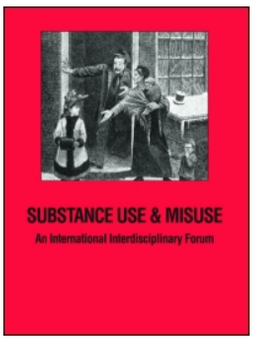

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ORIGINAL ARTICLE

The Physiological and Ergogenic Effects of Khat (*Catha edulis* Forsk) Extract

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ABSTRACT

Background: Khat (*Catha edulis* Forsk) is a natural psychoactive substance which contains two main addictive substances; Cathine and Cathinone. Khat is widely used in east Africa and southern Arabian Peninsula. Khat chewers believe that it improves work capacity and increases energy level and alertness. That is why we aimed in this study to investigate the physiological and ergogenic effects of khat extract. *Methods:* This study is an experimental study conducted at the Substance Abuse Research Centre in Jazan University, Saudi Arabia. Thirty healthy young volunteers were randomly assigned into two experimental groups. The first group ingested 45 g of grounded khat leaves extract mixed with juice in the first session then placebo (juice only) in the second session. While the second group ingested the placebo in the first session and the grounded khat leaves with juice in the second session. Experiments were done between December 2012 and March 2013. We recorded the blood pressure, heart rate, grip strength, and reaction time every 15 min for 75 min after each ingestion. The study proposal was reviewed and approved by Research Ethics Committee (REC) of the Medical Research Centre in Jazan University. Results: The results showed the consumption of 45 g of grounded khat leaves contributed to the increase in blood pressure (SBP & DBP) and reaction time ($p < 0.05$); but had no significant effect on heart rate and grip strength ($p > 0.05$). *Conclusions:* The findings of this study showed that Khat has an acute effect on some physiological parameters. These findings support the prohibition of cathinone and cathine by the World Anti-Doping Agency (WADA, 2016).

KEYWORDS
Khat chewing; ergogenic effect; repeated measurements; cycling

Background

Khat (*Catha edulis* Forsk) is a shrub of the family Celastraceae which grows in certain areas of East Africa such as Ethiopia and Kenya as well as in the southern Arabian Peninsula including Yemen and the southern areas of Saudi Arabia (Sheikh et al., 2014). Khat is traditionally chewed for its' euphoric and stimulating effects (Wabe, 2012). Chewers believe that it improves work capacity, increases energy levels, and alertness. Khat is a controlled substance in most western countries such as the United States and some European countries. In 2013, the classification of khat changed in UK and it is now a controlled drug in Table C. Netherland which is famous in its tolerance of drugs had prohibited the use of khat in 2012 (Sheikh et al., 2015; Sa'ed, 2015). Khat contains two main psychoactive ingredients; cathine and cathinone. Both affect the central and peripheral nervous system in a manner similar to amphetamine or cocaine (Kalix, 1992).

The amount of cathinon and cathin in the khat leaves is debatable. Few studies reported composition of khat leaves. An earlier review article reported the presence of 36 mg cathinone, 120 mg cathine, and 8 mg norephedrine per 100 g of leaves (Geisshusler & Brenneisen, 1987). A Kenyan publication reported that each 100 g of fresh khat leaves contain 102 mg cathinone, 86 mg cathine, and 47 mg norephedrine (Widler et al., 1994). In Frankfort University, they detected 114 mg cathinone, 83 mg cathine, and 44 mg norephedrine in 100 g of khat leaves (Toennes et al., 2003). A much wide range of cathinone concentrations (78–343 mg/100 g khat leaves) was reported from Yemen (Al-Motarreb, Baker, & Broadley, 2002). This study used type of khat called "Radaee" grown in Yemen. "Radaee is the main type of khat used in Jazan; that is why, it is used it in this experiment. Cathinone is present in higher concentration than Cathine in fresh, tender, leaves. Then, it is converted to Cathine and Norephedrine progressively (Al-Motarreb, Baker, & Broadley, 2002).

The misuse of drugs is common in sport, as in sports there is a need to be sharper and quicker

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than competitors. In many sports, the difference between success and failure can be as small as a fraction of a second. The ability to react quickly to a stimulus is therefore advantageous to athletes and may result in improved performance. There are so many different types of drugs used to enhance sports performance. The World Anti-Doping Agency (WADA) provides a list of prohibited substances that sportspersons are not allowed to take or use. WADA recently prohibited the use of cathinone and cathine by athletes in competitions as a specified stimulant (WADA, 2016). Therefore, the primary aim of this study is to investigate the physiological and ergogenic effects of consumption khat on young healthy men in Jazan region in Saudi Arabia. The experiment hypothesis tested was this: 'mean scores of the physiological measures in Khat treatment group are significantly higher than the mean scores of the placebo group.'

Methods

Study participants

The study participants were young healthy male volunteers. Their ages ranged between 20 and 30 years (mean 22.3 ± 2.3). Their weights ranged between 60 and 80 kg (mean 64.6 ± 6.47). Women were excluded for cultural reasons and experimental convenience. The inclusion criteria included not having heart problems, no chest pain on exertion, not currently under any medication for any health problem. The study participants were all non-professional football players and some of them were students, they were using khat in special occasions only like general festivals or family wedding, but never on regular bases. The study protocol was reviewed and approved by the Research Ethics Committee (REC) of the Medical Research Centre at Jazan University. In total, 30 healthy volunteers were recruited.

Design and procedures

All participants completed two experiments, one after ingesting a placebo and the other after ingesting grounded khat leaves. The order in which the experiments were conducted was randomized. The participants were blind to the nature of the experimental substance. A statistical power test on pilot data suggested that the number of subjects required for this experiment is 30. The sample size calculated was based on standard deviation of 1.0, expected effect size of 0.643 (Cohen's *d*, a measure of effect size), power level of 0.80, and alpha of 0.05 (Gore & Altman, 2001). Experiments took place in a laboratory of The Substance Abuse Research Centre (SARC) at Jazan University, Jazan, Saudi Arabia. The experiments were created between December 2012 and March 2013. The study participants were asked to visit the laboratory on two occasions. On the first visit, the volunteers ingested either 330 mL of fruit juice alone, as a placebo, or the juice mixed with 45g of grounded, filtered khat leaves. The least amount of khat used by khat users in Jazan is quarter of pile. That is why we calculated this quantity (45 g) as it equals the weight of the fresh leaves in a quarter of the pile of khat (date collected from focus group discussions and a cross-sectional survey in the process of publication). In the second visit, those who ingested khat were asked to ingest the placebo and those ingested placebo we asked to ingest the juice with khat. In both visits, the participants were blind to the ingested material.

Each visit lasted around one and half hour. In both visits, the participant's resting blood pressure, heart rate, reaction time, and grip strength were measured before ingestion and after ingestion every 15–75 min (Figure 1).

Reaction time test

The test measured simple reaction times in response to a visual stimulus. The testing equipment was pre-programmed to deliver a "get ready" and a "go" signal by illuminating small lamps. The volunteers reacted to the "go" signal by touching pad a few millimeters from their resting finger position. Before each stimulus the subject was given a signal that the test period has begun. The "go" signal was then presented after a randomized delay of 1–9 seconds. A set 10 repetitions was delivered in about 2–3 min. Each test was provided 10 reaction time

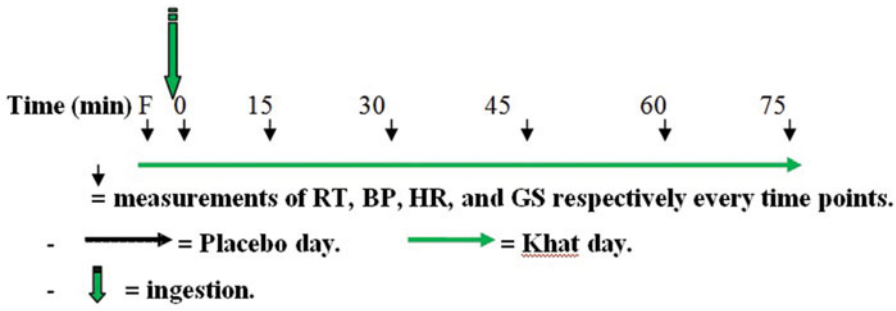

Figure 1. The protocol of the study.

Figure 2. Measurement of reaction times. The reaction timer is shown to the left. The touch switch and resting finger position are to the right.

measurements. This device was developed for another research project and full details of its design and construction used by Rizzi in his PhD thesis (Rizzi, 2011).

Blood pressure and heart rate

Blood pressure was measured after the reaction time measurements using an automatic cuff (Boso Medicus, Germany 2011, www.boso.de) using the manufacturer's standard protocols. This procedure is shown below in Figure 2. Before blood pressure measurement was measured each participant was asked to sit quietly and to have some time to relax. Three measurements were taken at 30 sec intervals. Average of the measurements was considered. The heart rate was measured at the same time with the same device. The heart rate recorded was the mean of the three readings.

Grip strength

We measured the grip strength for each participant while he was standing using a Grip Dynamometer (0–100 kg, No. 792003, Takei Kiki Kogyo, Tokyo, Japan). The manufacturers' standard protocol was followed (topendsports.com/testing/handgrip). These tests lasted for around 1–2 min. The measurements were recorded three times during this period. The mean of the three grip strength measurements was considered.

Statistical analysis

Repeated Measures Analysis of Variance (ANOVA) was utilized to find the effect of group differences in grip strength, reaction time, heart rate, systolic blood pressure, and diastolic blood pressure. We tested both the within-subject effects and between-subject effects of the model factors. The experimental design used was essentially a two-factor (time point and treatment) experiment with repeated measures of five responses on both factors. In each model, the subject is entered as a random factor while Time Point and Treatment (placebo and khat) and the interaction between Time Point and Treatment were entered as between-subjects factors. The Levene statistic test was used to assess the assumption of equality of variances in the study variable of the two trial groups.

Ethical approval

The experimental protocol was conducted in accordance with the ethical guidelines of the Helsinki Declaration and was approved by Research Ethics Committee (REC) of the Medical Research Centre (MRC), Jazan University. All volunteers were fully informed of the nature of the experiment. Each one signed a written informed consent. Participants were informed that they can withdraw from the experiment at any time. However, none of them withdrew during the experiment. Volunteers were paid only for their travel expenses.

Results

I. Graphic presentations

Systolic Blood Pressure (SBP): Figure 3 shows that after khat ingestion SBP rose within the first 30 min when it reached a plateau between 30 and 60 min when it started to drop for the last 15 min. On the other hand, SBP slightly dropped after placebo ingestion.

Diastolic Blood Pressure (DBP): Figure 4 show that the mean scores of DBP after consumption of khat was

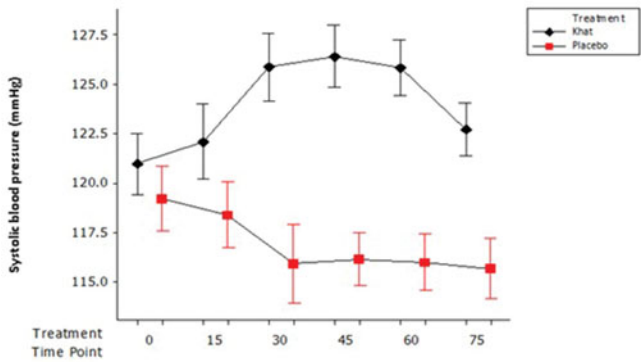

Figure 3. Mean and standard error of the mean (SEM) of systolic blood pressure after taking khat or Placebo.

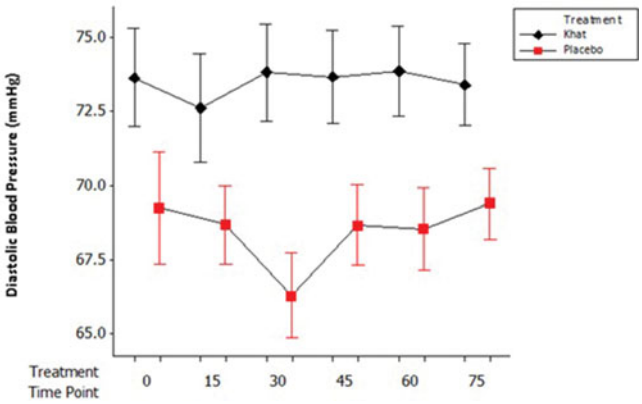

Figure 4. Mean and SEM of the diastolic blood pressure after taking the khat or Placebo.

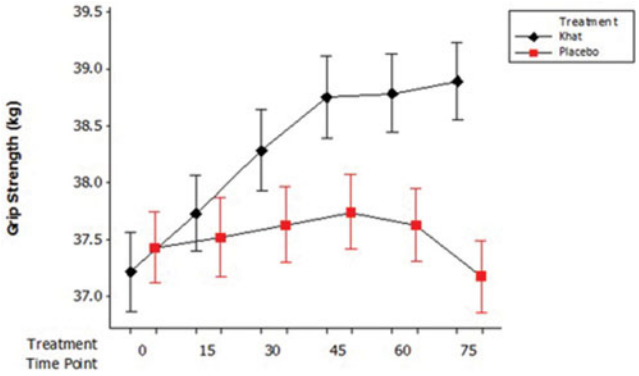

Figure 6. Mean and SEM of grip strength measured after taking khat or Placebo.

higher at all-time point compared with taking placebo. Changes in mean scores over time were stable in both experiment groups (khat and placebo), only there was one unexplained deep shock at time 30 min in placebo group.

Heart Rate (HR): Figure 5 shows that HR showed steady increase between 15 and 45 min after khat ingestion. Then, it started gradual decline but did not reach the original baseline after 75 min. In contrary, after ingestion of placebo HR showed steady decline all over the period of measurements.

Grip Strength (GS): Figure 6 shows that after khat consumption there was a steady increase in the GS. Then, it started to decline gradually. After khat consumption, the grip strength started at 37.2 + 6.4 kg and increased gradually over the next 75 min to 38.9 + 6.2 kg. On the other hand, after placebo mean grip strength was nearly the same; it increased slightly after 15 min until 45 min when it started a gradual decline.

Reaction Time (RT): Figure 7 shows the mean reaction times declines after consumption of khat till 60 min, then it starts to increase. After placebo consumption, changes in reaction time were negligible.

In summary, according to the graphical analysis in each of the study variables (SBP, DBP, HR, GS, and RT) the mean differences of the placebo group and khat treatment group did not show significant effect at earlier times of the trial, but later in the trial the mean differences of the two experiments (placebo and khat) get significant. Therefore, the graphical analysis provided inconclusive results; hence, we proceed to use Repeated Measures Analysis of Variance (ANOVA).

II. Repeated measures analysis (ANOVA)

The Mauchly's test indicated that the covariance matrix assumption was not fulfilled; therefore, the *F*-values were corrected using the Greenhouse–Geisser test. The results of the 'Within-subjects test indicated insignificant differences over time for SBP ($F = 1.239$, df1 = 5, df2 = 4.131, $p > 0.05$), DBP ($F = 0.886$, df1 = 5, df2 = 3.902, $p > 0.05$) and HR ($F = 1.659$, df1 = 5, df2 = 3.706, $p > 0.0$). On the other hand, significant differences were detected over time for GS ($F = 2.952$, $df_1 = 5$, $df_2 = 3.763$, $p < 0.05$) and RT ($F = 3.955$, $df_1 = 5$, $df_2 = 3.198$, $p < 0.05$). This means, after ingestion of khat, these variables do change over time and will get higher reaction time and higher grip strength over time.

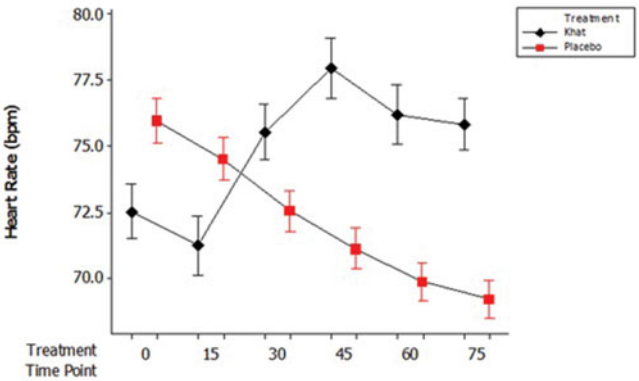

Figure 5. Mean and SEM of the heart rates after consuming khat or Placebo.

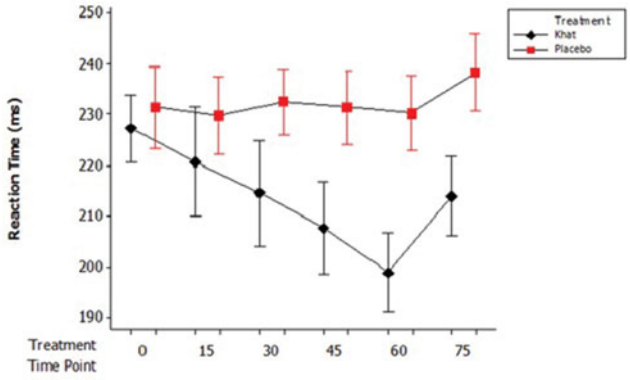

Figure 7. The mean and SE of reaction times after consuming khat and after taking the placebo.

Table 1. Summary of repeated measures analysis of variance (ANOVA).

Variables	Time	Time*Session	Main effect of a session
Systolic blood pressure	No	Yes	Yes
Diastolic blood pressure	No	No	Yes
Heart rate	No	Yes	No
Grip strength	Yes	Yes	No
Reaction time	Yes	Yes	Yes

In addition, the Within-subject test confirmed that there were significant interaction effects of time and session (khat & placebo) on the following variables: systolic blood pressure ($F = 7.103$, df $= 4.131$, $p < 0.001$); heart rate ($F = 14.139$, df $= 3.706$, $p < 0.001$); grip strength ($F = 2.756$, df $= 3.763$, $p < 0.05$) and reaction time ($F = 3.790$, df $= 3.198$, $p < 0.01$). While it only showed no significant interaction of time and session with diastolic blood pressure ($F = 1.390$, df $= 3.902$, $p > 0.05$). To conserve space, details of the results of the main effects plot and the interaction plot are available upon request.

The results of between-subjects effects indicated a significant main effect of a session (placebo and khat) on the following three variables: SBP ($F = 14.174$, df $= 1$, $p < 0.001$), DBP ($F = 7.029$, df $= 1$, $p < 0.05$), and RT ($F = 3.097$, df $= 1$, $p < 0.10$), *while no significant difference were found between HR and GS measurements after ingestion of placebo and khat* ($F = 1.283$, df $= 1$, $p > 0.05$ and $F = 0.240$, df $= 1$, $p > 0.05$ respectively); this means differences between condition means of HR and GS are likely due to chance and not likely due to khat consumption. Finally, the equality of variances condition was fulfilled as the *p*-values of Levene's test were greater than 0.05 across all the five variables in the study.

Table 1 provides the summary of repeated measures analysis of the study model. The variable time in column two provided information about whether there was significant difference of means – at the different time points – within each experiment groups (khat and placebo); on this regard, GS and RT variables had significant time effect in the model. Column three provided information about the interaction effect of *time* and *session* (khat and placebo); on this regard, all variables with the exception of DBP had shown significant interaction of time and session. The final column "Main effect of session" tells us the overall significant difference of means *between* experiment groups (khat vs. placebo); on this regard, khat experiment group had reported higher mean scores in SBP, DBP, and RT compared to placebo experiment group.

Discussion

We aimed through these series of experiments to investigate the effect of consuming khat leaves on some of physiological variables in a group of healthy young men. The study findings support the study's hypothesis that "the mean scores of the physiological measures in Khat group are significantly higher than the mean scores of the placebo group." We found that ingestion of khat leaves contribute to raising SBP & DBP, and reduce the RT of healthy young men. Khat did not affect heart rate nor grip strength. The effects on SBP are in agreement with the results of several earlier studies which reported that the systolic blood pressure increases after khat consumption (Widler et al., 1994; Toennes et al., 2003; Patel, 2000; Getahun, Gedif, & Tesfaye, 2010; Brenneisen et al., 1990; Hassan et al., 2000). The effect of khat on heart rate was not significant; although, it was higher at most of the time points compared with the placebo. The effect of khat on DBP was the only variable in disagreement with the results of earlier studies. May be this because we are recording the acute effect of khat use while other studies were mainly recording the long-term effects.

Khat has effects on both the peripheral and the central nervous system. The peripheral actions of khat are of the sympathomimetic type and they resemble those of amphetamine. Previous studies have found that the effects may appear rapidly after the consumption of khat. These include: increased heart rate, blood pressure, respiratory rate, and body temperature. The effect depends on the amount and potency of the material absorbed (Halbach, 1972; Margetts, 1967; Kalix, 1990). The central nervous system effects of khat consumption including euphoria, alertness, and feeling of wellbeing (Patel, 2000). The constituents of khat have been shown to exert their effects on two main neurochemical pathways: dopamine and noradrenaline. These effects are believed to result from the ability of cathinone to act as an indirect sympathomimetic agent and to facilitate the release of dopamine from central nervous system dopamine terminals and thus increase the activity of the dopaminergic pathways (Kalix & Braenden, 1985; Cox & Rampes, 2003).

The data shown in Figure 6 show that the consumption of khat is produced a small but statistically insignificant effect on grip strength. In our opinion, this is the first study of this type. The finding suggests that the volunteers were able to activate their muscle equally in both conditions. The sympathetic nervous system has no direct effect on the force development by skeletal muscle (Arreola, Calvo, Garcia, & Sanchez, 1987; Gonzalez-Serratos, Hill, & Valle-Aguilera, 1981). The lack of effect probably indicates that volunteers had no perceptual or motivational limitations on either day.

The results of this study would be for the first time that consumption of Khat leaves contributes to reduced reaction time. The mean reaction time falls progressively after consumption of khat and the changes are statistically significant between 45 and 60 min. This follows the likely

time course of changes in cathinone concentrations in plasma describe above. Previous studies have investigated the effects of long-term use of khat on reaction times (Colzato et al., 2011a; Colzato, Ruiz, van den Wildenberg, & Hommel, 2011b; Colzato, Ruiz, van den Wildenberg, & Hommel, 2012). These studies demonstrated that long-term khat users in general were slower to react than non-users across a range of tests of cognitive functions (Colzato et al., 2011a; Colzato, Ruiz, van den Wildenberg, & Hommel, 2011b; Colzato, Ruiz, van den Wildenberg, & Hommel, 2012). It is not surprising that short (stimulant phase) and long term (depressive phase) effects may be quite different.

In the present study, it clear that consumption of khat has a physiological action. This suggests strongly that sufficient cathinone and to a lesser extent cathine is present in the khat leaves to have biological action. Cathinone is present at higher concentration than cathine in fresh leaves then it converts to cathine and Norephedrine progressively (Patel, 2000; Ahmed, 2004; Griffiths et al., 2010; Kalix, 1992; Kalix, 1991). Cathinone is more potent than cathine some 7–10 times and both are activator for central nervous system (Griffiths et al., 2010; Pennings, Opperhuizen, & van Amsterdam, 2008; Al-Hebshi & Skaug, 2005). Therefore, the ergogenic effects are believed to be caused by central and peripheral actions. It is not possible to separate central and peripheral effects in the experiments described in this article. It is most likely that the reaction time changes are due to central actions on alertness but the effects on heart rate could be due to a mixture of central and peripheral actions.

Conclusion

This would be the first study to investigate the physiological and ergogenic effects of khat extract on healthy volunteers. The study results showed that the consumption of 45 g of khat leaves contributed to the increased SBP and DBP, while it reduced RT. On the other hand, this study found no significant effect on heart rate and grip strength. These findings showed that Khat use has an acute effect on some physiological variables. Therefore, these findings support the recent prohibition of cathinone by the World Anti-Doping Agency (WADA, 2016).

Study limitations

The main limitation of this study include: (1) we did it on healthy volunteers who are not using khat on regular bases. That is why we were able to measure the acute effects of khat use but not the chronic effect. (2) It was difficult to ask the volunteers to chew khat to simulate the khat session which was not accepted by the university as khat chewing is illegal in KSA although it is widely spread in Jazan region (Sheikh et al., 2014; Ageely, 2009). (3) We were unable to recruit female participants for cultural unacceptability and because the khat use among them in Jazan is much lower than among males (Sheikh et al., 2014). (4) We were unable to titrate the least dose to cause the physiologic effects and the least dose to tiger the ergogenic effect. These doses should be calculated, but it needs bigger sample size.

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Author contributions

MA is the principal investigator of the project, developed the protocol, participated in data acquisition, conducted the experiments, did the data analysis, and drafted the manuscript. KA participated in data collection, statistical analysis, and drafted the manuscript. RB enriched the protocol, provided guidance to the whole research process and critically reviewed the draft manuscript. MN assisted in statistical analysis, interpretation, and manuscript revision. AMH assisted in statistical analysis and manuscript revision. ME conducted the experiments, did the data analysis, and drafted the manuscript. This final article was read and approved by all authors.

Competing interests

None of the authors have any competing interests in the article.

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