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The Effectiveness Of Cotton Ointment Containing Marigold Cambium Aroma Extract On Mosquito Repellent Power

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ABSTRACT
The importance of controlling Aedes aegypti mosquitoes as vectors of dengue fever, by killing mosquito larvae, The use of chemical insecticides, has a negative impact on human health and the environment, such as using fogging, abate powder, which has an impact on the environment. Researchers are looking for natural larvicide solutions that are safe and effective. Researchers observed marigold plants at the research site. Marigold plants contain essential oils that are effective as larvicides on Aedes aegypti mosquitoes. This study was quasi-experimental. The aim was to test the effectiveness of cotton swabs containing Cambium Aroma extract of marigold plants on mosquito repellent power. The research location was in a room containing a mosquito net box containing 140 mosquitoes. Chi-square results obtained: P value = 0.040 <α 0.05, Statistically there was a significant efficiency of cotton swabs containing Cambium aroma extract compared to marigold plant stems in mosquito repellent power, with an odds ratio = 4.9 times. Students are advised to practice applying cotton swabs to the stem cambium and rubbing marigold plants indoors to repel mosquitoes.
Keywords: *Effectiveness; Aromatic Cotton Swab; Mosquitoes; and Marigold Plant Cambium*

INTRODUCTION

The importance of mosquito control lies in its role as a vector for dangerous diseases such as dengue fever. The use of chemical insecticides, although common, has negative impacts on human health and the environment. The *Aedes aegypti* mosquito can cause dengue fever. The response is to eradicate the vector's life cycle by killing mosquito larvae, using fogging and abate powder, which have environmental impacts (Aji, 2017; Aji, Kamaluddin, Salni, & Sriati, 2016; Aji, 2015). Researchers are seeking a safe and effective natural larvicidal solution. The researchers examined marigold plants at the study site. Marigold plants contain essential oils that are effective as larvicides against *Culex quinquefasciatus*, *Anopheles stephensi*, and *Aedes aegypti* mosquitoes (Aji et al., 2024).

This study is quasi-experimental. Mosquito control is important for the spread of disease, as mosquitoes are the primary vectors of various deadly diseases that can cause death and disability, especially in tropical regions. Health impact on the community, the occurrence of disease outbreaks caused by mosquitoes can burden the health system and disrupt socio-economic activities. Prevention is necessary, by means of effective mosquito control to reduce the spread of disease and protect public health (Aji, 2015).

The negative impact of chemical insecticide use can lead to mosquito resistance. Excessive use of insecticides can cause mosquitoes to become resistant (immune), thus reducing their effectiveness. Regarding human health, chemical insecticide sprays can cause various health problems in humans, such as respiratory problems, skin irritation, and poisoning (Aji et al., 2023). From an environmental perspective, chemical insecticide sprays can pollute the environment, kill non-target organisms, and damage ecosystems. Furthermore, the impact of residues on food. The use of insecticides on plants can leave residues in food consumed by humans, potentially causing long-term health problems. In organic farming, organic farming practices, which avoid the use of chemical pesticides, can be an alternative to reduce the negative impacts of chemical insecticide use (Aji, 2017).

Alternative mosquito control methods include biological control, using natural enemies of mosquitoes, such as bacteria, fungi, or larvae-eating fish, to control mosquito populations (Aji, Kamaluddin, Salni, & Sriati, 2016). Physical control methods include using mosquito traps, mosquito nets, or mosquito nets to

prevent mosquito bites. Improving sanitation, eliminating mosquito breeding sites, such as standing water, is a crucial step in vector control. Natural insecticides can include plants or natural ingredients with mosquito-repellent or mosquito-killing properties, including citronella, lavender, mint, rosemary, marigolds, and basil. These plants emit scents that mosquitoes dislike, making them effective in reducing mosquito populations around homes (Aji et al., 2024).

The World Health Organization (WHO, 2024) recorded a global increase in dengue fever (DHF) cases in 2024, with Indonesia among the countries experiencing a significant spike. As of the 17th week of 2024, Indonesia recorded 88,593 DHF cases and 621 deaths. This increase was also seen in the January–April 2024 period, where global dengue cases approached the total number of cases from the previous year, with the majority of cases coming from Brazil, according to the BBC. Globally, a significant increase in dengue cases was reported worldwide, with more than 13 million cases in North, Central, and South America, and the Caribbean in 2024, according to the CDC (WHO, 2024).

Dengue fever cases in Indonesia, until the 17th week of 2024, recorded 88,593 cases of dengue fever with 621 deaths. The number of cases increased to 119,709 with 777 deaths in the 22nd week (May 2024). The Ministry of Health (Kemenkes) recorded an increase of around 60% in dengue fever cases in September 2024 compared to the previous year. The death rate due to dengue fever also increased in 2024. Regions: Bali reported 15,570 cases of dengue fever in 2024, according to the Bali Health Office. Sumedang Regency recorded 2,341 cases of dengue fever with 7 deaths until October 2024, a sharp increase compared to the previous year. Depok City reported 4,825 cases of dengue fever with 10 deaths throughout 2024 (Director General of Disease Prevention and Control, Ministry of Health RI, 2024).

According to data from the Director General of Disease Prevention and Control (P2P) at the Indonesian Ministry of Health, in the 17th week of 2024 (around April 2024), there were 88,593 cases of Dengue Hemorrhagic Fever (DHF) with 621 deaths in Indonesia. However, in the 22nd week (May 2024), the number of cases increased to 119,709 with 777 deaths. This increase in cases is also influenced by the dry season which is expected to increase the frequency of mosquito bites, as well as the shortening of the annual cycle of dengue cases from 10 years to 3 years or less, caused by the El Niño phenomenon, according to the Ministry of Administrative and Bureaucratic Reform. Several important points regarding dengue cases in 2024. There is an increase in cases, there was a significant spike in dengue cases in 2024, especially in January to March, with a further increase in November and December 2024. The causes of the increase include climate change, a prolonged dry season, and a shortening of the annual cycle of dengue cases. Prevention efforts: The Ministry of Health continues to carry out various prevention efforts, including the 3M Plus Mosquito Nest Eradication (PSN) program (draining, closing, and recycling), as well as the implementation of the National Dengue Prevention Strategy (STRANAS) 2021–2025. Target in 2030: The Ministry of Health is targeting zero deaths due to DHF in 2030 through various prevention efforts and earlier handling. It is urged that the public always be vigilant in the dry season and remain cautious against DHF, especially during the dry season which is expected to increase the risk of mosquito bites, according to the Ministry of Administrative and Bureaucratic Reform (Director General of Disease Prevention and Control, Ministry of Health RI, 2024).

Dengue fever cases in Bengkulu Province in 2024 reached 1,537 cases, with 7 people dying. These DHF cases experienced a spike in March 2024, with 481 cases, but then showed a downward trend. In total, 1,537 DHF cases occurred throughout Bengkulu Province in 2024. Deaths: 7 people died from DHF in Bengkulu throughout 2024. Affected districts included Mukomuko (587 cases) and Bengkulu City (255 cases with 4 deaths). The peak of cases in March 2024 recorded 481 DHF cases, but cases began to show a downward trend in the 18th week of May 2024. The Head of the Bengkulu Provincial Health Office continues to urge the public to remain vigilant and implement preventive measures, including the 3M movement: draining, covering, and recycling (Director General of Disease Prevention and Control, Ministry of Health Bengkulu, 2024).

In several areas in Rejang Lebong Regency, there were 435 cases of dengue fever in 2024, occurring in 15 sub-districts. This is quite high compared to 2023, which only had 86 cases. Dengue fever remains a threat, especially since three of these cases resulted in deaths (Head of Prevention and Control of Infectious Diseases [P2PM], 2022).

Entering the transition period from the dry season to the rainy season, cases of Dengue Hemorrhagic Fever (DHF) in Indonesia have been observed to increase. The expected public behavior in *Healthy Indonesia 2025* is proactive behavior to maintain and improve health, prevent disease risks, protect oneself

from disease threats and other health problems, be aware of the law, and actively participate in public health movements, including creating a healthy and prosperous society—a safe/protected community (Indonesian Ministry of Health, 2021).

Previous research by Marini et al. (2018) revealed that phytochemical tests using the color test method on kenikir leaf extract successfully identified alkaloids, flavonoids, saponins, and tannins. The protective efficacy test showed that kenikir leaf extract lotion was ineffective as a repellent against *Ae. aegypti* mosquitoes, with protective efficacy above 90% lasting only two hours after application, at a concentration of 30% (Marini et al., 2018).

The results of Aji's (2017) research showed a real influence of citronella on the presence of *Aedes aegypti* larvae in water reservoirs (Aji, 2017).

Research results by Kamelia et al. (2020) showed that there was a very significant effect on mortality resulting from each extraction concentration administered. The study found that a 2% concentration resulted in the highest mortality rate for *Aedes* sp. mosquitoes, with an average of 92.5%, with a mortality rate of 37 out of 40 mosquitoes. Tahi Kotok (*T. erecta*) leaf extraction can be used as an alternative to control *Aedes* sp. mosquitoes. The results of this study can be used as a learning resource in the form of a module and are suitable for use with a validation result of 85.2% (Kamelia, 2020).

Research by Aji (2015) demonstrated the influence of mosquito larvae monitoring (jumantik) on the incidence of dengue fever in Rejang Lebong Regency. A novel aspect of this study was the determination of the side effects of soaking in the aroma of sliced leaves, bark, flower buds, flowers, and roots of the kenikir plant on mosquito repellent properties (Aji, 2015).

The results of Aji's research (2024), *The Effectiveness of Marigold Root Powder Aroma on Mosquitoes*, showed that almost all (98.57%) of the 138 mosquitoes avoided and were repelled, while the remaining 2 mosquitoes (1.43%) approached and landed, from a total of 140 mosquitoes in a mosquito net box soaked in 2 grams of marigold root powder for 10 minutes. Bivariate analysis showed that repellent power was the cause of mosquito avoidance, with a *p* value = 0.043. The aroma of marigold root powder soaking had a positive effect, which was statistically significant in its effectiveness as a mosquito repellent, with an odds ratio of 4.12 times (Aji et al., 2024).

Aji's (2024) research also found that the effectiveness of marigold bark powder soaking aroma as a mosquito repellent was significant. Almost all (90.71%) of the 127 mosquitoes were found to avoid and repel, while the remaining 13 mosquitoes (9.28%) approached and landed, from a total of 140 mosquitoes in a mosquito net box soaked in 2 grams of marigold bark powder. Bivariate analysis showed that repulsion was the cause of mosquito avoidance, with a *p*-value of 0.043. The aroma of marigold bark powder had a positive effect, which was statistically significant in its effectiveness as a mosquito repellent, with an odds ratio of 4.08 times (Aji et al., 2024).

Aji's (2024) research on the effectiveness of marigold flower aroma powder as a mosquito repellent showed that the majority (82.14%) of 115 mosquitoes did not resist and avoided the mosquito net box. The remaining 25 mosquitoes (17.86%) of the 140 mosquitoes approached and landed on the mosquito net box in less than 10 minutes. This observation was made when the box contained 2 grams of marigold flower powder. Bivariate analysis showed that repellent activity was a factor in mosquito repellent activity. Avoidance, with a *p*-value of 0.043, had a significant impact on marigold powder's effectiveness, as evidenced by a statistically significant odds ratio of 4.06 times its effectiveness as a mosquito repellent (Aji et al., 2024).

A survey conducted by researchers on Saturday, April 19, 2025, showed numerous marigold plants growing along roadsides, in residents' yards, and in the classrooms of State Senior High School 10 Rejang Lebong. However, the community is not yet aware of the benefits and efficacy of marigold plants as a mosquito repellent. The community's role in eradicating dengue mosquito breeding grounds at the research site has not been fully implemented optimally, due to the continued presence of mosquitoes, community habits when mosquitoes appear during the rainy season, community behavior in killing mosquitoes using sprays, mosquito coils, mosquito rackets, and avoiding mosquito bites using mosquito nets, among others.

The novelty of this study is to determine the side effects of cotton swabs containing marigold cambium extract on mosquito repellent activity. Based on the above background and considering the highest number of suspected cases of dengue fever in the research location, the author is interested in conducting

research: *The Effectiveness of Cotton Ointment Containing Marigold Plant Cambium Aroma Extract on Mosquito Repellent in SMA 10 Rejang Lebong.*

Research Objectives

This study aims to evaluate the effectiveness of cotton swabs containing marigold cambium extract as a mosquito repellent. Specifically, the research compares the repellent effect of cotton swabs infused with marigold cambium extract against a control group (unscented cotton swabs without extract). The results are expected to provide valuable information on the potential of marigold plants as a natural, environmentally friendly mosquito repellent.

METHODOLOGY

This study is a quasi-experimental study with a cross-sectional study design, which is a study that closely approximates a true experiment. The aim is to determine the effectiveness of cotton swabs containing marigold cambium extract on mosquito repellent.

The dependent variable was the number of mosquitoes that avoided and landed on cotton swabs containing Marigold Cambium Aroma Extract on Mosquito Repellent. The independent variable, namely the application of cotton swabs containing Marigold Cambium Aroma Extract, was analyzed using a 2 x 2 cross-tabulation, odds ratio calculation, and Chi-square test. The research sample consisted of 140 mosquitoes in a mosquito net box. The study will last three months.

Univariate analysis was used to determine the effectiveness of cotton swabs containing marigold cambium aroma extract on mosquito repellent and the proportion of each variable studied. Bivariate analysis was used to determine the positive effect of the independent and dependent variables.

Research Tools and Materials

The researchers used the following tools: knives, cotton swabs, scissors, cloth, drying boxes, bowls, mosquito nets, mosquito net boxes, stopwatches, clocks, stationery, and observation paper. The researchers used the following research materials: Cambium from marigold stems and branches.

How it Works

The process for making marigold cambium extract, applied to cotton balls placed in a bowl, is as follows:

1. Prepare a small bowl containing 1 gram of cotton balls.
2. Take 2 grams of cambium extract from each marigold stem and twig.
3. Place the cotton balls containing the marigold cambium extract into the bowls, each containing 2 grams of cambium extract from each marigold stem and twig. Then, mix them to allow the aroma of the cambium extract to penetrate.
4. Place the cotton balls containing the marigold cambium extract into the bowls and place them in a mosquito net box containing 140 mosquito nets.

The mosquito collection process is as follows:

1. Mosquitoes are collected using a mosquito net, selecting 140 normal mosquitoes (with legs).
2. Then, the 140 mosquitoes are placed in the prepared mosquito net box. The research procedure is as follows:
3. Prepare all necessary equipment and materials.
4. Take a cotton swab soaked in marigold stem and twig cambium extract from each bowl and place it in the bowl.
5. Prepare a stopwatch or clock, writing utensils, and observation paper.
6. Then, collect 140 mosquitoes and place them in the mosquito net box.
7. Use a stopwatch/clock and observe the effect of the cotton swab containing the marigold stem and twig cambium extract.
8. Then, record how many mosquitoes avoid and land on the bowl containing the cotton swab containing the marigold stem and twig cambium extract.
9. Tabulate the data obtained and then analyze it according to the statistical method used. The data obtained from the observation results were first analyzed using a cross-sectional study design, analyzed

using 2 x 2 cross-tabulations to determine the positive effect of applying the cotton swab containing the marigold stem and twig cambium extract.
10. Calculate the odds ratio and perform a Chi-square test. According to Nursalam (2018), the significance level was set at 0.05, with the null hypothesis (H_0) rejected if $p < 0.05$.

RESULTS

Univariate Analysis Results

The activities in this study included counting the number of mosquitoes that avoided and landed on a bowl of cotton swabs containing marigold stem and twig cambium extract after treatment. The observation process of 140 mosquitoes for a maximum of 10 minutes, for each mosquito that avoided and landed on a container containing 2 grams of cotton swab containing marigold stem and twig cambium extract, produced the results as shown in the following table:

Table 1: Effectiveness of Cotton Swabs Containing Marigold Stem Cambium Extract on Mosquito Repellent

Treatment	Mosquito Reaction	Reject (n)	Reject (%)	Approach (n)	Approach (%)	Total (n)	Total (%)
Yes (with extract)		134	95.71	6	4.29	140	100
No (control)		0	0.00	136	100.00	140	100

Source: Compiled by Aji (2025)

Based on Table 1, it can be seen that almost all mosquitoes (95.71%) avoided the cotton swabs treated with marigold stem cambium extract, while only 6 mosquitoes (4.3%) approached and landed. This indicates that cotton swabs containing 2 grams of marigold stem cambium extract were highly effective as mosquito repellents within 10 minutes of exposure.

Bivariate Analysis

The effectiveness of cotton swabs containing the aroma cambium extract of marigold plant stems.

Table 2: Effectiveness of Applying Marigold Stem Cambium Extract to Cotton on Mosquito Repellent

Mosquito Reaction	Mosquito Rejection (n, %)	Mosquito Approaches (n, %)	Total (n, %)	OR	p
Yes	134 (95.71)	6 (4.29)	140 (100)	4.8	0.039
No	0 (0)	136 (100)	140 (100)		

Source: Compiled by Aji (2025)

Based on Table 2 above, it can be seen that repulsion is a determining factor in mosquito repellent behavior. The avoidance response, with a p-value of 0.039, shows a positive effect of cotton swabs containing marigold stem cambium extract. This result is statistically significant, with an odds ratio (OR) of 4.8, indicating that the extract is effective as a mosquito repellent. The effectiveness of cotton swabs containing marigold stem cambium extract as a mosquito repellent is presented as follows:

Table 3: Effectiveness of Cotton Swabs Containing Marigold Twig Cambium Extract.

Mosquito Reaction	Mosquito Rejection (n, %)	Mosquito Approaches (n, %)	Total (n, %)
Yes	135 (96.43)	5 (3.57)	140 (100)
No	0 (0)	135 (100)	140 (100)

Source: Compiled by Aji (2025)

Based on Table 3 above, it can be seen that almost all mosquitoes (96.43%) were repelled. Out of 140 mosquitoes placed in the mosquito net box smeared with 2 grams of marigold twig cambium extract, only 5 mosquitoes (3.57%) approached and landed. In contrast, 135 mosquitoes showed avoidance behavior and did not land during the 10-minute observation period.

Table 4: Effectiveness of Marigold Twig Cambium Extract on Mosquito Repellent.

Bivariate Analysis

Mosquito Reaction	Mosquito Rejection (n, %)	Mosquito Approaches (n, %)	Total (n, %)	OR	p
Yes	135 (96.43)	5 (3.57)	140 (100)	4.9	0.040
No	0 (0)	135 (100)	140 (100)		

Source: Compiled by Aji (2025)

Based on Table 4 above, repellent activity is shown to be a key factor in mosquito avoidance. The avoidance response, with a p-value of 0.040, demonstrates a statistically significant positive effect. Cotton swabs containing the aroma extract of marigold twig cambium were effective, with an odds ratio of 4.9, confirming their role as a mosquito repellent.

DISCUSSION

Based on the observations from trials using cotton swabs containing the aroma extract of marigold stem cambium and twig cambium as mosquito repellents, the same formulation produced different numbers of mosquitoes avoiding or landing within the same observation period. The results can be summarized as follows:

Effectiveness: The effectiveness of cotton swabs containing the aroma extract of marigold stem cambium on mosquito repellent.

Based on Table 1, it was observed that almost all mosquitoes (95.71%) were repelled, amounting to 134 out of 140 tested. Of the total mosquitoes placed in the mosquito net box smeared with cotton swabs containing 2 grams of marigold stem cambium extract, only 6 mosquitoes (4.3%) approached and landed. In contrast, 134 mosquitoes avoided landing during the 10-minute observation. This indicates that the marigold stem cambium extract demonstrated a strong repellent effect within the given timeframe.

Based on Table 3 above, it can be seen that almost all (96.43%) of the 135 mosquitoes found were killed. Of the 140 mosquitoes in the mosquito net box covered with 2 grams of cotton containing marigold twig cambium extract, 5 (3.57%) approached and landed. Of the 135 mosquitoes, 135 approached and landed on the mosquito net box. These mosquitoes approached and landed on the mosquito net box covered with 2 grams of cotton containing marigold twig cambium extract for 10 minutes.

This finding is consistent with the study of Aji et al. (2023), which demonstrated the positive effect of the aroma of sliced marigold leaves on mosquito repellent. Their indoor experiments, conducted in a mosquito net box containing 136 mosquitoes, also showed strong repellent activity

The results of the Chi-square analysis show that, based on Table 2, repulsion is the primary factor in mosquito avoidance. The avoidance response, with a p-value of 0.039, demonstrates a positive effect of cotton swabs containing the aroma extract of marigold stem cambium. This effect is statistically significant, with an odds ratio of 4.8, confirming the effectiveness of marigold stem cambium extract as a mosquito repellent.

Similarly, Table 4 indicates that repellent activity is a determining factor in mosquito avoidance. With a p-value of 0.040, cotton swabs containing the aroma extract of marigold twig cambium also showed a statistically significant positive effect. The odds ratio of 4.9 further supports the effectiveness of marigold twig cambium extract as a mosquito repellent.

According to the research results of Kurniati Fitri (2021), there was a highly significant effect on mosquito mortality across different extract concentrations. A 2% concentration produced the highest mortality effect on *Aedes* sp. mosquitoes, with an average of 92.5%, corresponding to a death rate of 37 out of 40 mosquitoes. The extraction of Tahi Kotok (*Tagetes erecta*) leaves can therefore be used as an alternative in controlling *Aedes* sp. mosquitoes. The study concluded that the results could also be applied as a learning resource in the form of a module, validated at 85.2%.

This finding agrees with the research of Fabrick et al. (2020), which demonstrated a significant reduction in survival of pest species on *Tagetes patula* plants. Their test involving feed treated with liquid marigold leaf extract and methanol showed mortality rates dependent on concentration, suggesting the presence of one or more extractable toxicants. These data indicate that *T. patula* plants contain insecticidal constituents.

In line with the opinion of Marini et al. (2018), phytochemical tests using the color test method on marigold leaf extract successfully identified alkaloids, flavonoids, saponins, and tannins. However, their

protective efficacy test revealed that marigold leaf extract lotion was ineffective as a repellent against *Aedes aegypti*. Although the protective efficacy exceeded 90%, it lasted for only two hours post-application at a concentration of 30%.

This is consistent with the findings of Irfayanti et al. (2023), who reported that repellent sprays formulated with marigold essential oil demonstrated increasing protective efficacy with higher concentrations—50.67% against the negative control, 68.33% at 2.5%, 78.67% at 5%, 96% at 10%, and 100% against the positive control. The strongest repellent activity was observed at 10%, and results of the SNK (Newman Keuls) follow-up test showed that this concentration was not significantly different from the positive control.

The present study corroborates these findings. Almost all mosquitoes (95.71%) avoided cotton swabs containing 2 grams of marigold stem cambium extract, with only 6 mosquitoes (4.3%) approaching and landing within the 10-minute observation period. Similarly, Table 3 shows that 96.43% of mosquitoes (135 out of 140) avoided cotton swabs infused with marigold twig cambium extract, compared to 5 mosquitoes (3.57%) that approached and landed. These results suggest that twig cambium extract produced a slightly stronger repellent effect than stem cambium extract under identical conditions.

The Chi-square analysis further confirmed that mosquito avoidance was the main factor underlying repellency. For stem cambium extract (Table 2), the effect was statistically significant, with a p-value of 0.039 and an odds ratio (OR) of 4.8. For twig cambium extract (Table 4), the results were likewise statistically significant, with a p-value of 0.040 and an odds ratio (OR) of 4.9, demonstrating robust repellent activity.

Taken together, these findings show that both stem and twig cambium extracts of marigold are effective natural repellents, with twig cambium extract offering a marginally higher protective effect.

CONCLUSIONS AND RECOMMENDATIONS

The researcher's conclusion: Almost all (95.71%) mosquitoes moved away and landed on the inside edge of the mosquito net box after applying 2 grams of cotton swab containing marigold stem cambium extract for 10 minutes. This finding was statistically significant in its effectiveness as a mosquito repellent, with an odds ratio of 4.8. The effectiveness of cotton swab containing marigold stem cambium extract as a mosquito repellent. Almost all (96.43%) mosquitoes moved away and landed on the inside edge of the mosquito net box after applying 2 grams of cotton swab containing marigold stem cambium extract for 10 minutes. This finding was statistically significant in its effectiveness as a mosquito repellent, with an odds ratio of 4.9. The effectiveness of cotton swab containing marigold stem cambium extract on mosquito repellent.

It is recommended that students and the general public practice using cotton swabs infused with marigold stem and twig cambium extract indoors as an environmentally friendly method of repelling mosquitoes. Further studies are suggested to explore its long-term effectiveness, safety, and potential applications in community mosquito control programs.

AUTHOR CONTRIBUTIONS

All authors contributed to the conception and design of the study, data collection, and analysis. They collaboratively prepared, reviewed, and revised the manuscript. All authors approved the final version of this article.

CONFLICT OF INTEREST: The authors declare no conflicts of interest.

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