https://doi.org/10.23925/1984-4840.2024v26a18 **Revisão Sistemática** / *Systematic Review*

Insecticidal effect of *Cannabis*: a systematic review of toxicity on medically important insects

Efeito inseticida da Cannabis: uma revisão sistemática da toxicidade em insetos de importância médica

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ABSTRACT

Currently, there is a need for the development of vector insect control products that are ecologically viable, utilizing active principles available in nature. Natural compounds with insecticidal potential already identified in *Cannabis* are promising prospects for the control and management of vector arthropods of diseases. In this context, the work aims to investigate possible disparities in the toxicity effects of *Cannabis* in different formulations and at different stages of the vectors' life. This is a systematic review. Experimental studies describing the toxic effects of *Cannabis* on eggs, larvae, pupae, and adult vector insects were included. Articles in which the insect was characterized as a mechanical vector, literature review research, and ethnobotanical studies were excluded. The study revealed the potential insecticidal effect of *Cannabis* when applied in different formulations on *Ctenocephalides felis felis*, *Aedes albopictus*, *Anopheles stephensi*, *Anopheles gambiae*, and *Culex quinquefasciatus* at different stages of development. *Cannabis* proved to be a promising plant in terms of mortality and evidenced effects on insect fertility, birth rates, and adult emergence. The study revealed a potential insecticidal effect of *Cannabis*. However, further investigations are crucial to elucidate the role of this plant in vector insect control strategies.

Keywords: insect vectors; larva; oils, volatile; cannabis; toxicity.

RESUMO

Atualmente, há necessidade do desenvolvimento de produtos de controle de insetos vetores que sejam ecologicamente viáveis, utilizando princípios ativos disponíveis na natureza. Compostos naturais com potencial inseticida já identificados na *Cannabis* são perspectivas promissoras para o controle e manejo de artrópodes vetores de doenças. Neste contexto, o trabalho visa investigar possíveis disparidades nos efeitos de toxicidade da *Cannabis* em diferentes formulações e em diferentes estágios da vida dos vetores. Trata-se de uma revisão sistemática. Foram incluídos estudos experimentais que descreveram os efeitos tóxicos da *Cannabis* em ovos, larvas, pupas e adultos de insetos vetores. Foram excluídos artigos em que o inseto foi caracterizado como vetor mecânico, pesquisas de revisão de literatura e estudos etnobotânicos. O estudo revelou potencial efeito inseticida da *Cannabis* sendo aplicada em diferentes formulações sobre *Ctenocephalides felis felis*, *Aedes albopictus*, *Anopheles stephensi*, *Anopheles gambiae* e *Culex quinquefasciatus* em diferentes estágios de desenvolvimento. A *Cannabis* demonstrou ser uma planta promissora em termos de mortalidade e evidenciou efeitos na fertilidade dos insetos, nas taxas de natalidade e na emergência dos adultos. O estudo revelou um potencial efeito inseticida da *Cannabis*. Contudo, mais investigações são cruciais para elucidar o papel dessa planta em estratégias de controle de insetos vetores.

Palavras-chave: insetos vetores; larva; óleos voláteis; cannabis; toxicidade.

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INTRODUCTION

Analyzing medically important insects is of paramount importance in the current global scenario, given the crucial role they play in the spread of pathogens among humans and animals.[1] Among these insects, mosquitoes stand out for their significant biological capacity to act as vectors for viruses such as dengue, Zika, malaria, yellow fever, Chikungunya, among others.[2,3] Furthermore, it is crucial to consider the various life stages of these insects, ranging from larvae to adults, as each presents specific characteristics, behaviors, and physiological vulnerabilities.[4] This understanding of the different stages of insect development is essential for the development and implementation of effective control strategies integrated control is crucial for the reduction of the disease vectors.[4,5]

To control insect-borne diseases, synthetic insecticides are currently widely used, given their longer residual action and shelf life. However, these compounds can be harmful to the environment and toxic to non-target species.[6] In addition, there is a concern regarding the selection of insects that are resistant to these pesticides, causing these chemicals to become less efficient.[7] With the growing resistance of insects to a great number of currently available insecticides, there has been a search for new compounds that can replace them.[8] In addition, there is a surge in interest in the development of alternative ecologically friendly control products, using active ingredients available in nature.[9] Thus, effective and sustainable products to control insect-borne diseases are needed as a valid alternative to synthetic products.[10]

Plant derivatives have been used as raw material for the production of insecticides. Plants are large libraries of active molecules of pharmacological interest and industrial use; among these, *Cannabis* spp. has been cultivated in the world for several purposes over thousands of years. The genus *Cannabis* includes the flowering plant of the Cannabaceae family. The number of species of the genus *Cannabis* is controversial. Some authors consider the genus to be polyspecific, consisting of two to three species, namely *C. sativa*, *C. indica* and *C. ruderalis*, while others have admitted different varieties within the *C. sativa* species.[11]

A common feature of all *Cannabis* spp. genus plants is the presence of phytocannabinoids, which are predominantly produced in the trichomes present in the female inflorescence, such as tetrahydrocannabinol (THC) and cannabidiol (CBD), which have received increasing public and scientific attention.[12] In addition, the heads of the trichome glands are sensitive and burst easily, releasing terpenoids and phytocannabinoids, which subsequently oxidize and polymerize forming a resin on the trichome stem and on the leaves' surface. This resin can harm small insects, acting as a kind of mechanical control, as well as chemical control.[6]

Currently, *Cannabis* has become a popular plant due to its industrial, food, cosmetic and medicinal uses;[13] however, some newly discovered active ingredients may have insecticide potential characteristics that have not yet been detected. We quote for example, industrial hemp and varieties of *Cannabis* spp. that are largely cultivated to obtain the medicinal constituent cannabidiol.[14]

Although insects do not have cannabinoid receptors,[15] natural agents with insecticidal potential such as those found in *Cannabis* spp. are promising prospects for the control and management of arthropod vectors involved in the transmission of a number of diseases.[9,10,16–21] Among these are the terpenoids, which are the main constituents of *Cannabis* and are responsible for deterring arthropods.[6]

Furthermore, *Cannabis sativa* resin has already shown 80.00% and 68.00% inhibitory effect on acetylcholinesterase (AChE) and butyrylcholinesterase (BChE), respectively.[22] This feature is sought when investigating products that lead to insects' elimination, since cholinesterase inhibition causes dysfunction in the transmission of nervous impulses, leading to mortality. This important enzyme catalyzes the hydrolysis reaction of a choline ester (acetylcholine and butyrylcholine) into choline and acetic acid. Acetylcholine is an excitatory neurotransmitter that causes muscle contraction and stimulates the release of hormones.[23]

In this connection, this review article aims to investigate possible disparities in the toxicity effects of *Cannabis* spp. in different formulations for use during different life stages of vector insects, which contributes to the expansion of *Cannabis* spp. research and of *Cannabis* spp. effects against medically important insects' investigations.

MATERIALS AND METHODS

Articles search and data collection strategy

This study is based on a systematic review of articles found in the PubMed and ScienceDirect databases, retrieved until February 20, 2024, using the following search strategy: (Insecticide OR Insect) and *Cannabis*. "Research articles" as a search filter was used in ScienceDirect.

The selection of articles was carried out by two independent reviewers. First, the titles and abstracts were examined, subsequently, the papers considered eligible based on the inclusion and exclusion criteria were assessed in full. In case of divergence in the selection of articles, a third reviewer was called in.

Eligibility criteria

All the experimental studies that would describe the toxic effects of *Cannabis* spp. on eggs, larvae, pupae, and adults of insects of medical importance were selected. However, articles in which the insect was characterized as a mechanical vector, and literature review research as well as ethnobotanical studies were excluded.

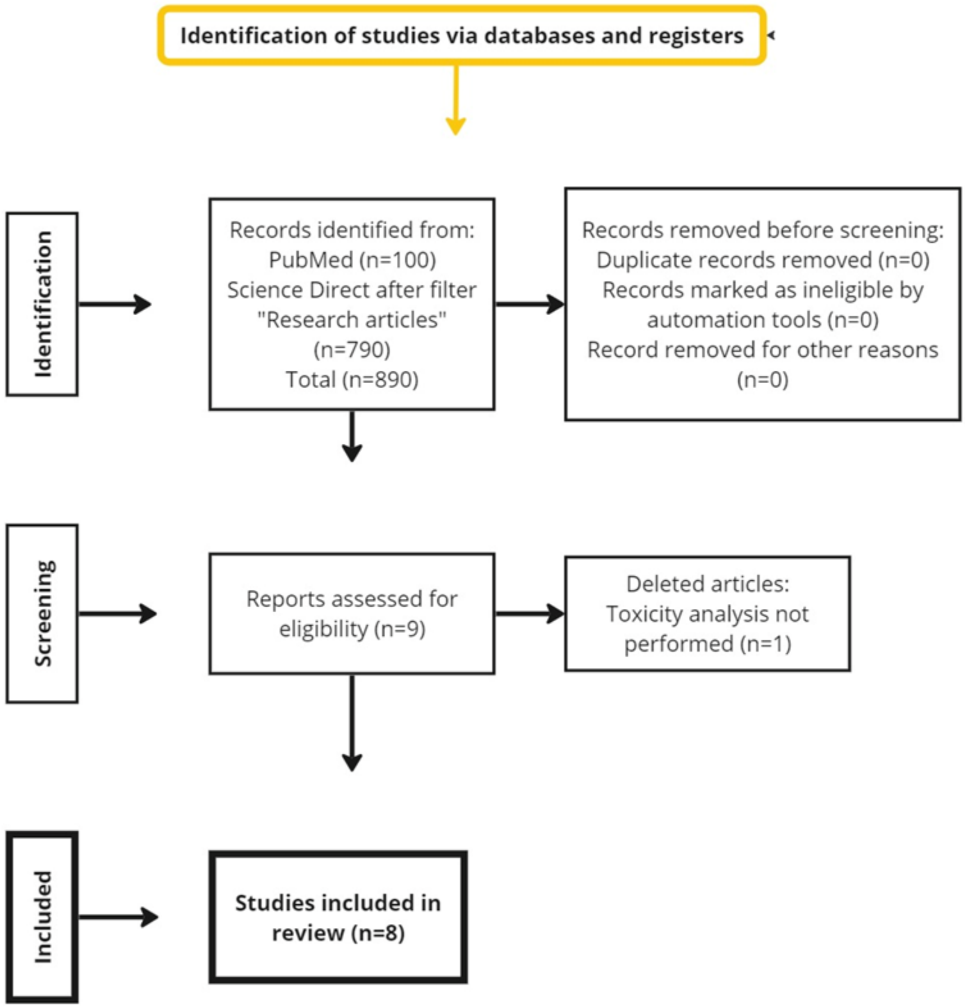
The results were analyzed and described qualitatively, presented in the form of tables, with a description of the study authorship, year, insect assessed, insect life stage, form of use of *Cannabis* spp., and results.

RESULTS

The search identified 890 publications on the toxic effects of *Cannabis* spp. on clinically important insects. Being 100 in PubMed and 790 in ScienceDirect (after using the “Research Articles” filter).

After validating the eligibility criteria, we obtained 8 articles that were included in the analysis of this work (Figure 1).[9,10,16–21]

Figure 1. PRISMA guideline-based article selection flowchart.



In total, the work focused on 5 species of medically important insects, namely: *Ctenocephalides felis felis* (n = 1),[18] *Aedes albopictus* (n = 1),[9] *Anopheles stephensi* (n = 1),[16] *Anopheles gambiae* (n = 1)[16] and *Culex quinquefasciatus*;[10,17,19–21] the latter had the largest number of articles (n = 5).

In all the articles, the authors aimed to evaluate the insecticidal effects caused by *Cannabis* spp. in certain stages of the insects' life cycle; all studies sought to evaluate the insecticidal effects at least in the larval phase.

Medically important insects were the focus of our survey; however, a large number of studies have compared the effects of *Cannabis* spp. on non-medically important insects, including *Daphnia magna*,[10] *Myzus persicae*,[19] *Musca domestica*,[19,20] *Spodoptera littoralis*,[19,20] *Harmonia axyridis*,[19] *Eisenia fetida*,[19] *Cloeondipterum*[9] and *Physella acuta*[9] (Table 1).

Table 1. Summary of the main characteristics of the studies reviewed. *Life stage of the medically important insects; **Information only from the insect medically important.

Author	Insect of medical importance	Objective	Life stage*	Other species	Conclusion
Mazzara *et al*., 2023[10]	*Culex quinquefasciatus*	Investigate the insecticidal efficacy of essential oil (EO) obtained from the "Kompolti" hemp variety and optimize it's formulation development into a nanoemulsion (NE).	Larvae	*Daphnia magna*	First time demonstration of the effectiveness of EO Kompolti and its nanoemulsion against larvae of *Culex quinquefasciatus*. Furthermore, non-target toxicity tests showed limited impact on the aquatic microcrustacean *Daphnia magn*a. As a result, the encapsulated form of this EO can be considered an ecological and sustainable mosquito larvicide.
Benelli *et al*., 2018[19]	*Culex quinquefasciatus*	To evaluate the potential of *Cannabis* EO as a botanical insecticide for the management of insect pests in organic crops.	Larvae and adult	*Myzus persicae*, *Musca domestica*, *Spodoptera littoralis*, *Harmonia axyridis* and *Eisenia fetida*.	The results demonstrate that the tested EOs can be used as a source of ecological botanical insecticides for Integrated Pest Management and in biological agriculture, particularly to manage populations of aphids and house flies.
Bedini *et al*., *2016*[9]	*Aedes albopictus*	EO from hemp and hops were chemically analyzed and their acute toxicity evaluated against larvae of *Aedes albopictus* and adults of *Physella acuta*, and against the mayfly *Cloeon dipterum.*	Larvae	*Cloeon dipterum* and *Physella acuta*	For both EOs, the most sensitive species was *Physella acuta,* followed by *Cloeon dipterum*, while the least sensitive species was *Aedes albopictus*. Both EOs are capable of exerting a good toxic effect against the invasive disease vectors *Aedes albopictus* and *Physella acuta*.
Pavela, 2009[21]	*Culex quinquefasciatus*	Test the larvicidal potential and oviposition deterrent effect of EOs from 22 species of aromatic plants.	Larvae**	-	EOs produced from other plants offered greater insecticidal potential than *Cannabis* spp.
Rossi *et al*., 2020[16]	*Anopheles stephensi* and *Anopheles gambiae*	Verify whether EOs obtained from hemp inflorescences may be of interest for the manufacture of botanical insecticides, as well as their safety profile for operators.	Larvae and pupae	-	The three EOs tested, coming from different cultivars and plant parts, were effective in killing the two malaria vectors. Notably, this work highlighted that male inflorescence, which is typically discarded during industrial hemp processing, can be a sustainable source of larvicidal compounds. The bioactivity observed in the larvicidal assays can be entirely attributed to the terpenoid fraction of the essential oils, since the cannabinoid fraction was almost absent.

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Soares *et al*., 2023[18]	*Ctenocephalides felis felis*	To evaluate the insecticidal activity of *Cannabis sativa* EO against the egg, larva, pupa and adult stages of *Ctenocephalides felis felis*.	Egg, larvae, pupae and adult.	-	Showed for the first time the potential of *Cannabis sativa* EO as a botanical insecticide against *Ctenocephalides felis felis*, especially in the egg and larval stages.
Benelli *et al*., 2018[20]	*Culex quinquefasciatus*	Explore the insecticidal potential of Eos obtained from hemp crop residues, such as leaves and inflorescences, against three target insects. Furthermore, evaluating the inhibitory activity exerted by EO on acetylcholinesterase (AChE), as well as its antioxidant capacity.	Larvae	*Spodoptera littoralis* and *Musca domestica*	In particular, the harvest residue provided by the hermaphrodite inflorescences obtained during fiber processing or before seed harvesting contains an effective, ecological, biodegradable, safe and legal (with regard to THC content) EO, which can be incorporated into insecticidal formulations to control mosquitoes, flies and agricultural pests.
Maurya *et al*., 2008[17]	*Culex quinquefasciatus*	Exploring the larvicidal potential of *Aloe barbadensis* and *Cannabis sativa* against the *filariasis* vector, *Culex quinquefasciatus*	Larvae	-	Among the extracts examined, the carbon tetrachloride extract of *Aloe barbadensis* was the most effective, however, the same type of *Cannabis* extract also showed larvicidal action.

The formulation of *Cannabis* spp. refers to the physical form in which the formulation was used in the studies, which could be as EO, extract or nanoemulsion based on EO.

In total, seven articles reviewed used only *Cannabis* spp. with EO formulation,[9,10,16,18–21] while one used extract[17] and another used EO and EO-based nanoemulsion[10] (Table 2). The effects of *Cannabis* spp. EO were tested on the egg,[18] larva,[9,10,16,18–21] pupa[16,18] and adult stages,[18,19] and also in the adult insect emergence and reproductive parameters including fecundity, fertility and birth rate.[10]

In contrast, the effects of *Cannabis* spp. extract were only studied on insects' larvae.[17] On the other hand, the effects of the nanoemulsion based on *Cannabis* EO have been verified on larvae, emergence of adults, fecundity, fertility, and birth rate of insects of medical importance.[1]

Table 2. Action of *Cannabis* spp. in connection with the species, life stage, reproductive pattern and formulation.

Formulation	Life stage or reproductive pattern	Insect	Outcome
Essential oil	Egg	*Ctenocephalides felis felis*[18]	Mortality rate was 100% at a concentration of 200 µg/cm^2
	Larvae	*Aedes albopictus*[9]	The LC^{50} value of *C. sativa* was 301.560 µL^{-1}
		Ctenocephalides felis felis[18]	Mortality rate was 100% at a concentration of 400µg/cm^2
		Anopheles stephensi[16]	At a concentration of 100 ppm, mortality was 82.7% (Feline 32), 90.2% (female CS) and 89.8% (male CS). The CL^{50} values were 78.80 respectively; 75.12 and 75.23 ppm respectively.
		Anopheles gambiae[16]	At a concentration of 100 ppm, mortality was 91.1% (Feline 32), 91.6% (female CS) and 89.8% (male CS). The LC^{50} values were 73.5; 75.54 and 75.04 ppm respectively.
		Culex quinquefasciatus[10,19–21]	The LC^{50} value was 252.5 mLL^{-1}
			The LC^{50} value was 127.3 µg/ml and presented an LC^{90} of 201.5 µg/ml
			The LC^{50} values were 152.3 and 124.5 µl/l for the leaf and inflorescence essential oil, respectively.
			The LC^{50} (LC^{90}) value was estimated at 56.8 (142.3) ppm
	Pupae	*Ctenocephalides felis felis*[18]	Mortality rate was 100% at the highest concentrations of 1600 µg/cm^2
		Anopheles stephensi[16]	At a concentration of 100 ppm, mortality was 100% (Feline 32), 94.2% (female CS) and 90.5% (male CS). The CL^{50} value was 54.41; 67.19 and 20.13 ppm respectively.
		Anopheles gambiae[16]	At a concentration of 100 ppm, mortality was 84.9% (Feline 32), 79.6% (female CS) and 79.7% (male CS). The CL^{50} value was 50.06; 41.51 and 50.27 ppm respectively.
	Adult	*Ctenocephalides felis felis*[18]	The mortality rate reached 90% at a concentration of 2,000 µg/cm^2
		Culex quinquefasciatus[19]	Presented a value of LC^{50} > 500 µgcm^{-2}
	Adult emergency	*Culex quinquefasciatus*[10]	Testing the impact of LC^{30} (35 ppm), a total reduction (males and females) in adult emergence of 60.9% was observed.
	Fecundity	*Culex quinquefasciatus*[10]	In experiments that tested the impact of LC^{30} (35 ppm), no significant effects on fertility were observed.
	Fertility	*Culex quinquefasciatus*[10]	Testing the impact of LC30 (35 ppm) 93.3% egg hatchability was observed.
	Natality	*Culex quinquefasciatus*[10]	Testing the impact of LC^{30} (35 ppm) a reduction in the birth rate of 40.4% was observed.

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Extract	Larvae	*Culex quinquefasciatus*[17]	LC^{50} of Carbon Tetrachloride extract was 88.51 and 68.69 ppm after 24 and 48 h, respectively, being more effective than the LC^{50} of Petroleum Ether extracts (294.42 and 73.32 ppm) and Methanol (160.78 and 71.71 ppm) after 24 and 48h.
Essential oil-based nanoemulsion	Larvae	*Culex quinquefasciatus*[10]	The LC^{50} (LC^{90}) value was estimated at 963.7 (2,763.5) ppm, equivalent to the EO result of 72.2 (207.2) ppm in the same article.
	Adult emergency	*Culex quinquefasciatus*[10]	Testing the impact of LC^{30} (35 ppm), a total reduction (males and females) in adult emergence of 59.2% was observed.
	Fecundity	*Culex quinquefasciatus*[10]	Testing the impact of LC^{30} (35 ppm) no significant effects were observed.
	Fertility	*Culex quinquefasciatus*[10]	Testing the impact of LC30 (35 ppm) 91.8% egg hatchability was observed.
	Natality	*Culex quinquefasciatus*[10]	Testing the impact of LC^{30} (35 ppm), a reduction in the birth rate of 45.1% was observed.

DISCUSSION

Different *Cannabis* formulations showed an insecticidal effect on the developmental stages of five species of medically important insects.

Regarding the toxic action of *Cannabis* formulations on eggs, a potential ovicidal effect on the species *Ctenocephalides felis felis* has been observed.[18] However, this is the only work that assessed the ovicidal effect of *Cannabis*, enhancing the need for further investigations to evaluate the potential ovicidal effect of this plant on different vectors. On the other hand, the toxicity of *Cannabis* in the vectors' larval stage was documented in all studies reviewed and for the three formulations used in the investigations.[9,10,16–21]

Since the EO formulation was the most used for the treatment of the larval stage,[9,10,16,18–21] additional studies with other *Cannabis* formulations are suggested with the aim of determining which formulation is most effective in this stage of the vectors' development. On the other hand in the vectors' pupa[16,18] and adult[18,19] development stages, the insecticidal effect of *Cannabis* EO formulation was assessed in two studies, respectively, thus enhancing the need for further studies that evaluate different formulations, to find out which is the best for these stages of the vectors' development life.

When it comes to the effects of *Cannabis* on the reproductive parameters, the lack of data becomes indisputable, since in only one study[10] information was found about *Cannabis* effects and specifically only on *Culex quinquefasciatus*. Besides, it was also the only study that compared the effects of two *Cannabis'* formulations (EO and EO-based nanoemulsion) on the reproductive and life stage parameters. Although no significant effects on the vectors' fertility were observed, a 93.3% egg hatchability in the fertility rate was observed with the use of EO.

The nanoemulsion based on *Cannabis* EO caused a 91.8% egg hatchability in the fertility rate. Regarding toxicity on the birth rate parameter, a 40.4% reduction was observed using the *Cannabis* EO formulation, as well as a 45.1% reduction using the EO-based nanoemulsion formulation. Regarding the emergence of adults, a total 60.9% emergence (males and females) was observed for the EO formulation and 59.2% for the EO-based nanoemulsion formulation.

The larval phase was the most studied; it was approached in all the articles reviewed and taking into account all the *Cannabis* formulation formats. However, we ought to clarify that despite the reported *Cannabis* insecticidal action on this insect vectors' stage of development, there are still few studies that have approached the effect of this plant on the vectors' larval phase that would allow an effective conclusion considering each formulation.

As to the action of *Cannabis* on the reproductive patterns, the potential use of this plant that has ovicidal, larvicidal, pupicidal and adulticidal properties is evident, but also with regard to aspects of fecundity, fertility, birth rate and adult insect's emergence.

CONCLUSION

Our study revealed a potential *Cannabis* insecticidal effect on *Ctenocephalides felis felis*, *Aedes albopictus*, *Anopheles stephensi*, *Anopheles gambiae* and *Culex quinquefasciatus* in different stages of development (egg, larvae, pupae and adult) when *Cannabis* was applied in different formulations (EO, extract and EO-based nanoemulsion). However, there are significant knowledge gaps, especially with regard to divergent insecticidal effects on the different stages of development of the same insect, as well as the effects of different

Cannabis formulations. *Cannabis* has been a promising plant in terms of insect vector mortality; it has also evidenced effects on insects' fertility, birth rates and adults' emergence. Therefore, further investigation is crucial to elucidate the role of *Cannabis* against insects of medical importance as well as to expand our knowledge about the plant's toxic action, and also to explore its potential in insect vectors' control strategies.

Conflicts of Interest

The authors declare that they have no conflicts of interest. This work was carried out with the financial support of the *Coordenação de Aperfeiçoamento de Pessoal de Nível Superior* (CAPES, Coordination for the Improvement of Higher Education Personnel) - Brazil - Financing Code 001. The funding agency had no role in the design, analysis, interpretation of data, writing of the manuscript, or decision to publish.

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