$). Antioxidant enzymes, non-enzymatic markers, and indicators of oxidative damage were analyzed in the heart, liver, and kidneys. In the liver and kidneys, there were no changes in enzymatic activities. In the heart, catalase activity increased only in the SCO group. Non-enzymatic markers did not differ between groups in any tissue. In all tissues, the lipid damage marker in the SCO group increased significantly, but only in the liver was there a reduction in this parameter with the co-administration of CU. These results indicate that scopolamine had an impact on the redox state of these tissues, particularly on lipid structures, and the *C. urens* extract was unable to modulate antioxidant enzymes, but had a protective effect against lipid peroxidation in liver tissue.
**Keywords:** oxidative stress; antioxidants; cansanção-branco.

## Avaliação do estado redox de camundongos *Swiss* tratados com *Cnidoscolus urens* e escopolamina

**RESUMO:** A atividade antioxidante de uma espécie vegetal promissora, a *Cnidoscolus urens* (CU), pode ser investigada por meio de seus efeitos sobre o estado redox de um organismo exposto à escopolamina (ESC), um indutor de estresse oxidativo. Neste estudo, avaliou-se o efeito do extrato etanólico de CU sobre o estado redox de camundongos *Swiss* tratados com ESC. Os animais foram divididos em três grupos: controle (C; solução fisiológica), ESC (0,8 mg $kg^{-1}$) e ESC+CU (0,8 mg $kg^{-1}$ + 150 mg $kg^{-1}$). Foram analisados enzimas antioxidantes, marcadores não enzimáticos e indicadores de dano oxidativo no coração, no fígado e nos rins. No fígado e nos rins, não houve alterações nas atividades enzimáticas. No coração, a atividade da catalase aumentou apenas no grupo ESC. Os marcadores não enzimáticos não diferiram entre os grupos em nenhum dos tecidos. Em todos os tecidos, o marcador de dano lipídico no grupo ESC aumentou significativamente, mas somente no fígado houve redução nesse parâmetro com a coadministração de CU. Esses resultados indicam que a escopolamina teve impacto no estado redox desses tecidos, particularmente nas estruturas lipídicas, e que o extrato de *C. urens* não foi capaz de modular enzimas antioxidantes, mas teve efeito protetor contra a lipoperoxidação no tecido hepático.
**Palavras-chave:** estresse oxidativo; antioxidantes; cansanção-branco.

## 1. INTRODUCTION

According to the World Health Organization (WHO), the leading causes of death worldwide are chronic noncommunicable diseases (NCDs), which mainly affect the cardiovascular, respiratory, and nervous systems, such as ischemic heart disease, chronic obstructive pulmonary disease, stroke, Alzheimer's disease, diabetes mellitus, etc. (WHO, 2024). The etiology of these diseases is complex, involving genetic and environmental factors. Lifestyle factors have a major impact on the development of NCDs (NYBERG et al., 2020).

The increase in the incidence of NCDs may be linked to the overall rise in the elderly population, particularly in developed countries (HAMBLETON et al., 2023). In Brazil, the Brazilian Institute of Geography and Statistics (IBGE) estimates that by 2060, the population over 60 years of age will represent 36% of the total population (IBGE, 2024). This segment of the population is more susceptible to NCDs due to prolonged exposure to risk factors and reduced cell repair capacity (PADRÓN-MONEDERO, 2023).

The physiopathological processes that lead to the development of these comorbidities are not fully understood. However, there is consensus in the literature that oxidative stress plays a key role in the onset of these pathologies (JOMOVA et al., 2023). Oxidative stress is a condition characterized by an imbalance between the production of oxidative species and the body's antioxidant defenses. Oxidative species consist of free radicals, reactive oxygen species (ROS), and reactive nitrogen species (RNS), which are produced by cellular metabolism even under physiological conditions. At high concentrations, these substances become harmful to cells and cause damage to lipids, proteins, and nucleic acids (KATERJI et al., 2019).

Antioxidant defense mechanisms act by preventing the formation of free radicals, neutralizing free radicals that have already formed, or repairing damage caused by ROS and RNS (JOMOVA et al., 2023). The body's main enzymatic defenses include superoxide dismutase (SOD), glutathione-S-transferase (GST), glutathione peroxidase (GPx), and catalase (CAT). The main non-enzymatic antioxidants are reduced glutathione (GSH), ascorbic acid (ASA), and vitamins A and E (MAS-BARGUES et al., 2022).

Exogenous substances may contribute to oxidative stress by inducing the production of oxidative species or inhibiting antioxidant defenses. One such substance is scopolamine, an alkaloid originally extracted from *Hyoscyamus niger*. Currently, this drug is used in the symptomatic treatment of gastrointestinal and genitourinary tract and biliary tract spasms, as well as motion sickness (BRUNTON et al., 2018).

Scopolamine acts by antagonizing muscarinic receptors and, in appropriate doses, can cross the blood-brain barrier and produce effects on the central nervous system. Blocking muscarinic receptors in the brain negatively affects cholinergic transmission, similar to neurodegenerative diseases such as Alzheimer's disease. In addition, it is also capable of producing oxidative stress in nervous tissue (AKBARIAN et al., 2022). Thus, this drug is particularly useful for inducing cholinergic dysfunction and oxidative stress in animal models. However, its effects on visceral organs have not been studied.

In recent years, plant species have been the main source of new molecules with therapeutic potential. Ethnopharmacology has been the main strategy employed by the academic community to discover new substances with medicinal properties. In this perspective, the genus *Cnidoscolus* is promising because it contains several species traditionally used in folk medicine to treat a wide variety of diseases. Preliminary studies have demonstrated anti-inflammatory, antinociceptive, antioxidant, hypoglycemic, and hepatoprotective activities in numerous species of the genus (NASCIMENTO et al., 2025).

*Cnidoscolus urens* L. Arthur (*Euphorbiaceae*) is a shrubby plant belonging to the genus *Cnidoscolus* with wide distribution in different geographical regions, such as the Atlantic Forest, Caatinga, Amazon, and Cerrado (MAYA-LASTRA et al., 2020). Several *Cnidoscolus* species have demonstrated antioxidant, anti-inflammatory, cardioprotective and hypoglycemic activities in rodent models, with oral doses typically ranging from 100 to 500 mg $kg^{-1}$ (MOURA et al., 2019). Recently, Dutra et al. (2024) found phenols, anthocyanins, flavonoids, steroids, saponins, and coumarin in the crude extract of *C. urens* leaves. These secondary metabolites play important roles in the adaptation of plants to their environments and are commonly associated with therapeutic properties (BORGES; AMORIM, 2020). Thus, the aim of this study was to evaluate the possible effects of the ethanolic extract of *C. urens* and scopolamine on the heart, liver, and kidneys of *Swiss* mice, since most studies in this experimental model focus only on nervous tissue.

## 2. MATERIAL AND METHODS

### 2.1. Preparation of *C. urens* extract

To prepare the ethanolic extract of *C. urens*, only the leaves, without stalks or stems, were harvested and separated from dirt and contaminants using a brush. The plant material was kept in a forced-ventilation oven at a temperature of 40 °C for 7 days. After drying, the material was ground to obtain a powder with an average particle size of 1.0 mm.

The extract was obtained by macerating 100 g of plant material with 1000 mL of 80% ethanol, which was left in contact for 15 days in a dark place, with the mixture being stirred once a day. After this period, the extract underwent vacuum filtration, and the solvent was evaporated in a rotary evaporator under reduced pressure until an ethanolic extract with a paste-like consistency was obtained. This product was stored at a temperature of –20 °C until use.

### 2.2. Experimental protocol

This research was submitted to the Animal Use Ethics Committee (CEUA) of the Federal University of Mato Grosso, through process no. 23108.007432/2023-43, and approved in accordance with the ethical principles adopted by the National Council for the Control of Animal Experimentation (CONCEA). Twenty-four male *Swiss* mice were obtained from the central animal facility of the Federal University of Mato Grosso, Cuiabá Campus. The animals underwent a 15-day acclimatization period, receiving water and feed *ad libitum*. Throughout the experiment, temperature and humidity were controlled, with a 12-hour day and night cycle, air circulation, and exhaust.

After the acclimatization period, the animals were divided into three groups of eight animals each. To analyze the possible antioxidant effect of the extract of *C. urens*, the animals were treated once a day, orally (gavage) and intraperitoneally (i.p.) for 15 days, as described in Table 1. Since no standardized protocol exists specifically for *C. urens*, the dose of 150 mg $kg^{-1}$ of extract was chosen based on the dose range reported by Moura et al. (2019) for this initial *in vivo* characterization. Additionally, unpublished oral acute toxicity data (OECD 423 protocol) from our research group showed no signs of toxicity at this dose.

Table 1. Experimental protocol of the research.
Tabela 1. Modelo experimental da pesquisa.

| Group | Treatment |
|---|---|
| C | Water (orally) and sterile physiological solution (i.p.) |
| SCO | Water (orally) and scopolamine 0.8 mg/kg (ip.) |
| SCO+CU | *C. urens* extract 150 mg/kg (orally) and scopolamine 0.8 mg/kg (ip.) |

All groups received maximum volumes of 100 µL orally or intraperitoneally according to the above treatments. A sterile physiological solution was used as a vehicle for scopolamine. After 15 days, the animals were anesthetized with ketamine 50 mg $kg^{-1}$, xylazine 2 mg $kg^{-1}$, and

acepromazine 2 mg $kg^{-1}$, administered intraperitoneally. Euthanasia was then performed by cervical dislocation. The hearts, livers, and kidneys were removed. After washing with sterile physiological solution, the samples were safely stored at –80 °C until analysis. The oxidative stress markers described below were measured.

### 2.3. Enzymatic markers analysis

The activities of the enzymes superoxide dismutase (SOD), catalase (CAT), glutathione-S-transferase (GST), and glutathione peroxidase (GPx) were analyzed. SOD activity was measured using the method adapted from Misra and Fridovich (1972), which consisted of spectrophotometric monitoring of the rate of adrenochrome formation at 480 nm. The results of the analysis were expressed in UI SOD/mg protein. CAT activity was analyzed according to Nelson; Kiesow (1972). The change in hydrogen peroxide absorbance in this method enabled the calculation of CAT activity in µmol $H_2O_2$/min/mg protein.

GST activity was measured according to Habig et al. (1974), using 1-chloro-2,4-dinitrobenzene (CDNB) to determine enzyme activity, expressed as µmol GS-DNB/min/mg protein. GPx activity was measured using the method described by Paglia and Valentine (1967) and expressed in the results as µmol/min/mg protein.

### 2.4. Analysis of non-enzymatic markers

The non-enzymatic antioxidants reduced glutathione (GSH) were also analyzed using the method adapted from Sedlack and Lindsay (1968), and ascorbic acid (ASA) was analyzed following the methodology described by Roe (1954). Both analyses involve comparing the analytical signal of the samples with a calibration curve prepared with solutions of known concentrations (GSH and ASA, respectively). GSH levels were expressed in µmol GSH/mg protein, and ASA levels in µmol ASA/g of tissue.

### 2.5. Analysis of oxidative damage markers

The oxidative damage markers evaluated were thiobarbituric acid reactive substances (TBARS) and carbonylated proteins (PCO). TBARS levels were determined according to the adapted technique of Buege and Aust (1978), which is based on the formation of a complex between malondialdehyde and thiobarbituric acid. The results were expressed in nmol MDA/mg protein. PCO levels were determined by the method described by Colombo et al. (2016) and expressed in nmol PCO/mg protein.

The protein content of the tissues was also determined to calculate the other biochemical parameters, except ASA. The Bradford method (1976) was used, which employs Coomassie Brilliant blue dye, which interacts with the proteins in the sample. The results were obtained by comparison with a standard curve of bovine serum albumin.

### 2.6. Statistical analysis

GraphPad Prism® version 8.0 software was used for statistical analysis, and the significance level was set at 5%. The data were submitted to the D'Agostino & Pearson normality test, and the comparison between groups was performed using one-way analysis of variance (ANOVA) followed by Tukey's post hoc test or Kruskal-Wallis nonparametric test followed by Dunn's post hoc test. Data that followed a normal distribution were expressed as mean and standard deviation. Those that did not follow a normal distribution were expressed as median and total range. Some data was transformed using square root or logarithmic functions.

## 3. RESULTS

### 3.1. Enzyme markers

In the heart, SOD, GST, and GPx enzyme activities remained unchanged in all treatments. However, CAT activity showed a statistically significant increase in the SCO group compared to the C group (Table 2). In the liver (Figures 1A to 1D) and kidneys (Figures 2A to 2D), no significant differences were observed between treatments for any of the enzyme markers analyzed.



### 3.2. Non-enzymatic markers

There were no significant differences between any of the treatments in cardiac (Table 2), hepatic (Figures 1G and 1H), and renal (2G and 2H) tissues.

Table 2. Results of the enzymatic and non-enzymatic biomarkers analyzed in cardiac tissue.
Tabela 2. Resultados dos biomarcadores enzimáticos e não-enzimáticos analisados no tecido cardíaco.

| Biomarker | C | SCO | SCO+CU |
|---|---|---|---|
| SOD (UI SOD/mg protein) | 14.02 ± 2.85 a | 14.13 ± 2.43 a | 12.07 ± 2.24 a |
| CAT (µmol $H_2O_2$/min/mg protein) | 15.71 ± 2.29 a | 20.51 ± 2.69 b | 17.77 ± 2.55 ab |
| GST (µmol GS-DNB/min/mg protein) | 314.0; 170.0 a | 329.8; 106.1 a | 346.7; 62.0 a |
| GPx (µmol/min/mg protein) | 1.36 ± 0.23 a | 1.40 ± 0.23 a | 1.26 ± 0.35 a |
| TBARS (nmol MDA/mg protein) | 0.47 ± 0.15 a | 0.72 ± 0.20 b | 0.54 ± 0.14 ab |
| PCO (nmol PCO/ mg protein | 1.27 ± 0.08 a | 1.17 ± 0.16 a | 1.16 ± 0.16 a |
| GSH (µmol GSH/mg protein) | 0.62 ± 0.32 a | 0.87 ± 0.12 a | 0.74 ± 0.35 a |

Data expressed as mean ± standard deviation. For GST, the result was expressed as median and total range. Data followed by the same letters in each column are not statistically different ($p > 0.05$).
Os dados são expressos como média ± desvio padrão. Para GST, o resultado foi expresso como mediana e amplitude total. Dados seguidos pelas mesmas letras em cada coluna não diferem estatisticamente ($p > 0,05$).

### 3.3. Oxidative damage markers

In the heart, PCO levels remained similar between treatments (Table 2), as well as in the liver (Figure 1F) and kidneys (Figure 2F). In contrast, TBARS levels in cardiac, hepatic, and renal tissues increased significantly in the SCO group compared to the C group, but only in the liver was it possible to observe a significant reduction in this parameter in the SCO+CU group.

## 4. DISCUSSION

There is extensive literature on the effects of scopolamine on the redox state of the brain, and therefore

it is widely used in cognitive deficit models (Lima et al., 2026; Yadang et al., 2020), which typically use doses ranging around 1 mg $kg^{-1}$. However, the analysis of oxidative stress markers is often limited to brain tissue. In this sense, the present study is innovative in analyzing the effect of scopolamine on the redox state of visceral organs.

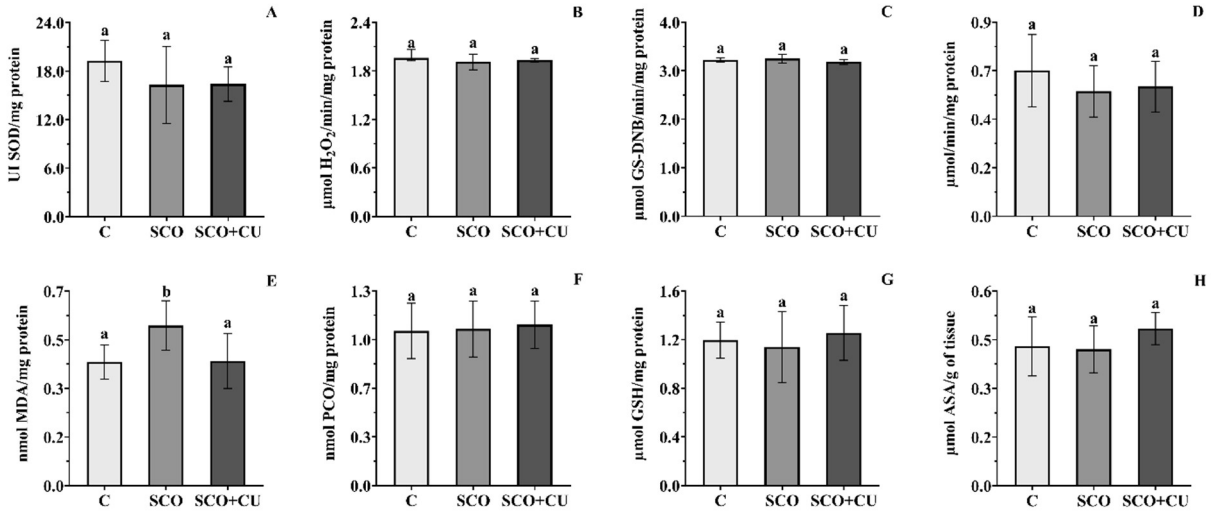


Figure 1. Results of the enzymatic and non-enzymatic biomarkers analyzed in hepatic tissue.
SOD (A), CAT (B), GST (C), GPx (D), TBARS (E), PCO (F), GSH (G) and ASA (H). Data expressed as mean ± standard deviation (A, C, D, E, F, G, and H) and median and total range (B). Identical letters indicate data that do not differ statistically ($p > 0.05$). Logarithmic functions transformed data in B, C, D, F, and G, and data in H were transformed by square root functions.
Figura 1. Resultados dos biomarcadores enzimáticos e não-enzimáticos analisados no tecido hepático.
SOD (A), CAT (B), GST (C), GPx (D), TBARS (E), PCO (F), GSH (G) e ASA (H). Os dados são expressos como média ± desvio padrão (A, C, D, E, F, G e H) e mediana e intervalo total (B). Letras idênticas indicam que os dados não diferem estatisticamente ($p > 0,05$). Os dados em B, C, D, F e G foram transformados por funções logarítmicas, e os dados em H foram transformados por funções de raiz quadrada.



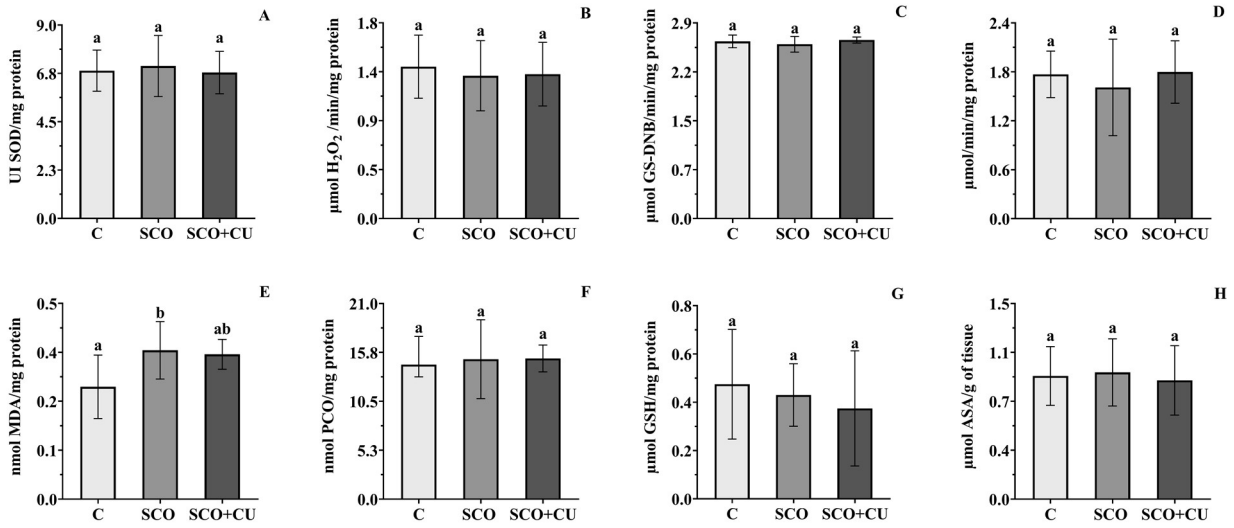


Figure 2. Results of the enzymatic and non-enzymatic biomarkers analysed in renal tissue.
SOD (A), CAT (B), GST (C), GPx (D), TBARS (E), PCO (F), GSH (G) and ASA (H). Data expressed as mean ± standard deviation (A, B, C, D, E, G, and H) and median and total range (F). Identical letters indicate data that do not differ statistically ($p > 0.05$). Logarithmic functions transformed data in B, C, and G, and data in E and H were transformed by square root functions.
Figura 2. Resultados dos biomarcadores enzimáticos e não-enzimáticos analisados no tecido renal.
SOD (A), CAT (B), GST (C), GPx (D), TBARS (E), PCO (F), GSH (G) e ASA (H). Os dados são expressos como média ± desvio padrão (A, C, D, E, F, G e H) e mediana e intervalo total (B). Letras idênticas indicam que os dados não diferem estatisticamente ($p > 0,05$). Os dados em B, C, D, F e G foram transformados por funções logarítmicas, e os dados em H foram transformados por funções de raiz quadrada.

The results demonstrate that the enzymatic response to drug administration was selective. SOD, GST, and GPx activities remained unchanged in all tissues. Increased expression or activity of antioxidant enzymes is a crucial adaptive response of tissues to oxidative stress (JI; YEO, 2021). The absence of this observation suggests that the drug-induced oxidative stress in this study was insufficient in magnitude or duration to elicit an adaptive response and modulate the activity of SOD, GST, and GPx. The same observation can be made for the non-enzymatic markers GSH and ASA, whose levels remained constant in all groups in the heart, liver, and kidneys.

Interestingly, CAT activity was only affected by scopolamine administration in the heart, an organ that is extremely sensitive to disturbances in redox status. This result is possibly associated with an adaptive response to increased ROS in the heart. In this tissue, ROS play important roles in signaling pathways, regulating cardiomyocyte development and maturation, intracellular calcium levels, excitation-contraction coupling, and vascular tone (PEOPLES et al., 2019). Thus, it is of utmost importance that ROS are maintained at physiological levels.

Contrary to expectations, no positive modulation of antioxidant enzymes was observed by the ethanolic extract of *C. urens* in any of the organs analyzed. Similar studies with this species were not found. However, some studies with *Cnidoscolus aconitifolius* obtained more promising results. Obichi et al. (2015) found increased SOD and CAT activity, as well as decreased TBARS levels, in the plasma of diabetic *Wistar* rats after treatment with the aqueous extract of the *Cnidoscolus aconitifolius* leaves at doses of 400 to 800 mg $kg^{-1}$.

On the other hand, Ezebuiro et al. (2020) observed an increase in SOD and glutathione reductase (GR) activity and a reduction in malondialdehyde (MDA) levels in the plasma of *Wistar* rats after administration of the hydromethanolic extract of *C. aconitifolius* at doses of 200 to 400 mg $kg^{-1}$. Compared to these methodologies, treatment with *C. urens* extract in this study had a lower dose and duration. In addition, these authors used different solvents and analyzed plasma samples, which may explain the discrepancy between the results of these species.

In contrast to enzymatic markers, more pronounced effects of scopolamine were observed on markers of lipid oxidative damage, specifically in TBARS concentrations, an important marker of lipid peroxidation. No similar studies were found on cardiac, hepatic or renal tissues. However, many experiments in nervous tissue had related results. Woo et al. (2020), for example, observed an increase in TBARS in nervous tissue after treating C57BL/6J rats with scopolamine at a dose of 1 mg $kg^{-1}$. PCO levels, on the other hand, were not altered by the treatments in the heart, liver, and kidneys. Thus, it is evident that scopolamine administration has systemic repercussions, particularly on the lipid structures of tissues.

The effect of the *C. urens* extract on markers of oxidative damage was also modest. There was protection against lipid peroxidation only in the liver, where the concentration of TBARS decreased significantly with the co-administration of the ethanolic extract of *C. urens* and scopolamine. In line with this result, Pérez-González et al. (2018) also reported protection of the liver against lipid peroxidation by a plant of the same genus, *Cnidoscolus chayamansa*, albeit with higher doses and a longer treatment period. The reduction of TBARS in the liver may be attributed to the oral route of administration of the extract and the organ's central role in xenobiotic metabolism. As the primary site of first-pass metabolism, the liver is potentially exposed to higher concentrations of antioxidant compounds and their metabolites, although it must be acknowledged that tissue accumulation is highly compound-specific (LU et al., 2022). There was also a reduction in TBARS levels in the SCO+CU group in the heart, although it was not statistically significant ($p > 0.05$).

Although the effects of the ethanolic extract of *C. urens* on the markers analyzed in this study were modest, this plant should not be disregarded for future studies evaluating its antioxidant capacity. The therapeutic potential of this species has already been demonstrated in studies such as that by Dutra et al. (2024). Still, currently, there is a lack of *in vivo* studies on oxidative stress markers to support the use of *C. urens* extract as an antioxidant.

## 5. CONCLUSIONS

In this study, intraperitoneally administered scopolamine was able to induce systemic oxidative damage in the heart, liver and kidneys of *Swiss* mice, predominantly evidenced by increased lipid peroxidation, while leaving major enzymatic and non-enzymatic antioxidant defenses unaffected under the present experimental conditions. Similarly, oral administration of the ethanolic extract of *C. urens* exhibited hepatoprotective activity by mitigating oxidative damage to liver lipid structures caused by scopolamine, without significantly modulating enzymatic antioxidant defenses. However, the lack of a positive control group, use of single-dose treatments and short treatment period require the results to be interpreted cautiously. Moreover, the scarcity of prior *in vivo* investigations with *C. urens* hinders direct comparison of our findings with those from other experimental models.

Thus, to further advance our understanding of the effects of this species on redox state markers, future studies should evaluate the repercussions of *C. urens* extract in alternative chronic oxidative stress models, with multiple, higher doses and longer exposure, and assess if the observed effects involve solely free radical scavenging. These approaches will elucidate the effects of *C. urens* extract on oxidative stress markers and clarify whether this species holds promise for therapeutic antioxidant applications.

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