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Research Article

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Anxiolytic and Potential Neurotoxic Effects of *Salvia hypoleuca* in Mice

Marjan Talebi[a], Reyhaneh Alinejad[a], Nima Naderi[b], Faraz Mojab[a,c*]

[a] *Department of Pharmacognosy, School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran.*
[b] *Department of Toxicology and Pharmacology, School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran.*
[c] *Pharmaceutical Sciences Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran.*

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Abstract

Anxiety disorders are prevalent worldwide, significantly impacting various aspects of patients' lives. The use of *Salvia* species in ethnobotanical medicine has been well documented, with applications as diuretics, analgesics, anti-hyperhidrosis agents, laxatives, antipyretics, and antitussives. Among these, *Salvia hypoleuca*, an endemic plant in Iran, is recognized for its tonic, carminative, digestive, antispasmodic, anti-inflammatory, antioxidant, antimicrobial, and anti-nociceptive properties. The objectives of this study were to assess the anxiolytic effects of *S. hypoleuca* ethanolic extract and its potential neurotoxicity using established pharmacological models in mice. Animals were randomly allocated into five groups: one control group, three groups underwent treatment that received oral doses of *S. hypoleuca* at 30, 100, and 300 mg/kg, and a positive control group given diazepam at 10 mg/kg. Behavioral evaluations were performed using the light/dark test (LDT) and the elevated plus maze (EPM) tests. To evaluate potential neurotoxic effects, open-field and rotarod tests were also performed. The results specified that *S. hypoleuca* extract at doses of 30 and 100 mg/kg significantly enhanced entries and time spent in the open arms of the EPM, suggesting anxiolytic effects. In the LDT, the 30 mg/kg dose notably increased the time spent in the light box. However, the rotarod test showed a slight decrease in latency to fall at both 30 and 300 mg/kg doses, indicating possible motor impairment at higher concentrations. Open-field analysis revealed significant reductions in total distance moved and velocity at 30 and 300 mg/kg doses, suggesting potential locomotor suppression.

Additionally, the total phenolic and total flavonoid contents of *S. hypoleuca* ethanolic extract were measured as 47.26 ± 2.87mg GAE/g DW and 31.73 ± 5.38 mgRE/g DW, respectively. In conclusion, our efforts suggest that oral administration of *S. hypoleuca* extract exhibits anxiolytic effects in mice, as demonstrated by improved performance in the EPM and LDT. However, the observed locomotor impairment at higher doses warrants further investigation to determine the optimal therapeutic dose and potential safety concerns.

Keywords: Anxiety; Flavonoids; Neurotoxicity; Phenolic compounds; Phytochemicals; Plant extract; *Salvia hypoleuca*.

1. Introduction

Although there are many medications available for the treatment of neurological and psychological disorders, the clinical outcomes and quality of care for many patients continue to be less than ideal [1]. A significant number of patients either cannot tolerate

*** Corresponding Author**:
Faraz Mojab, Department of Pharmacognosy, School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran. E-mail: sfmojab@sbmu.ac.ir.

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pharmacological treatments or do not respond adequately to existing therapies, which often exhibit only modest efficacy [2]. Consequently, there is a substantial demand for more advanced, better-tolerated, and therapeutic options [3]. Medicinal plants, which contain a diverse array of pharmacologically active metabolites, present a promising alternative therapeutic approach. They can be utilized either as standalone treatments or synergistically with conventional medications to manage various mood and neurological disorders [4]. Anxiety, which is marked by heightened sympathetic activity, muscle tension, and increased alertness, impacts about one-eighth of the world's population. It is the most common type of psychological disorder and greatly diminishes the well-being of those who experience it [5, 6]. While several pharmacotherapeutic agents, such as benzodiazepines, are commonly prescribed for anxiety disorders, these medications often come with considerable adverse effects [7–9]. Throughout history, herbal medicines have been employed to address central nervous system (CNS)-related disorders like anxiety. In contemporary society, many individuals prefer natural products due to their lower incidence of unwanted side effects and cost-effectiveness [10, 11].

A variety of medicinal plants, such as those from the *Salvia* genus, are acknowledged in Traditional Persian Medicine for their diverse therapeutic benefits. The Salvia genus, commonly referred to as sage, is one of the largest within the Lamiaceae family, containing nearly 900 species found worldwide [12]. In Iran, approximately 58 species of this genus are documented, with 17 being endemic. These plants are well-known and utilized for their flavoring, fragrances, and pharmaceutical applications. Traditionally, *Salvia* species have been employed to treat a range of conditions, including colds, digestive problems, bronchitis, infections, and inflammatory diseases, showcasing their extensive traditional applications [13–15].

Sage species are aromatic botanical specimens with a considerable body of scientific literature supporting their biological and therapeutic properties, as well as their phytochemical compositions. They find numerous applications in food technology, pharmaceuticals, nutraceuticals, and cosmetics, providing significant economic benefits [16–18]. *Salvia hypoleuca* Benth. is one of the 17 endemic species in Iran. This plant naturally grows in various regions, particularly on the slopes of the Alborz mountains in provinces such as Alborz, Guilan, Mazandaran, Tehran, and Qazvin, where it is locally known as "Maryami." [15]. Previous studies have reported numerous pharmacological properties for *S. hypoleuca*, including anti-nociceptive, anti-stress, anti-inflammatory, carminative, tonic, antimicrobial, and antioxidant effects [19–21]. The essential oil of *S. hypoleuca* contains several phytochemical compounds identified as its main components: caryophyllene oxide, caryophyllene, bicyclogermacrene, germacrene D, viridiflorol, spathulenol, δ-elemene, β-pinene, and α-pinene [13, 22]. Additionally, other compounds such as rosmarinic acid [23] and various sterols [13] and terpenoids [24][25] have also been detected.

Additionally, *Salvia* species are known for their neuroprotective effects. They can affect the central nervous system and demonstrate anti-seizure, anti-depressant, anxiolytic, anti-Alzheimer's, and anti-nociceptive properties, thanks to their beneficial secondary metabolites, such as phenolic compounds. While several *Salvia* species_ including *S. officinalis* [26], *S. reuterana* [27], *S. elegans* [28], *S. miltiorrhiza* [29], *S. verticillata* [30], *S. limbata* [31], and *S. divinorum* [32]_ have been extensively studied for their neuropharmacological activities, there is limited information available on *S. hypoleuca* [14].

Therefore, this study aims to evaluate the anxiolytic and potential neurotoxic effects of *S. hypoleuca* ethanolic extract through various behavioral experiments conducted in mice.

2. Materials and Methods

2.1. Chemicals and Reagents

All solvents and chemical agents utilized for extraction and pharmacological tests were of suitable purity and sourced from Merck (Darmstadt, Germany).

2.2. Plant Collection, Identification, Extraction, and Standardization

The aerial parts of *Salvia hypoleuca* were collected by Mr. M. Kamalinejad in June 2023 from Sar Ziarat, located in Karaj County, Alborz Province, Iran. A qualified pharmacognosist identified the plant, Dr. F. Mojab, and a voucher specimen of *S. hypoleuca* Benth. (HPSRC-105) was deposited at the Herbarium of the PSRC at SBMU. The dried plant material was ground

and macerated in 96% ethanol to create extracts. These extracts were filtered through Whatman paper and concentrated using a Heidolph rotary evaporator (Schwabach, Germany) at 45°C and 90 rpm. The resulting dried extract was stored at 4°C until the commencement of pharmacological testing.

The Folin-Ciocalteu colorimetric assay was utilized to quantify the total phenolic content (TPC), with gallic acid employed as the calibration reference. TPC values were expressed as milligrams of gallic acid equivalents per gram of dry extract. Similarly, the total flavonoid content (TFC) was measured using the aluminum chloride method combined with UV spectrophotometry, where rutin served as the calibration standard [33, 34].

2.3. Animals and Study Design

The pharmacological studies were performed using male NMRI albino mice weighing between 20 and 25 g. These mice were bred in the Animal House of the School of Pharmacy at SBMU. These animals were housed in a controlled environment with a temperature of 24 ± 2 ºC and a 12-hour light/dark cycle, where the light phase lasted from 7:00 AM to 7:00 PM. They had unlimited access to water and food, except during behavioral tests. All behavioral evaluations were conducted between 9:00 AM and 4:00 PM, with groups assigned randomly (n = 10). Mice were divided into five groups: control (saline), diazepam (positive control), and *S. hypoleuca* extract at 30, 100, and 300 mg/kg, administered orally 30 minutes prior to behavioral testing. Prior to testing, the animals were acclimatized to the laboratory conditions for one hour. All procedures adhered to the guidelines of the National Institutes of Health for animal care and use. The study protocol received approval code of IR.SBMU.Pharmacy.REC.1403.078.

2.4. Elevated Plus Maze

The elevated plus maze (EPM) apparatus used in this study consisted of four arms, each measuring 40 cm in length. Two of the arms were enclosed by walls that were 20 cm high, while the other two arms remained open. The configuration of the maze placed the closed arms opposite each other, as well as the open arms. The maze was elevated 50 cm above ground level. Given that anxious mice typically exhibit an innate avoidance of open spaces and a preference for enclosed areas, the effects of *S. hypoleuca* were assessed based on these behavioral tendencies [35]. Data analysis was conducted using Ethovision® XT software version 8, developed by Noldus Information Technology (Wageningen, The Netherlands). The maze environment was sanitized with 70% ethanol between trials to prevent any confounding effects [36].

2.5. Light/Dark Test

The apparatus for the LDT consisted of a dark plastic compartment occupying one-third of the testing area (16 cm × 50 cm) and a light compartment covering the remaining two-thirds (34 cm × 50 cm). An 80W light source illuminated the light section, while the dark section received minimal ambient light from its surroundings. A central opening (7 cm × 7 cm) at floor level connected the two compartments. Mice were allowed to explore the light-dark arena for 30 minutes after being administered either *S. hypoleuca* extract or diazepam, which served as a positive control. Following this, the behavior of each mouse was observed for 5 minutes, during which the number of entries into the light section and the time spent in the light compartment were recorded. An increase in these measures was interpreted as evidence of the anxiolytic effect of the extract [30].

2.6. Open Field Test

The study included an assessment of locomotor activity using an open-field arena made of transparent Plexiglas, measuring 40 cm × 40 cm × 40 cm in size. Thirty minutes after oral administration of the plant extract, each mouse was individually placed in the arena, and its movements were recorded for 10 minutes. The distance traveled by each mouse was analyzed using the video tracking software Ethovision® XT, following the methodology outlined by Jones et al. [37].

2.7. Rotarod Test

The rotarod test was employed to assess the animal's motor coordination and balance. Mice were positioned on a rotating rod with a 3 cm diameter, which initially began at a speed of 4 rpm for 300 seconds, and the rotation speed progressively increased from 4 rpm to 40 rpm. Throughout the test, the time each mouse stayed on the rod was meticulously recorded. Each animal underwent three trials, and the average duration on the rod was calculated. A 10-minute rest period was provided between each trial [38].

2.8. Statistical Analysis

Statistical analysis was performed using GraphPad Prism version 10 software (La Jolla, CA, United States). The experimental results were presented as mean ± standard error of the mean (SEM). One-way analyses of variance (ANOVA) were conducted, followed by Dunnett's test for multiple comparisons. Statistical significance was determined at a P-value of less than 0.05. Significance levels were categorized as $P < 0.05$, $P < 0.01$, $*P < 0.001$, and $****P < 0.0001$, with comparisons made to the control group (n=10 in all groups).

3. Results and Discussion

3.1. TPC and TFC

The yield of dried *S. hypoleuca* ethanolic extract was found to be 16.1% (W/W) of the initial plant material. The TPC and TFC of *S. hypoleuca* ethanolic extract were measured at 47.26 ± 2.87 mg GAE/g DW and 31.73 ± 5.38 mg RE/g DW, respectively.

3.2. Results of the Elevated Plus Maze

The EPM results are presented in **Figure 1**, with statistical evaluation performed using one-way ANOVA and Dunnett's post hoc test. As illustrated in **Figure 1A**, diazepam (10 mg/kg) significantly increased both the percentage of time spent in the open arms and the number of open arm entries compared to the control group ($P < 0.001$), confirming the validity of the EPM model. Notably, *S. hypoleuca* extract at 30 mg/kg also significantly increased open arm duration ($P < 0.05$). **Figure 1B** shows that mice administered *S. hypoleuca* ethanolic extract at a dose of 100 mg/kg ($P < 0.05$) exhibited a significant increase in entries into the open arms compared to the control group.

3.3. Results of Light/Dark Test

As demonstrated in **Figure 2A**, administration of diazepam (2 mg/kg) resulted in a significant increase in the time spent in the light compartment compared to the control group ($P < 0.05$), validating the LDT model. Similarly, *S. hypoleuca* extract at 30 mg/kg significantly increased the time spent in the light box ($P < 0.05$), with this effect being comparable to that observed with diazepam. However, as shown in **Figure 2B**, neither diazepam nor the extract significantly altered the number of entries into the light compartment.

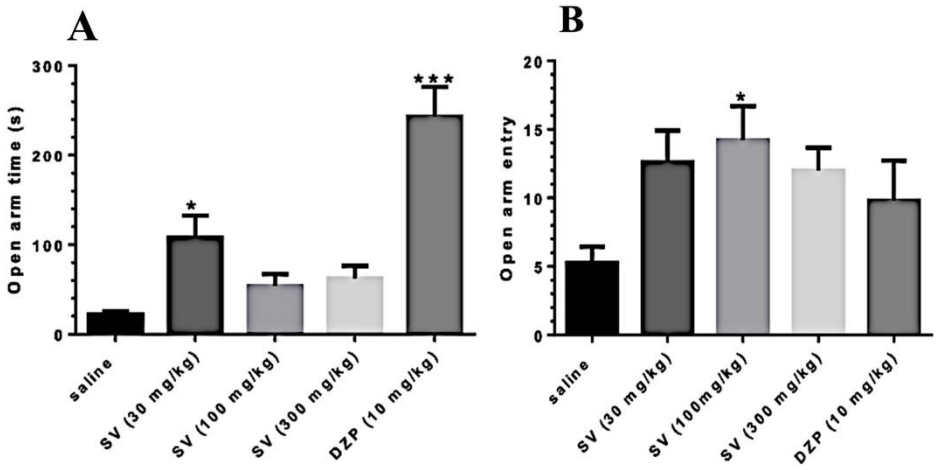

Figure 1. Effects of *S. hypoleuca* ethanolic extract on anxiety-like behavior in the Elevated Plus Maze. (A) The percentage of time spent in the open arms and (B) number of entries into the open arms were measured. Diazepam (10 mg/kg) served as a positive control. Statistical significance is denoted as $P < 0.05$ and $**P < 0.001$ compared to the control group. Data were analyzed using one-way ANOVA followed by Dunnett's post hoc test and are presented as mean ± SEM (n = 10).

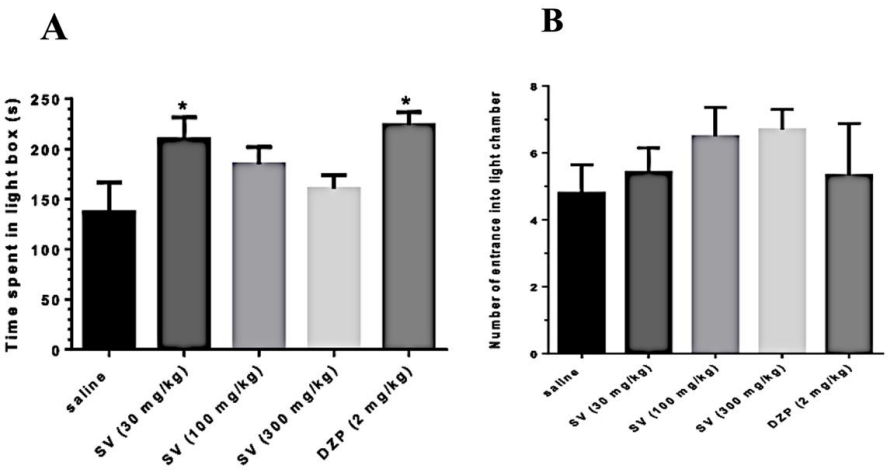

Figure 2. Effects of *S. hypoleuca* ethanolic extract on anxiety-like behavior in the Light/Dark Test (LDT). (A) Time spent in the light box and (B) number of entries into the light chamber were evaluated. Diazepam (2 mg/kg) was used as a positive control. Statistical significance is indicated as $P < 0.05$ compared to the control group. Data were analyzed using one-way ANOVA followed by Dunnett's post hoc test and are expressed as mean ± SEM (n = 10).

3.4. Results of the Open Field Test

The findings from the OFT highlighted the effects of *S. hypoleuca* ethanolic extract on spontaneous motor activity in mice. As shown in **Figure 3A**, treatment with the extract at doses of 30 mg/kg and 300 mg/kg significantly reduced the distance moved compared to the control group, with significance levels of $P < 0.01$ and $P < 0.001$, respectively.

Figure 3B illustrates that mice administered *S. hypoleuca* ethanolic extract at doses of 30 mg/kg and 300 mg/kg also exhibited a significant decrease in velocity compared to the control group, with P values of < 0.01 and < 0.001, respectively.

As presented in **Figure 3C**, no significant differences were observed among treatment groups regarding the time spent in the central zone ($P > 0.05$).

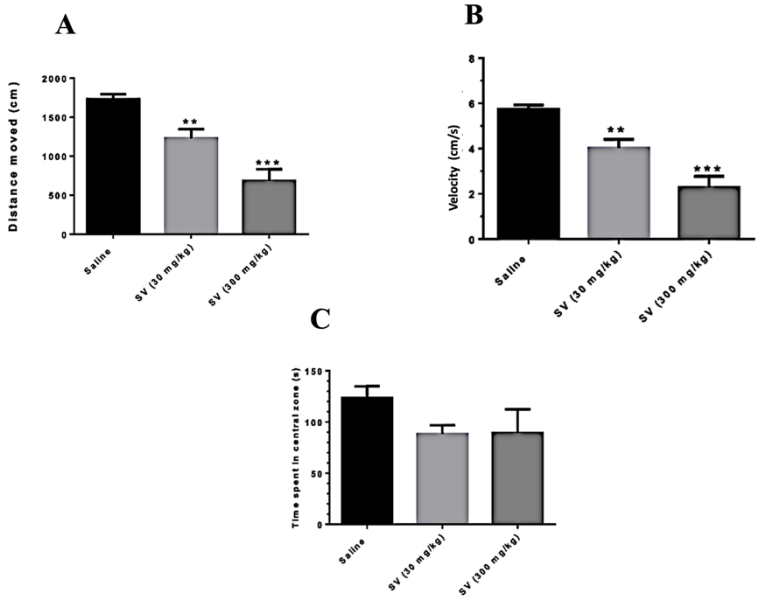

Figure 3. Effects of *S. hypoleuca* ethanolic extract on locomotor activity in the Open Field Test. (A) Distance moved, (B) velocity, and (C) time spent in the central zone were evaluated. Mice treated with *S. hypoleuca* extract at 30 mg/kg and 300 mg/kg showed significant reductions in distance moved (**P < 0.01 and ***P < 0.001) and velocity (**P < 0.01 and ***P < 0.001) compared to controls. No significant differences were observed in central zone exploration time ($P > 0.05$). Statistical analysis was performed using one-way ANOVA followed by Dunnett's post hoc test. Data are expressed as mean ± SEM (n = 10).

3.5. Results of the Rotarod Test

The rotarod test was employed to assess motor coordination and balance in animals, serving as indicators for evaluating the neurotoxicity of *S. hypoleuca*. In this study, 10% of the animals treated with *S. hypoleuca* ethanolic extract at a dose of 30 mg/kg, and 20% of those receiving 300 mg/kg fell from the rod. These results suggest a low level of neurotoxicity associated with the ethanolic extract of *S. hypoleuca* at the doses used in this study.

3.6. Discussion

Although *S. hypoleuca* is commonly used in traditional medicine for treating various ailments, there is a notable lack of scientific studies investigating its neuropharmacological properties. This research provides evidence that oral administration of *S. hypoleuca* ethanolic extract at different doses induces anxiolytic effects in mice without significantly impairing their natural motor activity. In the EPM test, mice treated with the extract exhibited behavioral responses similar to those treated with diazepam, with no significant differences observed between the two groups.

The results showed that mice receiving *S. hypoleuca* ethanolic extract at doses of 30 and 100 mg/kg had a significant increase in both the number of entries into and the time spent in the open arms during the EPM test compared to the saline control group. In the LDT, mice treated with 30 mg/kg of the extract spent significantly more time in the light chamber than the control mice. The rotarod test revealed that 10% of mice treated with 30 mg/kg and 20% of those receiving 300 mg/kg fell from the rotating rod, indicating potential motor effects. In the OFT, both total distance moved and velocity were significantly reduced at doses of 30 and 300 mg/kg compared to the control group.

Non-dose-dependent anxiolytic effects, similar to those observed in our study with *S. hypoleuca*, have also been reported for other *Salvia* species and plant extracts. For example, studies on *S. reuterana* demonstrated that the anxiolytic effect was most pronounced at an intermediate dose, with higher or lower doses producing less consistent results. This non-linear dose-response relationship is not unique to the genus *Salvia*; it has also been reported in other medicinal plants with complex phytochemical profiles. Such phenomena are generally attributed to the multifaceted interactions among the diverse secondary metabolites present in crude plant extracts, which may exert synergistic, antagonistic, or threshold-dependent effects on neuropharmacological pathways. Consequently, the lack of a clear dose-dependent anxiolytic response in our findings is consistent with the broader literature on plant-based anxiolytics. It highlights the importance of considering phytochemical complexity when interpreting pharmacological outcomes [27, 39].

Pharmacological studies have shown that plants from the Salvia genus, as well as some of their chemical components, such as essential oils and flavonoids, exhibit depressant effects on the nervous system. For example, the flavonoid apigenin selectively binds with high affinity to central benzodiazepine receptors and demonstrates significant anxiolytic effects. Herrera-Ruiz et al. highlighted the anxiolytic potential of *S. elegans* hydroalcoholic extract using EPM and LDT assays [28].

A recent study by Lin et al. found that ethanolic extract of *S. miltiorrhiza* exhibited anxiolytic effects through activation of benzodiazepine and 5-HT_{1A} receptors [29]. Additionally, Rabbani et al. reported that the hydroalcoholic extract of *S. reuteri* displayed anti-anxiety effects at a dose of 100 mg/kg (i.p.) in the EPM test in mice [27]. At the same time, Motaghi and Teimouri found that *S. officinalis* hydroalcoholic extract exerted an anxiolytic effect at a dose of 10 mg/kg (i.p.) in the same test [40].

Research conducted by Monsef Esfahani et al. revealed that administration of methanolic and hydroalcoholic extracts of *S. hypoleuca* at a dose of 500 mg/kg (i.p.) resulted in a statistically significant increase in the duration spent in the central zone and head-dipping behavior compared to the normal control group in open field and hole-board behavioral experiments [14].

Previous phytochemical studies have identified various phenolic acids, flavonoids, and related compounds in *Salvia* species, including *S. hypoleuca* and its relatives [41]. For example, rosmarinic acid, caffeic acid, luteolin, quercetin, and other polyphenols are commonly reported in *Salvia* species extracts and have demonstrated neuroprotective and anxiolytic properties in preclinical models [42–45]. Therefore, the anxiolytic activity observed in our study may be partially attributed to these phenolic constituents, in line with findings from other *Salvia* species and related plant extracts.

4. Conclusion

In summary, our findings indicate that the oral administration of *S. hypoleuca* ethanolic extract produces anxiolytic effects in mice. While the experimental tests employed in this study provided valuable insights into motor activity and anxiety, they do not allow for a clear elucidation of the underlying mechanisms through which *S. hypoleuca* exerts its effects. The lack of an apparent dose-dependent effect may be attributed to pharmacological variability and the complex chemical composition of the crude ethanolic extract. Further research is needed to confirm and expand upon these findings.

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Conflict of interest

The authors state that they have no conflicts of interest that could influence or be perceived as affecting their research or its interpretation.

Data availability

The data that support the findings of this study are available on request from the corresponding author.

Authors Contributions

Conception and design of the study: Faraz Mojab and Nima Naderi
Analysis and interpretation of data: Reyhaneh Alinejad, Nima Naderi, Faraz Mojab, and Marjan Talebi
Drafting the article: Marjan Talebi and Faraz Mojab
Revising the article: Marjan Talebi and Faraz Mojab
Supervisor of the project: Faraz Mojab

Authors Orcid numbers:

Marjan Talebi: https://orcid.org/0000-0001-5513-3204
Nima Naderi: https://orcid.org/0000-0003-4591-8918
Faraz Mojab: https://orcid.org/0000-0003-2415-2175

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Using artificial intelligence chatbots

There was no use of artificial intelligence in the making of this article.

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