

Effects of a Standardized Saffron Extract on Premenstrual Symptoms: An Open-Label, Exploratory, Real-World Consumer Study



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Submission: 14 April, 2026

Accepted: 05 May, 2026

Published: 08 May, 2026

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Keywords: Premenstrual syndrome; Women's health; *Crocus sativus*; Open study; Saffron extract

Abstract

Background: Premenstrual syndrome is a common cyclical condition characterized by emotional and physical symptoms that may affect daily functioning and quality of life. Because many women rely on analgesics to manage these symptoms, interest is growing in complementary approaches that may help support both psychological-related and physical complaints.

Objective: To assess the tolerability and perceived effects of a patented standardized saffron extract (Safr'Inside™) on premenstrual symptoms under real-life conditions.

Methods: An open-label, exploratory, real-world consumer study with medical oversight was conducted in California in women aged 20-45 years reporting recurrent premenstrual symptoms. Participants consumed one capsule containing 30 mg of a standardized saffron extract during a 10-day perimenstrual window over two consecutive cycles. PMS-related symptoms were assessed at baseline and after each supplemented cycle using an identical structured questionnaire (Q0, Q1 and Q2). The questionnaire captured 16 psychological and physical symptoms rated on a 0-10 Visual Analogue Scale (VAS), as well as treatment use, satisfaction, tolerability, and compliance.

Results: Across both supplemented cycles, Safr'Inside™ use was associated with self-reported improvements in emotional and physical symptoms. Participants reported improvements in both psychological-related outcomes (including quality of life impact, emotional imbalance, irritability, and nervousness) and physical symptoms (including appetite changes, digestive discomfort, physical fatigue, and water retention). Compliance was high and no adverse effects were reported.

Conclusions: In this open-label, exploratory, real-world consumer study, 10-day supplementation with a standardized saffron extract, administered 5 days before the onset of menstruation, was associated with self-reported improvements in both emotional and physical premenstrual symptoms under everyday conditions. These findings should be interpreted cautiously and considered as preliminary complementary real-world evidence.

List of abbreviations

EFSA: European Food Safety Authority; 5-HIAA: 5-Hydroxyindoleacetic Acid; PMDD: Premenstrual Dysphoric Disorder; PMS: Premenstrual Syndrome; SERT: Serotonin Transporter; SSRI: Selective Serotonin Reuptake Inhibitor; UHPLC: Ultra-High-Performance Liquid Chromatography; UV: Ultraviolet; VAS: Visual Analogue Scale.

Introduction

Premenstrual syndrome (PMS) is a common cyclical condition characterized by the recurrence of emotional and physical symptoms during the late luteal phase of the menstrual cycle, typically resolving with the onset of menstruation or shortly thereafter [1]. Symptom onset generally occurs within the 2 to 7 days preceding menses, although in some women symptoms may begin earlier, up to approximately 14 days before menstruation. PMS encompasses a broad spectrum of manifestations that vary in intensity and may

substantially affect daily functioning and quality of life. In its most severe form, symptoms may meet criteria for premenstrual dysphoric disorder (PMDD), a condition associated with marked distress and functional impairment.

Premenstrual symptoms are highly prevalent worldwide. It has been estimated that 70% to 90% of women of reproductive age experience at least some premenstrual symptoms, while 20% to 40% report symptoms sufficiently bothersome to interfere with daily activities. PMDD is estimated to affect approximately 3% to 8% of women [1]. In the United States, up to three out of four women report having experienced PMS symptoms at some point in their lives, highlighting the broad relevance of this condition in routine practice [2]. PMS symptomatology is heterogeneous and includes both psychological and physical manifestations, such as irritability, emotional lability, anxiety, headaches, abdominal cramps, breast tenderness, fatigue, digestive discomfort, and changes in appetite or eating behavior. Consistent with this multidimensional presentation, an online quantitative study conducted in France in 2022 among

146 women reporting PMS found that 98% experienced physical symptoms and 97% psychological symptoms, with abdominal pain, fatigue, emotional swings, and lack of energy among the most frequently reported complaints [3].

Given the frequency and multidimensional nature of PMS, symptom management often relies on repeated use of conventional treatments, particularly analgesics for pain-related symptoms. However, recurrent use of such medications may raise tolerability concerns in some women. Self-medication with painkillers for PMS-related symptoms is common, and survey data indicate substantial rates of analgesic use among women experiencing premenstrual discomfort. In parallel, selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine, have demonstrated efficacy for both psychological and physical symptoms of PMS and may act rapidly in this context, sometimes within days. Together, these observations support the relevance of serotonergic pathways in PMS and underscore the interest of complementary, well-tolerated, non-pharmacological approaches that may be suitable for recurrent use and broader symptom management [4-7].

The pathophysiology of PMS is considered multifactorial, with converging evidence implicating ovarian hormone fluctuations and downstream modulation of neurotransmission systems involved in mood regulation, particularly the serotonergic pathway. PMS is closely linked to ovulatory cycles and appears to emerge during the late luteal phase, when progesterone and estrogen levels decline in the absence of pregnancy [8].

Estrogen has been described as supporting serotonergic neurotransmission through modulation of serotonin synthesis, receptor signaling, reuptake, and degradation. Consequently, the late-luteal decline in estrogen may contribute to serotonergic vulnerability and to the emergence of emotional symptoms such as irritability, anxiety, emotional instability, and sleep disturbances (Figure 1) [9]. This mechanistic framework is further supported by observations in PMDD, where increased serotonin transporter (SERT) activity near menstruation has been proposed as one contributor to reduced synaptic serotonin availability and symptom exacerbation. Beyond mood regulation, serotonin also contributes to pain modulation, suggesting that altered serotonergic signaling may be involved not only in the emotional manifestations of PMS, but also in its physical symptom dimension. In addition to hormonal and

neurochemical factors, other contributors such as stress, smoking, and nutritional or dietary factors may further influence symptom expression, reinforcing the multifactorial nature of PMS and the need for multidimensional management strategies [10,11].

In this context, saffron (*Crocus sativus* L.) has attracted increasing scientific interest as a potential nutraceutical approach for emotion- and stress-related conditions. Its main bioactive compounds, notably crocins and safranal, have been associated with effects on neurotransmission pathways involved in emotional regulation, including possible interactions with the serotonergic system, as well as antioxidant and anti-inflammatory activities. This multimodal profile is of interest in PMS, where psychological and physical symptoms coexist [12-14].

Several randomized, double-blind, placebo-controlled studies have reported improvements in both psychological and physical symptoms following saffron supplementation. In one trial including 50 women aged 20-45 years, supplementation with 30 mg/day of saffron extract (2% safranal, UV) for two months significantly improved both physical and emotional symptoms from the first month onward. After two months, PMS severity was reduced by at least 50% in 76% of supplemented participants, and depressive symptoms decreased by at least 50% in 60% [15]. A second randomized, double-blind, placebo-controlled trial in 78 women aged 18-35 years using the same daily dose for two months also reported significant improvements in PMS severity and symptom dimensions compared with placebo [16]. Finally, a third randomized, double-blind, placebo-controlled study investigated saffron's volatile fraction in 35 women aged 19-26 years. Participants were exposed to saffron stigma oil odor for 20 minutes, resulting in a significant reduction in salivary cortisol. These findings support a possible role of saffron volatiles, largely attributed to safranal, in stress-related and emotional outcomes [17]. Mechanistically, safranal has been described as a potential modulator of serotonin reuptake, while crocin may interact with other monoaminergic pathways, providing biological plausibility for the observed clinical effects [18]. Furthermore, *ex vivo* data suggest that Safr'Inside™ may modulate serotonin-related pathways under stress-related conditions [19].

Although these controlled studies support the potential of saffron for the management of premenstrual symptoms, additional data obtained with a well-characterized and standardized saffron extract may help further document its use in this setting. Complementary evidence generated under real-world conditions may also be informative, particularly regarding adherence, tolerability, perceived symptom evolution, and acceptability in routine use. Such data are of interest given that PMS is commonly managed through everyday self-care strategies and that dietary supplement use is widespread, particularly among women in the United States [2].

The aim of this open-label, exploratory, real-world consumer study with medical oversight was therefore to evaluate the tolerability and self-reported effects of Safr'Inside™, a standardized saffron extract (0.2% safranal, 3% crocins, analyzed by HPLC, and 12% saframotivines analyzed by UV), in women experiencing recurrent premenstrual symptoms, by documenting changes in psychological and physical symptom dimensions across two consecutive supplemented menstrual cycles under real-life conditions.

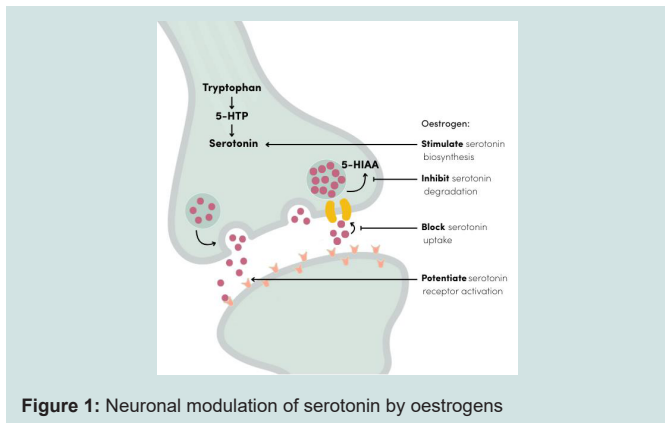


Figure 1: Neuronal modulation of serotonin by oestrogens

Materials and methods

Study design and participants

This open-label, exploratory, real-world consumer study with medical oversight was conducted in California (USA) in 40 women reporting premenstrual symptoms. The study aimed to evaluate the tolerability and self-reported effects of a standardized saffron extract consumed during a targeted 10-day perimenstrual window over two consecutive menstrual cycles.

No formal sample size calculation was performed, as this was an exploratory consumer-use study intended to generate preliminary descriptive real-world data on tolerability, acceptability, and self-reported symptom evolution. A sample of 40 participants was considered appropriate for the exploratory objectives of the study.

The study population consisted of American women aged 20 to 45 years (mean age 33), with a balanced distribution between the 20-33 and 34-45 age groups. Inclusion required a baseline PMS-related discomfort score $\geq 4/10$ and a baseline PMS-related pain score $\geq 3/10$ on a VAS, as well as written informed consent prior to participation. Women who were pregnant or breastfeeding, who had given birth within the previous year, who reported endometriosis, who were perimenopausal or menopausal, or who has used PMS-targeted products (dietary supplements, medications, antispasmodics, anti-inflammatory, etc) within 30 days prior to baseline assessment were not eligible.

Intervention

The intervention consisted of one daily capsule providing 30 mg of Safr'Inside™, a full-spectrum standardized saffron extract (*Crocus sativus L.*) developed by Activ'Inside (Beychac-et-Caillau, France). This saffron extract is produced according to patent WO2018/020013A1 and is standardized to contain $>3\%$ crocins and $>0.2\%$ safranal, quantified by UHPLC. Participants consumed the supplement over two consecutive menstrual cycles, during a 10-day peri-menstrual period in each cycle, from five days before menstruation onset to five days after menstruation onset (Figure 2).

Evaluation protocol

PMS-related symptoms were assessed using a structured online questionnaire developed by a gynecologist and intended as a pragmatic, non-validated tool to capture the consumer experience under real-world conditions. Evaluations were performed at

three time points: baseline (Q0, before supplementation), after the first supplemented menstrual cycle (Q1), and after the second supplemented cycle (Q2) (Figure 2).

The same questionnaire was administered at Q0, Q1, and Q2. It was designed to capture the most common and clinically relevant manifestations of PMS encountered in routine gynecological practice. It included items related to symptom-management behaviors, as well as psychological and physical symptom domains.

At each time point, participants rated 16 PMS-related symptoms on a 0-10 Visual Analogue Scale (VAS), where 0 corresponded to the absence of the symptom and 10 to the highest perceived intensity/frequency depending on the item. The 16 items were: impact of PMS on quality of life, stress, nervousness, emotional imbalance, sensitivity, irritability, lack of enthusiasm, menstrual pain, appetite changes, physical fatigue, breast discomfort, muscle discomfort, digestive discomfort, weight gain, water retention, and headache. No global score was calculated. Improvement was defined as a lower score compared with Q0.

All questionnaire data were reviewed and interpreted by the medical assessor.

The baseline questionnaire (Q0) was sent on Day 0 (D0) and asked participants to retrospectively report PMS symptoms experienced during unsupplemented menstrual cycles preceding study entry. As a result, Q0 reflects recalled pre-intervention symptom experience rather than prospectively recorded baseline data. Responses were collected again after the first supplemented cycle (Q1) and after the second supplemented cycle (Q2), allowing within-subject comparison over time.

Statistical analysis

No formal statistical analysis was performed. Only descriptive summary measures were planned for this exploratory study. No inferential analyses were performed. Measures of dispersion were not available for reporting in the present manuscript, which limits the reader's ability to assess inter-individual variability in symptom ratings. Given the exploratory and descriptive nature of this open-label real-world study, results were summarized using mean scores, percentage changes versus baseline, and proportions of participants reporting improvement. No hypothesis-testing framework was pre-specified, and no imputation procedure was applied for missing data.

Satisfaction, tolerability and compliance

At the end of the study, participants completed an acceptability questionnaire regarding perceived changes in their menstrual cycles and premenstrual symptoms and reported on ease of use, tolerability, and compliance.

Results

Psychological outcomes

Participants rated psychological symptoms on a 0-10 Visual

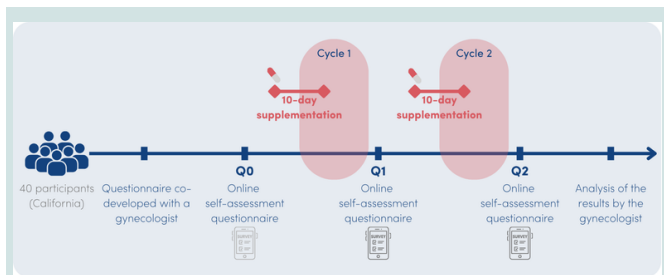


Figure 2: Design of the real-world study

Analogue Scale (VAS) at Q0, Q1, and Q2. Mean ratings and percentage changes versus baseline are presented in (Table 1).

The proportion of participants reporting improvement versus baseline at Q2 was high for several psychological outcomes, including emotional imbalance (95%), irritability (95%), nervousness (85%), and sensitiveness (85%). These findings suggest a consistent pattern of perceived improvement across psychological domains (Figure 3).

Physical outcomes

Using the same 0-10 scale at Q0, Q1, and Q2, participants also rated physical symptoms. Mean ratings and percentage changes versus baseline are presented in (Table 2).

At Q2, a high proportion of participants reported improvement versus baseline for several physical outcomes, including water retention (100%), digestive discomfort (100%), physical fatigue (95%), menstrual pain (83%), and breast discomfort (60%). This pattern suggests perceived improvement across multiple somatic symptoms (Figure 4).

At baseline, mean scores for psychological symptoms ranged from 6.9 to 8.0 out of 10, indicating a moderate-to-high self-reported symptom burden.

After the first supplemented cycle (Q1), mean scores were lower than baseline across all psychological items, suggesting an early favorable trend. After two supplemented cycles (Q2), mean scores decreased further, ranging from 5.3 to 6.6 out of 10. The largest relative reductions were observed for emotional imbalance (-32.1%), irritability (-30.0%), sensitivity (-25.6%), and nervousness (-23.7%).

Table 1: Self-reported ratings of psychological symptoms across the study period and percentage change vs. baseline.

Psychological symptoms	Mean score /10			% change vs Q0	
	Q0	Q1	Q2	Q1	Q2
Impact of PMS on quality of life	7.7	7.2	6.6	-6.49%	-14.29%
Stress	6.9	6.6	5.8	-4.35%	-15.94%
Nervousness	7.6	7.3	5.8	-3.95%	-23.68%
Emotional imbalance	7.8	7.4	5.3	-5.13%	-32.05%
Sensitivity	7.8	7.3	5.8	-6.41%	-25.64%
Irritability	8	7.5	5.6	-6.25%	-30%
Lack of enthusiasm	7.5	6.9	5.9	-8%	-21.33%

Table 2: Self-reported ratings of physical symptoms across the study period and percentage change vs. baseline.

Physical symptoms	Mean score /10			% change vs Q0	
	Q0	Q1	Q2	Q1	Q2
Menstrual pain	8.1	7.6	6.7	-6.17%	-17.28%
Appetite changes	8	6.5	5.8	-18.75%	-27.5%
Physical fatigue	7.3	6.9	5.6	-5.48%	-23.29%
Breast discomfort	7.7	7.4	6.6	-3.9%	-14.29%
Weight gain	7.7	7.4	6	-3.9%	-22.08%
Water retention	8	7.7	6.6	-3.75%	-17.5%
Headache	6.8	6.3	5.4	-7.35%	-20.59%
Muscle discomfort	8.1	7.6	6.9	-6.17%	-14.81%
Digestive discomfort	8.3	7.9	6.3	-4.82%	-24.1%

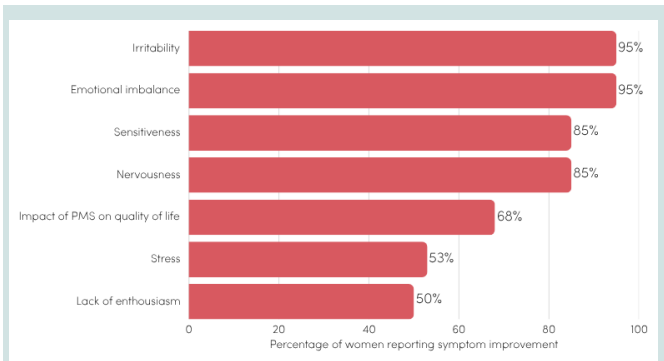


Figure 3: Proportion of participants reporting improvement in emotional symptoms of PMS after two supplemented cycles vs. baseline

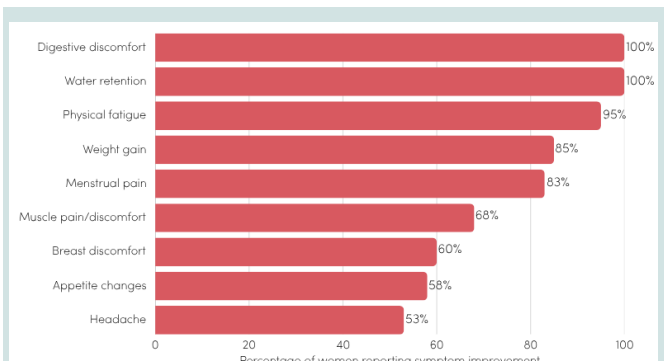


Figure 4: Proportion of participants reporting improvement in physical symptoms of PMS after two supplemented cycles vs. baseline

At baseline, mean scores for physical symptoms ranged from 6.8 to 8.3 out of 10, indicating a high self-reported symptom burden.

After the first supplemented cycle (Q1), mean scores were lower than baseline for all physical items, suggesting an early favorable trend. After two supplemented cycles (Q2), mean scores ranged from 5.4 to 6.9 out of 10. The largest relative reductions were observed for appetite changes (-27.5%), digestive discomfort (-24.1%), physical fatigue (-23.3%), weight gain (-22.1%), and headache (-20.6%).

Participant satisfaction and acceptability

In addition to symptom-related outcomes, qualitative questions were used to document participant satisfaction, perceived usability, and acceptability of Safr'Inside™ under real-world conditions.

Most participants reported a positive overall experience with the supplement, together with favorable perceptions of usability and acceptability. These findings are presented as supportive secondary observations rather than efficacy outcomes. Notably, 90% of participants reported a rapid onset of action, with noticeable benefits perceived within an average of four days of use.

Tolerability and compliance

Compliance was high throughout both intervention cycles: 95% of participants reported taking the supplement in full without missing

any doses, while 5% reported missing 2 to 3 doses. No side effects were reported during the study, supporting the product's safety and tolerability.

Discussion

This open-label, exploratory, real-world consumer study with medical oversight conducted over two consecutive menstrual cycles suggests that daily supplementation with a standardized saffron extract (Safr'Inside™), administered during a targeted 10-day perimenstrual window, was associated with self-reported improvements in both psychological and physical premenstrual symptoms under everyday conditions.

These observations are directionally consistent with previous randomized, placebo-controlled clinical studies in women with PMS, in which oral supplementation with 30 mg/day of saffron extract administered continuously over two menstrual cycles was associated with improvements in both psychological and physical symptoms. However, direct comparison should remain cautious given the important differences in study design, population, assessment tools, and supplementation regimen.

From a biological perspective, these self-reported improvements are compatible with current understanding of PMS pathophysiology and with the known properties of saffron bioactives. PMS has been linked to cyclical changes in ovarian hormone levels, which may influence serotonergic neurotransmission and thereby contribute to emotional symptoms such as irritability, mood instability, stress sensitivity, and nervousness.

Additional mechanistic plausibility comes from an *ex vivo* clinical approach performed with Safr'Inside™, in which serum collected after intake of the extract attenuated stress-induced changes in serotonin-related markers in a human neuron culture model, including serotonin release, serotonin transporter expression, and 5-HIAA levels [19]. While such *ex vivo* findings cannot be directly extrapolated to clinical efficacy, they support the hypothesis that circulating metabolites derived from Safr'Inside™ may help preserve serotonergic tone under stress-related conditions. In the context of PMS, where altered serotonergic regulation and stress reactivity have both been implicated in emotional symptom expression, these findings are biologically consistent with the improvements reported here, particularly in psychological symptom domains.

This serotonergic hypothesis may also be relevant, at least in part, to the physical symptom improvements observed in the present study. Beyond its role in mood regulation, serotonin is also involved in nociceptive processing, with effects that vary according to receptor subtype, anatomical level, and pain context [10]. Because saffron has been proposed to influence serotonergic signaling, including pathways related to serotonin reuptake, it is plausible that some of the observed improvements in pain-related symptoms may reflect, indirectly, modulation of serotonin-related mechanisms. However, this interpretation remains hypothetical and was not specifically assessed in the present study.

This study was specifically designed to evaluate outcomes under real-life conditions, with minimal disruption to participants' usual

dietary and lifestyle habits. Such an approach enhances ecological validity and provides insight into how supplementation may be perceived and used in everyday settings. It should not, however, be considered as providing the same level of evidence as a randomized controlled trial.

Several important methodological limitations should nevertheless be acknowledged. First, the study used an open-label, non-controlled design, and therefore expectancy effects and natural cycle-to-cycle symptom variability may have contributed to the observed changes. Second, the sample size was limited. Third, the baseline assessment (Q0) was retrospective, whereas follow-up assessments referred to prospectively experienced supplemented cycles; therefore, recall bias may have inflated baseline symptom burden and amplified the apparent magnitude of change. Fourth, symptom evaluation relied on a pragmatic questionnaire that was not formally validated, although it was developed by a gynecologist to reflect common and clinically relevant PMS manifestations encountered in practice. Finally, no formal statistical analysis was performed in this exploratory study. Results are therefore presented descriptively as mean scores, percentage changes versus baseline, and proportions of participants reporting improvement. Accordingly, the findings should be interpreted as preliminary real-world observations rather than confirmatory evidence.

Conclusion

In conclusion, this open-label, exploratory, real-world consumer study conducted in California suggests that supplementation with Safr'Inside™, a standardized saffron extract, taken once daily during a targeted 10-day perimenstrual window over two consecutive cycles, was associated with self-reported improvements in psychological and physical premenstrual symptoms under everyday conditions.

Because baseline symptoms were retrospectively recalled and no control group was included, the magnitude of the observed changes should be interpreted cautiously.

Overall, these findings provide complementary preliminary real-world evidence that is directionally consistent with previously published randomized, placebo-controlled trials of saffron supplementation, while remaining distinct in design and evidentiary strength.

Future studies should confirm these observations in randomized, double-blind, placebo-controlled designs using validated PMS instruments and prospective symptom tracking across multiple cycles.

Acknowledgements

The authors thank the participants for their time and cooperation.

Funding

This study was funded by Activ'Inside (Beychac-et-Caillau, France), the developer of Safr'Inside™. The sponsor provided the study material and covered operational costs but had no role in data collection, statistical analysis or interpretation of the results.

Conflicts of interest

All authors are full-time employees of Activ'Inside, the company that developed the product tested in this study. This affiliation did not influence the objectivity of the research or the interpretation of the results.

Ethics approval and consent to participate

This interventional study was based on the voluntary use of a food supplement for 10 days during two menstrual cycles. All participants provided informed consent before inclusion. In accordance with the non-pharmacological and real-world nature of the study, no formal ethics committee approval was obtained.

Availability of data and materials

All relevant data supporting the conclusions of this study are presented in this article.

Authors' contributions

E.A. and I.G. contributed to the development of the study protocol, supervised the study, performed data analysis and interpretation, and were involved in manuscript writing. M.J. contributed to its critical revision, and approved the final version for publication.

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