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Formulation and Physical Evaluation of Kratom (*Mitragyna speciosa* Korth.) Leaf Extract Emulgel as Analgesic in Mice (*Mus musculus*)

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Abstract

Background: *Kratom leaves contain major alkaloid compounds, particularly mitragynine and 7-hydroxymitragynine which have demonstrated anti-pain or analgesic properties.* ***Objective:*** *This study aims to evaluate the effectiveness of kratom leaf extract emulgel in reducing pain when applied topically in mice.* ***Methods:*** *This study was conducted on male mice that had been induced with acetan acid intraperitoneally. Following induction, emulgel formulations were applied topically and pain responses were recorded every five minutes over 30 minutes period. Group 1 (emulgel base without active ingredient), Group 2 (voltaren emulgel), Group 3 (emulgel with 5.6% extract concentration), Group 4 (emulgel with 11.6% extract concentration) and Group 5 (emulgel with 17.6% extract concentration).* ***Results:*** *The results of physical evaluations of emulgel formulations met the applicable standards. Observations of pain responses indicated optimal analgesic effect in the emulgels containing 11.6% and 17.6% extract concentration with analgesic values of 51.52% and 63.06% respectively. An active substance is considered to have analgesic activity whent it demonstrates ≥50% effectiveness.* ***Conclusion:*** *This study concluded that emulgels formulated with kratom leaf extract exhibited analgesic activity as evidenced by the decreased in the writhing response of mice every five minutes.*

Keywords*: analgesic, emulgel, kratom leaf, Mitragyna speciosa, physical evaluation*

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INTRODUCTION

Pain is a common and significant health issue, particularly among middle-aged and elderly individuals. It is often caused by severe tissue damage or necrosis, which leads to discomfort during daily activities (Raja et al., 2020). Therefore, pain management is necessary. However, the use of non-steroidal drugs or analgesics may result in adverse side effects, such as gastrointestinal disorders, nausea, increased blood pressure, and melena. Acute or chronic pain conditions, such as musculoskeletal pain, can also be managed with the use of topical drugs, which offer potential benefits by reducing systemic side effects (Wang et al., 2018).

Traditionally, kratom leaves have been used to boost stamina, relieve pain, and treat conditions such as rheumatism, gout, hypertension, stroke symptoms, diabetes, insomnia, wounds, diarrhea, cough, cholesterol, typhoid, and to increase appetite (Wahyono et al., 2019). The primary compound in kratom leaves is mitragynine, which has a strong affinity for opioid receptors and exhibits opioid-like analgesic activity (Nugraha et al., 2018). Research conducted by Anindita (2023) on kratom leaf ethanol extract cream formulations at concentrations of 0.26 grams, 0.56 grams, and 0.86 grams showed that the cream containing 0.86 grams of kratom leaf ethanol extract demonstrated the strongest antinociceptive activity (Anindita et al., 2023).

An emulgel is a topical preparation composed of two phases: a gel phase and an emulsion phase (Vanpariya et al., 2021). Emulgels can serve as formulations with a prolonged-action mechanism as they are suitable for both hydrophobic and hydrophilic active ingredients and are advantageous for active ingredients with a short half-life (Patel et al., 2022). Other advantages of emulgel formulations include ease of spreading, easy removal, non-staining, acceptability, transparency, and long-lasting effects (Vanpariya et al., 2021).

Based on the aforementioned descriptions, there has been limited research on topical formulations of kratom leaf extract, with most studies focusing only on the antinociceptive or analgesic activity of the extract itself. Therefore, this study aims to develop and physically evaluate kratom (*Mitragyna speciosa* Korth.) leaf extract emulgel formulations as an anti-pain or analgesic agent in mice (*Mus musculus*). The concentrations of the kratom leaf extract used in the emulgel formulations (*Mitragyna speciosa* Korth.) were adapted from Anintida's research (2023) in which initial extract amounts of 0.26, 0.56 and 0.86 grams corresponded to concentrations of 2.6%, 5.6% and 8.6% and were adjusted to 5.6%, 11.6% and 17.6%.

MATERIALS AND METHODS

Material

The chemical materials used included kratom leaf extract, Carbopol 940 (Arcypol, Ahmehabad, India) , propylene glycol (SamirasChem, Indonesia), liquid paraffin (Rofa Laboratorium Centre, Bandung, Indonesia), Span 80 (KOLB, Swiss), Tween 80 (LG H&H, Korea), TEA (Methan Tirta Kimia, Bekasi, Indonesia), methylparaben (Golden Era, India), propylparaben (UENO, Japan), distilled water (Rofa Laboratorium Centre, Bandung, Indonesia), peppermint essential oil, 95% ethanol (JK Care, Indonesia), glacial acetic acid (Merck, Germany), Mayer's reagent (Merck, Germany), $FeCl_3$ (Merck, Germany), and NaOH (Merck, Germany).

Method

Extraction

The extraction process began by weighing 100 g of dried powdered leaves, which was then placed in a previously prepared round bottom flask. A 96% ethanol solvent was added to the flask up to 500 ml and a boiling stone was inserted to keep the temperature stable. The soxhlet process was then carried out for three hours at 78^{o}C. Due to the limited availability of soxhlet apparatus, the extraction was repeated several times to obtain the desired quantity of extract. The resulting extract was filtered and the filtrate collected was concentrated using a rotary evaporator at a temperature of ± 45°C (Mutiara et al. 2023). The thickened extract was then subjected to several evaluations including: organoleptic test, extract yield, total ash content, drying shrinkage and phytochemical screening.

Phytochemical screening

Alkaloid tests

The kratom leaf extract was dissolved in chloroform and placed into a test tube. Subsequently, one or two drops of ammonia were added, then mixture was shaken and filtered. Following this, 1-3 ml of 2N sulfuric acid was added. The upper layer formed was collected using a dropper pipette and distributed into three separate test tubes, each treated with a different reagent Wagner, Mayer and Dragendorff's reagents. The presence of alkaloids was indicated by the formation of a white precipitates with Mayer's reagent, a red to orange precipitate with Wagner's reagent, and a reddish brown precipitates with Dragendorff's reagent (Tiaravista et al., 2019).

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Flavonoid test

The kratom leaf extract was dissolved in ethanol, followed by the addition of Mg and concentrated HCL solution. The presence of flavonoid compounds in the extract was indicated by a red color change (Tiaravista et al., 2019).

Steroid test

The kratom leaf extract was dissolved in ethanol, and glacial acetic acid and concentrated sulfuric acid were added. A positive result for steroids was indicated by the appearance of a green to blue color (Tiaravista et al., 2019).

Quinone test

A total of 5 ml of extract dissolved in ethanol was mixed with 1N NaOH. A sample positive result forquinone compounds was indicated by the appearance of a red color (Sofia et al., 2022).

Tannin test

A total of 0.5 g of extract was added to hot water, folllowed bya few drops of 1% FeCl3. The presence of tannin compounds was indicated by the formation of a dark blue or blackish green color (Sofia et al., 2022).

Saponin test

A total of 0.5 g of kratom leaf extract was dissolved in distilled water, shaken and left for 10 minutes. Then one drop of 1% hydrochloric acid was addes. A positive for saponins was indicated by the formation of a stable foam (Sofia et al., 2022).

Formulation optimization

The formulations of kratom leaf extract emulgel were modified from the methods described by Firmansyah et al., (2023).

Preparation of emulgel

Carbopol 940 was dispersed in a mortar containing preheated distilled water (70–80°C) for 30 minutes, followed by trituration for 15 minutes until fully dispersed. TEA was added to the gel base in the mortar and stirred for 15 minutes until a clear gel base was formed. Separately, nipagin, nipasol, and Na EDTA were dissolved in propylene glycol using a porcelain dish and then mixed into the gel base. The emulsion base preparation began with the oil phase (Span 80 and liquid paraffin), which was melted in a porcelain dish at 60–70°C. The aqueous phase was prepared by melting Tween 80 and distilled water at 70°C in a porcelain dish. Both phases were combined by pouring the oil phase into the aqueous phase and stirred until a homogeneous emulsion mass was formed. The prepared emulsion mass was immediately mixed into the gel base in the mortar, followed by the addition of kratom leaf extract at varying concentrations and peppermint essential oil. The mixture was triturated until homogeneous, resulting in the emulgel mass. The final emulgel was then transferred into appropriate containers and subjected to evaluation (Firmansyah et al., 2023).

Evaluation parameters of emulgel

Organoleptic test

The organoleptic test was conducted by directly observing the emulgel formulation in terms of its appearance, color, and odor. Gel formulations are expected clear with a semi-solid consistency.

Table 1. Kratom leaf extract emulgel formulations

Materials	Concentration (%)					Function of Materials
	K-*	F1	F2	F3	K+*	
Kratom leaf extract	-	5.6%	11.6%	17.6%	Voltaren emulgel containing diclofenac diethylamine	Active ingredient
Carbopol 940	0.5%	0.5%	0.5%	0.5%		Gelling agent
Propylene glycol	10%	10%	10%	10%		Humectant
Liquid paraffin	5%	5%	5%	5%		Emollient
Span 80	5%	5%	5%	5%		Emulsifying agent
Tween 80	5%	5%	5%	5%		Emulsifying agent
Na EDTA	0.1%	0.1%	0.1%	0.1%		Chelating agent
TEA	2%	2%	2%	2%		Emulgator
Methyl paraben	0.1%	0.1%	0.1%	0.1%		Preservative
Propyl paraben	0.1%	0.1%	0.1%	01%		Preservative
Peppermint essential oil	2 drips	2 drips	2 drips	2 drips		Perfume
Aquadest	Ad 10 gr	Ad 10 gr	Ad 10 gr	Ad 10 gr		Solvent

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Homogeneity test

This test involved applying the emulgel onto a glass slide and observing its color distribution to ensure uniformity and the absence of fine granules. According to SNI standards, a good gel formulation should not contain coarse particles or clumps (Firmansyah et al., 2023).

Spreadability test

The spreadability test was performed by weighing 0.5 grams of the emulgel, placing it on a transparent glass surface, and covering it with another glass plate. A 150-gram weight was applied for one minute, and the increase in spread diameter was measured. The spreadability of a semi-solid formulation is considered good if it meets the standard requirement of 3–5 cm (Voigt., 1994).

Adhesion test

The adhesion test was conducted using an adhesion testing device by spreading the emulgel on a glass slide, covering it with another glass slide, and applying a 250-gram weight for five minutes. After releasing the lever, a stopwatch was used to measure the time taken for the glass slides to separate. An adhesion value greater than four seconds is considered good (Firmansyah et al., 2023).

pH Test

The pH test was conducted by diluting 0.5 grams of the emulgel in 5 ml of distilled water, and the pH was measured using a pH meter. According to SNI standards, a good gel formulation should have a pH suitable for the skin, which is 4.5–8 (Chandra & Rahmah, 2022).

Analgesic test

A total of 25 mice were prepared and fasted for 18 hours, with free access to water. The mice were weighed and divided into five groups. Pain induction was performed by intraperitoneally administering 1% glacial acetic acid at a dose of 10 ml/kg body weight or 0.2 ml/20g body weight. The mice were left for 10 minutes before treatment. Group 1 received emulgel without active ingredients, group 2 received voltaren emulgel containing diclofenac diethylamine, group 3 received with emulgel containing 5.6% kratom leaf extract, group 4 received emulgel containing 11.6% kratom leaf extract and group 5 received emulgel containing 17.6% kratom leaf extract. Observations were conducted over a 30 minutes at 0, 5, 10, 15, 20, 25, and 30 minutes. Each group consisted of five mice, and each treatment was repeated five times, to obtain an average response value. The analgesic response of the mice in this test was evaluated based on their behavior, specifically writhing movements characterized by pulling both legs backward and pressing their abdomen against the surface of the cage. The percentage of pain relief activity was then calculated.

This study was declared ethically appropiate according to the seven 2011 WHO standards. The animal experiment ethics approval number is No.3088 /UN22.9/PG/2023.

$$\text{Analgesic Activity} = 100 - \left[\frac{\text{Treatment groups}}{\text{Negative control}} \times 100\right] \%$$

RESULTS AND DISCUSSION

Non-specific parameter tets

The concentrated extract obtained weighed 75.8 g after processing with a rotary evaporator. The results of the non-specific parameter tests were as follows yield of 25.27%, drying shrinkage of 0.56% and total ash content of 0.7171%. Phytochemical screening indicated that the kratom leaf extract contained alkaloids, flavonoids, steroids, quinones, tannins and saponins. These non-specific parameter tests were carried out to determine the quality of the extract to ensure suitability.

Phytochemical screening

The purpose of this test was not only to identify the class of compounds present in the extract but also to evaluate the effect of the hot extraction methods (soxhletation) on the extraction chemical compounds in kratom leaves. This is consistent with the findings of Mutiara et al., (2023) who reported that heat-assisted extraction methods such as reflux and soxhlet can extract more secondary metabolite compounds. Heating facilities the extraction of compound that are difficult to dissolve at room temperature by activating low-molecular-weight polymer subunits into high-molecular-weight, thereby improving extraction efficiency (Mutiara et al., 2023). The results shows that the kratom leaf extract tested positive for alkaloids, flavonoids, steroids, quinones, saponins and tannins. These findings are consistent with the studiest by Anindita et al., (2023) which also reported the presence of these compounds in kratom leaves positive for alkaloid, flavonoids, tannins and saponins.

Organoleptic test

Observations of the emulgel formulations containing kratom leaf extract revealed that F1 was light brown in color, with a characteristic peppermint aroma, and a semi-solid consistency. F2 produced a dark brown, emulgel with a slight blackish tint, retaining the characteristic peppermint aroma, and exhibiting a semi-solid consistency. Meanwhile, F3 resulted in a blackish-brown emulgel, maintaining the characteristic

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peppermint aroma, and also presenting a semi-solid consistency. Homogeneity testing was conducted to assess the uniformity of the emulgel components. The results indicated that the formulations were homogeneous, as evidenced by the absence of coarse particles or clumps.

Spreadability test

The spreadability of the emulgel formulations was assessed over one month, encompassing five cycles. The average spreadability ranged from 4.3 to 5 cm, meeting the requirements for effective spreadability. The spreadibility of formulation is influenced by its consistency; specifically, as the consistency increas, its spreadability decreases (Bagiana & Kresnawati, 2020).

Statistical analysis was conducted to evaluate the spreadability data. The Shapiro-Wilk normality test indicated that spreadability data were normally distributed, as evidenced by a significance value greater than 0.05. Homogeneity testing of the three formulations also show homogeneous data, as indicated by a significance value of 0.456 ($p > 0.05$). Additionally, the ANOVA test yielded, a significance value of 0.008 ($p > 0.05$), suggesting no significant differences among the three formulations.

Adhesion test

The adhesion test results over one month with five cycles presented in Table 4. The adhesion capability of the emulgel formulation in this study exceeded four seconds, meeting the criteria for good adhesion. A high adhesion value of a formulation enhances the absorption of active substances into the skin by increasing the contact time between the skin and the formulation.

The Shapiro-Wilk normality test revealed that the adhesion data were normally distributed, as evidenced by a significance value greather than 0.05. Homogeneity testing of the three formulastions also showed homogeneous data, as indicated by a significance value of 0.092 ($p > 0.05$). In the ANOVA test, a significance value of 0.000 ($p < 0.05$), indicating a significant difference among the three formulations. Duncan's test identified that the third formulation, containing 17.8% emulgel concentration, exhibited significant differences compared to F1 and F2.

pH test

The pH test result, conducted over one month yielded an average value ranging from 6.74 to 7.41, indicating that the emulgel formulation maintained a good pH value in accordance with the Indonesian National Standard SNI 16-3499-1996. This standard stipulates that a good pH range for emulgel formulations intended for use on the skin is 4.5-8 (Chandra & Rahmah, 2022). Throughout the one-month testing period, changes in pH were observed weekly, likely influenced by to factors such as storage temperature and exposure to light.

The Shapiro-Wilk normality test for the pH values confirmed a normal distribution, with a significance value greather than 0.05. Homogeneity testing of the three formulations also showed homogeneous data, as indicated by a significance value of 0.786 ($p > 0.05$). In the ANOVA test, a significance value of 0.001 ($p < 0.05$), indicating a significant difference among the formulations. Furthermore, post-hoc testing revealed that F3 exhibited significant differences when compared to F1 and F2.

The results presented in Figure 1 indicated in F1, with a concentration of 5.6%, provided a relatively weaker analgesic effect, whereas F2 and F3, with concentrations of 11.6% and 17.6% respectively, achieved analgesic protection rates of 51.25% and 63.06%. These values can be classified as demonstrating analgesic effects, with the percentage of pain relief increasing with higher concentrations of the extract. This trend indicated that the effectiveness of the formulation is positively correlated with the concentration of the kratom leaf extract, suggesting that higher extract concentrations lead to greater analgesic efficacy. A test substance is considered to possess analgesic or pain-relieving properties if it achieves a percentage value of ≥50% when tested on laboratory animals (Lara et al., 2021).

Table 3. Organoleptic test results of kratom leaf extract emulgel

Formula	Organoleptic			
	Color	**Form**	**Odor**	**Homogeneity**
FI (5.6%)	Soft brown	Semisolid	Peppermint	Homogenous
F2 (11.6%)	Brown	Semisolid	Peppermint	Homogenous
F3 (17.6%)	Dark brown	Semisolid	Peppermint	Homogenous

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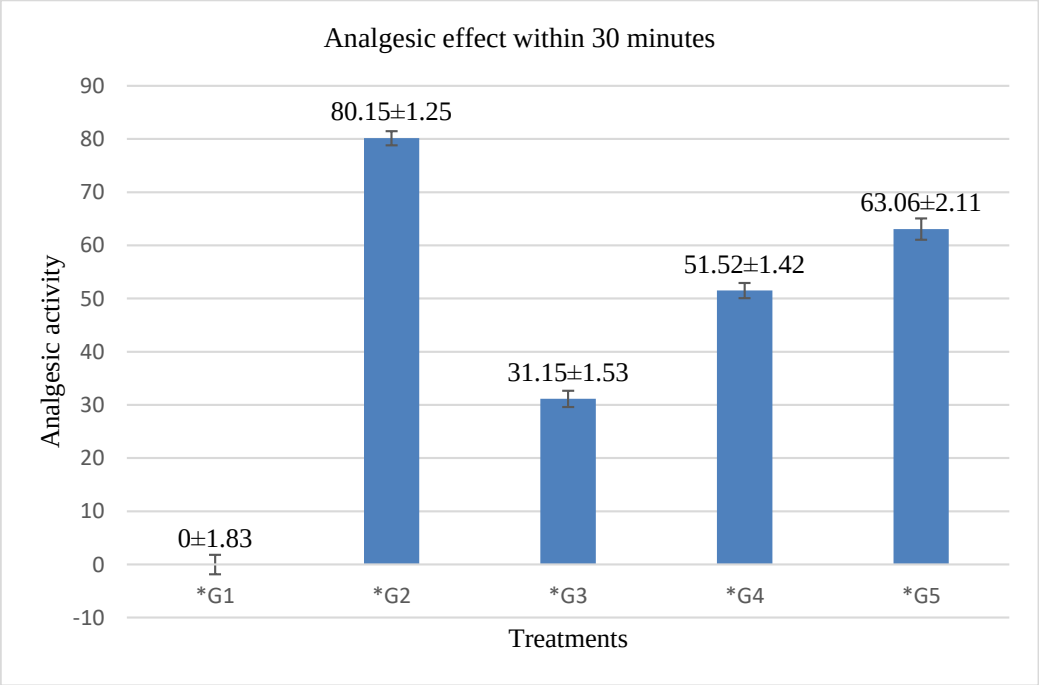
Table 4. Physical evaluation results of kratom leaf extract emulgel

Test	Formula	Result ± SD	Requirement	Sig ANOVA ($p < 0.05$)
Spreadability Test	F1 (5.6%)	5 ± 0.37	3–5 cm	0.008
	F2 (11.6%)	4.76 ± 0.60		
	F3 (17.6%)	4.32 ± 0.63		
Adhesion Test	F1 (5.6%)	14.24 ± 0.90	> 4 seconds	0.092
	F2 (11.6%)	15.098 ± 0.74		
	F3 (17.6%)	15.876 ± 0.32		
pH Test	F1 (5.6%)	7.4 ± 0.203411	4.5-8	0,001
	F2 (11.6%)	7.1 ± 0.127373		
	F3 (17.6%)	6.7 ± 0.232499		



*G1 = group 1 mice treated with emulgel without active ingredients
*G2 = group 2 mice treated with voltaren emulgel containing diclofenac diethylamine
*G3 = group 3 mice treated with emulgel containing 5.6% kratom leaf extract
*G4 = group 4 mice treated with emulgel containing 11.6% kratom leaf extract
*G5 = group 5 mice treated with emulgel containing 17.6% kratom leaf extract

Figure 1. Analgesic test in mice within 30 minutes

Kratom leaves contain at least 66% of alkaloid compounds (Rybarczyk, 2019). The compounds responsible for the analgesic activity of kratom leaf emulgel are alkaloids, which play a role in inhibiting the formation of prostaglandins, particularly in the cyclooxygenase (COX) enzymatic pathway of the arachidonic acid route (Tamimi et al. 2020). According to Kruegel (2019), in vitro evaluations of mitragynine and 7-hydroxymitragynine in kratom leaves (*Mitragyna speciosa*) on mouse liver preparations suggested a potential interaction with mu-opioid receptors mediated by cytochrome P450 3A. This study found high concentrations of mitragynine in the brains of mice; however, it did not directly activate opioid receptors. Kruegel further stated that the analgesic effects of these compounds may vary depending on the route of administration (Kruegel et al., 2019).

The principle underlying topical medications or drug administration through the skin is passive diffusion, wherein active substances move from one area to another. Absorption occurs when drug molecules penetrate the skin into the tissue and subsequently enter the bloodstream through passive diffusion (Bagiana & Kresnawati, 2020). Based on this mechanism, it can be

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concluded that the alkaloid compounds in kratom leaf extract emulgel serve as analgesics by moving from the skin into the bloodstream.

The Shapiro-Wilk normality test for pain relief data confirmed a normal distribution, with a significance value greater than 0.05. Homogeneity testing of the three formulas also showed homogeneous data, as indicated by the significance value of 0.013 ($p>0.05$). ANOVA yielded a significance value of 0.000 ($p<0.05$), indicating significant differences among the three formulas. Subsequent tests were conducted to identify formulas that exhibited differences. The follow-up test demonstrated significant differences among all emulgel formulations of kratom leaf extract, as evidenced by the fact that each formulation occupied different locations in the Duncan test. The results confirmed that the 17.6% kratom leaf extract emulgel concentration differed from that of the other two formulas. These findings are consistent with those of Anindita et al. (2023), who suggested that higher doses of kratom leaf extract administered to experimental animals are associated with decreasing response rates, as reflected by smaller responses from the test subjects (Anindita et al., 2023). This study has limitations regarding the writhing response given by mice, which if the researcher is a different person, then maybe the results obtained will be different, because this study was only visually observed for the writhing response by mice. So, it is suggested that future research to use a more advanced analgesic method that is limited to being observed visually.

CONCLUSION

Based on the physical evaluations conducted, the emulgel formulation met the requirements of a good emulgel, as evidenced by successful organoleptic, homogeneity, spreadibility, adhesion, and pH tests. The efficacy of an emulgel formulation containing kratom leaf extract at three different concentrations was evaluated for analgesic properties. Notably, the formulation at a concentration of 17.6% demonstrated a significant analgesic effect, achieving an efficacy rate of 63.06%. This was followed by the formulation at a concentration of 11.6%, which exhibited an analgesic effect of 51.52%. These findings suggest that the concentration of kratom leaf extract directly influences its analgesic capacity, highlighting its potential as a therapeutic agent for pain management..

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AUTHOR CONTRIBUTIONS

Conceptualization: I.Z., K.D., J.D.; Methodology, I.Z., K.D., J.D.; Software, I.Z.; Validation, I.Z., J.A., KD.; Formal Analysis, I.Z., K.D., J.D.; Investigation: I.Z., K.D., J.D.; Resources, I.Z., K.D., J.D.; Data Curration; I.Z., K.D., J.D.; Writing - Original Draft, I.Z., K.D., J.D.; Writing - Review and Editing, I.Z., K.D., J.D.; Visualization, I.Z., K.D., J.D.; Supervision: I.Z., K.D., J.D.; Project Administration, I.Z., K.D., J.D.; Funding Acquisition, I.Z., K.D., J.D.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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