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Antidiabetic, antioxidant, and therapeutic effects of *Salvia balansae* leaf and stem extracts on sexual function in diabetic male rats

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Abstract: This study investigates the *in vitro* antioxidant and antidiabetic effects, and *in vivo* the pro-sexual activities of aqueous extracts from *Salvia balansae* leaves (LAE) and stems (SAE) in streptozotocin (STZ)-induced diabetic male rats. The total polyphenol and flavonoid contents, as well as the antioxidant activity of the extracts, were assessed using the DPPH radical scavenging and FRAP assays. Following the induction of diabetes by intraperitoneal injection of STZ (40 mg/kg), diabetic rats received 200 mg/kg of LAE/SAE. Acute oral toxicity, glycemic levels, sexual behavior parameters, and serum testosterone levels were assessed. *S. balansae* extracts exhibited high levels of total polyphenols and flavonoids, reflecting an antioxidant capacity. Acute toxicity tests confirmed a high safety margin, with no observed toxicity at doses up to 2 g/kg. In diabetic rats, LAE and SAE administration reduced hyperglycemia and enhanced sexual function, as evidenced by increased male-female interaction frequency, decreased latency times, and elevated serum testosterone levels, pointing to an aphrodisiac effect. This work demonstrates the therapeutic potential of *S. balansae* leaf and stem extracts in improving reproductive function in diabetic rats, potentially through its antioxidant, antihyperglycemic and aphrodisiac properties.

Keywords: *Salvia balansae* Noë ex Coss, antioxidant, acute toxicity, aphrodisiac, antihyperglycemic

INTRODUCTION

Sage (*Salvia*), the largest genus of herbaceous perennial plants in the Lamiaceae family, occupies a special place, recognized since ancient times for its healing properties [1]. The genus name *Salvia*, derived from the Latin word "salvare" (to save), underscores its long-standing reputation for medicinal properties [2,3]. Originating from the Mediterranean basin, eastern and southwestern Asia [1], there are around 1,000 species of sage worldwide [4], with particular diversity in Algeria, where around 30 species have been identified [2]. The Mostaganem region of Algeria has a wealth of endemic and rare *Salvia* species, including *Salvia balansae* [5]. *Salvia balansae* Noë ex Coss, whose local name is "hchichet koul blia" (plant that cures all ills), is used in traditional medicine to treat a wide range of illnesses in local communities. Its distribution is limited to the Chelif Valley, in the coastal region of Oranie and the Aures Mountains, and *S. balansae* is strictly endemic to Algeria [6]. Differences in climate lead to variations in flower color and leaf morphology in the Aures mountain species [6]. The genus *Salvia* is rich in polyphenolic compounds such as phenolic acids, flavonoids, and anthocyanins, which are major classes of bioactive phytoconstituents. They exert a wide range of biological and pharmacological activities such as antioxidant [7], antimicrobial, anticancer, antitumor, antiinflammatory [8], anti-neurodegenerative activities, as well as anti-enzymatic

activities such as anticholinesterase, anti-urease, anti-tyrosinase, and anti-elastase activities [1,9]; they also exert antipyretic, analgesic, hepatotoxic, cytotoxic, and insecticidal activities [1,10,11]. Ethnobotanical studies have shown that sage has traditionally been used in the Mediterranean region to regulate blood sugar and increase male fertility. Indigenous people from different tribes living in Algeria use different species of *Salvia* for these purposes [12].

In the context of modern medicine, diabetes mellitus has emerged as one of the most prevalent and challenging chronic diseases, associated with a wide range of complications [13]. Characterized by persistent hyperglycemia, diabetes affects multiple organs and systems and is often associated with reduced libido, erectile dysfunction, and other pro-sexual impairments that significantly affect the quality of life [14,15]. The use of plants, such as sage, has become an area of growing interest in the management of diabetes and its multifaceted complications. *Salvia officinalis* extract has been shown to improve testicular function, reduce blood glucose levels, and enhance lipid profiles in diabetic animal models [16]. These effects are attributed to the bioactive phytoconstituents of this plant, which act as antioxidants and help regulate blood glucose levels [9]. However, the specific effects of the aqueous extracts of the leaves (LAE) and stems (SAE) of *S. balansae* on diabetes-induced male reproductive dysfunction are poorly explored. Only three papers to date have specifically addressed *S. balansae* from Mostaganem. Mekki et al. [17] examined its leaves, showing antioxidant and antidiabetic effects, including improved metabolic parameters, testosterone levels, and testicular structure in a high-fat, diet-induced diabetic model; other studies have examined its *in vitro* biological properties [18,19]. The photoprotective properties of the same Salvia species found in the Aures Mountains have also been investigated [6].

We hypothesized that the polyphenolic and flavonoid compounds in *S. balansae* leaf and stem aqueous extracts possess anti-diabetic and antioxidant properties capable of alleviating diabetes-induced male reproductive dysfunction. More specifically, these bioactive constituents may improve sexual behavior parameters (mounting, intromission, ejaculation) and restore hormonal balance, including testosterone levels. We evaluated these potential therapeutic effects in a streptozotocin (STZ)-induced diabetic model and provide a different perspective from the high-fat, diet-induced diabetic model investigated by Mekki et al. [19].

MATERIALS AND METHODS

Ethics statement

Sexually active male and female Wistar rats weighing 220±4 g were obtained from the Biology Department, Faculty of Life and Nature Sciences, University of Saïda. The animals were maintained in well-ventilated polypropylene cages under standard laboratory conditions (12-h light-dark cycle at 22±3°C.) The study was conducted in accordance with the ethical standards set by the Faculty Scientific Council (PV N22 of 07/12/2020) and the guidelines specified by the Algerian Association of Sciences in Animal Experimentation, with approval No. 45/DGLPAG/DVA/SDA/14, ensuring animal welfare. Special attention given to Algerian legislation, Law 12-235/2012, and the European directive 2010/63/EU.

Nomenclature

The medicinal plant used in this study is *Salvia balansae* Noë ex Coss. The plant was identified botanically by Dr. Mostari from the University of Mostaganem, Algeria, and Dr. Véla from the University of Montpellier, France. A reference voucher was kept in the university herbarium and the Muséum National d'Histoire Naturelle in Paris (MNHN-P-P02876546).

Plant material

The leaves and stems of *Salvia balansae* Noë ex Coss used in the present study were collected in the Chelif valley, Mostaganem province, during the active flowering month of April 2023. The material was cleaned and dried in the shade, and then ground to a fine powder using an electric grinder.

Preparation of extracts

The extraction procedure adopted is based on that reported by Kowalczyk [20]. Briefly, a 10% decoction was prepared by adding 100 g of leaves or stem

powder to 1 L of distilled water and heating in a water bath at 90°C for 30 min with continuous stirring. The cooled residue was filtered through a Wattman No. 1 filter and lyophilized to a powder in an Alpha 1-2 LD plus freeze-dryer. The yields of the leaf aqueous extract (LAE) and the stem aqueous extract (SAE) were calculated using the following expression:

$$\text{Yield (\%)} = (w/w) \times 100$$

where m=mass of dry extract, M=mass of dry plant powder.

Determination of total polyphenol and flavonoid contents in the extract

Total polyphenol content (TPC)

According to the microplate assay method described by Bouzana et al. [21], the total phenolic content in LAE and SAE was measure using the Folin-Ciocalteu reagent. Absorbance was measured at 765 nm using a Perkin Elmer EnSpire 96-well microplate reader. Data are presented as µg GAE/mg extract, based on the calibration equation R^2=0.984 and y=0.0032x+0.2363.

Total flavonoid content (TFC)

Flavonoid contents were determined by measuring the complex formation between flavonoids and Al^{3+} [22]. The results were expressed as µg QE/mg using the equation of the curve

$$y=0.0048X, R^2=0.997.$$

***In vitro* antioxidant properties**

DPPH free radical-scavenging assay

The assessment of the scavenging activity of free radicals was conducted as described [6]. Forty µL of LAE or SAE was combined with 160 µL DPPH solution. The solution was kept at ambient temperature in the dark for 30 min. Absorbance was measured using a 96-well microplate reader at 517 nm. The findings were compared to butylated hydroxyanisole (BHA). The comparison was based on their 50% inhibitory concentration (IC_{50}; µg/mL).

Ferric-reducing antioxidant power assay (FRAP)

The reducing power was assessed based on the procedure described previously [6]. After mixing 10 µL of LAE or SAE with 50 µL of 1% $K_3Fe(CN)_6$ and 40 µL of 0.2 M phosphate buffer (pH 6.6), the plate was incubated at 50°C for 20 min. Forty µL of distilled water, 50 µL of 10% trichloroacetic acid (TCA), and 10 µL of 0.1% $FeCl_3$ were added. Using a 96-well microplate reader, the absorbance of the mixture was measured at 700 nm. The results were compared to antioxidant standards (α-tocopherol) and expressed as the absorbance ($A_{0.5}$ µg/mL), representing the concentration resulting in 0.5 absorbance.

Acute oral toxicity of LAE and SAE

Single oral dosing was employed for acute toxicity studies in accordance with the guidelines provided by the Organization for Economic Co-operation and Development [22] utilizing an up and down procedure. In this study, 54 rats were divided into 9 groups, each consisting of 6 rats (3 males and 3 females). The groups were treated with single oral doses of 0.2, 0.6, 1, and 2 g/kg body weight of either LAE or SAE, while the control group received distilled water. Subsequently, the rats had limitless access to water and food. They were monitored for toxicological and mortality indicators initially for 30 min, then periodically over the next 24 h, and daily for a total of 14 days.

Evaluating the combined antidiabetic and pro-sexual effects of LAE and SAE

Preselection of male rats and receptivity of female rats

Male rats that were sexually experienced were preselected for the study of sexual behavior before diabetes induction following the protocol established by Olvera-Roldán et al. [13]. To induce receptivity in female rats, an injection of 10 µg estradiol benzoate was administered, followed by a dose of 2 mg progesterone 4 h before mating. Estrous females exhibited typical paracopulatory behaviors such as ear wagging and lordosis.

Type I diabetes rat model and batch allocation

For the type I diabetes model, male rats, except for the control, LAE (200 mg/kg), and SAE (200 mg/kg) groups, were rendered diabetic by a single intraperitoneal injection of STZ at 40 mg/kg after a period of fasting. Five percent glucose was added to their drinking water for 48 h to prevent hypoglycemia. The control group received only citrate buffer. After 72 h, the diabetic status of rats with fasting blood glucose levels above 2.50 (g/L) was confirmed using a glucometer [23]. The rats were randomly divided into six groups (n=7 each) as follows: Group I – control, Group II – LAE: 200 mg/kg for 12 weeks, Group III – SAE: 200 mg/kg for 12 weeks, Group IV – STZ: hyperglycemic control, Group V – STZ-LAE: diabetic rats treated with LAE at 200 mg/kg for 12 weeks, and Group VI – STZ-SAE: diabetic rats treated with SAE at 200 mg/kg for 12 weeks. The initial and final fasting blood glucose levels were measured.

Copulation behavior testing

Rats were placed in a maze for observation of sexual behavior. As previously described [13], copulatory behavior tests were carried out during the first 3 h of the nocturnal period in a tranquil room with subdued red lighting. The male rats were placed in a transparent Plexiglas box containing sawdust for 5 min to acclimate. Subsequently, a receptive female was introduced for 30 min during which interaction was permitted. Various copulatory parameters were recorded: mount frequency (MF), intromission frequency (IF), ejaculation frequency (EF), post-ejaculatory interval (PEI), mount latency (ML), intromission latency (IL), and ejaculation latency (EL). Rats that did not engage in sexual behavior within 10 min were excluded. At the conclusion of the mating behavior, vaginal smears from the female rats were examined microscopically for the presence of spermatozoa, confirming successful mating.

Testosterone assay

The total testosterone concentration in serum was measured using the electrochemiluminescence (Elecsys) method. The serum was obtained by centrifuging blood samples collected in heparin-free tubes after euthanasia, and stored at -20°C.

Statistical analysis

All analyses were performed using Sigma Stat version 3.5. A P value below 0.05 was deemed statistically significant. Group comparisons were made using Tukey's test following a one-factor ANOVA for statistical analysis. Quantitative data were expressed as the mean±SD for *in vitro* results and as the mean±SEM for *in vivo* results.

RESULTS

The extraction yield, total phenolic and flavonoid contents of *S. balansae*

The findings shown in Table 1 show the extraction yield, the total phenolic and flavonoid contents of *S. balansae* leaf and stem aqueous extracts.

In vitro antioxidant properties

The antioxidant capacity of *S. balansae* LAE and SAE was evaluated using two techniques, expressed as IC_{50} (µg/mL) and $A_{0.5}$ (µg/mL), and compared with the standards BHA, ascorbic acid and α-tocopherol (Table 2).

Table 1. Extraction yield, total phenolic content (TPC), and total flavonoid content (TFC), of the LAE and SAE

Samples	Yield %	TPC (µgGAE/mg Extract) [1]	TFC (µgQE/mg Extract) [2]
LAE	16.73%	178.22±0.68	46.74±0.15
SAE	16.82%	144.98±0.45	45.97±0.59

Values were expressed as means±SD of three parallel measurements. [1] – Total phenolics were expressed as µg gallic acid equivalent /mg of extract (µg GAE/mg); [2] – flavonoid content expressed as µg quercetin equivalent /mg of extract (µg QE/mg).

Table 2. Antioxidant activities of the LAE and SAE

Samples	Antioxidant activity	
	DPPH assay	Ferric reducing power assay
	IC_{50} (µg/mL)	$A_{0.5}$ (µg/mL)
LAE	62.90±1.06	55.54±1.04
SAE	87.50±0.70	69.99±1.21
BHA	5.73±0.41	/
α-Tocopherol	/	34.93±2.38

Values are expressed as the means±S.D. of three parallel measurements.

Acute oral toxicity of LAE and SAE

The acute toxicity of *S. balansae* LAE and SAE revealed a promising safety profile. The results showed that it is non-toxic when administered orally, with no lethality observed in rats, even at high doses of 2 g/kg, making it difficult to determine an exact LD_{50} value. This indicates a high margin of safety for consumption. Consequently, we selected one-tenth of the maximum tolerated dose as the therapeutic dose, which is 200 mg/kg, ensuring both safety and therapeutic efficacy.

Fasting blood glucose level

As shown in Fig. 1, diabetic rats exhibited significant hyperglycemia (P<0.001). Administration of LAE and SAE to diabetic rats (STZ-LAE and STZ-SAE, respectively) significantly reduced serum glucose concentrations (P<0.001 for both) by the end of the treatment period, confirming their glycemic normalization effect.

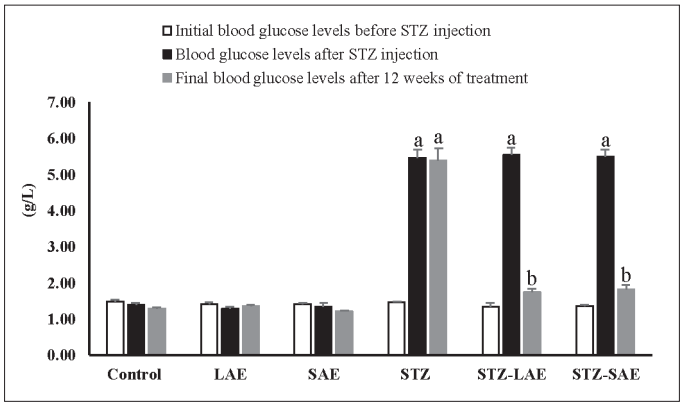

Fig. 1. Blood glucose levels of the different experimental groups before and after diabetes induction, and after 12 weeks of treatment. STZ – streptozotocin. LAE – leaf aqueous extract; SAE – stem aqueous extract. Each bar indicates the mean±SEM (n=7); P<0.001 indicates a highly significant difference vs the (a) control LAE, SAE, and (b) STZ.

Copulation behavior test

Statistical analysis of the copulation behavior test showed that the number and latency of mounts in the sexually active male rats with chronic hyperglycemia were significantly different from control rats with the number and the latency of mounts higher (P<0.001, P<0.001 respectively) in diabetic rats than in control rats. The administration of LAE and SAE to diabetic rats significantly reduced the number of mounts (P<0.001 and P<0.01, respectively), and mount latency (P<0.01 and P<0.001, respectively) compared to untreated diabetic rats (Fig. 2A and B). The results obtained for intromission frequency and latency showed that diabetic rats have a significantly lower intromission frequency (P<0.001) compared to the control group. The intromission latency of diabetic rats was significantly higher than that of control rats (P<0.001). The administration of LAE and SAE to the diabetic rats significantly increased the number of intromissions compared to diabetic control rats (P<0.001 and P<0.001, respectively). Regarding intromission latency, there was a significant decrease after the administration of LAE and SAE to diabetic rats (P<0.01, P<0.001, respectively) (Fig. 2C and D).

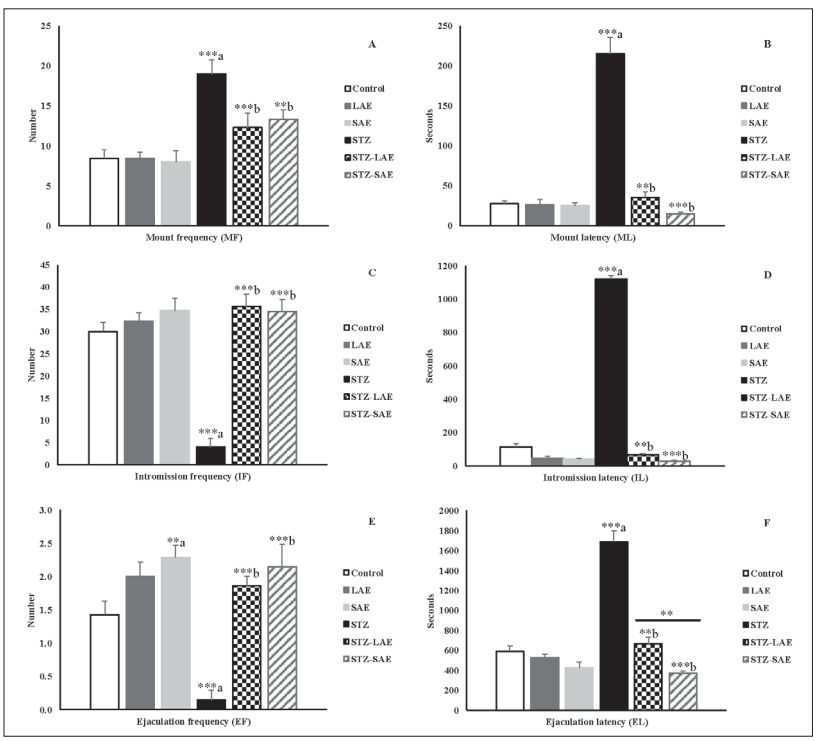

Fig.2. Effect of *S. balansae* LAE and SAE on copulatory behavior of diabetic rats. **A** - Mount frequency (MF). **B** – Mount latency (ML). **C** – Intromission frequency (IF). **D** – Intromission latency (IL). **E** – Ejaculation frequency (EF). **F** – Ejaculation latency (EL). STZ – streptozotocin; LAE – leaf aqueous extract; SAE – stem aqueous extract. Each bar indicates the mean±SEM (n= 7); **P<0.01; indicates a very significant difference; ***P<0.001 indicates a highly significant difference vs (a) control, LAE, SAE, and (b) STZ.

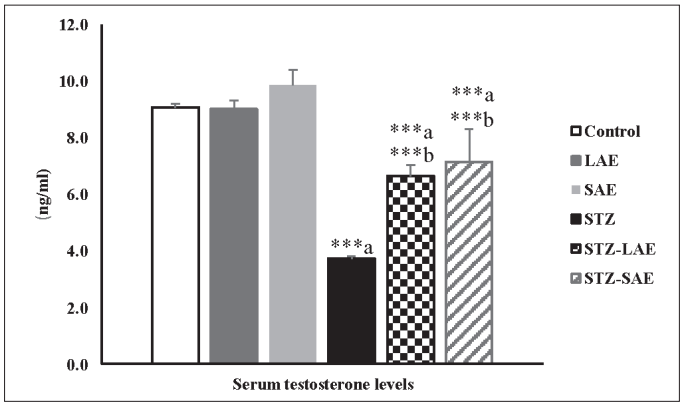

Fig. 3. Testosterone serum level (ng/mL) in different experimental groups. STZ – streptozotocin; LAE – Leaf aqueous extract; SAE – stem aqueous extract. Each bar indicates the mean±SEM (n= 7); ***P<0.001 indicates a highly significant difference vs (a) control, LAE, SAE, and (b) STZ.

Fig. 2E and F show that diabetic rats differed from control rats, as there was a highly significant decrease in the number of ejaculations in diabetic rats (P<0.001). The ejaculation latency of diabetic rats was significantly increased compared to control rats (P<0.001). In addition, ejaculation frequency after LAE and SAE administration was highly significantly increased compared to diabetic control rats (P<0.001, P<0.001 respectively). In terms of ejaculatory latency, there was a significant decrease after administration of LAE and SAE (P<0.01 and P<0.001, respectively) compared with diabetic control rats, and a significant difference (P<0.01) between the two treatments. Similarly, control rats treated with SAE showed a significantly increased ejaculation frequency compared to control rats (P<0.01).

Testosterone assay

Fig. 3 shows the serum testosterone concentration. The diabetic rats exhibited a significant reduction (P<0.001) in serum testosterone levels compared to non-diabetic rats. Administration of LAE and SAE to diabetic rats resulted in a significant increase (P<0.001 and P<0.001, respectively) in blood testosterone levels compared to diabetic rats.

DISCUSSION

Diabetes mellitus adversely affects sexual function in male rats [24]. Research suggests that natural remedies, such as sage extract with its antioxidant properties, may offer therapeutic benefits by mitigating reproductive disorders associated with diabetes [16]. To the best of our knowledge, there is no research on the effects of *S. balansae* aqueous leaf and stem extracts in models of sexual dysfunction and its antioxidant capacity in diabetes models.

The extraction yields of *S. balansae* LAE and SAE were 16.73% and 16.82%, respectively. Our findings are similar to those obtained recently for the same species from the Aures Mountains for a hydroalcoholic extract prepared from leaves and stem, while the leaf extract showed a slightly higher value [6]. This difference in yield can be attributed to geographical origin, the species type, harvesting period, drying conditions, extraction technique, and polarity of the solvent.

The medicinal effects of our LAE and SAE may arise from different secondary metabolites, such as flavonoids and phenols. The TPC in the extracts ranged from 178.22±0.68-144.98±0.45 µg GAE/mg extract, which is higher than previously reported for the same species using ultrasound-assisted extraction (49.63±6.31 mg GAE/g DW) and aqueous infusion (134.91±0.230 mg GAE/g extract) [17,19]. Similar TPC values were obtained by Bendrihem et al. [6] in ethanolic and methanolic extracts of leaves and stems of the same species collected in June 2019 at the end of the development and flowering season in 'Ichmoul', a commune in the wilaya of Batna. The values were 82.61±0.38 and 113.12±0.38 µg GAE/mg extract for leaves, and 60.80±0.42 and 99.85±0.10 µg GAE/mg extract for stems. The TFC in our extracts ranged from 46.74±0.15 and 45.97±0.59 µg QE/mg extract for LAE and SAE, respectively. Higher TFC values were found in the 70% ethanolic (61.79±0.63 µg QE/mg) and 80% methanolic (60.22±0.40 µg QE/mg) extracts of *S. balansae* leaves [6]. Moreover, a relatively low amount of TFC was recorded in the 70% ethanolic and 80% methanolic extracts of S. balansae stems, with values of 17.58±0.35 mg QE/g extract and 17.23±0.06 mg QE/g extract, respectively [6].

The high phenolic compound content of an extract indicates its high antioxidant capacity [25], as is the case with sage infusion [26]. Our results showed greater scavenging capacity (62.90±1.06 µg/mL) than

the different IC_{50} values recorded for the hydroethanolic extract from *S. balansae* leaves (545.03±3.267 µg/mL) and the methanolic extract of *S. balansae* (242.7±7.44 µg/mL) [18,19]. Bendrihem et al. [6] found a capacity to neutralize DPPH radicals close to our own in a methanolic extract from *S. balansae* followed by acetone extracts, particularly in the leaf extract. For the stem extract our result for antioxidant activity as assessed by the DPPH method (87.50±0.70 µg/ml) is higher than recorded for *S. balansae* collected from the Aures Mountains, with an IC_{50} of 97.72 µg/mL. Furthermore, the reducing power assay showed an $A_{0.5}$ (µg/mL) of 55.54±1.04 for LAE close to the results of *S. balansae* leaves collected from the Aures Mountains, while the stems extract showed an $A_{0.5}$ of 69.99±1.21 µg/mL, which was greater than the one collected from Aures Mountains [6].

The toxicity of the aqueous extracts of *S. balansae* leaves and stems reveals a promising safety profile. The results show that they are non-toxic when administered orally, with no lethality observed in rats, even at high doses up to 2 g/kg, making it difficult to determine an exact LD_{50} value. This indicates a high margin of safety for consumption. Consequently, we selected one-tenth of the maximum tolerated dose as the therapeutic dose (200 mg/kg), ensuring both safety and therapeutic efficacy. The non-toxicity of sage is supported by its key active compounds, which exhibit strong antioxidant and antiinflammatory properties. The compounds present in our extract contribute to the herb's ability to protect against oxidative stress and inflammation, further affirming its safe use [27].

Experimental diabetes was induced in rats using streptozotocin (STZ), which is a widely used model for experimental Type 1 diabetes mellitus [28]. Low doses impair β-cell function, while higher doses cause necrosis [29]. In this study, adult male Wistar rats injected with STZ developed hyperglycemia within five days, showing significantly elevated blood glucose levels. This confirms previous findings of increased blood glucose in untreated diabetic rats [30]. However, administration of LAE and SAE to diabetic rats restored blood glucose to near normal levels. Flavonoids and phenolic compounds in these extracts contribute to glucose homeostasis by regulating insulin release through signaling pathways [31,32].

Sexual function in male rats was affected by hyperglycemia and insulin deficiency. Rats with diabetes had prolonged ML, IL, EL, and less MF, IF, and EF than normoglycemic rats [33]. According to our research, increased ML and decreased MF in diabetic rodents were evidence of diminished sexual arousal. Our findings align with those of Huang et al., [33], who demonstrated that chronic hyperglycemia disrupts the dopaminergic system in the medial preoptic area (MPOA), thereby impairing sexual motivation and the initiation of copulatory behavior. Increased IL and decreased IF were suggestive of sexual impotence and significant penile erectile dysfunction, primarily caused by endothelial dysfunction and reduced nitric oxide (NO) synthesis, both critical for smooth muscle relaxation and penile vasodilation. These results are consistent with observations by Olvera-Roldán et al. [13]. The administration of *S. balansae* LAE and SAE to male diabetic rats resulted in improved sexual interaction, with a notable increase in the MF, IF, and EF. The treatment resulted in a reduction in ML, IL, EL, reinforcing the notion that the treatment possesses aphrodisiac properties. The observed pro-sexual effects in rats may be correlated with the phenolic acid and flavonoid contents of the extracts, which are known for their antioxidant properties.

Phenolic acids, such as protocatechuic acid, function as potent antioxidants by reducing oxidative stress and restoring nitric oxide (NO) bioavailability through the Akt-eNOS pathway [34], which is essential for endothelial function and smooth muscle relaxation, ultimately enhancing erectile function [32]. Higher NO levels can lead to an increase in dopamine in male rats when exposed to female rats, which boosts sexual desire (libido), potentially affecting motor performance and the initiation of sexual activity [35]. Comparable effects have been observed with *Stevia rebaudiana* extract, which exhibits aphrodisiac properties in STZ-induced diabetic rats by preserving Leydig cell function and enhancing sexual function, as evidenced by increased male-female interaction [36]. These parallels suggest that the bioactive compounds in both *S. balansae* and *Stevia rebaudiana* may mitigate diabetes-induced male reproductive dysfunctions through shared mechanisms, including the modulation of oxidative stress and hormonal balance.

Diabetic rats show significant reductions in serum testosterone levels compared with control rats,

supporting previous findings that in diabetic rats, low testosterone may contribute to decreased sexual performance [13]. This dysregulation disrupts the hypothalamic-pituitary-gonadal (HPG) axis, altering testosterone secretion [37,38], and may also affect the vascular plexus of the corpora cavernosa, leading to erectile dysfunction (ED) and, consequently, impaired reproductive function [39]. Treatment with LAE and SAE resulted in a significant increase in serum testosterone levels in diabetic rats. Flavonoids have a core structure similar to steroids and cholesterol, allowing them to interact with androgen receptors in Sertoli cells and enzymes of steroidogenesis [40]. This interaction stimulates androgen production in Leydig cells by increasing the expression of steroidogenic acute regulatory protein (StAR), crucial for cholesterol transport and testosterone production [41]. These bioactive compounds also help maintain appropriate levels of reproductive hormones like testosterone, FSH, and LH by stimulating the HPG axis [42], further elucidating the mechanisms behind the observed improvements in reproductive function and sexual performance.

CONCLUSIONS

The results of this study indicate that aqueous extracts of the leaves (LAE) and stems (SAE) of *S. balansae* have significant antioxidant, antihyperglycemic, and prosexual properties. In streptozotocin-induced diabetic male rats, these extracts effectively reduced hyperglycemia, improved sexual behavior parameters, and increased serum testosterone levels, supporting their potential in the treatment of diabetic complications. Given their high content of polyphenols and flavonoids, which contribute to their antioxidant capacity, and their demonstrated safety profile, LAE and SAE show promise as candidates for further investigation into diabetes-related metabolic and reproductive health interventions.

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Author contributions: Writing - Original Draft, Investigation, Conceptualization, Sendous W. Souidi; Supervision, Visualization, Validation, Mansouria Belhocine; Investigation, Methodology, Ines Feknous and Chawki Bensouici; Resources, Tayeb Sitayeb and Abdelkader A. Dahou. All authors have read and agreed to the published version of the manuscript.

Conflict of interest disclosure: The authors declare no conflict of interest.

Data availability: The data underlying the reported findings have been provided as a raw dataset available here: https://www.serbiosoc.org.rs/NewUploads/Uploads/Souidi%20et%20al_Dataset.pdf

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