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Original Article

Relaxing effect of *Sideritis raeseri* Boiss. & Heldr. on the uterus is dependent on calcium and nitric oxide signaling pathways

[Efecto relajante de *Sideritis raeseri* Boiss. & Heldr. sobre el útero depende de las vías de señalización del calcio y el óxido nítrico]

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Abstract

Context: *Sideritis raeseri* Boiss. & Heldr. (*Lamiaceae*), commonly known as "mountain tea," is a medicinal plant with a long-standing use in traditional medicine.

Aims: To evaluate the effects of *Sideritis raeseri* ethanol extract (SRE) on uterine smooth muscle contractility and elucidate its underlying mechanisms of action.

Methods: An ethanol extract was prepared from the aerial parts of SRE. Isolated rabbit uterine rings were suspended in organ baths containing physiological salt solution at 37°C, continuously bubbled with 95% O_2 and 5% CO_2. The relaxant effects of SRE (0.5–2 mg/mL) were assessed on spontaneous and induced uterine contractions. Uterine contractions were stimulated using carbachol (1 µM), high K^+ (80 mM), oxytocin (5 nM), or indomethacin (10 µM). The involvement of Ca^{2+} influx and NO/cGMP signaling was investigated using L-NAME (100 µM, NO synthase inhibitor) and bradykinin (100 nM, NO synthase activator).

Results: SRE significantly inhibited spontaneous uterine contractions in a concentration-dependent manner. It also reduced Ca^{2+}-induced contractions under all tested stimuli. The relaxant effect was attenuated by L-NAME and enhanced by bradykinin, suggesting the involvement of NO-mediated pathways.

Conclusions: These results indicate that the uterine relaxant activity of SRE involves both calcium modulation and NO-dependent signaling pathways. SRE shows potential as a natural tocolytic agent for the management of uterine hyperactivity or related disorders.

Keywords: NO signaling; organ bath; *Sideritis raeseri*; smooth muscle relaxation; tocolytic agent; uterus.

Resumen

Contexto: *Sideritis raeseri* Boiss. & Heldr. (*Lamiaceae*), conocida comúnmente como «té de montaña», es una planta medicinal con un uso antiguo en medicina tradicional.

Objetivos: Evaluar los efectos del extracto etanólico de *S. raeseri* (SRE) sobre la contractilidad del músculo liso uterino y dilucidar sus mecanismos de acción subyacentes.

Métodos: Se preparó un extracto etanólico a partir de las partes aéreas de SRE. Se suspendieron anillos uterinos aislados de conejo en baños de órganos que contenían solución salina fisiológica a 37°C, burbujeados continuamente con 95% de O_2 y 5% de CO_2. Se evaluaron los efectos relajantes de la SRE (0,5-2 mg/mL) sobre las contracciones uterinas espontáneas e inducidas. Las contracciones uterinas se estimularon con carbacol (1 µM), K^+ elevada (80 mM), oxitocina (5 nM) o indometacina (10 µM). Se investigó la participación del influjo de Ca^{2+} y la señalización NO/cGMP utilizando L-NAME (100 µM, inhibidor de NO sintasa) y bradicinina (100 nM, activador de NO sintasa).

Resultados: La SRE inhibió significativamente las contracciones uterinas espontáneas de forma dependiente de la concentración. También redujo las contracciones inducidas por Ca^{2+} bajo todos los estímulos probados. El efecto relajante fue atenuado por L-NAME y potenciado por bradicinina, lo que sugiere la participación de vías mediadas por NO.

Conclusiones: Estos resultados indican que la actividad relajante uterina de la SRE implica tanto la modulación del calcio como vías de señalización dependientes de NO. La SRE muestra potencial como agente tocolítico natural para el tratamiento de la hiperactividad uterina o trastornos relacionados.

Palabras Clave: agente tocolítico; baño de órganos; relajación del músculo liso; señalización de NO; *Sideritis raeseri*; útero.

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Abbreviation: [Ca2+]i: Intracellular concentration of free calcium ions; CCh: Carbachol; cGMP: Guanosine 3',5'-cyclic monophosphate; COX: Cyclooxygenase; IND: Indomethacin; L-NAME: NG-nitro-ʟ-arginine methyl ester; NO: Nitric oxide; NOS: Nitric oxide synhase; Oxt: Oxytocin; PSS: Physiological salt solution; SM: Smooth muscle; SR: *Sideritis raeseri*; SRE: *Sideritis raeseri* extract.

INTRODUCTION

Humans have used medicinal herbs for thousands of years, both in traditional medicine and culinary applications (Favarin et al., 2013). In many countries, herbal remedies are employed to prevent and treat a wide array of diseases, including uterine disorders and uterine cancer (Santana et al., 2016). In recent years, numerous natural compounds with significant therapeutic potential have been identified from plants, offering promising avenues for treating various human illnesses (Fukahori et al., 2014; Santana et al., 2016; Srancikova et al., 2013; Stagos et al., 2012).

During the past decade, many plant-derived compounds have been approved for medical use (Cheng et al., 2016; Romanucci et al., 2017). However, the precise molecular mechanisms underlying their effects often remain poorly understood. Investigating their pharmacological actions and mechanisms is essential to expanding our understanding of medicinal plants and discovering novel therapeutic agents.

The genus *Sideritis* L. (*Lamiaceae*) includes approximately 150 species, with *Sideritis raeseri* Boiss. & Heldr. (SR) being one of the most notable. It is widely distributed in the Mediterranean region—especially in the Balkans and the Iberian Peninsula—as well as in Macaronesia (Romanucci et al., 2017; Stagos et al., 2012). Known colloquially as "mountain tea" or "shepherd's tea," SR has a long-standing history of use in traditional medicine for its antiulcerogenic, antimicrobial, digestive, and anti-inflammatory properties, as well as its use as a beverage (Romanucci et al., 2017). Additionally, it has been used to treat conditions such as rheumatism, bronchitis, gastrointestinal disorders, flu, and as a diuretic.

The traditional use of *S. raeseri* in female reproductive health is still prevalent in various regions. Although its medicinal value has been documented extensively (Romanucci et al., 2017; Stagos et al., 2012), no study to date has investigated its effects on uterine contractility or its underlying mechanisms of action. Understanding these effects is particularly relevant given the need for cost-effective therapies to manage uterine hyperactivity and related disorders (Gruber and O'Brien, 2011).

Phytochemical analyses have revealed that *Sideritis* species contain a wide range of bioactive constituents, including terpenoids, coumarins, sterols, flavonoid aglycones, and glycosides (Kostadinova et al., 2007; Romanucci et al., 2017; Stagos et al., 2012). Compounds isolated from *Sideritis* spp. have been reported to exhibit diverse biological activities, including antioxidant, anti-inflammatory, antimicrobial, antitussive, antinociceptive, immunomodulatory, vasoprotective, antiulcer, and hypotensive effects (Gabrieli et al., 2005; Kitic et al., 2012; Petreska et al., 2011; Romanucci et al., 2017).

Our group's previous studies revealed novel effects of certain medicinal plants, including a new tracheorelaxant effect of SRE (Krasniqi et al, 2020) and both tracheorelaxant (Thçci et al, 2020) and vasorelaxant (Thaçi et al, 2022) effects of *Vitex agnus-castus*. Despite these findings, the effects of SR on uterine smooth muscle and the potential mechanisms involved have not been elucidated.

Given the clinical relevance of uterine contractility regulation, this study was designed to investigate the in vitro relaxant effects of *Sideritis raeseri* extract (SRE) on isolated rabbit uterine rings. The primary objective was to determine whether SRE modulates uterine activity and to identify the signaling pathways involved. This work aims to provide pharmacological justification for the traditional use of *S. raeseri* in the treatment of gynecological disorders.

MATERIAL AND METHODS

Plant material collection and extraction

Aboveground parts (shoot system) of *Sideritis raeseri* were manually collected during the summers of 2018 and 2019 from two mountainous regions in Albania: Dry Mountain (40°48′30.09″N, 20°50′17.33″E, 1585 m a.s.l., 12 July 2018) and Ostrovica Mountain (40°33′30.70″N, 20°27′24.85″E, 1700 m a.s.l., 25 June 2019). The plant material was authenticated by Prof. Dr. Lulëzim Shuka, and voucher specimens were deposited at the Herbarium of the Department of Biology, University of Tirana (Herb. Shuka No. 7524 & No. 7947).

The collected aerial parts were cleaned, shade-dried at room temperature (avoiding direct sunlight and wind), and ground into a coarse powder using a laboratory grinder (IKA® MF 10 Basic Microfine Grinder Drive, Germany). The powder was soaked in 80% aqueous ethanol (1:10, w/v) for 24 hours at room temperature with intermittent shaking. The mixture was filtered through Whatman No. 1 filter paper, and the filtrate was concentrated under reduced pressure using a rotary evaporator. The resulting ethanol extract (SRE) was dried, stored at 4°C in airtight containers, and freshly diluted in physiological salt solu-

tion (PSS) to the desired concentrations (0.5–2 mg/mL) before use.

Reagents

All reagents used were of analytical grade. Oxytocin (Oxt), carbachol (CCh), NG-nitro-L-arginine methyl ester (L-NAME), bradykinin, and indomethacin (IND) were purchased from Sigma-Aldrich (Germany). Indomethacin (50 mg/mL) was dissolved in ethanol, and bradykinin was prepared in 0.1 M acetic acid. All other compounds were dissolved in distilled water. Stock solutions were freshly prepared on the day of the experiment.

Animals and tissue preparation

Adult female rabbits (800–1200 g) were maintained under standard laboratory conditions (temperature 19–23°C, 12 h light/dark cycle) with ad libitum access to food and water. All animal procedures conformed to Directive 2010/63/EU (Carbone, 2012a, 2012b) on animal experimentation and were approved by the Ethical Committee of the Faculty of Medicine, University of Prishtina (approval code: 870-07.09.2018).

Animals were humanely sacrificed by a blow to the back of the head, and the uterus was immediately excised and placed in ice-cold PSS with the following composition (in mM): NaCl (115), KCl (4.7), $CaCl_2$ (2.0), $MgSO_4$ (1.16), KH_2PO_4 (1.18), $NaHCO_3$ (22), and D-glucose (7.88), pH 7.4 (Alotaibi, 2016).

Under a stereomicroscope (Leica Microsystems, Germany), the uterus was cleared of connective tissue and blood clots. Uterine strips (2–3 mm wide) with intact endometrium were dissected and mounted vertically in 10 mL organ baths (DMT 750TOBS, Danish Myo Technology, Denmark) containing PSS at 37°C, bubbled continuously with a 95% O_2 and 5% CO_2 gas mixture.

Experimental protocols

Uterine tension was measured isometrically using force transducers (DMT 750, Danish Myo Technology, Denmark) and recorded with LabChart software (ADInstruments, Denmark) (Dupont et al., 2014; Krasniqi et al., 2020; Thaçi et al., 2020; 2022). Each uterine strip was equilibrated for 45–60 minutes under a resting tension of 1 g. During equilibration, PSS was refreshed every 15–20 minutes.

To investigate the relaxant effects of SRE, cumulative concentrations (0.5, 1, 1.5, and 2 mg/mL) were applied to spontaneous uterine contractions. Additional experiments evaluated the effect of SRE on contractions induced by carbachol (1 μM), KCl (80 mM), oxytocin (5 nM), or indomethacin (10 μM). In mechanistic studies, uterine strips were pretreated with L-NAME (100 μM) or bradykinin (100 nM) to assess the involvement of nitric oxide (NO) pathways in SRE-induced responses.

Statistical analysis

Contractile activity was expressed as a percentage of the maximum response induced by CCh, Oxt, or KCl. Data are presented as mean ± SEM from at least four independent experiments. Statistical comparisons were performed using one-way ANOVA followed by Student's t-test. A p-value < 0.05 was considered statistically significant. Statistical analysis was performed using GraphPad Prism version 6 (GraphPad Software, USA).

RESULTS

SRE induces dose-dependent relaxation of spontaneous uterine contractions

Cumulative application of SRE at concentrations of 0.5, 1, 1.5, and 2 mg/mL significantly attenuated spontaneous uterine contractions in a concentration-dependent manner. Even the lowest dose of 0.5 mg/mL significantly reduced spontaneous contractile activity ($p<0.001$, $n = 4$), with higher concentrations producing progressively stronger relaxant effects (Fig. 1A-B). These findings indicate a clear tocolytic potential of SRE.

SRE attenuates CCh- and oxytocin-induced uterine contractions

To further evaluate its pharmacological action, SRE was tested against contractions induced by carbachol (CCh, 1 μM) and oxytocin (Oxt, 5 nM). In both cases, SRE (0.5–2 mg/mL) significantly and dose-dependently relaxed precontracted uterine strips (Fig. 2A-B). The extent of inhibition was comparable for both CCh- and Oxt-induced contractions, confirming that SRE acts as a broad-spectrum uterine relaxant.

SRE reverses high K^+-induced uterine contractions

To assess whether the extract interferes with membrane depolarization-dependent mechanisms, uterine strips were contracted with high extracellular potassium (80 mM K^+). SRE, particularly at 2 mg/mL, significantly reduced high K^+-induced contractions ($p<0.001$, $n = 4$), suggesting its potential role as a calcium channel blocker (Fig. 3).

Indomethacin and SRE exhibit comparable uterine relaxant effects

To compare the efficacy of SRE with a standard tocolytic agent, indomethacin (10 μM) was tested under identical experimental conditions. As shown in Fig. 4,

indomethacin significantly inhibited both spontaneous and Oxt-induced contractions, exhibiting a relaxant profile similar to that of SRE at 2 mg/mL.

Nitric oxide pathway mediates SRE-induced uterine relaxation

To investigate the involvement of the nitric oxide (NO) pathway in SRE-induced relaxation, uterine strips precontracted with Oxt were treated with SRE (2 mg/mL) alone or in combination with either bradykinin (100 nM, a NOS stimulator) or L-NAME (100 µM, a NOS inhibitor). SRE alone induced significant uterine relaxation ($p<0.001$, n = 5), which was potentiated by bradykinin ($p<0.05$) and markedly attenuated by L-NAME ($p<0.001$), as shown in Fig. 5. These results confirm the partial dependence of SRE-mediated relaxation on NO signaling pathways.

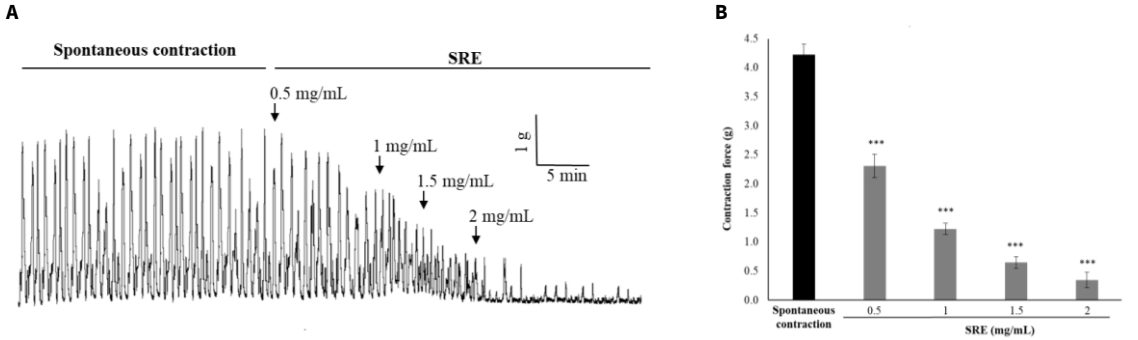


Figure 1. The dose-dependent relaxant effect of SRE on spontaneous contractions of the uterus.

Original representative current tracings demonstrating the force/time effects of dose-dependent (0.5–2 mg/mL) *S. raeseri* extract-induced smooth muscle relaxation on isolated uterus rings **(A)**. Arithmetic means ± SEM (n = 4 ring segments, each taken from a different uterus of a female rabbit) of the relaxant function of SRE (0.5–2 mg/mL, gray bars) on uterus muscle contraction **(B)**. The values are the means of contraction responses in g of muscle contraction force. ***This indicates that the presence of SRE (gray bars) made a statistical difference ($p<0.001$; t-test), as compared to spontaneous contraction (black bar).

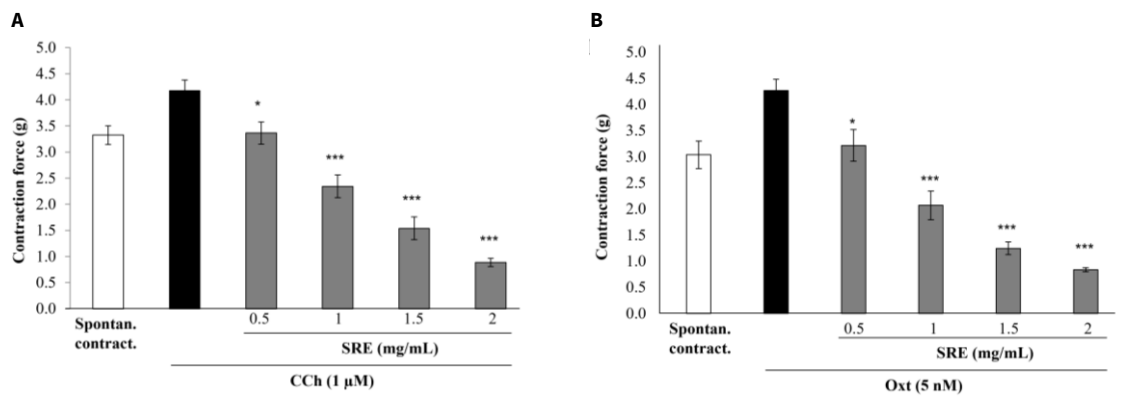


Figure 2. The dose-dependent relaxant effect of SRE on uterine smooth muscle following precontraction with CCh or Oxt.

Arithmetic means ± SEM (n = 5 uterus rings, each collected from a separate rabbit) of the uterus relaxant effects of SRE (0.5–2 mg/mL, gray bars) on uterus muscle contraction induced with either CCh (1 µM) **(A)** or Oxt (10 µM) **(B)**. Results are expressed relative to values obtained as the mean of contraction responses compared to g muscle contraction force. *Denotes statistical significance ($p<0.05$; t-test) from the absence of SRE (CCh alone, black bar). ***Indicates significance ($p<0.001$; t-test) from the absence of SRE.

DISCUSSION

The present study demonstrates that *Sideritis raeseri* ethanol extract (SRE) exerts significant relaxant effects on uterine smooth muscle. These effects were observed both during spontaneous contractions and after contractions induced by various stimuli, including oxytocin (Oxt), carbachol (CCh), indomethacin, and high extracellular potassium (K^+). The findings suggest that SRE-induced relaxation may involve inhibition of Ca^{2+} influx, as well as nitric oxide (NO)-dependent signaling pathways.

Uterine smooth muscle contraction is primarily mediated by increases in intracellular free calcium ion concentration ($[Ca^{2+}]_i$), which result from either the influx of extracellular Ca^{2+} via voltage-gated Ca^{2+} channels or release from the sarcoplasmic reticulum. Depolarization by high extracellular K^+ induces Ca^{2+} influx across the plasma membrane, while CCh

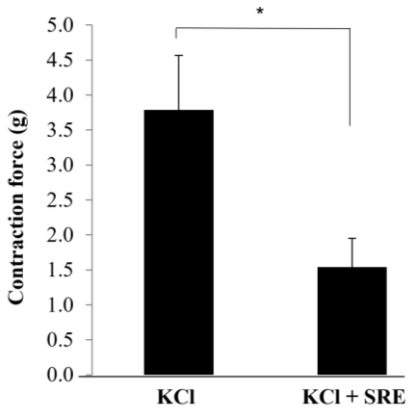


Figure 3. The uterine relaxant effect of SRE on high KCl-induced smooth muscle contractions.

Arithmetic means ± SEM (n = 5 uterine segments, each collected from a separate rabbit) of the relaxant function of SRE (2 mg/mL) on uterus muscle contraction induced by KCl (80 mM). Results are expressed relative to values obtained at 1 g of contraction force. *Denotes statistical significance (p<0.05; t-test) from the absence of SRE.

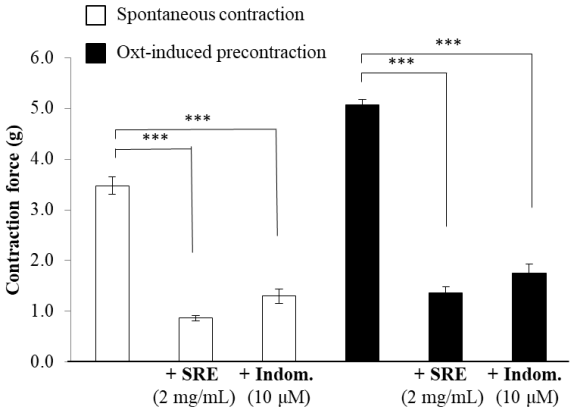


Figure 4. Spontaneous contraction and Oxt-induced precontraction without or with SRE or indomethacin.

Arithmetic means ± SEM (n = 4 uterine segments) of the relaxant function of SRE (2 mg/mL) and indomethacin (10 µM) on uterus muscle muscles under spontaneous contraction or induced by Oxt (5 nM). Results are expressed relative to values obtained at 1 g of contraction force. ***Denotes a statistically significant difference (p<0.001; t-test) from the absence of SRE and indomethacin, respectively.

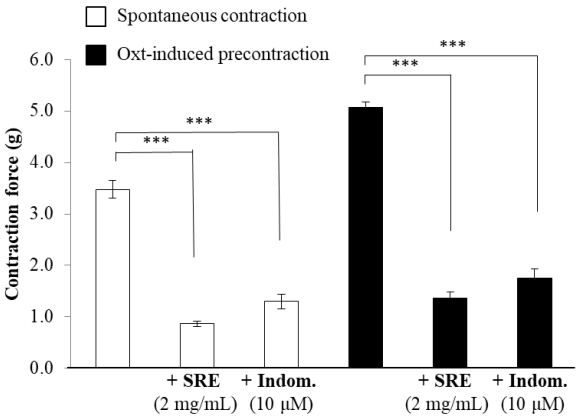


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stimulates contraction through both Ca^{2+} influx and intracellular release (Dërmaku-Sopjani et al., 2014; Dërmaku-Sopjani and Sopjani, 2019; Saito et al., 2004; Sopjani et al., 2015; Sopjani and Dërmaku-Sopjani, 2016). In our study, SRE significantly inhibited contractions elicited by both high K^+ and CCh, indicating that it may interfere with both extracellular and intracellular Ca^{2+} signaling pathways.

These findings align with previous work reporting the tracheorelaxant effect of SRE (Krasniqi et al., 2020), suggesting that the extract acts as a non-specific smooth muscle relaxant. Similar mechanisms have been reported for *Vitex agnus-castus*, another medicinal plant with smooth muscle-relaxant properties in trachea and aorta (Thaçi et al., 2020; 2022).

Indomethacin, a cyclooxygenase (COX) inhibitor, has long been used as a tocolytic agent to manage preterm labor. While effective, its use is associated with adverse prenatal outcomes (Arrowsmith et al., 2010). In our experiments, SRE demonstrated relaxant effects comparable to or exceeding those of indomethacin, suggesting its potential as a safer alternative. Indomethacin's tocolytic effect is mediated by reduced prostaglandin synthesis and, potentially, COX-independent mechanisms affecting calcium mobilization (Sawdy et al., 1998).

Furthermore, the role of NO in SRE-induced uterine relaxation was confirmed using pharmacological modulators. Pretreatment with L-NAME (a NOS inhibitor) reduced SRE efficacy, whereas bradykinin (a NOS stimulator) enhanced it. This clearly implicates NO-mediated signaling in the extract's mechanism of action, consistent with the known role of NO in uterine smooth muscle relaxation (Moncada et al., 1989; 1991; Murad, 2006).

Phytochemical studies of *Sideritis* species have identified several bioactive compounds, including terpenoids, sterols, coumarins, and especially flavonoids (Romanucci et al., 2017). Although our current study evaluated the whole extract, future studies should isolate individual constituents to determine whether a specific compound—or a synergistic combination—is responsible for the observed uterine relaxant activity.

CONCLUSION

This study provides the first evidence that *Sideritis raeseri* ethanol extract (SRE) exerts potent uterine-relaxant effects. These effects are mediated by inhibition of calcium entry and modulation of nitric oxide signaling pathways. Taking together, these findings suggest that SRE may serve as a promising candidate for the development of novel phytotherapeutic agents aimed at treating uterine hyperactivity and related disorders. Further studies are warranted to isolate active compounds and assess safety and efficacy in *in vivo* models.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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AUTHOR CONTRIBUTION:

Contribution	Krasniqi B	Thaçi S	Dërmaku-Sopjani M	Abazi S	Sopjani M
Concepts or ideas	x				x
Design			x		x
Definition of intellectual content				x	x
Literature search					
Experimental studies	x	x			
Data acquisition	x	x			
Data analysis	x	x	x	x	x
Statistical analysis	x	x			x
Manuscript preparation			x		x
Manuscript editing	x	x	x	x	x
Manuscript review	x	x	x	x	x

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