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Association Between the Frequency of rs4680 *COMT* Polymorphism in Elite Iranian Male Athletes: An Experimental and *In Silico* Study

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A B S T R A C T

Introduction: The *COMT* gene, with its influence on motivation, emotions, stress tolerance, self-control, pain processing, perception, and neurodegeneration, may underpin variations in sports competition outcomes. Thus, this study aims to explore the frequency of the *COMT* gene rs4680 polymorphism in elite Iranian male athletes in the domains of basketball and wrestling.

Materials & Methods: A total of 60 wrestlers, 55 basketball players, and 60 non-athletes were included as subjects. Saliva samples were used for DNA extraction, and the Tetra ARMS PCR method was employed for genotype determination. The impact of mutations on mRNA second structure and *COMT* gene function was assessed using RNAsnp and PolyPhen-2 servers, respectively. SPSS22 software facilitated data analysis, with the chi-square test applied to evaluate genotype frequency.

Results: The study did not reveal any association between the *COMT* rs4680 polymorphism and elite wrestlers and basketball players. Significant differences in genotype distributions or allele frequencies were not observed among (1) wrestlers and basketball players; (2) wrestlers and non-athletes; (3) basketball players and non-athletes. However, further replication studies are warranted ($P < 0.05$).

Conclusion: No significant association was identified between the *COMT* rs4680 polymorphism and the elite status of wrestlers and basketball players in the studied population. Nevertheless, additional replication studies are imperative for a comprehensive understanding of these relationships.

Keywords: *COMT*, rs4680, polymorphism, elite athletes

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Introduction

An individual's physical performance is influenced by a multifaceted interplay of developmental, behavioral, environmental factors, and genetic background, with an estimated heritability of athlete status at around 66% (1-3). Genetic factors, including various gene variants affecting power, strength, endurance, and other traits, are recognized as significant contributors to physical performance (1,4). However, often overlooked is the association between genetic polymorphisms and cognitive abilities such as motivation, stress tolerance, and self-control (5,6).

The midbrain dopaminergic system, a principal regulator of cognitive abilities, plays a crucial role in the development of fatigue during exercise, influencing motor control, thermoregulation, motivation, and the reward system (7, 8). Studies have confirmed an association between dopamine system genes and physical activity-related behaviors (9). Specifically, the catechol-O-methyl transferase (*COMT*) gene has been implicated in individual differences in cognitive abilities, potentially influencing remarkable achievements in professional sports and everyday physical activity (5). However, the role of *COMT* in the development of physical performance across diverse populations remains underexplored, necessitating additional replication studies.

The human *COMT* gene, located on chromosome 22q11.21, encodes the catechol-O-methyl transferase enzyme, a key regulator of dopaminergic and adrenergic neurotransmission (12). The rs4680 polymorphism generates multiple gene transcription forms, resulting in high (Val/Val), medium (Val/Met), or low (Met/Met) expression, leading to a 3 to 4-fold difference in enzyme activity (13, 14). *COMT*'s involvement extends beyond neurotransmission regulation, impacting diseases, neuropsychiatric disorders, neurobiology, cognitive characteristics, emotions, behavior, sleep regulation, pain processing, perception, addiction, and neurodegeneration (5).

The A allele of the *COMT* gene, associated with the amino acid methionine, decreases enzyme activity, elevating dopamine levels and enhancing cognitive abilities and sports performance (1). In contrast, the G allele decreases dopamine levels, influencing cognitive flexibility and executive control in aerobic sports (5, 16). The Val158Met polymorphism (rs4680), resulting from a guanine-to-adenine change, further modulates enzyme activity and dopamine levels, with the A allele linked to improved performance in specific sports (5, 10). This polymorphism has shown positive associations with Iranian martial arts performance and Asian swimmers (10).

Given the pivotal role of the dopamine system and its inhibitors in regulating cognitive abilities, potentially influencing elite athlete potential, this study aimed to investigate the frequency of the *COMT* rs4680 polymorphism among elite wrestlers and basketball players (17). However, comprehensive studies in this field are warranted to deepen our understanding of these relationships.

Materials and Methods

Study Population

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The study comprised 175 volunteers, including 60 wrestlers, 55 basketball players, and 60 non-athletes, all finalists in the Iranian National Championships. Notably, three participants had Olympic Games experience, and 23 had competed in the Asian Championships or World Championships. The demographic information of these athletes is shown in Table 1. Ethical approval (Ethical Approval Code: IR.SSRC.REC.1402.132) was obtained from the Institutional Review Board/Independent Ethics Committee of Tehran Physical Training School, Iran. All participants provided informed consent.

Table 1. Body Composition Description (Mean ± Standard Deviation) for Non-Athletes, Basketball Players, and Wrestlers

Variables	Wrestlers	Basketball Players	Non-Athletes
Age (years)	24.07±1.98	22.95±2.78	23.43±2.78
Height (meters)	1.75±0.064	1.92±0.061	1.84±0.111
Weight (kg)	73.21±15.28	88.90±3.80	80.51±15.19
Body Mass Index (BMI)	23.65±3.20	23.41±1.27	22.76±2.28

DNA Extraction and Genotyping of BDNF SNP

Saliva samples (~5 mL) were collected from elite athletes before morning training and processed using a Genomic DNA Extraction Kit (Biot Elixir Futuristic, Iran). DNA concentration and purity were assessed with a NanoDrop® ND-1000 UV-Vis Spectrophotometer (Thermo Fisher Scientific™, Waltham, MA, USA). Genotyping of the *COMT* rs4680 SNP was performed using the polymerase chain reaction (PCR)-Tetra ARMS PCR method. The specific primer sequences are detailed in Table 2. PCR amplification was conducted on an Applied Biosystems™ Thermal Cycler (Thermo Fisher Scientific, Waltham, MA, USA) with cycling conditions as described. Electrophoresis on a 2% agarose gel visualized the amplified DNA segments, and genotypes were determined.

Table 2. Primer Specifications in the Study

Gene	Primer sequence (5'→ 3')	Product Length (bp)
COMT (Catechol-O-methyltransferase)	F- CCAACCCTGCACAGGCAAGAT R- CAAGGGTGACCTGGAACAGCG	G allele: 626, 222
	F- CGGATGGTGGATTTCGCTGACG R- TCAGGCATGCACACCTTGTCCTTTAT	A allele: 626, 451

Statistical Analysis

IBM SPSS Statistics, Version 22.0, was employed for statistical analysis, considering $P \leq 0.05$ as statistically significant. Descriptive statistics represented quantitative variables as means ± standard deviations. The Hardy-Weinberg Equilibrium (HWE) for *COMT* SNP was assessed using the Chi-square test. Logistic regression

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analysis under three genetic models evaluated the association of *COMT* rs4680 SNP with physical performance, presenting odds ratios (OR) and corresponding 95% confidence intervals (95% CI). The impact of amino acid substitution on protein function was analyzed using Polyphen-2. Genotype frequencies were assessed with the chi-square test.

Results

Association of COMT SNP with Physical Performance in Iranian Elite Male Wrestlers and Basketball Players

This study investigated the frequency of alleles and genotypes of the *COMT* gene polymorphism among elite male wrestlers and basketball players compared to non-athletes. Figure 1 represents the PCR products for the COMT gene. Statistical analyses presented in Table 3 revealed no significant differences in genotype frequencies (GG, GA, AA) and the A allele between elite wrestlers and basketball players (P=0.989). Similarly, Table 4 indicated no significant distinctions in genotype frequencies between elite wrestlers and non-athletes (P=0.119), and Table 5 demonstrated no significant differences between elite basketball players and non-athletes (P=0.138).

Comment [11]: Figure 1 represents the PCR products for the *COMT* gene.

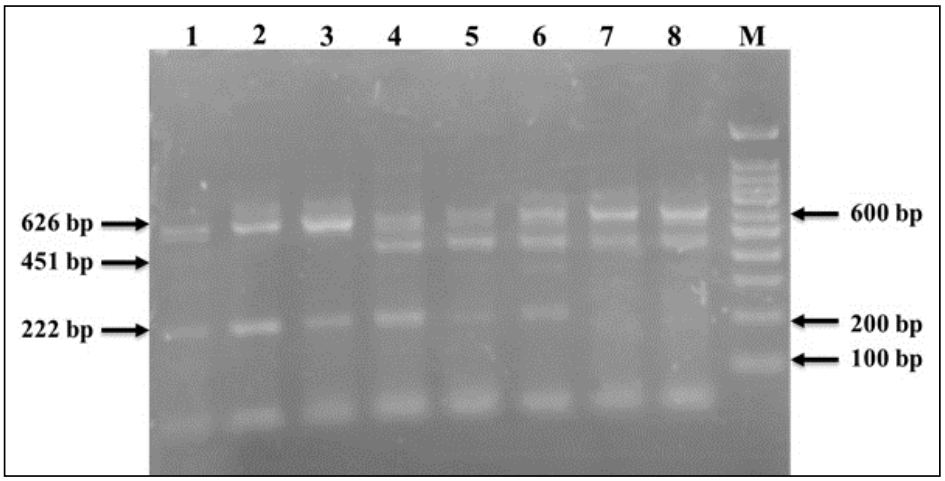


Figure 1. Representative Agarose Gel Electrophoresis of PCR Products for *COMT* Gene. Lanes 1,2,3: GG genotype (626, 222bp), Lanes 4, 5, 6: GA genotype (626, 222, 451bp) and Lanes 7,8: AA genotype (626,451bp). M Lane: 100 bp DNA Ladder

Table 3. Comparison of Allelic and Genotypic Frequency of *COMT* Gene Polymorphism Between Elite Wrestlers and Basketball Players

Genotype/ allele (*COMT* rs4680 G/A Polymorphism)	Basketball players N (%)	Wrestlers N (%)	OR (95% CI)	P- value
GG	29 (52.37)	32 (53.33)	1.000	0.98
GA	19 (34.54)	20 (33.33)	0.95 (0.426 – 2.13)	0.535

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AA	7 (12.73)	8 (13.33)	1.03 (0.33 – 3.12)	0.590
A	33 (/30.00)	36 (30.00)	1 (0.56-1.75)	0.556
Genetic comparison				
Dominant (GG vs. GA+AA)	-	-	0.750 (0.304 - 1.846)	0.532
Recessive (GG+GA vs. AA)	-	-	1.576 (0.350 - 7.095)	0.714

OR: Odd ratio, CI: Confidence interval

Table 4. Comparison of Allelic and Genotypic Frequencies of *COMT* Gene Polymorphism Between Elite Wrestlers and Non-Athletes

Genotype/ allele (*COMT* rs4680 G/A Polymorphism)	Wrestlers N (%)	Non- Athletes N (%)	OR (95% CI)	P- value
GG	32 (53.33)	21 (35.00)	1.000	0.119
GA	20 (33.33)	26 (43.33)	(0.888 – 4.416) 1.981	0.069
AA	8 (13.33)	13 (21.66)	2.47(0.87 – 6.99)	0.071
A	36 (30.00)	52 (43.33)	1.78(1.048-3.036)	0.061
Genetic comparison				
Dominant (GG vs. GA+AA)	-	-	0.601 (0.264 - 1.359)	0.290
Recessive (GG+GA vs. AA)	-	-	1.156 (0.272 - 4.898)	1.000

OR: Odd ratio, CI: Confidence interval

Table 5. Comparison of Allelic and Genotypic Frequencies of *COMT* Gene Polymorphism Between Elite Basketball players and Non-Athletes

Genotype/ allele (*COMT* rs4680 G/A Polymorphism)	Basketball Players N (%)	Non- Athletes N (%)	OR (95% CI)	P- value
GG	29 (52.37)	21 (35.00)	1.000	0.138
GA	19 (34.54)	26 (43.33)	(0.835 – 4.272) 1.881	0.091
AA	7 (12.73)	13 (21.66)	2.56(0.873 – 7.52)	0.069
A	33 (/30.00)	52 (43.33)	1.78(1.035-3.076)	0.073
Genetic comparison				
Dominant (GG vs. GA+AA)	-	-	0.801 (0.350 - 1.825)	0.672
Recessive (GG+GA vs. AA)	-	-	0.693 (0.198 - 2.431)	0.744

OR: Odd ratio, CI: Confidence interval

The findings of this study lead to the conclusion that *COMT* SNP gene genotypes do not confer a specific advantage for achieving elite status in wrestling and basketball. To further understand the molecular implications, the study utilized the RanSnp server and PolyPhen-2. Figure 2 illustrates the mRNA structure with nucleoside G present in the DNA molecule, while Figure 3 depicts the state where nucleoside G is replaced by nucleoside A. A comparative analysis of these structures suggests that the *COMT* rs4680 mutation induces a change in the mRNA's secondary structure. This alteration can potentially impact the *COMT*

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gene's expression level and mRNA stability, influencing the development of a functional system suitable for athletes

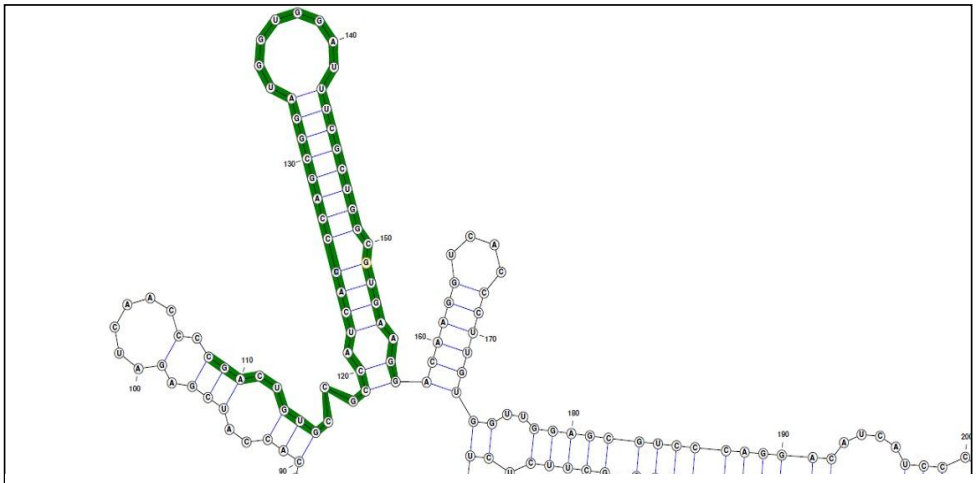


Figure 2. RNAsnp Analysis of *COMT* rs4680 (158G>A SNP in Wild-Type). The mRNA structure corresponding to the wild-type state (nucleoside G present in the DNA molecule) of the *COMT* rs4680

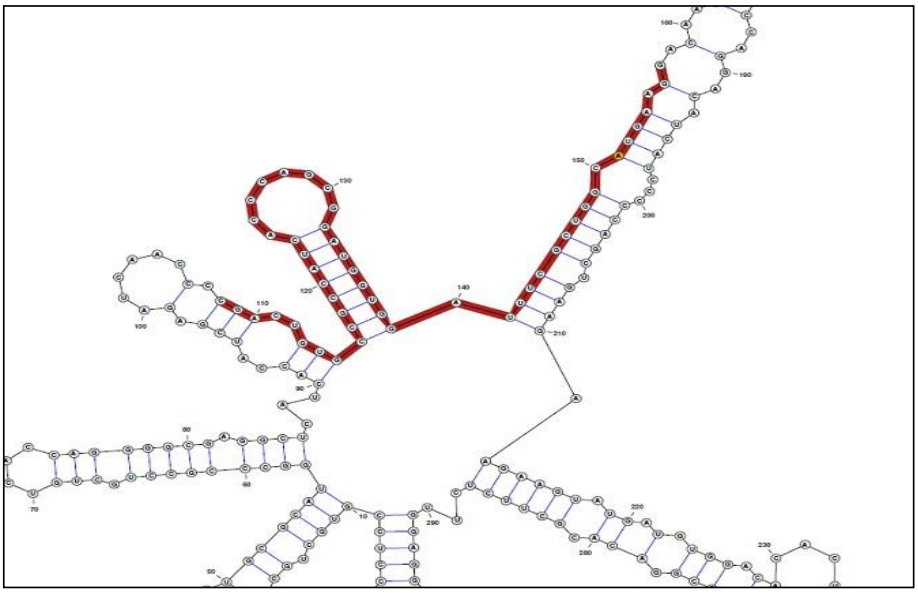


Figure 3. RNAsnp Analysis of *COMT* rs4680. Secondary RNA structure (158G>A SNP in Mutant), illustrating the state where nucleoside G is replaced by nucleoside A

Figure 4 delves into the investigation of replacing methionine with valine at position 158 on protein function using the online server PolyPhen-2.

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According to Figure 4, the *COMT* rs4680 mutation demonstrates no discernible effect on protein function

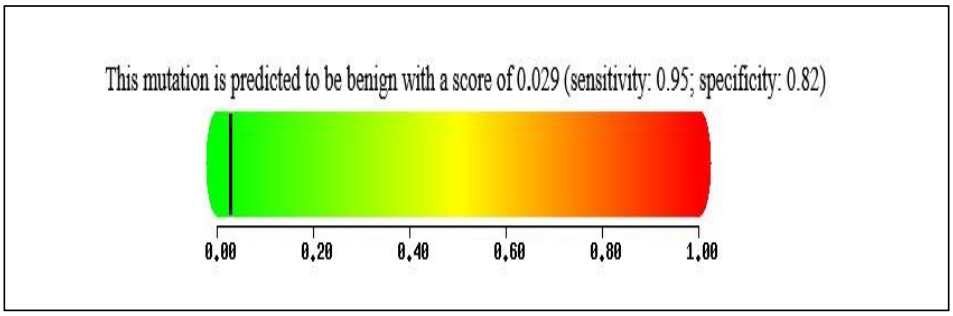


Figure 4. PolyPhen-2 Analysis of *COMT* rs4680 SNP. PolyPhen-2 Predicts Mutation Impact on the *COMT* Protein Structure and Indicates No Effect on Protein Function.

Discussion

The present study was conducted with the aim of investigating the frequency of rs4680 polymorphism of the *COMT* gene in Iranian elite male athletes in wrestling and basketball. The main finding of this research was that in the non-athlete group, the frequency of allele A was higher than in the elite athlete group, and the elite athletes were not superior in any of the genotypes compared to the control group. These results show that the (RS4680) polymorphism of the *COMT* gene does not play a significant role in becoming an elite athlete in these two disciplines. Therefore, more studies are needed to prove the role of this polymorphism in elite wrestlers and basketball players.

Although, the athletic phenotype is complex and depends on a combination of many elements, such as environmental variables and experience (training and diet) and biological and genetic factors (18), But in our study, the genetic role of the *COMT* gene in the elite was not significant. The *COMT* gene is responsible for the degradation of catecholamines. This has been linked to genotypes associated with dopamine availability in the brain. *COMT* gene variants are engaged in a number of psychological roles, e.g., cognition, anxiety, and stress response (19). However, *COMT* gene results are controversial. In accordance with the present findings, Leźnicka et al. (20), no significant relationship ($p = 0.286$ and $p = 0.43$) between the *COMT* rs4680 GG genotype and elite martial arts athletes exists (20).

Piotr Zmijzewski et al. (2021) evaluated the relationship between the *COMT* Rs4680 polymorphism and the competitive performance of swimmers and reported that there was no evidence for the relationship between the *COMT* rs4680 polymorphism and the state of elite swimming athletes, and observed that no significant difference in genotypic or allelic distribution was observed between (1) male and female athletes (2) short and long-distance swimmers (3) all athletes and sedentary group (4). Recent studies have also shown that *COMT* is catabolized by estrogen and has a sex-dependent interaction with psychiatric characteristics, including psychological abilities, and personality traits (21). It has been shown that

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COMT gene expression in the frontal cortex of the brain (perifrontal) is more in men than in women (21).

In contrast to our findings, Tatar et al. (2020) demonstrated a significantly higher frequency of the GG (fighter) phenotype in combat sports athletes compared to the control group ($p = 0.003$) (22). Ferfer et al. (2023) investigated the relationship between *COMT* gene polymorphism. They observed that there is a significant relationship between elite and control groups, Val/Met genotype carriers, and Met allele carriers in the athletes' group. Professionals were more frequent. They suggested that athletes with Val/Met genotype frequency may achieve high status in combat sports (10). Another study performed on 75 participants undergoing 17 weeks of running training demonstrated that individuals with the Val/Val genotype showed superior executive control abilities after aerobic exercise training compared to the Met allele carriers. It was concluded that a rise in physical fitness causes improved cognitive functioning via dopaminergic modulation (23). Another study showed that the *COMT* Val genotype may be a novel genetic factor in sports that require aggressiveness under high-stress conditions. These findings indicate that environmental factors, such as stress conditions, and genetic factors affect athletic performance, thereby causing difficulty in identifying genes involved in the dopaminergic system that tend to elite athletic status (23).

The relatively high frequency of the *COMT* rs4680 polymorphism, together with its key role in regulating catecholamine catabolism, rapidly led to several efforts to establish its possible significance to a range of neuropsychiatric phenotypes (14). The amino acid change (Met → Val substitution at codon 158) makes the enzyme susceptible to distortion of the active site and aggregation of polypeptide at physiological temperature, leading to a lower enzyme activity in Met allele carriers, whereas higher activity is observed in Val allele carriers (13). The Met/Met genotype gives a three- to four-fold decrease in *COMT* activity relative to the Val/Val genotype, with heterozygotes demonstrating medium activity (12). The frequency of the Met allele in diverse ethnic groups has ranged from 0.01 to 0.62, e.g., 0.49–0.54 in Caucasians, 0.49 in Southwest Asians, 0.18–0.3 in East Asians, and 0.03–0.04 in African Americans and Africans (12). Bilder et al. hypothesized that the Met allele leads to higher tonic DA levels and reciprocal decreases in phasic DA in subcortical regions and enhanced D1 receptor transmission cortically. This mechanism may give higher stability but lower flexibility to the neural network activation states that underlie significant aspects of working memory and executive functions. These effects may be advantageous or disadvantageous depending on the phenotype, as well as numerous endogenous and environmental factors (24). In the other study, the authors suggested that the chronic levels of physical activity, as seen in ultra-endurance athletes, show increased novelty-seeking in Met (158) homozygous allele carriers, supporting the hypothesis that there is an association between personality traits and *COMT* Val158Met (rs4680) genotype (25). The study of Lesinka et al. (2015) showed that the Val/Val homozygous genotype showed less sensitivity than the Val/Met heterozygous genotype and the Met/Met homozygous genotype (17).

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The animal experiments concerning the effect of physical activity on brain function demonstrated that exercise initiation leads to increased levels of serum calcium, which is transported to the brain, where it stimulates DA synthesis through a calmodulin-dependent system. Consequently, the higher DA levels regulate various brain functions (26). In contrast, the decrease in DA concentration which is observed as physical activity continues is probably due to the inhibitory effects of serotonin. The activity of the DA system is correlated with the development of fatigue through associated modulation circuits that are linked to thermoregulatory regulation, motor control, motivation and the reward system (7, 27). During exercise, a rise in DA system activity seems to impact tolerance to higher core temperatures before stopping exercise. This observation was confirmed by the administration of blockers of the D1 and D2 receptors, which resulted in impaired running performance by decreasing the tolerance to heat storage. The blockade also weakens the dissipation of exercise-induced heat and recovery of metabolic rate during the post-exercise period. Thus, the authors suggested that the DA system and its inhibitors are essential for heat balance and exercise performance (7, 28). However, in humans, the biological mechanisms underlying the improvement of cognitive abilities correlated with exercise-induced changes in the brain are still unclear and have not been comprehensively studied, though the DA system seems to play a key role (23).

Conclusion

The study found no evidence for an association between the *COMT* rs4680 polymorphism and elite wrestlers and basketball players. We did not observe significant differences in the genotype distributions or allele frequencies between (1) wrestlers and basketball players; (2) wrestlers and non-athletes; (3) basketball players and non-athletes. However, more replication studies are needed.

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Conflict of Interests

The authors affirm the absence of any conflict of interest.

Authors' Contributions

VT participated in sampling, laboratory work, and drafting the initial manuscript. MR conceptualized the work, provided scientific revisions to the manuscript, and contributed to the article's methodology. MF also contributed to laboratory work and statistical analysis.

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