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Sub-chronic and acute toxicity of aqueous extracts *Salvia blancoana* subsp. *mesatlantica* (Maire) Figuerola to rodents

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ABSTRACT

Background: *Salvia blancoana* subsp. *mesatlantica* (Maire) Figuerola (SBm) is a plant endemic to Morocco and is one of the less studied species of Salvia. Herbal therapy is becoming more and more popular, especially in underdeveloped nations where access to medicinal herbs is affordable. However, some plants demonstrated toxic effects in animals and humans.
Objective: Our study aimed to evaluate the SBm-extract for both acute and sub-chronic toxicity.
Methods: Aqueous extracts were obtained from the aerial parts of SBm collected from Immouzer Kander commune (Middle Atlas, Morocco). Total Phenolic Content (TPC) and Flavones and flavonols Content (FFC), Antioxidant activity (2,2-diphenyl-1-picrylhydrazyl (DPPH) and reducing power) was determined, and chemical composition was determined by High-Performance Liquid Chromatography with Diode Array Detection (HPLC-DAD). Toxicity tests were conducted on mice and rats.
Results: In acute toxicity, Swiss albino mice (mass of 25–35 g) received SBm-extract orally and intraperitoneally at doses (0.5–11 g/kg, bm). The sub-chronic toxicity was tested in Wistar albino rats (mass of 200–240 g) for 90 days at doses of 0, 250, 500, or 1000 mg/kg, bm. Values of TPC and FFC were estimated to be 157.56 ± 0.32 mg GAE/g DW and 7.89 ± 0.05 mg QE/g DW, respectively. DPPH scavenging (IC_{50}) was estimated to be 26.9 ± 0.08 μg/mL while reducing power was 12.41 ± 0.03 μg/mL. No toxicity or deaths were observed in acute tests after oral exposure, while intraperitoneal administration resulted in dose-dependent acute toxicity, with an LD_{50} value of 6.82 g/kg. In sub-chronic tests, most hematological and biochemical parameters remained unchanged, except for transient fluctuations in specific blood constituents and a transitory reduction in serum

Abbreviations: ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; BW, Body Mass; DPPH, 2,2-diphenyl-1-picrylhydrazyl; HCT, Hematocrit; HE, Haematoxylin and Eosin; HGB, Hemoglobin; IC_{50}, Half Maximal Inhibitory Concentration; LD50, Lethal Dose 50; LOAEL, Lowest-Observed-Adverse-Effect Level; MCHC, Mean Corpuscular Hemoglobin Concentration; MCV, Mean Corpuscular Volume; MCV, Mean RBC Volume; NOAEL, No-Observed-Adverse-Effect-Level; OECD, Organization for Economic Co-operation and Development; PLT, Platelet Count; RBC, Red Blood Cells, S.E.M., Standard Error of Mean; SBm-extract, *Salvia blancoana* subsp. *mesatlantica* aqueous extract; FFC, Flavones and flavonols Content; TPC, Total Phenolic Content; HPLC-DAD, High-Performance Liquid Chromatography with Diode Array Detection; WBC, White Blood Cells.

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glucose levels observed at elevated dosages. Histopathological investigation revealed no organ abnormalities. The SBm-extract exhibited minimal toxicity, supporting its safe use.
Conclusions: Despite the relevant results of this study, future studies need to confirm these findings and expand our understanding of the safety characteristics of *Salvia*. Further investigations are needed to explore the effects of other solvents on the extraction of bioactive compounds from the underground and aerial parts of this endemic species. Evaluation of other biological properties such as anti-microbial, anti-cancer, and anti-inflammatory activities are needed.

1. Introduction

Various indigenous medical traditions have harnessed plants for their therapeutic properties [1,2]. During the last decades, herbal therapy is becoming more and more popular, especially in underdeveloped nations where access to medicinal herbs is affordable and readily available [3,4]. Indeed, herbal medicine constitutes the predominant healthcare approach for a substantial proportion of the global populace, spanning from 60 % to 80 % [5,6]. These plants serve in addressing health issues like digestive and stomach disorders [7,8]. Their medicinal efficacy stems from the diverse chemical compounds found in their flowers, leaves, stems, and roots [7,8]. However, despite the beneficial effects of medicinal herbs, some plants demonstrated toxicity effects in animals and humans [9]. For example, the essential oil of *Salvia officinalis* showed acute and chronic toxicities in the liver and kidneys of rats [9,10]. In Morocco, public health issues related to poisoning from medicinal plants remain concerning due to a lack of strict regulations and adequate knowledge. Among the plants most commonly involved in these poisonings are glue thistle (*Atractylis gummifera*, known as Addad), cannabis (*Cannabis sativa*), and harmel (*Peganum harmala*), which have significant morbidity rates [11]. In the absence of appropriate controls, these plants pose a toxicological threat, particularly to children. Therefore, it is imperative to establish a monitoring system to assess the therapeutic efficacy and toxic risks of plant-based products [12].

Chemical components in medicinal plants control their biological characteristics, including their toxic and therapeutic effects [13,14]. The essential oils, extracts, and infusions of medicinal plants are rich in a wide range of bioactive molecules [11,12]. For example, 56, 54, and 49 chemical compounds were identified from the essential oils of *Salvia pilifera* (Montbret & Aucher), *Salvia viscosa* Jacq., and *Salvia adenophylla* Hedge & Hub.-Mor., respectively [15]. Some of the major components were β-pinene (14.4 %) and α-pinene (16.2 %) in Eos of *Salvia adenophylla*, myrcene (9.0 %) and β-pinene (24.9 %) in Eos of *Salvia pilifera*, and β-caryophyllene (10.8 %) and α-copaene (13.0 %) in Eos of *Salvia viscosa*. Extracts of medicinal plants demonstrate significant quantities of polyphenols and flavonoids [16,17]. Compounds in plants vary based on species, origin, and extraction techniques. Essential oils and extracts contain constituents with important biological functions, such as antioxidants and potential toxicity effects [15,18].

In traditional medicine, the Lamiaceae family holds prominence due to its extensive distribution, encompassing around 236 genera and over 6000 species among various plant families [19,20]. Among the Lamiaceae, *Salvia* (*Salvia spp*.) is the largest genus and consists of approximately 900 species worldwide [21,22]. Many of these species are highly valued for their advantageous qualities, which make them useful in a range of applications like traditional remedies, perfumes, and cosmetics [23]. One of the most extensively cultivated species, Common Sage (*Salvia officinalis* L.) possesses vital essential oils, polar extracts, and biological potential [24,25]. Its various applications make it crucial for research [26]. Sage is a medicinal herb, prevalent in Europe, the Mediterranean, and the Middle East, that treats various conditions by use as antiseptic, antibacterial, and cognitive impairments [23,27]. Another member of the genus *Salvia*, *S. lavandulifolia* Vahl, is native to the Mediterranean and is used in traditional medicine for its antiseptic, anti-inflammatory, and analgesic properties. It has fungicidal, virucidal, and bactericidal activities and is favored by diabetic patients as a hypoglycemic treatment [26,28–30]. The species of this family are rich in chemical compounds and contribute to their biological activities. For example, Sharma et al., [31] recorded significant quantity of total polyphenols, flavonoids, and terpenoids in extracts of *Salvia officinalis* L. These compounds support various biological properties, such as toxicity effects, antioxidant activity, and anti-microbial inhibition [32]. Despite the significant importance of the Lamiaceae family for research investigations and therapeutic uses, many species belonging to this family have not yet been investigated. Therefore, more research is needed to explore the chemical compounds and biological properties in other plants and this is suggested to add new data for medicine and phytochemicals.

Salvia blancoana subsp. *mesatlantica* (Maire) Figuerola, previously known as *Salvia lavandulifolia* subsp. m*esatlantica* (Maire) Rosua & Blanca, is endemic to Morocco thriving particularly in elevated regions such as the Middle Atlas mountains [33].

In Moroccan traditional medicine, the leaves of *S. lavandulifolia* subsp. *mesatlantica* are widely acknowledged for their antiseptic, healing, choleretic, astringent, hypoglycemic and antidiabetic properties. The leaves and areal parts of these plants are used in herbal tea, vapor inhalation, and hydroalcoholic extract to manage diseases of the respiratory, digestive, circulatory, and genitourinary systems [34].

Although *S. blancoana* subsp. *mesatlantica* (Maire) is well-known for its medicinal attributes, it is essential to recognize that natural remedies can also entail potential adverse effects. To the best of our knowledge, there is limited laboratory research available regarding the chemical compounds and biological properties of this particular species. Therefore, this study aimed to evaluate the quantity of total polyphenols and flavonoids in aqueous extracts of wild *Salvia blancoana* subsp. *mesatlantica*. Antioxidant activity and toxicity effects of the extracts were assessed. Both acute and chronic effects were assessed on mice and rats, respectively.

2. Material and methods

2.1. Plant Material

In the present study, we used leaves from *S. blancoana* subsp. *mesatlantica* sourced from the Immouzer Kander commune (33.731° N, 5.015° W) situated within the Sefrou province of the Middle Atlas region in Morocco. The collection of the plants was realized during the period from April to June 2022. The sampled plants were transferred to the laboratory for identification and chemical experiments. Drs. M. Fennane and M. Ibn Tattou of the Department of Botany and Plant Ecology, Scientific Institute, Mohammed V University, Rabat, confirmed the identity of the plant. To serve as a permanent reference, a voucher specimen (RAB 112040) was deposited into the institute's Herbarium Fig. 1.

2.2. Preparation of aqueous extracts

The aerial parts of *S. blancoana* subsp. *mesatlantica* were promptly washed with running water. After seven days of air drying in a dark environment at room temperature, they were crushed into a powder using a Willey mill. Following this, the aqueous extract of the plant was prepared by boiling 100 g of the powder in 1000 milliliters of distilled

water under reflux conditions for 20 min. The resulting decoction was then centrifuged, filtered, and frozen at −20°C. Subsequently, it underwent lyophilization using a FreeZone® Dry 4.5 lyophilizer, yielding approximately 11 % (w/w) of residue. The residue was preserved at −20°C until needed. Before each experiment, the residue (referred to as SBm-extract) was meticulously prepared by dissolving it in distilled water [35].

2.3. Chemical analysis of SBm Extract

2.3.1. Quantification of total phenolic content (TPC)

The total phenolic content (TPC) was quantified using the Folin-Ciocalteu reagent-based colorimetric method, following the procedure described by Singleton et al. (1999) [36]. 50 μL of the sample or a reference solution was mixed with 450 μL of a 10 % Folin-Ciocalteu reagent solution. The mixture was vortexed and incubated for 5 min. Then, 450 μL of a 75 $g.L^{-1}$ sodium carbonate solution was added and vortexed again. After a 2-hour incubation period at room temperature (25 ± 1 °C), the absorbance was measured at 760 nm. The quantification of TPC in the dry plant material was based on gallic acid used as the reference standard. TPC was expressed as Eq GAE/g DW by applying the reversion equation derived from the calibration curve constructed with gallic acid.

2.3.2. Quantification of flavones and flavonols content (FFC)

The aluminum chloride (AlCl3) method, originally described by Miguel et al. [37], was applied with minor adjustments to quantify the flavones and flavonols content. In short, 500 μL of the diluted sample and 500 μL of 2 % AlCl3 solution were combined. The combination was incubated for one hour in the dark at ambient temperature. Next, each solution's absorbance was measured at 420 nm in relation to a blank.

Fig. 1. Sampling Site Map.

2.4. Identification of phenolic compounds by HPLC-DAD (High-Performance Liquid Chromatography with Diode Array Detection)

High-performance liquid chromatography (HPLC) fitted with a UV detector (wavelength range: 210–400 nm) was used to identify and quantify chemical constituents. A ternary mobile phase consisting of acetonitrile, methanol, and water was used to separate phenolic compounds by HPLC on a reverse-phase column (C18) measuring 4 mm × 250 mm and having a particle size of 5 μm. The column's flow rate stood at 1 mL/min. A 40 μl injection volume was used, and the column temperature was maintained at 30°C. Phenolic compounds present in the hydroethanolic extract had been previously quantified so that 50 mg/mL of the extract was made, then filtered through 0.45 μm microfilters [32,33].

2.5. Antioxidant activity in SBm-extract

Dried aqueous extracts of *S. blancoana* subsp. *mesatlantica* were re-dissolved in water to a concentration of 4 mg/mL for the determination of their antioxidant activity.

2.5.1. DPPH free radical scavenging activity

The SBm-extract's overall capacity to scavenge free radicals was assessed using the previously described technique [38]. Briefly, 50 μL of the SBm-extract at different concentrations (ranging from 12.5 to 50 mg/mL) was combined with 825 μL of DPPH ethanol solution. Following thorough mixing, the mixture was allowed to incubate at room temperature in the absence of light for one hour. Additionally, measurements of the DPPH radical absorption for the blank were conducted. Each measurement was performed in triplicate for accuracy. The DPPH antioxidant activity was computed with the following formula:

$$\text{Inhibition}(\%) = \frac{\text{Abs control} - \text{Abs sample}}{\text{Abs control}} \times 100 \quad (1)$$

In this equation, Abs sample represents the absorbance of the extract, while Abs control corresponds to the absorbance of the control. By analyzing the graph depicting the inhibition rate exhibited by the plant extract, the IC_{50} value of DPPH was established [39].

2.5.2. Reducing power

The reducing capacity of the sample was evaluated following the ferrous ion reduction method outlined by Oyaizu, [40]. Briefly, 50 μL of the sample was diluted with 250 μL of 0.2 M sodium phosphate buffer (pH=6.6) and then mixed with 250 μL of a 1 % potassium ferricyanide solution. The resultant mixture was sealed and subjected to incubation at 50°C for 20 min. After the incubation period, 250 μL of 10 % trichloroacetic acid was introduced to the reaction mixture, followed by centrifugation for 10 min. The supernatant was combined with 250 μL of distilled water and 60 μL of a 0.1 % ferric chloride solution. Subsequently, the absorbance of the resultant solution was measured at 700 nm, with ascorbic acid serving as the standard. All experiments were performed in triplicate, and the outcomes were presented as the mean ± standard error of the mean (SEM).

2.6. Experimental animals

Swiss albino mice of both sexes, weighing between 25 and 35 g, were used to assess acute toxicity, while Wistar albino rats of both sexes, weighing between 200 and 240 g, were utilized to evaluate subchronic toxicity. The animals were obtained from the animal house at the Faculty of Sciences Dhar El Mahraz, USMBA in Fez, Morocco. All ethical regulations were strictly followed. The animals were maintained in a controlled environment with a temperature set at 25 ± 1 °C, with a 12-hour light-dark cycle (12 L/12 D) to allow for proper acclimation. They were acclimated to these conditions for seven days before the start of the experiments, allowing them to adjust effectively to their new environment. Access to tap water and food was provided ad libitum, and we took great care to ensure their well-being and comfort. Our institutional animal protection committee approved our study procedures, and we adhered to ethical guidelines, as demonstrated by our ethical approval registration number L.20. USMBA-SNAMOPEQ 2020–03.

2.7. Acute toxicity of SBm-extract

The acute toxicity test was conducted in accordance with OECD 423 guidelines to ensure rigor and standardization [41]. A total of 180 Swiss albino mice, both males and females, were used to assess the acute toxicity of different doses of SBm extract dissolved in distilled water, administered via two distinct routes: intraperitoneal and oral. The mice were divided into two groups based on the administration route. The first group received the doses orally, which mimics human use, while the second group was treated via the intraperitoneal route, ensuring systemic exposure to the medication. Each group was further subdivided into 9 batches of 10 mice, equally composed of 5 males and 5 females, according to the doses administered, which were 0, 0.5, 2.0, 3.5, 5.0, 6.5, 8.0, 9.5, and 11.0 g/kg BW. The test substances were administered at constant volumes: 0.4 mL per 20 g BW for the intraperitoneal route and 0.5 mL per 20 g BW for the oral route [35].

Following the treatment, the animals were continuously monitored for one hour, followed by intermittent monitoring for four hours. Any behavioural modifications, toxicity-related signs, or symptoms of mortality, including the death latency period, were tracked throughout a 24-hour span. The animals were given food and water for 14 days, during which time their daily food and water intake, body weight, and any changes in appearance were noted. The Litchfield and Wilcoxon approach was utilized to ascertain the LD50 (Lethal Dose 50) values [42].

2.8. Sub-chronic toxicity of SBm-extract

2.8.1. Experimental design

Male and female Wistar albino rats, weighing between 200 and 240 g, were housed in gender-segregated plastic cages. Throughout the acclimation period, they were divided into four groups of 10 individuals, ensuring an equal representation of 5 males and 5 females in each group. Each cage contained 2–3 rats, in accordance with animal welfare guidelines.

The SBm extract, mixed with distilled water and adjusted to a final volume of 10 mL/kg per dose, was administered daily by oral gavage for 90 days to groups 1 through 4 at doses of 0, 250, 500, and 1000 mg/kg of BW, respectively. The choice of these dosages was determined based on multiple factors, including recommendations from the Dep of Commerce in United States [43], human dosage practices in traditional medicine, and the results obtained from the acute (single dose) study conducted in mice.

During the duration of the trial, toxic symptoms and mortality were carefully tracked every day. After each 30-day cycle, precise measurements of body weights were noted. Under light anesthesia, blood samples were taken together with the administration of an anticoagulant (200 mL of blood and 50 mL of 4 mM ethylenediamine tetra acetate or heparin) to ensure accurate analysis. Blood samples treated with ethylenediamine tetra acetic acid were promptly utilized for hematological parameter assessments, while heparinized blood was subjected to centrifugation at 2000 x g for 10 min at 4°C. The resulting plasma was carefully preserved at −20°C until analyzed for biochemical parameters.

Upon completion of the 90-day experimental period, blood samples were obtained through cardiac puncture. Subsequently, the liver, kidneys, and spleen were subjected to precise dissection, and their weights were meticulously recorded to determine any potential changes in organ mass. To facilitate further examination, selected portions of these organs were fixed in a 10 % formalin solution to prepare histopathological slides for microscopic evaluation.

2.8.2. Hematology and clinical chemistry analysis

A Sysmex KX-21 blood analyzer (Sysmex Corporation, Japan) was utilized to assess an extensive panel of hematological characteristics, including total red blood cells, neutrophils, eosinophils, basophils, lymphocytes, mean RBC volume, monocytes, platelet count, hematocrit, mean RBC hemoglobin concentration and hemoglobin. This compact analyzer utilizes a variety of light sources, such as a halogen lamp for hemoglobin dimension, a tungsten halogen lamp for white blood cell count, and a helium/neon light for RBC and platelet counts, ensuring precise and accurate measurement of each parameter.

The biochemical analyses were performed using 1 mL of blood samples collected in heparinized Eppendorf tubes. The resulting plasma was obtained by centrifuging the samples at 2000 x g for 10 min. Several key biochemical parameters, including aspartate aminotransferase, glucose, serum creatinine, triglycerides, urea, alanine aminotransferase, total cholesterol, and total bilirubin, were measured using (Beckman Coulter, Japan), an automated serum biochemistry analyzer.

2.8.3. Histopathology

After performing a simple laparotomy, internal organs, including the spleen, kidneys and liver were removed under sterilized conditions for determination of relative masses and macroscopic examination. Organs were quickly preserved in 10 % buffered formalin (pH 7.4). Following fixation, tissue samples were cleaned with toluene, dried with a graded series of ethanol (70–100 %), and then embedded in paraffin. Using a microtome, thin slices of 5 μm were created, and they were then stained with hematoxylin and eosin (HE) for microscopic examination. The treated groups' microscopic characteristics were contrasted with those of the control group, and photomicrographs were recorded for future reference.

2.9. Statistical analysis

The data were imported into a Microsoft Office Excel 2016 file and GraphPad Prism 8.0 V for Windows was used for analysis. The normality of data was tested using the Shapiro-Wilks test and homogeneity of variance was assessed using Levene's test. Results were expressed as mean values ± SEM. We performed a one-way ANOVA followed by post-hoc Tukey's test to compare the groups, and the results were considered significant at the $p < 0.05$ level.

3. Results

3.1. Quantification of TPC, FFC, and antioxidant activity

The TPC in aqueous extract was esteemed at 157.56 ± 0.32 mg GAE/g DW. Further, the value of FFC was measured at 7.89 ± 0.05 mg QE/g DW. In terms of antioxidant activity, the value of IC_{50} (DPPH scavenging) was measured at 26.9 ± 0.08 μg/mL. Moreover, the reducing power of SBm-extract was 12.41 ± 0.03 μg/mL.

3.2. Phenolic compounds in extract

The chemical components of the *S. blancoana* subsp. *mesatlantica* extract were examined using high-performance liquid chromatography coupled with a diode array detector (HPLC-DAD). Fig. 2 depicts the HPLC chromatogram illustrating the identified polyphenols, and Table 1 provides the documentation of retention times and percentage areas of the compounds in the SBm-extract. In total, 10 chemical compounds were identified in the aqueous extracts of *S. blancoana* subsp. *mesatlantica*. The predominant chemical compounds were Naringin (56.9 %), followed by Cinnamic acid (14.96 %) and Rutin (8.4 %). A medium quantity of Apigenin (4.76 %), Kaempferol (4.51 %), and Vanillic acid (3.1 %) were also identified. In contrast, p-coumaric acid and Sinapic acid were the less dominant compounds with 0.97 % and 0.29 %, respectively.

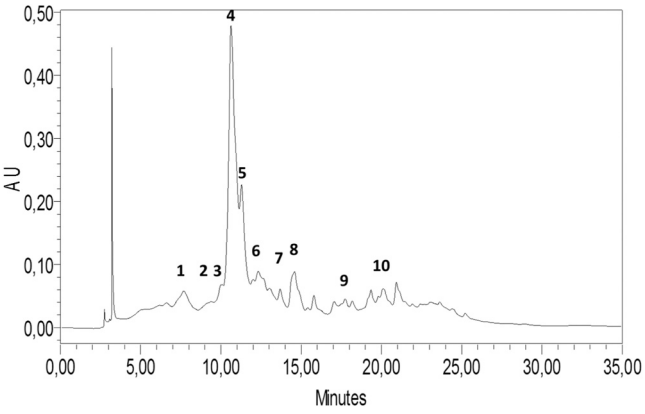

Fig. 2. HPLC-DAD chromatogram of *S. blancoana* subsp. *mesatlantica* extract) - at 320 nm using the following standards: 1: vanillic acid, 2: 3-hydroxybenzoic acid, 3: naringin,4: cinnamic acid, 5: p-coumaric acid, 6: sinapic acid, 7: succinic acid, 8: rutin, 9: kaempferol, and 10: apigenin.

Table 1
Bioactive compound identified in the aqueous extract of *Salvia blancoana* subsp. *mesatlantica* leaves.

Phytochemical		Retention Time (min)	Area (%)
Vanillic acid	1	7,66	3,1
3-hydroxybenzoic acid	2	9887	1,81
Naringin	3	10,46	56,9
Cinnamic acid	4	11,33	14,96
p-coumaric acid	5	11,858	0,29
Sinapic acid	6	12,247	0,97
Succinic acid	7	13,69	1,39
Rutin	8	14,484	8,4
Kaempferol	9	17,48	4,51
Apigenine	10	21,10	4,76

3.3. Acute toxicity

Following acute administration of single oral doses of the SBm-extract at various doses up to and including the maximum dose tested at 11 g/kg bm mice exhibited no toxicity or lethality (Table 2). This indicates that the SBm-extract is safe for oral consumption, with the greatest dose tested being established for both sexes of animals for example the no-observed-adverse-effect level (NOAEL). However, it's crucial to remember that intraperitoneal injection of the SBm-extract increased the rate of acute toxicity and death in a dose-dependent manner. Mortality of essentially 0 % at doses as great as 2 g SBm-extract/kg, bm, but it progressively rose to 100 % at the greatest dose investigated, 11 g/kg, bm.

The LOAEL, which denotes the lowest observed adverse effect level, was determined to be 2 g/kg for both sexes, while the NOAEL, based on intraperitoneal injection was found to be 0.5 g/ kg, bm. Some adverse consequences, including anorexia and lethargy, were observed later and were more prominent at greater dosages, lasting until death. Immediate adverse effects, like hypoactivity, piloerection, and asthenia, were observed shortly after injection. The LD_{50} for intraperitoneally administered SBm-extract in mice was calculated to be 6.82 g/kg, bm.

3.4. Sub-chronic toxicity

3.4.1. Body mass

The Fig. 3 presents the results of body weight of studied animals treated with SBm-extract. Female rats, in both control and treated groups (Groups 2–4), did not exhibit any significant changes in their body weight over time (Fig. 3.**B**). Nevertheless, following a 30-day treatment period, male rats in Group 3 that received 500 mg/kg of

Table 2
Investigations on the acute toxicity of giving mice an oral and intraperitoneal dose of *Salvia blancoana* subsp. *mesatlantica* aqueous extract.

Dose (g/kg BW)	Sex	Administration route					
		Oral			Intraperitoneal		
		Dead/Treated mice	Latency	Toxic symptoms	Dead/Treated mice	Latency	Toxic symptoms
Control	Male	0/5	–	None	0/5	–	None
	Female	0/5	–	None	0/5	–	None
0.5	Male	0/5	–	None	0/5	–	None
	Female	0/5	–	None	0/5	–	None
2.0	Male	0/5	–	None	1/5	> 48 h,< 72 h	Piloerection, asthenia, hypoactivity, anorexia
	Female	0/5	–	None	0/5	> 48 h,< 72 h	
3.5	Male	0/5	–	None	1/5	> 48 h,< 72 h	Piloerection, asthenia, hypoactivity, anorexia
	Female	0/5	–	None	0/5	> 48 h,< 72 h	
5.0	Male	0/5	–	None	2/5	< 48 h	Piloerection, asthenia, hypoactivity, anorexia
	Female	0/5	–	None	1/5	< 48 h	
6.5	Male	0/5	–	None	3/5	< 48 h	Piloerection, convulsions, asthenia, hypoactivity, anorexia
	Female	0/5	–	None	1/5	< 48 h	
8.0	Male	0/5	–	None	2/5	< 24 h	Piloerection, convulsions, extreme lethargy, paralysis,
	Female	0/5	–	None	4/5	< 24 h	anorexia
9.5	Male	0/5	–	None	5/5	< 2 h	Piloerection asthenia, extreme lethargy, convulsions,
	Female	0/5	–	None	5/5	< 2 h	paralysis, syncope
11.0	Male	0/5	–	None	5/5	< 1 h	Piloerection asthenia, extreme lethargy, convulsions,
	Female	0/5	–	None	5/5	< 1 h	paralysis, syncope

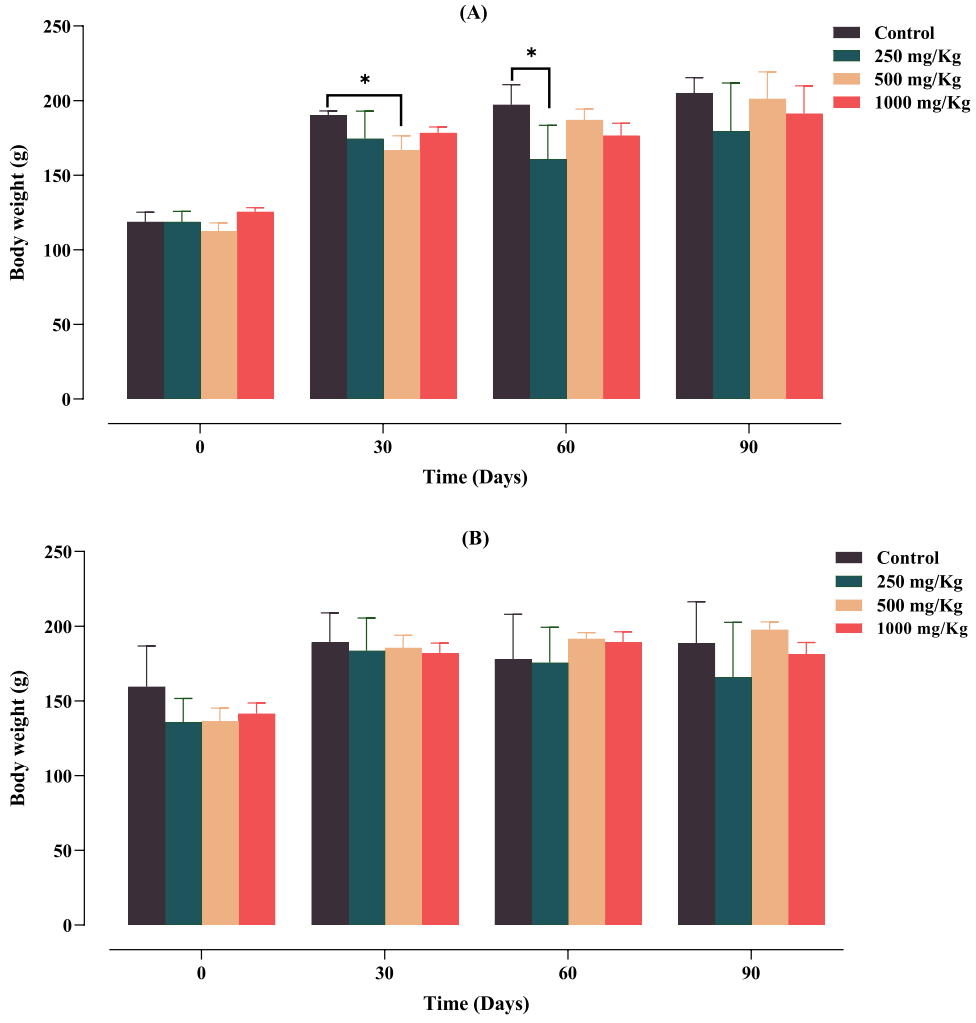

Fig. 3. Changes in the body mass of male (A) and female rats (B) after sub-chronic oral treatment with a lyophilised aqueous extract of *Salvia blancoana* subsp. *mesatlantica*. * Denote significant difference at $p < 0.05$.

SBm-extract had a significant reduction in body weight ($p < 0.05$). Furthermore, following 60 days of treatment, Group 2, which received 250 mg/kg of SBm-extract, had a decrease in body weight ($p < 0.05$) (Fig. 3.**A**). Interestingly, no deaths were reported at any dose during the 90-day treatment, even at the maximum dose of 1000 mg/kg.

3.4.2. Hematological parameters

Tables 3 and 4 present the results of a sub-chronic oral administration of SBm-extract on a number of hematological parameters, including RBC, HGB, HCT, MCV, MCHC, and PLT. Following careful examination, it was found that there was no discernible variation in male rates, suggesting negligible impacts. With the exception of group 4, which received a higher dosage of up to 1000 mg/kg, these results were consistent with observations made in females. Interestingly, after the first month of treatment, there was a notable decrease in this group's red blood cell (RBC) count of 24.4 % and hematocrit (HCT) levels of 23.4 % when compared to the control group. It's crucial to remember that this pattern was only temporary because RBC and HCT levels returned to normal after two months of treatment and as the trial came to a conclusion.

After sixty days of sub-chronic oral administration of SBm-extract, no discernible changes to numbers of white blood cells in male or female Wistar rats (Tables 5 and 6) with the exception of Group 4 receiving 1000 mg/kg, bm, which showed a 61.8 % decrease in eosinophils in comparison to the control group. After one month of treatment, basophil counts were significantly ($p < 0.05$). greater in female rats treated with 500 and 1000 mg/kg, bm, respectively, following two months of treatment, these same groups demonstrated a significant ($p < 0.05$ decrease in eosinophils of approximately 60 %). After 30 days of dosing, Group 4 contained significantly (76.1 %) fewer monocytes. Differences in white blood cell counts between the treated group and the control group were only temporary and returned to normal at the end of the treatment period.

Table 3
The effect of sub-chronic oral administration of a lyophilized aqueous extract of *Salvia blancoana* subsp. *mesatlantica* on certain hematological parameters in male Wistar rats.

Parameter	Treatment period (days)			
	Day_0	Day_{30}	Day_{60}	Day_{90}
Group 1 (Control)				
RBC (10^6/µL)	7.88 ± 0.31	6.51 ± 0.20	9.20 ± 0.13	8.02 ± 0.10
HGB (g/dL)	14.25 ± 0.32	11.05 ± 0.38	15.65 ± 0.20	12.50 ± 0.06
HCT (%)	47.65 ± 3.49	39.05 ± 1.59	49.80 ± 0.46	42.75 ± 0.72
MCV (fL)	55.80 ± 1.60	60.00 ± 0.58	54.50 ± 0.87	52.67 ± 0.33
MCHC (pg)	17.25 ± 0.32	17.50 ± 0.29	17.00 ± 1.15	15.50 ± 0.29
PLT (10^5/µL)	7.11 ± 1.08	5.62 ± 0.39	8.43 ± 0.11	6.21 ± 0.18
Group 2 (SBm dose, 250 mg)				
RBC (10^6/µL)	7.83 ± 0.10	6.43 ± 0.07	8.08 ± 0.68	7.72 ± 0.93
HGB (g/dL)	12.90 ± 0.00	10.60 ± 0.17	13.15 ± 1.99	12.53 ± 1.86
HCT (%)	41.60 ± 4.90	37.00 ± 0.64	46.33 ± 5.27	42.93 ± 5.32
MCV (fL)	51.93 ± 4.03	59.00 ± 1.00	51.50 ± 0.87	50.00 ± 1.73
MCHC (pg)	16.80 ± 0.06	17.00 ± 1.15	16.50 ± 0.29	14.50 ± 0.87
PLT (10^5/µL)	7.95 ± 1.37	6.01 ± 0.23	8.17 ± 1.69	7.05 ± 1.13
Group 3 (SBm dose, 500 mg)				
RBC (10^6/µL)	7.91 ± 0.24	7.44 ± 0.43	7.86 ± 0.27	8.51 ± 0.17
HGB (g/dL)	14.35 ± 0.09	13.00 ± 1.15	12.45 ± 0.78	13.85 ± 0.14
HCT (%)	50.30 ± 0.57	41.38 ± 3.08	42.63 ± 2.58	47.70 ± 0.69
MCV (fL)	60.95 ± 0.95	58.00 ± 1.00	52.50 ± 0.87	54.67 ± 0.33
MCHC (pg)	17.65 ± 0.38	17.00 ± 0.58	16.00 ± 0.00	16.00 ± 0.58
PLT (10^5/µL)	7.58 ± 0.72	7.50 ± 0.89	8.01 ± 0.36	6.57 ± 0.64
Group 4 (SBm dose, 1000 mg)				
RBC (10^6/µL)	7.56 ± 0.32	6.07 ± 0.15	9.66 ± 0.15	8.14 ± 0.07
HGB (g/dL)	12.58 ± 0.79	10.25 ± 0.38	16.20 ± 0.29	12.50 ± 0.29
HCT (%)	44.35 ± 3.90	35.23 ± 1.29	51.78 ± 1.08	41.90 ± 1.21
MCV (fL)	59.43 ± 2.42	56.50 ± 1.50	54.50 ± 0.29	52.00 ± 2.31
MCHC (pg)	17.30 ± 0.17	17.00 ± 1.00	16.50 ± 0.20	15.± 0.58
PLT (10^5/µL)	6.25 ± 0.50	7.10 ± 1.01	10.81 ± 0.47	6.78 ± 0.28

Over the course of 90 days, male Wistar rats (n = 5) were given the whole plant's lyophilized aqueous extract orally on a daily basis.
Hematological parameters (HBG: hemoglobin**, HCT**: hematocrit, **RBC:** red blood cells, **MCHC**: Mean corpuscular hemoglobin concentration, **MCV**: Mean corpuscular volume, **PLT**: platelet.)

Table 4
The effect of sub-chronic oral administration of a lyophilized aqueous extract of *Salvia blancoana* subsp. *mesatlantica* on certain hematological parameters in female Wistar rats.

Parameter	Treatment period (days)			
	Day_0	Day_{30}	Day_{60}	Day_{90}
Group 1 (Control)				
RBC (10^6/µL)	7.95 ± 0.30	8.10 ± 0.16	9.13 ± 0.30	7.76 ± 0.10
HGB (g/dL)	14.10 ± 0.90	13.85 ± 0.20	16.60 ± 0.07	13.10 ± 0.12
HCT (%)	45.08 ± 0.59	49.65 ± 1.01	51.85 ± 0.43	48.28 ± 2.78
MCV (fL)	57.73 ± 2.23	61.50 ± 0.87	54.00 ± 0.58	54.50 ± 4.50
MCHC (pg)	18.33 ± 0.49	17.50 ± 0.29	17.00 ± 0.58	17.00 ± 0.58
PLT (10^5/µL)	6.08 ± 0.10	7.27 ± 0.37	8.80 ± 0.21	7.26 ± 0.21
Group 2 (SBm dose, 250 mg)				
RBC (10^6/µL)	7.71 ± 0.42	7.52 ± 0.22	9.64 ± 0.17	7.99 ± 0.87
HGB (g/dL)	14.10 ± 0.06	13.20 ± 0.92	16.60 ± 0.23	12.75 ± 1.10
HCT (%)	49.30 ± 0.57	45.60 ± 2.94	52.82 ± 0.22	49.13 ± 1.23
MCV (fL)	59.65 ± 0.33	61.00 ± 1.15	54.50 ± 0.87	50.00 ± 2.00
MCHC (pg)	17.57 ± 0.47	17.50 ± 0.26	17.00 ± 1.00	16.00 ± 1.25
PLT (10^5/µL)	7.65 ± 0.85	7.36 ± 0.06	7.92 ± 0.04	6.57 ± 0.64
Group 3 (SBm dose, 500 mg)				
RBC (10^6/µL)	7.67 ± 0.19	7.31 ± 0.30	8.93 ± 0.07	8.42 ± 0.21
HGB (g/dL)	13.85 ± 0.55	13.00 ± 0.98	16.10 ± 0.23	14.68 ± 0.55
HCT (%)	48.38 ± 0.63	45.15 ± 3.49	51.35 ± 1.13	51.05 ± 0.14
MCV (fL)	60.32 ± 3.70	62.00 ± 0.58	57.50.± 1.50	59.00 ± 1.00
MCHC (pg)	18.03 ± 0.03	18.00 ± 0.58	18.± 1.53	18.00 ± 0.58
PLT (10^5/µL)	6.80 ± 0.27	7.88 ± 0.10	9.28 ± 1.39	6.24 ± 0.07
Group 4 (SBm dose, 1000 mg)				
RBC (10^6/µL)	7.32 ± 0.42	6.12 ± 0.15***	8.04 ± 0.05	8.24 ± 0.30
HGB (g/dL)	11.60 ± 0.75	11.15 ± 0.38	14.25 ± 0.38	14.85 ± 0.20
HCT (%)	44.68 ± 2.39	38.05 ± 1.47 *	46.95 ± 0.38	50.35 ± 0.61
MCV (fL)	60.23 ± 2.23	61.33 ± 0.67	56.00 ± 0.58	58.50 ± 0.29
MCHC (pg)	17.72 ± 0.36	18.00 ± 1.00	18.00 ± 0.58	17.50 ± 0.29
PLT (10^5/µL)	6.37 ± 0.02	7.51 ± 0.03	8.46 ± 1.87	6.74 ± 0.09

Over the course of 90 days, female Wistar rats (n = 5) were given the whole plant's lyophilized aqueous extract orally on a daily basis. (* denote significant difference at $p < 0.05$ and ***>**>*)
Hematological parameters (HBG: hemoglobin**, HCT**: hematocrit, **RBC:** red blood cells, **MCHC**: Mean corpuscular hemoglobin concentration, **MCV**: Mean corpuscular volume, **PLT**: platelet.)

3.4.3. Serum biochemical parameters

Tables 7 and 8 exhibit the male and female biochemical profiles of the treated and control rats, respectively. The effects of reiterated oral administration of SBm-extract were evaluated in male Wistar rats over a period of 90 days, using a daily dose of up to 500 mg/kg BW. The parameters including plasma levels of urea, creatinine, glucose, total cholesterol, total bilirubin, cholesterol, triglycerides, and liver marker enzymes (ALT and AST) did not significantly change after SBm-extract administration. In contrast, male rats administered 1000 mg/kg of SBm-extract demonstrated significant increases in urea and total bilirubin levels after 30 and 60 days of treatment, respectively. Moreover, after a 60-day course of treatment, the glucose level was significantly lower.

The effects observed in females treated with SBm-extract showed variability. The majority of biochemical indicators in female rats were found to be similar, except a decrease in creatinine levels. In contrast, following a 30-day course of administration, creatinine levels were significantly lower in the groups treated with 500 mg/kg and 1000 mg/kg (*p*-values less than 0.01 and 0.001 respectively). It's also important to keep in mind that these changes were temporary and did not continue for the full ninety-day course of treatment with SBm-extract.

3.4.4. Mass of organs

The results of organ weight in both male and females of Wistar rats treated by SBm-extract for 90 days are presented in Fig. 4. Obtained

Table 5
The effect of sub-chronic oral administration of a lyophilized aqueous extract of *Salvia blancoana* subsp. *mesatlantica* on white blood cells count in male Wistar rats.

Parameter	Treatment period (days)			
	Day_0	Day_{30}	Day_{60}	Day_{90}
Group 1 (Control)				
Neutrophils (10^3/μL)	1.86 ± 0.31	3.38 ± 0.19	2.30 ± 0.31	1.64 ± 0.04
Eosinophils (10^2/μL)	2.51 ± 0.67	3.43 ± 0.88	6.26 ± 0.94	3.60 ± 0.06
Basophils (10^2/μL)	5.01 ± 1.30	6.40 ± 1.79	5.33 ± 1.48	5.55 ± 1.85
Lymphocytes (10^3/μL)	2.86 ± 0.57	3.45 ± 0.15	4.95 ± 0.98	3.78 ± 0.16
Monocytes (10^2/μL)	7.79 ± 2.23	9.10 ± 0.55	9.69 ± 0.79	9.72 ± 1.81
Group 2 (SBm dose, 250 mg)				
Neutrophils (10^3/μL)	2.08 ± 0.09	3.15 ± 0.75	3.18 ± 0.22	2.57 ± 0.32
Eosinophils (10^2/μL)	4.03 ± 0.15	2.54 ± 0.59	6.45 ± 1.11	2.60 ± 0.61
Basophils (10^2/μL)	4.58 ± 0.43	7.42 ± 0.51	8.10 ± 2.77	4.58 ± 1.91
Lymphocytes (10^3/μL)	3.33 ± 0.05	2.22 ± 0.19	3.22 ± 0.26	3.30 ± 0.32
Monocytes (10^3/μL)	10.82 ± 4.73	6.32 ± 0.97	7.68 ± 2.42	5.41 ± 1.58
Group 3 (SBm dose, 500 mg)				
Neutrophils (10^3/μL)	1.72 ± 0.10	2.43 ± 0.13	3.80 ± 0.83	2.46 ± 0.64
Eosinophils (10^2/μL)	3.73 ± 0.68	4.67 ± 1.40	4.21 ± 0.20	3.58 ± 0.78
Basophils (10^2/μL)	4.76 ± 0.66	5.23 ± 0.40	7.05 ± 1.84	8.70 ± 2.03
Lymphocytes (10^3/μL)	4.13 ± 1.18	3.35 ± 0.32	4.05 ± 0.16	4.47 ± 0.97
Monocytes (10^2/μL)	8.36 ± 2.27	10.08 ± 2.80	9.38 ± 0.16	8.92 ± 0.80
Group 4 (SBm dose, 1000 mg)				
Neutrophils (10^3/μL)	1.84 ± 0.37	4.24 ± 0.99	1.72 ± 0.12	2.22 ± 0.22
Eosinophils (10^2/μL)	2.73 ± 0.83	3.11 ± 0.85	2.39 ± 0.08 *	3.90 ± 0.38
Basophils (10^2/μL)	3.05 ± 1.03	7.59 ± 0.90	4.84 ± 0.85	5.06 ± 0.43
Lymphocytes (10^3/μL)	2.56 ± 1.00	2.58 ± 0.40	3.14 ± 0.07	5.00 ± 0.61
Monocytes (10^2/μL)	7.73 ± 2.01	10.41 ± 1.26	4.46 ± 0.02	4.90 ± 0.67

Over the course of 90 days, male Wistar rats (n = 5) were given the whole plant's lyophilized aqueous extract orally on a daily basis. (*denote significant difference at $p < 0.05$).

Table 6
The effect of sub-chronic oral administration of a lyophilized aqueous extract of *Salvia blancoana* subsp. *mesatlantica* on white blood cells count in female Wistar rats.

Parameter	Treatment period (days)			
	Day_0	Day_{30}	Day_{60}	Day_{90}
Group 1 (Control)				
Neutrophils (10^3/μL)	1.84 ± 0.12	2.35 ± 0.26	2.15 ± 0.38	1.50 ± 0.08
Eosinophils (10^2/μL)	3.16 ± 0.75	3.43 ± 0.88	6.60 ± 1.28	4.34 ± 0.93
Basophils (10^2/μL)	5.65 ± 0.39	5.11 ± 0.46	5.71 ± 0.24	4.45 ± 0.37
Lymphocytes (10^3/μL)	4.02 ± 0.46	4.99 ± 1.55	4.78 ± 0.47	3.96 ± 0.99
Monocytes (10^2/μL)	5.69 ± 1.56	9.62 ± 0.62	7.03 ± 0.02	6.33 ± 1.70
Group 2 (SBm dose, 250 mg)				
Neutrophils (10^3/μL)	2.01 ± 0.07	2.24 ± 0.21	2.04 ± 0.08	2.63 ± 1.18
Eosinophils (10^2/μL)	3.63 ± 1.32	2.54 ± 0.59	5.86 ± 0.97	2.17 ± 0.20
Basophils (10^2/μL)	4.96 ± 0.55	3.41 ± 0.55	6.23 ± 0.70	5.48 ± 1.38
Lymphocytes (10^3/μL)	4.83 ± 0.95	3.69 ± 0.13	3.87 ± 0.25	2.52 ± 1.44
Monocytes (10^2/μL)	5.98 ± 2.68	7.85 ± 1.18	8.74 ± 2.94	4.30 ± 1.47
Group 3 (BmL dose, 500 mg)				
Neutrophils (10^3/μL)	1.55 ± 0.47	3.77 ± 0.54	2.98 ± 0.68	1.75 ± 0.08
Eosinophils (10^2/μL)	1.80 ± 0.46	4.73 ± 1.23	2.64 ± 0.41 *	2.36 ± 0.40
Basophils (10^2/μL)	5.42 ± 1.77	8.05 ± 0.29 * *	4.57 ± 0.70	7.02 ± 0.89
Lymphocytes (10^3/μL)	2.51 ± 0.58	4.95 ± 0.17	3.68 ± 0.38	2.87 ± 0.01
Monocytes (10^2/μL)	3.74 ± 1.39	8.13 ± 0.64	6.07 ± 2.21	3.05 ± 1.36
Group 4 (SBm dose, 1000 mg)				
Neutrophils (10^3/μL)	1.64 ± 0.13	3.29 ± 0.05	2.50 ± 0.36	1.50 ± 0.23
Eosinophils (10^2/μL)	2.93 ± 0.64	3.11 ± 0.85	2.71 ± 0.33 *	3.78 ± 1.52
Basophils (10^2/μL)	4.44 ± 1.21	8.64 ± 0.20**	5.28 ± 0.56	5.07 ± 0.77
Lymphocytes (10^3/μL)	2.29 ± 0.26	3.25 ± 1.12	5.01 ± 0.53	5.11 ± 1.48
Monocytes (10^2/μL)	3.34 ± 1.16	2.29 ± 0.98**	5.85 ± 0.04	4.55 ± 1.04

Over the course of 90 days, female Wistar rats (n = 5) were given the whole plant's lyophilized aqueous extract orally on a daily basis (*denote significant difference at $p < 0.05$ and **>*).

findings revealed that the relative weight of kidneys, spleen and liver were similar for both male and female rats after treatment for 90 days. The administration of SBm-extract did not demonstrate any impact on the weight of these organs in either gender.

3.4.5. Histological analysis

The histological analysis of rates treated with SBm-extract from *Salvia blancoana* subsp. *mesatlantica* are presented in Figs. 5, 6 and 7. Upon macroscopic inspection, neither the male nor female Wistar rats' organs showed any anomalies. There were no histologically visible differences between the control and treatment groups. None of the animals' liver sections displayed any signs of vacuolation, degeneration, inflammation, or hepatic necrosis.

The liver sections of the rats in group treated with a dosage of 250 mg/kg (B) and control group showed the characteristic lobular architecture, with hepatocyte trabeculae arranged radially around a centrilobular vein. In contrast, histological analysis of liver sections from rates treated with 500 mg/kg (group C) and 1000 mg/kg (group B) revealed minor hepatic congestion.

The renal sections from rats in the control and treatment groups (B, C, and D) were found to have normal cortical and medullary regions, proximal and distal tubules, urine space, and intact glomeruli. In both the test and normal groups, the spleen architecture was normal. These findings imply that the drug under test does not seem to be very toxic to the liver, kidneys, or spleen.

4. Discussion

In this study, we evaluated the quantity of total polyphenols, flavones, flavonols, and antioxidant activity in the aqueous extract of *Salvia blancoana* subsp. *mesatlantica*, then we identified their chemical compounds. Equally, we evaluated the acute and chronic toxicity of this extract in mice and rats animals. The obtained results demonstrated the first data on the chemical composition of the extracts from this endemic plant. Equally, this study confirmed new biological properties (antioxidant and toxicity effects) of the extracts from *Salvia blancoana* subsp.

Table 7
The effect of sub-chronic oral administration of a lyophilized aqueous extract of *Salvia blancoana* subsp. *mesatlantica* on certain biochemical parameters in male Wistar rats.

Parameter	Treatment period (days)			
	Day_0	Day_{30}	Day_{60}	Day_{90}
Group 1 (Control)				
Urea (mmol/L)	10.06 ± 1.00	9.50 ± 0.29	9.50 ± 0.50	7.67 ± 0.19
Creatinine (µmol/L)	37.71 ± 3.14	46.50 ± 2.31	37.15 ± 2.57	41.30 ± 2.68
Glucose (mmol/L)	5.45 ± 0.71	3.09 ± 0.18	4.89 ± 0.45	3.05 ± 0.06
Total cholesterol (mmol/L)	2.29 ± 0.20	2.36 ± 0.26	2.38 ± 0.13	1.85 ± 0.14
Triglycerides (mmol/L)	0.72 ± 0.07	0.95 ± 0.03	1.05 ± 0.12	1.18 ± 0.10
ALAT (UI/L)	73.67 ± 2.96	84.00 ± 9.24	110.00 ± 1.15	145.83 ± 3.03
ASAT (UI/L)	159.67 ± 30.88	253.00 ± 2.89	202.33 ± 16.48	269.00 ± 9.29
Total bilirubin (µmol/L)	0.75 ± 0.14	0.73 ± 0.12	0.70 ± 0.12	0.57 ± 0.18
Group 2 (SBm dose, 250 mg)				
Urea (mmol/L)	10.50 ± 0.29	10.75 ± 0.14	10.11 ± 0.39	8.75 ± 0.80
Creatinine (µmol/L)	30.67 ± 0.67	41.60 ± 6.12	37.60 ± 4.33	46.50 ± 5.37
Glucose (mmol/L)	3.52 ± 0.99	2.58 ± 0.02	3.26 ± 0.43	2.78 ± 0.22
Total cholesterol (mmol/L)	1.84 ± 0.23	2.16 ± 0.10	2.25 ± 0.02	1.80 ± 0.13
Triglycerides (mmol/L)	0.71 ± 0.06	0.92 ± 0.21	1.09 ± 0.12	1.01 ± 0.21
ALAT (UI/L)	94.67 ± 10.73	109.33 ± 8.97	97.00 ± 10.39	107.67 ± 12.41
ASAT (UI/L)	185.00 ± 34.44	263.00 ± 31.53	276.00 ± 44.07	332.67 ± 22.65
Total bilirubin (µmol/L)	0.77 ± 0.07	0.63 ± 0.07	0.93 ± 0.15	0.63 ± 0.07
Group 3 (SBm dose, 500 mg)				
Urea (mmol/L)	9.36 ± 0.59	11.17 ± 1.25	8.44 ± 0.34	7.25 ± 0.43
Creatinine (µmol/L)	30.33 ± 3.92	35.85 ± 1.30	31.40 ± 0.75	45.60 ± 5.37
Glucose (mmol/L)	4.61 ± 0.23	2.61 ± 0.51	3.88 ± 0.31	2.67 ± 0.07
Total cholesterol (mmol/L)	2.17 ± 0.27	2.36 ± 0.09	2.07 ± 0.23	1.83 ± 0.15
Triglycerides (mmol/L)	0.67 ± 0.04	1.07 ± 0.19	0.84 ± 0.18	1.27 ± 0.21
ALAT (UI/L)	68.00 ± 4.62	101.50 ± 4.33	105.00 ± 4.62	121.50 ± 10.25
ASAT (UI/L)	152.00 ± 42.72	233.50 ± 23.96	238.00 ± 4.62	303.00 ± 22.65
Total bilirubin (µmol/L)	0.85 ± 0.09	0.73 ± 0.15	0.97 ± 0.03	0.77 ± 0.07
Group 4 (SBm dose, 1000 mg)				
Urea (mmol/L)	11.09 ± 1.21	14.00 ± 0.38**	8.50 ± 0.50	8.33 ± 0.44
Creatinine (µmol/L)	30.04 ± 4.05	41.15 ± 5.34	39.85 ± 2.05	57.55 ± 1.01
Glucose (mmol/L)	4.02 ± 0.49	2.22 ± 0.44	2.24 ± 0.30 *	2.48 ± 0.18
Total cholesterol (mmol/L)	1.99 ± 0.12	2.35 ± 0.34	2.27 ± 0.24	1.82 ± 0.05
Triglycerides (mmol/L)	0.85 ± 0.11	0.69 ± 0.07	1.17 ± 0.22	1.30 ± 0.21
ALAT (UI/L)	82.50 ± 10.10	116.00 ± 5.20	95.00 ± 4.62	134.50 ± 7.22
ASAT (UI/L)	166.67 ± 34.28	225.00 ± 19.05	286.50 ± 6.61	309.00 ± 23.01
Total bilirubin (µmol/L)	0.85 ± 0.09	0.77 ± 0.07	**1.47 ± 0.27***	0.70 ± 0.12

Over the course of 90 days, male Wistar rats (n = 5) were given the whole plant's lyophilized aqueous extract orally on a daily basis (*denote significant difference at $p < 0.05$ and **>*).

Table 8
The effect of sub-chronic oral administration of a lyophilized aqueous extract of *Salvia blancoana* subsp. *mesatlantica* on certain biochemical parameters in female Wistar rats.

Parameter	Treatment period (days)			
	Day_0	Day_{30}	Day_{60}	Day_{90}
Group 1 (Control)				
Urea (mmol/L)	8.33 ± 0.19	8.67 ± 0.37	11.44 ± 2.64	12.16 ± 0.86
Creatinine (µmol/L)	37.20 ± 3.06	57.95 ± 0.78	34.27 ± 0.85	41.15 ± 3.32
Glucose (mmol/L)	3.25 ± 0.08	3.53 ± 0.40	3.50 ± 0.90	3.53 ± 0.53
Total cholesterol (mmol/L)	2.42 ± 0.11	3.25 ± 0.35	2.56 ± 0.20	2.21 ± 0.13
Triglycerides (mmol/L)	0.60 ± 0.06	0.76 ± 0.09	1.41 ± 0.20	1.50 ± 0.07
ALAT (UI/L)	88.00 ± 6.93	104.50 ± 4.91	114.00 ± 7.51	107.33 ± 4.41
ASAT (UI/L)	242.00 ± 9.24	282.00 ± 17.62	256.00 ± 7.51	283.00 ± 28.29
Total bilirubin (µmol/L)	0.53 ± 0.09	0.63 ± 0.07	0.67 ± 0.20	0.67 ± 0.12
Group 2 (SBm dose, 250 mg)				
Urea (mmol/L)	9.08 ± 0.43	8.58 ± 0.72	10.33 ± 2.36	12.99 ± 1.15
Creatinine (µmol/L)	37.08 ± 8.73	51.35 ± 1.53	31.93 ± 1.13	49.55 ± 6.67
Glucose (mmol/L)	3.22 ± 0.10	3.43 ± 0.41	2.64 ± 0.27	2.75 ± 0.11
Total cholesterol (mmol/L)	2.25 ± 0.28	2.88 ± 0.27	1.94 ± 0.13	1.67 ± 0.43
Triglycerides (mmol/L)	0.65 ± 0.03	0.76 ± 0.09	1.41 ± 0.20	1.38 ± 0.14
ALAT (UI/L)	95.00 ± 10.97	115.33 ± 5.33	92.50 ± 9.53	108.33 ± 9.28
ASAT (UI/L)	196.00 ± 38.00	311.33 ± 23.18	293.00 ± 7.51	297.00 ± 33.38
Total bilirubin (µmol/L)	0.67 ± 0.03	0.60 ± 0.06	1.03 ± 0.20	0.50 ± 0.12
Group 3 (SBm dose, 500 mg)				
Urea (mmol/L)	7.75 ± 0.07	8.00 ± 0.29	9.33 ± 1.60	12.08 ± 0.99
Creatinine (µmol/L)	26.93 ± 2.87	45.60 ± 1.27 * *	44.07 ± 5.72	50.43 ± 7.74
Glucose (mmol/L)	4.29 ± 0.97	3.58 ± 0.37	3.53 ± 0.08	2.97 ± 0.54
Total cholesterol (mmol/L)	1.90 ± 0.28	2.54 ± 0.09	1.80 ± 0.08	2.16 ± 0.02
Triglycerides (mmol/L)	0.69 ± 0.10	0.90 ± 0.18	1.02 ± 0.08	1.09 ± 0.03
ALAT (UI/L)	83.50 ± 2.02	120.50 ± 3.18	102.50 ± 6.06	102.50 ± 7.22
ASAT (UI/L)	188.00 ± 5.13	306.00 ± 15.18	270.00 ± 18.15	327.00 ± 47.16
Total bilirubin (µmol/L)	0.53 ± 0.09	0.63 ± 0.13	1.30 ± 0.35	0.80 ± 0.10
Group 4 (SBm dose, 1000 mg)				
Urea (mmol/L)	9.16 ± 0.77	7.08 ± 0.14	8.16 ± 1.26	9.41 ± 0.63
Creatinine (µmol/L)	26.48 ± 2.61	41.60 ± 2.54***	39.53 ± 4.42	46.07 ± 4.34
Glucose (mmol/L)	3.27 ± 0.49	3.48 ± 0.23	2.92 ± 0.53	2.86 ± 0.34
Total cholesterol (mmol/L)	1.98 ± 0.32	2.73 ± 0.13	2.24 ± 0.11	1.90 ± 0.31
Triglycerides (mmol/L)	0.68 ± 0.04	0.63 ± 0.21	1.00 ± 0.03	1.16 ± 0.10
ALAT (UI/L)	97.00 ± 9.81	138.50 ± 15.10	113.50 ± 7.22	79.33 ± 9.39
ASAT (UI/L)	241.00 ± 32.33	298.33 ± 29.73	273.00 ± 4.04	309.00 ± 42.44
Total bilirubin (µmol/L)	0.60 ± 0.06	0.70 ± 0.12	0.87 ± 0.27	0.83 ± 0.07

Over the course of 90 days, female Wistar rats (n = 5) were given the whole plant's lyophilized aqueous extract orally on a daily basis (* denote significant difference at $p < 0.05$ and ***>**>*)

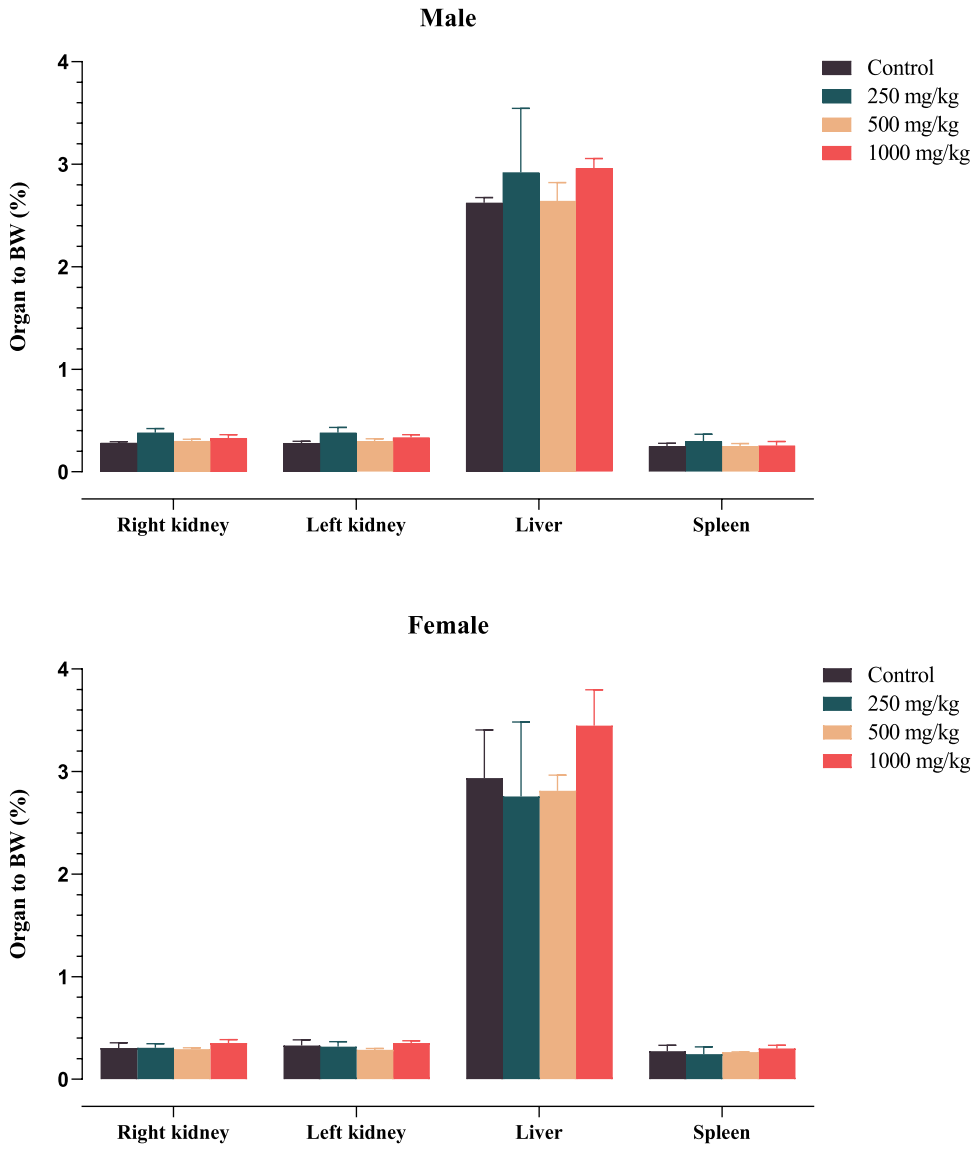

Fig. 4. The effect of sub-chronic oral treatment with the aqueous extract of *Salvia blancoana* subsp. *mesatlantica* on relative organ mass (spleen, liver and kidney) in female and male Wistar rats.

mesatlantica.

Currently, Maache et al., [33] revealed important chemical compounds in the essential oils of *Salvia blancoana* subsp. *mesatlantica.* This study presents first data on the chemical content and antioxidant activity in the aqueous extracts of leaves from *Salvia blancoana* subsp. *mesatlantica.* The obtained results showed significant quantity of total polyphenols and flavonoids in the study extract. The investigation of polyphenols and flavonoids was deep in other subspecies of *Salvia blancoana* and *Salvia lavandulifolia.* For example, Remok et al., [44] investigated the total polyphenols and flavonoids in aqueous extracts from leaves of *Salvia lavandulifolia* Vahl and recorded an estimated values of TFC and TPC respectively of 23.80 ± 0.12 mg EQ quercetin/g DE and 246.51 ± 1.69 mg EQ of gallic acid/g DE. In another study, Boutahiri et al., [45] evaluated the quantity of total polyphenols in aqueous extracts from *Salvia rosmarinus* Spenn. And *Salvia lavandulifolia* Vahl and revealed an estimated values respectively of 290.63 ± 7.69 mg GAE/g Ext and 252.67 ± 5.40 mg GAE/g Ext. These results (our study and literature) showed a variable quantity of TPC and TFC depending on the subspecies of Salvia and their geographical environment, which is in agreement with [38,39] who demonstrated that the phytochemicals such as polyphenols and flavonoids vary depending on the plant species and the geographical sampling sites. In fact, each species is influenced by the climatic and soil factors characterizing each areas and these are capable to impact the biosynthesis of chemicals in plants [40–43]. Equally, the biosynthesis of chemical is different between species and even subspecies of the same plan. In terms of antioxidant activity, many studies have demonstrated its close relationship to the quantity of total polyphenols and flavonoids [44,46]. Which is in agreement with our results. To compare with other study, the IC_{50} and total antioxidant capacity in aqueous extracts of *Salvia lavandulifolia* Vahl were 5.81 ± 0.23 μg/mL and 527.03 ± 5.95 mg EQ of ascorbic acid/g DE [44].

This research is the first to evaluate the toxicity in *Salvia blancoana* subsp. *mesatlantica*'s extract. Substances are generally considered non-toxic if their LD50 values are larger than 5 g/kg, and low toxicity if their values fall between 1 and 5 g/kg [47,48]. Therefore, our results confirm that the aqueous extract derived from *Salvia blancoana* subsp. *mesatlantica* is safe for oral consumption in mice, even at high doses tested up to 11 g/kg. These indicate that these extracts are non-toxic [49]. In comparison, the toxicity was investigated in a wide range of sage species including *Salvia scutellarioides*, *Salvia przewalskii*, *Salvia verbenaca*, *Salvia officinalis*, and *Salvia rhytidea*, and results were variable depending on the used doses, type of extracts, and tested animals [9,

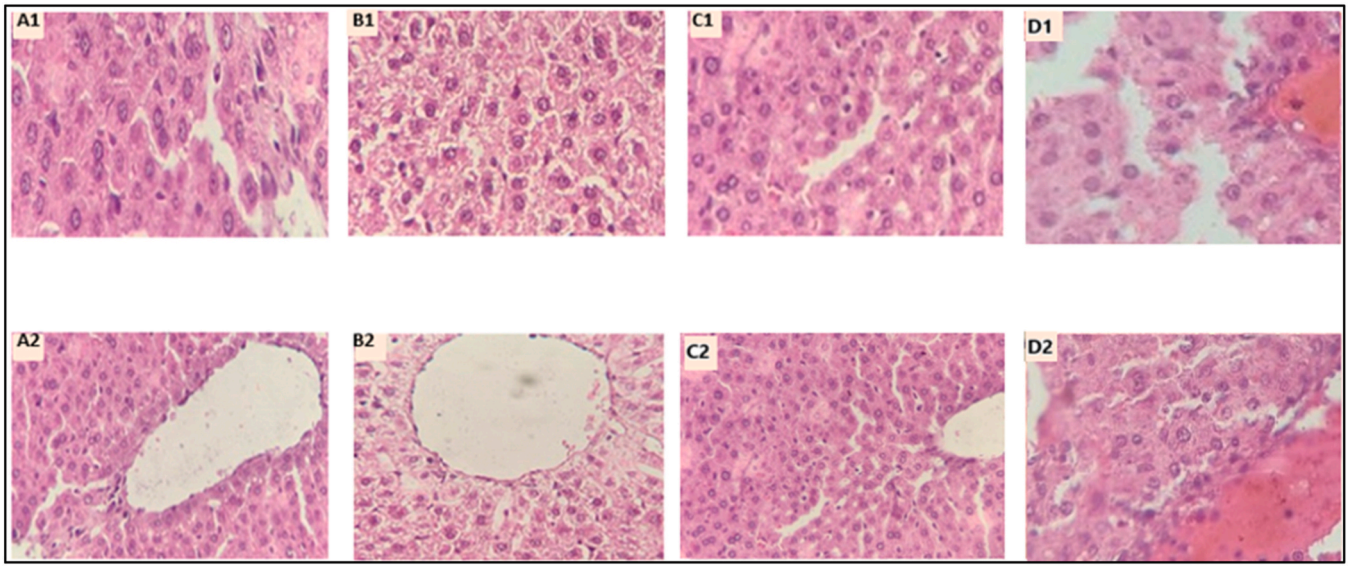

Fig. 5. Histological examination of the liver in male and female Wistar rats following subacute treatment with the aqueous extract of *Salvia blancoana* subsp. *mesatlantica*. A1 (Control, HE 400 ×, male), B1 (250 mg/kg, HE 400 ×, male), C1 (500 mg/kg, HE 400 ×, male), D1 (1000 mg/kg, HE 400 ×, male), A2 (Control, HE 400 ×, female), B2 (250 mg/kg, HE 400 ×, female), C2 (500 mg/kg, HE 100 ×, female), D2 (1000 mg/kg, HE 100 ×, female).

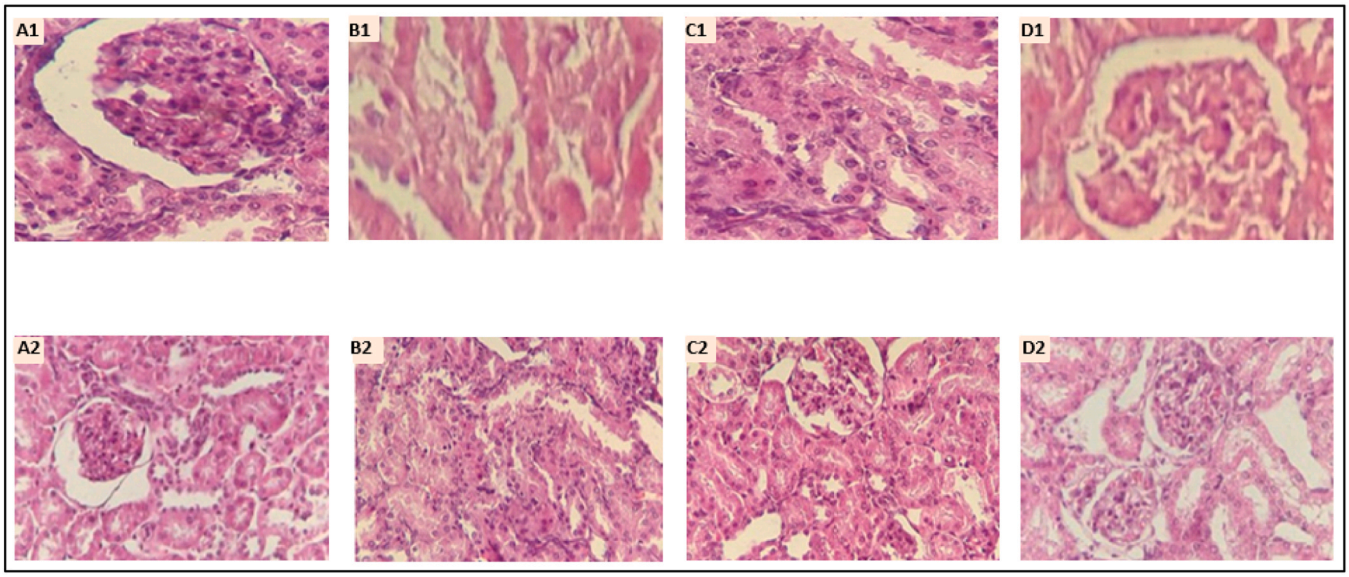

Fig. 6. Histological examination of the kidney in male and female Wistar rats following subacute treatment with the aqueous extract of *Salvia blancoana* subsp. *mesatlantica*. A1 (Control, HE 400 ×, male), B1 (250 mg/kg, HE 400 ×, male), C1 (500 mg/kg, HE 400 ×, male), D1 (1000 mg/kg, HE 400 ×, male), A2 (Control, HE 400 ×, female), B2 (250 mg/kg, HE 400 ×, female), C2 (500 mg/kg, HE 400 ×, female), D2 (1000 mg/kg, HE 400 ×, female).

50–53]. For example, Li et al., [54] evaluated the acute toxicity of ethanol extracts from *Salvia przewalskii* in rodents. The test was realized on Healthy Kunming strain mice weighing between 18 and 22 g with a single dose of extract (87 %, 70 %, and 80 %). *Salvia przewalskii* ethanol extract resulted in mortality and dose-dependent negative effects on general behavior. When administered by gavage, intramuscular, or intraperitoneal methods, the extract's no-observed adverse effect levels (NOAEL) were 1723, 288, and 500 mg/kg, respectively, while its lowest-observed adverse effect levels (LOAEL) were 1981, 840, and 781 mg/kg. With LD_{50} values of 2547.8, 901.3, and 780.8 mg/kg for oral, intramuscular, and intraperitoneal injection, respectively, mortality rose with higher doses. In our case, single intraperitoneal doses of the extract did produce adverse effects and mortality, but only at high doses with an LD_{50} of 6.82 g/kg BW in mice. Our results and those of literature are significantly different. This difference could be governed by various factors such as the quantity of toxic compounds in our extracts [49,55] or the lower absorption of these compounds by tested animals [56]. Interestingly, the polyphenols (the major components in our extracts) from medicinal plants exhibited lower toxicity across a wide range of animals, including mice [57,58], which is in agreement with our results. Instead, the polyphenols are showed higher anti-toxic effects, particularly against Lead [59] and Cadmium toxicities [60]. Equally, polyphenols such as rutin (recorded in our extracts) showed lower absorption and this is suggested to reduce their effects on tested animals [61].

Plants produce more than 10,000 different secondary metabolites, which serve primarily to protect themselves from parasites, pathogens, and predators [62]. The most important classes of compounds produced are alkaloids, saponins, total phenols, tannins, glycosides, cyanogenic, triterpenoids/steroids, and toxic amino acids. These classes of chemicals

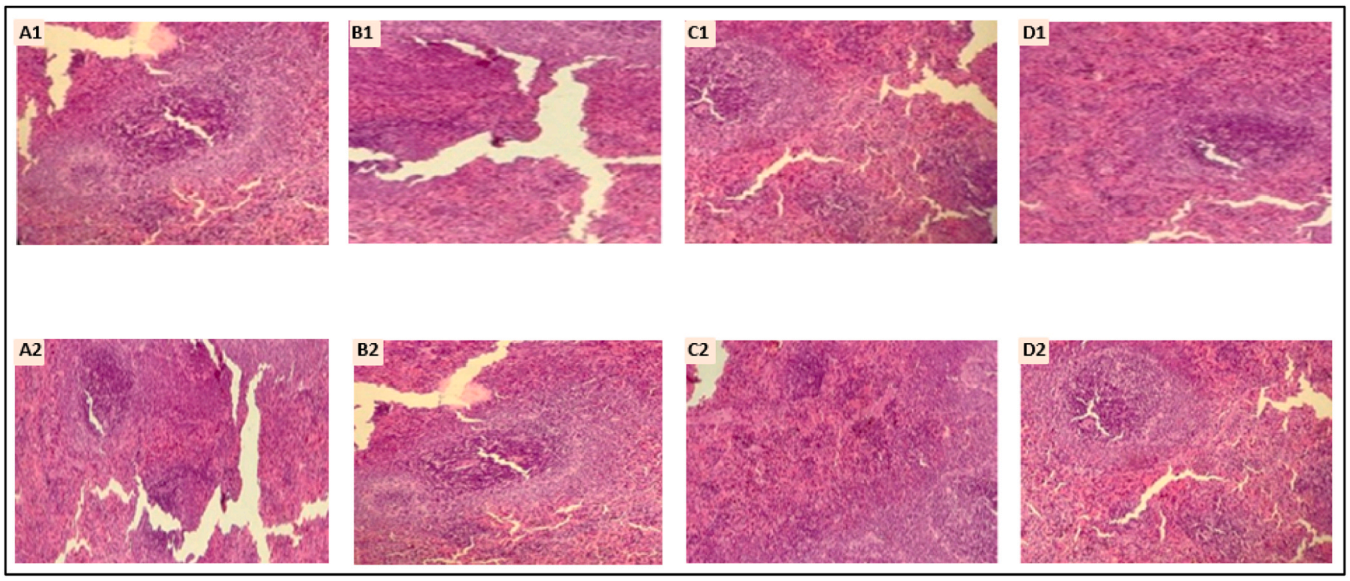

Fig. 7. Histological examination of the spleen in male and female Wistar rats following subacute treatment with the aqueous extract of *Salvia blancoana* subsp. *mesatlantica*. A1 (Control, HE 100 ×, male), B1 (250 mg/kg, HE 100 ×, male), C1 (500 mg/kg, HE 100 ×, male), D1 (1000 mg/kg, HE 100 ×, male), A2 (Control, HE 100 ×, female), B2 (250 mg/kg, HE 100 ×, female), C2 (500 mg/kg, HE 100 ×, female), D2 (1000 mg/kg, HE 100 ×, female).

have been linked to a wide range of biological activities [61–63]. Here are some examples linking certain chemical compounds to animal toxicity. Cardenolide and bufadienolide, specific glycosides, alter cardiac muscle function by increasing the force of contractions through Na-K/ATPase inhibition, which in some cases may trigger cardiac arrest [64]. Neurotoxic compounds from plants can also harm the brain, potentially causing cognitive and neurological impairment. For example, Veratrum species contain harmful steroidal alkaloids, and Aconitum species' aconitine can lead to both severe arrhythmias and neurotoxicity [64–66]. Similarly, pyrrolizidine alkaloids are a large group of hepatotoxins characterized by the presence of a pyrrolizidine nucleus in their structure and are capable of causing hepatocellular necrosis. On the other hand, Aristolochia species are now acknowledged as toxic herbs. Aristolochic acids, commonly found in Aristolochia, are responsible for the toxic effects of this genus [67]. Aristolochic acids primarily target renal proximal tubular epithelial cells. Regular intake of herbs containing aristolochic acids is associated with the progression of renal interstitial fibrosis, ultimately leading to nephropathy [68]. Yet, the SBm extract is rich in compounds, primarily polyphenols, such as naringin, cinnamic acid, rutin, apigenin, kaempferol, and vanillic acid. With notable antioxidant properties, these compounds offer health benefits such as cardiovascular support and anti-inflammatory effects. They are also being studied for their therapeutic potential in metabolic regulation and cancer prevention. Typically, these compounds have very low to moderate toxicity [68–70].

In the subchronic testing, alterations in body mass were utilized as a measure to assess potential detrimental impacts of the supplied pharmaceutical substances. According to our findings, female rats treated with SBm-extract or in the control group did not exhibit appreciable variations in body mass over time. However, male rats administered with 500 mg/kg and 250 mg/kg of SBm-extract experienced a statistically significant but temporary reduction in body mass after 30 and 60 days of treatment, respectively. It is noteworthy that the repeated administration of the extract for 90 days did not have a negative impact on the body mass of the rats overall. This observation could be attributed, at least in part, to the extract's lack of influence on appetite or food intake. In comparison in other subspecies, Guaouguaou et al., [55] investigated the subchronic toxicity of *Salvia verbenaca's* extracts in rats and mice, while Mandegary et al., [71] evaluated the toxicity of extracts from *Salvia rhytidea* against Mice. The results obtained from the study indicated that the administration of *S. Verbenaca* extracts at a dosage of 2000 mg kg−1 rat b.w. on a daily basis did not result in significant alterations in the body mass of male and female rats. Moreover, it was discovered that the animals in the treated test groups had a typical progression of body mass, indicating that they gained mass gradually in relation to their feed intake, comparable to the control group [55]. These are in agreement with our results. On the other hand, the measurement of organ mass can serve as a valuable indicator of animal health and overall well-being [56,72]. In our case, results showed that the relative mass of liver, kidneys, and spleen were similar in both male and female rats after treatment for 90 days. The administration of SBm-extract did not demonstrate any impact on the mass of these organs in either gender. Seo et al., [73] conducted a sub-chronic toxicity of extract mixture from *Salvia plebeian* and *Panax ginseng* on rats and demonstrated that the administration of the extracts for 28 days. The results demonstrated that the weight of Brain Heart Lung Liver Spleen Kidney Adrenal Gland Testis did not change upon experiment completion, which is in agreement with our findings.

The circulatory system is the primary pathway for the distribution of nutrients and foreign substances throughout the body, resulting in the consistent exposure of blood constituents, including leukocytes, erythrocytes, hemoglobin, and platelets to toxic substances [54]. Hence, the assessment of blood restrictions holds importance in the evaluation of risks posed by exposure to toxins, owing to the heightened predictability of human toxicity based on changes in the hematological system, which are discerned by translating findings from animal experiments to humans [74]. In general, our findings have identified transient variations that can be summarized as follows: male rats showed no significant variation which is consistent with similar observations in females, except for group 4, which received a higher dosage. This group had a significant, but transient, reduction in red blood cell count and hematocrit levels after a month of treatment. Previous study has observed that the reduction in red blood cell count subsequent to the administration of the product can be ascribed to hemolysis and/or the suppression of hematopoiesis, which are induced by the bioactive constituents included in the extract [75]. Several plant chemicals have been discovered to modify the metabolism of erythrocytes and cause damage to their cell membranes, resulting in hemolysis [76].

Regarding the white blood cell count, male rats exhibited no significant changes, except for Group 4 treated with 1000 mg/kg, which

showed a decrease specifically in eosinophils. In females, Group 3 and 4 treated with 500 mg/kg and 1000 mg/kg respectively showed increased basophils after one month, and decreased eosinophils after two months. Group 4 also showed decreased monocytes after 30 days. The observed white blood cell count variations were transient and returned to normal levels by the end of the treatment period. The SBm-extract appeared to influence the white blood cell counts, albeit transient. However, the observed variations suggest a temporary influence on the immune system of rats. In general, it appears that the SBm-extract did not cause any damage to the tissues or immune system, as evidenced by the lack of significant changes observed in the neutrophil and lymphocyte counts. Additionally, the significant changes detected in the eosinophil, basophil, and monocyte counts remained within the internationally recognized range, suggesting that the extract did not have any harmful effects on these particular cell types [77].

This study found that iterative oral administration of SBm-extract up to a daily dose of 500 mg/kg did not result in significant changes in most biochemical parameters. However, treatment with 1000 mg/kg caused significant rises in urea and total bilirubin levels and a reduction in glucose heights in male after 30 and 60 days of treatment, respectively. Female rats showed a temporary decrease in creatinine levels with SBm-extract treatment, but this effect did not persist throughout the 90-day period. The decrease in blood glucose levels observed in our study corroborates the earlier findings of Zarzuelo et al., [78], who demonstrated that an extract of a closely related species, *Salvia lavandulifolia* Vahl, has hypoglycemic effects. The hypoglycemic action of this substance may be attributed to various mechanisms, such as the enhancement of insulin release triggered by glucose, heightened uptake of glucose in peripheral tissues, reduction in the absorption of glucose in the intestines, and the observed hyperplasia of pancreatic islet beta cells, which becomes apparent following long-term treatment. Additionally, *Salvia lavandulifolia* has been shown to inhibit both of α-amylase and α-glucosidase, which are involved in the digestion of carbohydrates into simple sugars [62,79]. Inhibition of these enzymes slows the digestion of carbohydrates, which can lead to a reduction in postprandial plasma glucose levels [63,80].

Substance that results in elevated levels of urea and total bilirubin could be due to its impact on the liver's capacity to metabolize bilirubin, leading to its accumulation in the bloodstream. Alternatively, it could affect the kidney's ability to excrete urea, leading to its buildup in the bloodstream. Another potential explanation is that the substance might trigger physiological responses or have other side effects that contribute to the elevation of both urea and bilirubin levels. To understand the precise mechanism of action of the substance and any other potential impacts on the body, further investigation is necessary [64,65]. Nevertheless, it is worth mentioning that repeated administration of the SBm-extract only produces transient and reversible effects on urea and bilirubin levels, without affecting other liver and kidney function indicators such as creatinine, transaminases (ALT, AST), and total cholesterol. Based on these findings, it is reasonable to conclude that the SBm-extract does not pose a significant risk of liver or kidney damage. The results were corroborated by histological examination, which did not uncover any notable harm or modification in the liver and kidney tissues.

5. Conclusion

This study presents new data on the chemical compounds and biological features of extracts from *Salvia blancoana* subsp. *mesatlantica*. We investigated the total polyphenol, flavones, and flavonol contents, as well as the identification of polyphenols within the aqueous extracts obtained from the leaves of this particular plant species. Equally, we evaluated the extract's antioxidant activity and toxicity. The obtained results demonstrated a significant quantity of total polyphenol, flavones and flavonols content, while the analysis identified 10 polyphenols in the aqueous extract of *Salvia blancoana* subsp. *mesatlantica*. The antioxidant activity was significantly important. In the acute toxicity, based on the LD_{50} values, SBm-extract was found to have no acute toxicity in both oral and intraperitoneal routes. Similarly, the oral administration of SBm-extract for 90 days in the sub-chronic toxicity test did not produce any severe toxic effects on vital organs. Despite the relevant results of this study, future studies need to confirm these results and to expand our understanding of the safety profile of this plant. Then, deeper investigations are required to explore the effects of other solvents on the extraction of bioactive constituents from the areal and underground parts of this endemic species. Equally, the evaluation of other biological effects such as anti-microbial, anti-cancer, and anti-inflammatory activities are needed.

Ethics approval and consent to participate

All animal experiments in this study were approved by the First Affiliated Hospital Ethics Committee of Heilongjiang University of Chinese Medicine (2022062703). All methods described in the present study were conducted according to the relevant guidelines and regulations for handling laboratory animals. Euthanasia methods are consistent with the commonly accepted norms of veterinary best practice. In our study, the rats were subjected to light anesthesia using pentobarbital administered intraperitoneal at a dose of 30 mg/kg. For the euthanasia of rats, pentobarbital was used at a dose of 60 mg/kg administered intraperitoneal. All experiments were performed based on the ARRIVE guidelines. The consent to participate is not applicable.

Author agreement statement

We the undersigned declare that this manuscript is original, has not been published before and is not currently being considered for publication elsewhere.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed.

We understand that the Corresponding Author is the sole contact for the Editorial process. He is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs

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Author statement

SM, AT, and IE contributed to the manuscript writing. AT conducted data analysis. HS and JPG contributed to writing-review & editing of the original manuscript. DA and MAMAS contributed to writing-review & editing, resources, funding, and visualization. NS, MB AAB, and GN contributed to visualization. BL and IE contributed to supervision. All authors read and approved the final manuscript.

CRediT authorship contribution statement

Ghizlane Nouioura: Visualization. **Abdessamad Ait Benlabchir:** Visualization. **Dara Aldisi:** Visualization, Resources, Funding acquisition. **Mohammed Bouslamti:** Visualization. **Ilham Elarabi:** Supervision. **Souad Maache:** Writing – original draft. **Badiaa Lyoussi:** Supervision. **Najoua Soulo:** Visualization. **Adel Tahraoui:** Formal analysis. **Mourad. A. M. Aboul-Soud:** Visualization, Resources, Funding acquisition. **John P. Giesy:** Visualization, Resources, Funding acquisition. **Hamza Saghrouchni:** Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data Availability

Data will be made available on request.

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