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The effect of *Rosmarinus officinalis* L infusion supplementation on blood pressure among healthy volunteers and grade 1 hypertensive patients

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ABSTRACT

Background: Rosmarinus officinalis L, has been traditionally used to manage various ailments. Preclinical trials have reported the antihypertensive effect of the bioactive compounds in rosemary. However, clinical studies on its effects on hypertension are lacking.
Objective: This study aimed to explore the efficacy, safety, and tolerability of a 45-day administration of rosemary infusion in both healthy participants and individuals with grade 1 hypertension.
Methods: A total of 18 healthy subjects and 35 grade 1 hypertensive patients were enrolled and instructed to consume a daily infusion prepared by steeping 2 g of powdered rosemary leaves in 100 ml of boiled water. The study was completed by 15 healthy participants and 30 hypertensive patients. Baseline and post-intervention clinical and biochemical parameters, such as systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP), heart rate (HR), and pulse pressure (PP), were measured using ambulatory blood pressure monitoring (MBP).
Results: In the hypertensive group, rosemary infusion consumption over 45 days led to a significant reduction in 24-h SBP ($P = 0.005$), DBP ($P = 0.003$), daytime SBP and DBP ($P = 0.003$ and $P = 0.002$, respectively), MBP ($P = 0.003$), and Nocturnal SBP dipping ($P = 0.04$). In contrast, no significant changes in SBP or DBP were observed among healthy participants. Biochemical safety assessments showed no significant differences between baseline and post-intervention values for both groups. Additionally, no adverse effects were reported, further supporting the safety and efficacy of rosemary infusion.
Conclusion: This preliminary trial allowed the exploration of the effectiveness of rosemary infusion in reducing SBP and DBP in hypertensive patients with grade 1 hypertension over a 45-day period.

Abbreviations: ABPM, Ambulatory blood pressure monitoring; ACE, Angiotensin-I-converting enzyme; BP, Blood Pressure; CVD, Cardiovascular diseases; DBP, Diastolic blood pressure; HPLC, high-performance liquid chromatography; HR, Heart rate; HT, Hypertension,; MBP, Mean blood pressure; Nocturnal SBP dipping, relative daytime, nighttime SBP change; Nocturnal DBP dipping, relative daytime, nighttime DBP change; Nocturnal dipping status, relative daytime, nighttime BP change; PP, Pulse Pressure; RA, Rosmarinic Acid; SBP, Systolic blood pressure.

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1. Introduction

Hypertension (HT) is a condition characterized by high blood pressure, defined as a systolic blood pressure (SBP) of 140 mmHg or higher, and/or a diastolic blood pressure (DBP) of 90 mmHg or higher (Williams et al., 2018b). Arterial hypertension is categorized into three grades based on systolic and diastolic blood pressure measurements: grade 1 (SBP between 140–159 mmHg and/or DBP between 90–99 mmHg), grade 2 (SBP between 160–179 mmHg and/or DBP between 100 and 109 mmHg) and grade 3 (SBP $\geq$ 180 mmHg and/or DBP $\geq$ 110 mmHg) (Williams et al., 2018b). HT is mainly represented by two types: essential HT, the more frequent type encountered in approximately 95% of hypertensive patients, and secondary HT, which accounts for approximately 5–10 % (Rimoldi et al., 2014). Over the past several decades, the prevalence of HT has steadily increased worldwide, affecting all age groups in both high-income and low- to middle-income countries. In fact, in 2015, HT affected 24.1 % of males and 20.1 % of females (Zhou et al., 2021), and by 2025, it is estimated that 29.2 % of the adult population will be hypertensive, with 29.0 % of males and 29.5 % of females expected to be affected (Kearney et al., 2005). As a result, the total number of adults with HT is predicted to increase by approximately 60 %, reaching 1.56 billion by 2025 (Salutondok and Tanggo, 2022). In addition, HT has been linked to an increased risk of cardiovascular diseases (CVD) and other complications, including kidney failure, stroke, and dementia (Salutondok and Tanggo, 2022; Nadar and Lip, 2021; Fuchs and Whelton, 2020; Buonacera et al., 2019). Beyond reducing quality of life, it is a leading cause of premature mortality, particularly due to CVD (WHO, 2013; Williams et al., 2018). Indeed, the risk of cardiovascular mortality doubles for every 20/10 mmHg increase in SBP/DBP (Attique et al., 2019). Thus, HT is a significant public health concern globally.

Regular intake of the angiotensin-I-converting enzyme (ACE) inhibitors alone or with other chemical drugs, including diuretics, thiazide diuretics, angiotensin receptor II blockers, and calcium channel blockers, remains the most conventional treatment for hypertension. Despite the effectiveness of this treatment, patients, especially those with moderate hypertension, tend to avoid these drugs because of their side effects, such as dry cough, taste disturbances, and rashes (Konnoth, 2019; Stuermer et al., 2019). In addition, 10–20 % of patients fail to respond to conventional treatment, and only 30% of patients undergoing treatment achieve normalization of their blood pressure (BP)(Fuchs and Whelton, 2020; Mazzaglia et al., 2009; Tocci et al., 2015). Therefore, research has shifted towards developing new methods to serve as alternatives to traditional hypertension treatments. One such approach involves the use of medicinal plant extracts. According to a review by Verma et al (Verma et al., 2021), several plants are thought to have potent antihypertensive properties. The primary bioactive compounds believed to play a role in reducing or normalizing hypertension are polyphenols (Castro et al., 2010; Marhuenda et al., 2021; Shekarriz et al., 2021; Somova et al., 2003; Verma et al., 2021).

Rosmarinus officinalis L (Rosemary) is an aromatic, shrubby plant native to the Mediterranean region, thriving especially in the subhumid, semi-arid, and arid areas of central and north-western Tunisia. This edible plant has long been used for culinary and medicinal purposes (Ribeiro-Santos et al., 2015). Both fresh rosemary and its dried, ground powder are commonly used to flavor and preserve food. Additionally, rosemary tea has traditionally been consumed for the treatment of headaches, respiratory conditions, and various neuropsychiatric disorders (Upadhyay et al., 2021). Analytical and phytochemical studies on the plant extracts have reported its diversity in phenolic acids and flavonoids found under free forms (known as aglycones) and/or conjugated forms (Achour et al., 2018). One of these compounds, rosmarinic acid (RA), has been investigated for its potential antihypertensive properties. Its effectiveness is attributed to its ability to inhibit angiotensin-converting enzyme (ACE) (Ferreira et al., 2018; Kwon et al., 2006). Moreover, RA has demonstrated anti-anxiolytic (Achour et al., 2022; Dahchour, 2022; Nematolahi et al., 2018; Verma et al., 2023) anti-inflammatory and antioxidant properties, which may contribute to the regulation of blood pressure. The antihypertensive effects of RA have been evaluated through in vitro studies and experiments on laboratory animals (Ferreira et al., 2018; Karthik et al., 2011; Kwon et al., 2006; Prasannarong et al., 2019). However, to our knowledge, there is no scientific evidence supporting the antihypertensive effect of rosemary in hypertensive patients.

The objective of our study was to assess the impact of daily rosemary infusion consumption over 45 days on SBP and DBP, measured using ambulatory blood pressure monitoring (ABPM), while also evaluating its tolerability and safety through biochemical markers in both healthy participants and grade 1 hypertensive patients.

2. Materials and methods

2.1. Plant material

Rosmarinus officinalis L (family Lemnaceae), a plant, growing wild in Tunisia, was collected by our team from Mount Zaghouan (Hamem Zeriba) during April–May 2021, and identified by a botany expert from the Higher Institute of Biotechnology of Monastir according to the Flora of Tunisia (Pottier-Alapetite, 1981).

The collection was carefully carried out by our team. Only mature, undamaged leaves were selected and visually inspected for appearance and condition to avoid contamination or alteration of the active compounds. The collected material was washed with water, air-dried at room temperature, and stored out of direct sunlight for three weeks. The dried plant material was then stored in hermetically sealed containers for future use. The leaves were ground using Moulinex type LM 240 (France) to obtain a fine powder ready for use. Tea bags containing rosemary powder (2 g each) were given to the patients along with instructions on preparing the infusion at home. The chosen dose has been traditionally used since the dawn of time. In addition, quantification of the infusion showed a significant RA content.

2.2. Infusion preparation and analysis of its bioactive components

The rosemary infusion was prepared by soaking a tea bag containing 2 g of powdered leaves in 100 ml of hot water for 15 min. The infusion was analyzed using a validated high-performance liquid chromatography (HPLC) method (UHPLC-DAD, SHIMADZU 8045). The system included a thermostatic autosampler, a binary pump, and a diode array detector (DAD). Separation was achieved with a reversed-phase Kinetex Evo C18 column, and the chromatograms were recorded at 324 nm. Prior to injection, a 20 µl sample of the rosemary infusion was filtered using a 0.2 µm PVDF filter.

The major compounds in the rosemary infusion were identified based on a previous study conducted in our laboratory, which identified key compounds in an infusion made from the intact leaves of the plant (Achour et al., 2018), along with three authenticated standard compounds purchased from Sigma-Aldrich (coumaric acid, trans-ferulic acid, and sinapic acid). Pure standard compounds were dissolved in 10% DMSO in deionized water before being injected into the HPLC system. Polyphenol quantification in rosemary was carried out using the compound itself or one with a similar structure.

2.3. Study settings and participant recruitment

This research was carried out at the Laboratory of Biophysics in collaboration with the Cardiovascular and Pulmonary Interaction Laboratory at the Faculty of Medicine of Sousse, University of Sousse. Participants were recruited from the Regional Blood Bank consultations at the Farhat Hached University Hospital Center in Sousse. The study received approval from the Research Ethics Committee of the Faculty of Medicine of Sousse (registration number CEFMS 89 /2021) on May 22,

2021. All participants provided written informed consent before joining the study.

2.4. Study participants

Ninety individuals in total were eligible for the study. Of these, 24 were excluded (10 lived far away and 14 could not be contacted). Finally, 53 participants, consisting of 18 healthy individuals and 35 patients with hypertension, were included in the study.

We did not perform a formal sample size calculation for this study. Given the exploratory nature of the research, the primary objective was to gather preliminary data on clinical and biochemical responses, identify potential side effects, and assess feasibility for future large-scale trials. The number of participants was based on practical considerations, including participant availability, study duration, and resource. Our approach aligns with common practices in early-phase studies where the focus is on exploring outcomes rather than achieving strong statistical power.

2.4.1. Inclusion criteria

Participants of both genders, aged between 19 and 66 years, were enrolled in the study. The inclusion criteria for healthy participants were as follows: having normal and optimal blood pressure according to ESC/ESH 2018 guidelines (Williams et al., 2018b), not having any chronic diseases, and not taking any medication or dietary supplements for other health conditions. For participants with grade 1 HT, the inclusion criteria were a SBP of 140–159 mmHg and/or DBP of 90–99 mmHg (Williams et al., 2018b) and the absence of antihypertensive treatment. participants were screened for BMI during the recruitment phase.

2.4.2. Exclusion criteria

The exclusion criteria for both groups were as follows: secondary hypertension, renal failure, autoimmune diseases, history of cardiovascular disease, pharmacological treatment for hypertension or other health conditions, and major gastrointestinal problems.

To ensure that any observed effects on blood pressure changes are due to the rosemary infusion and not these external variables, we took several measures during the study design and analysis to manage and control for these factors. At baseline, participants were asked to provide detailed information about their diet and exercise habits using validated questionnaires. We excluded individuals with extreme diet patterns or irregular exercise regimens that could potentially confound the effects of the intervention. Participants were asked to maintain their usual diet routines throughout the study period to avoid any lifestyle changes that could affect blood pressure. We screened participants for current and previous use of antihypertensive medications or any other drugs that could potentially impact blood pressure. Participants on medications that might interfere with the study's outcome (e.g., blood pressure-lowering drugs) were also excluded. Additionally, at baseline, we screened participants for common comorbidities such as diabetes, cardiovascular disease, and other chronic conditions that could influence blood pressure. Participants with significant comorbidities that might confound the study's outcomes were excluded. We recorded participants' BMI at baseline as an important factor known to influence blood pressure. Participants with extreme BMI values (either underweight or severely obese) were excluded to minimize potential confounding. Thus, by carefully examining and expelling patients with extreme or irregular diets, significant comorbidities, and patients taking hypotensive medications that could skew the results and adjusting the BMI, we ensured that the results of this study reflect the true effects of rosemary infusion on blood pressure, thus minimizing the potential impact of these confounding factors in this preliminary study.

2.5. Study design, assessment, and outcomes

A pilot, non-randomized clinical trial was conducted to investigate the effectiveness and safety of daily Rosemary infusion consumption during 45 days among healthy subjects and grade 1 hypertensive patients.

The vegetal material was supplied to participants in tea bag, each containing 2 g of rosemary powder (45 tea bag per participant). The treatment was prepared at home by steeping the tea bag in 100 ml of boiling water for 15 min and was taken once daily for a duration of 45 days.

The initial screening of participants with normal blood pressure and stage 1 hypertension took place at the Regional Blood Bank consultations of the Farhat Hached University Hospital Center in Sousse. Baseline blood pressure readings were obtained at the start of the study. The investigator measured participants' blood pressure at the brachial artery using an oscillometric sphygmomanometer while they were seated, after at least 5 min of rest and fasting. The measurement was repeated every 5 min for a total of 15 min. The average of these three measurements for SBP and DBP was used. The oscillometric sphygmomanometer was only employed for the selection of study participants, not as a diagnostic tool for the study. Therefore, the participants were instructed to visit the Department of Biophysics at the Faculty of Medicine twice consecutively.

During the first visit, subjects performed BP monitoring over 24 h. The device was set to measure blood pressure every 30 min throughout the day and at 1-h intervals at night. The next day, patients went back to the department to return the device. If the diagnosis was confirmed, the investigator explained the study protocol to eligible patients, administered a questionnaire to record anthropometric data, BMI was measured using standard procedures. Height was measured to the nearest centimeter, and weight was recorded to the nearest kilogram. BMI was then calculated as weight (kg) divided by height (m^2). Then investigator collected a fasting blood sample. Patients classified as range 2 hypertensive were transferred to the cardiology clinic.

If a hypertensive emergency was identified with BP $\geq$ 180/110 mmHg, the patient was immediately referred to the emergency department. The study lasted for 45 days, during which eligible participants were instructed to consume 100 mL of freshly prepared rosemary infusion daily after breakfast. They were also asked to maintain their regular dietary habits throughout the study period. Weekly follow-ups were conducted via telephone. Upon completion of the study, participants provided new ABPM readings and blood samples. Therapeutic tolerance was measured through the presence of side effects (reported by the patient) and variations in both groups biochemical parameters measured after 45 days of infusion consumption. The antihypertensive effect was calculated as the difference between the basal BP and that obtained at the end of the study using ABPM.

2.5.1. Measurement of ambulatory blood pressure

ABPM was utilized to improve the accuracy of the clinical trial while minimizing the required number of participants. Blood pressure measurements were taken at the brachial artery using a Holter SunTech Medical Oscar 2 device (INC S07Air Port Blvd, Suite 117, Morrisville, NC, USA) to monitor BP over a 24-hour period. The device was set to record BP every 30 min during the day and every hour at night. The cuff was placed on the non-dominant arm, enabling the participants to carry on with their normal activities. They were instructed to stay still during cuff inflation.

The sleep and wake times for programming the Holter device were established based on a question asked to the subjects during their visit. These measurements were recorded on Day 0 (D_0) and Day 45 (D_{45}) to assess the impact of the rosemary infusion on blood pressure. We assessed the following blood pressure parameters: 24-h, daytime, and nighttime SBP and DBP, mean blood pressure (MBP), heart rate (HR), and nocturnal dipping status. Variations in SBP, DBP, MBP, HR, and nocturnal dipping status were quantified by calculating the standard deviation (SD) of the measurements during both the waking and sleep periods.

2.5.2. Biochemical analysis

Blood samples were collected from the cubital vein of subjects both at baseline and after the study, following a 12-h fasting period. The samples were drawn into three distinct tubes: an EDTA-coated tube, a heparin-coated tube, and a sodium fluoride/potassium oxalate-coated tube. These samples were immediately subjected to centrifugation for 20 min at 3000 rpm, then stored at −80 °C until further analysis.

Plasma aliquots were transferred to the biochemistry laboratory for the determination of various biochemical parameters and ionic constituents in the blood, including ASAT, ALAT, total bilirubin, direct bilirubin, γ-GT, alkaline phosphatase, cholesterol, triglycerides, HDL, LDL, glucose, urea, creatinine, uric acid, albumin, Na+, and K+. Analyses were conducted at the Biochemistry Department of Farhat Hached Hospital in Sousse using the Unicell DXC 600 Synchron analyzer by Beckman Coulter. LDL cholesterol levels were calculated using the Friedewald formula.

2.6. Ethical statement

The study adhered to the principles outlined in the Declaration of Helsinki and received approval from the Ethics Committee of the Faculty of Medicine of Sousse (Ethical Approval Number: CEFMS 89/2021, granted on May 22, 2021). Written informed consent was obtained from all participants.

2.7. Statistical analysis

Statistical analyses for this study were conducted using IBM SPSS software, version 20. The data are presented as mean values with their corresponding standard deviations (SD). To assess the normality of distribution for each variable, the Shapiro-Wilk test was employed. Descriptive statistics were used to summarize the characteristics of the study population. For within-group comparisons between baseline and D_{45} measurements, paired *t*-tests were used for variables with a normal distribution, while the Wilcoxon signed-rank test was applied for non-normally distributed data. To compare the differences in parameters between the healthy volunteers and hypertensive patients, unpaired *t*-tests were used for parametric continuous variables, while the Mann-Whitney U test was applied for nonparametric continuous variables. Fisher's Exact Test was used for analyzing categorical variables. Statistical significance was considered at a threshold of $P \leq 0.05$. Finally, we applied BMI adjustment using the ANCOVA test to control the effects of BMI on the primary and secondary outcome variables

3. Results

3.1. Chromatographic and phytochemical analyses

Fig. 1 illustrates typical chromatographic profiles of the tea prepared by infusing 2 g of dried rosemary leaves (blue chromatogram) and 2 g of fine powder from the crushed leaves (red chromatogram) in 100 ml of boiling water. As can be seen, the two chromatograms are qualitatively similar, showing the same peaks corresponding to the extracts. These are represented by 11 peaks named 1–11(Table 1). Except for peaks 3,4,5 all others, these were identified using previous LC-MS data (Achour et al., 2018). Peaks 3, 4 and 5 are identified on the basis of the retention time of the three standard compounds (coumaric acid, Trans-Ferulic acid and sinapic acid) as shown in Table 1.

However, there was a notable enhancement in the extraction yields of the identified compounds when the infusion was prepared using fine powder (red chromatogram). Notably, for the compounds identified, extraction yields increased by 0 to 33 times, depending on the compound, when using powdered leaves compared with dried leaves, as shown in Table 1. From these results, RA is the major compound found

Table 1
Phenolic composition of dried and fine powder leaves of Rosmarinus officinalis infusion.

Compounds	Peak number	Retention time (min)	Concentration (μg/1g dried rosemary leaves)	Concentration (μg/1g powder of rosemary leaves)
Chloroginic acid	1	6,19	20	80
Caffeic acid	2	7,46	40	160
Coumaric Acid	3	11,59	10	10
Trans-Ferulic Acid.	4	13,6	9	12
Sinapic Acid	5	14,16	6,4	50
Rosmarinic acid	6	23	910	8950
Feruloylnepitrin-Isomer 1	7	26	220	5800
Luteolin-3′-o-(2′′-o-acetyl)-β-D-glucuronide -Isomer 2	8	31.78	78	510
Feruloylnepitrin -Isomer 2	9	32.07	220	1680
Luteolin	10	32.97	20	190
Luteolin-3′-o-(2-o-acetyl)-β-D-glucuronide -Isomer 3	11	34.70	60	2020

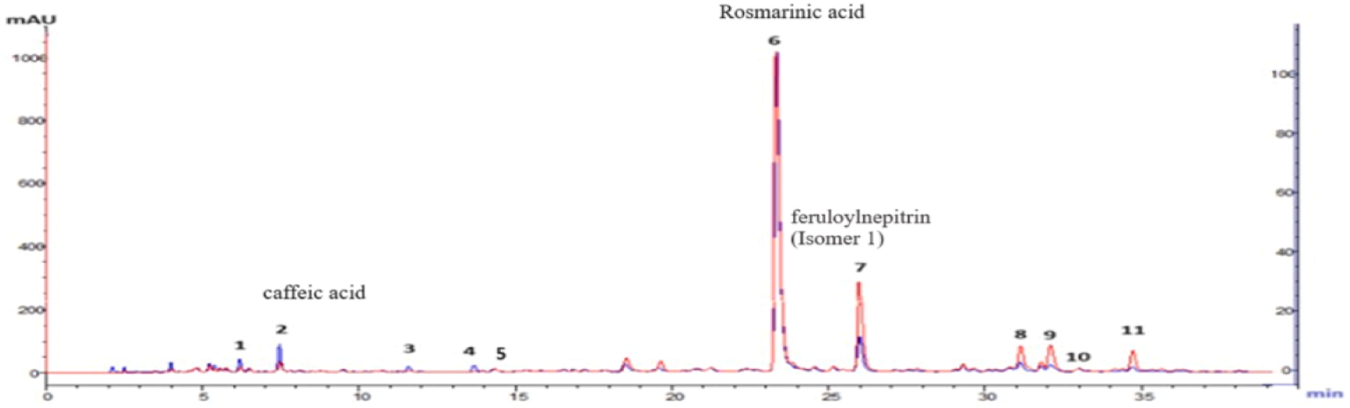

Fig. 1. Typical chromatograms recorded at 324 nm, of dried rosemary leaves infusion (blue chromatogram) and rosemary fine powder infusion (red chromatogram). 1: chloroginic acid(80 μg/1 g), 2: caffeic acid (160 μg/1 g) 3: coumaric acid (10 μg/1 g), 4: trransfurilic acid (12 μg/1 g), 5:sinapic acid (50 μg/1 g), 6:Rosmarinic acid (8950 μg/1 g), 7: feruloylnepitrin (Isomer 1) (5800 μg/1 g), 8: luteolin-30 -O-(200-O-acetyl)-β-D-glucuronide (Isomer 2) (510 μg/1 g), 9: feruloylnepitrin (Isomer 2) (1680 μg/1 g), 10: luteolin(190 μg/1 g), 11: luteolin-30 -O-(200-O-acetyl)-β-D-glucuronide (Isomer3) (2020 μg/1 g).

in fine powder infusion, with about 8950 μg/ g wish representing 45.9 % of the total quantified component of fine powder. All other components exhibited low extraction yields, as shown in Table 1. Taking into account the quantification results, the daily infusion intake of 2 g of rosemary powder contains approximately 38 mg of polyphenols, 18 mg of phenolic acid, and 20 mg of flavonoid.

3.2. Enrollment of study participants

A total of 90 participants were initially recruited. Twenty-four of the participants were excluded: ten lived far away and forty could not be contacted. Finally, 66 participants completed screening with ambulatory blood pressure measurement. Of these, 13 were considered ineligible, five refused ABPM, and eight had ambulatory SBP and DBP above the inclusion values. Ultimately, 53 participants, including 18 healthy volunteers and 35 hypertensive grade 1 patients, were enrolled and allocated to consume Rosemary infusion after providing informed consent. During follow- up, three patients in the healthy group and five participants among hypertensive patients were lost to follow-up. Finally, 15 healthy volnteers and 30 hypertensive patients completed the 45-day follow-up study. The trial flow chart of the study is shown in Fig. 2.

3.3. Baseline characteristics

The baseline characteristics of the study participants, including healthy volunteers (Group 1) and Grade 1 hypertensive patients (Group 2), are summarized in Table 2. We recognize that there is a notable imbalance in the sex ratios between the healthy (9 males, 6 females) and hypertensive groups (24 males, 6 females). This discrepancy may introduce potential biases or limit the generalizability of the findings. The imbalance may reflect differences in recruitment patterns, where more males were recruited into the hypertensive cohort due to a higher prevalence of hypertension among men in the study population. Hypertension is more common in men at younger ages, which may have contributed to the larger number of male participants in the hypertensive group. Additionally, it is possible that recruitment efforts or participation rates varied between the sexes, with fewer females being eligible or consenting to participate in the hypertensive cohort. This

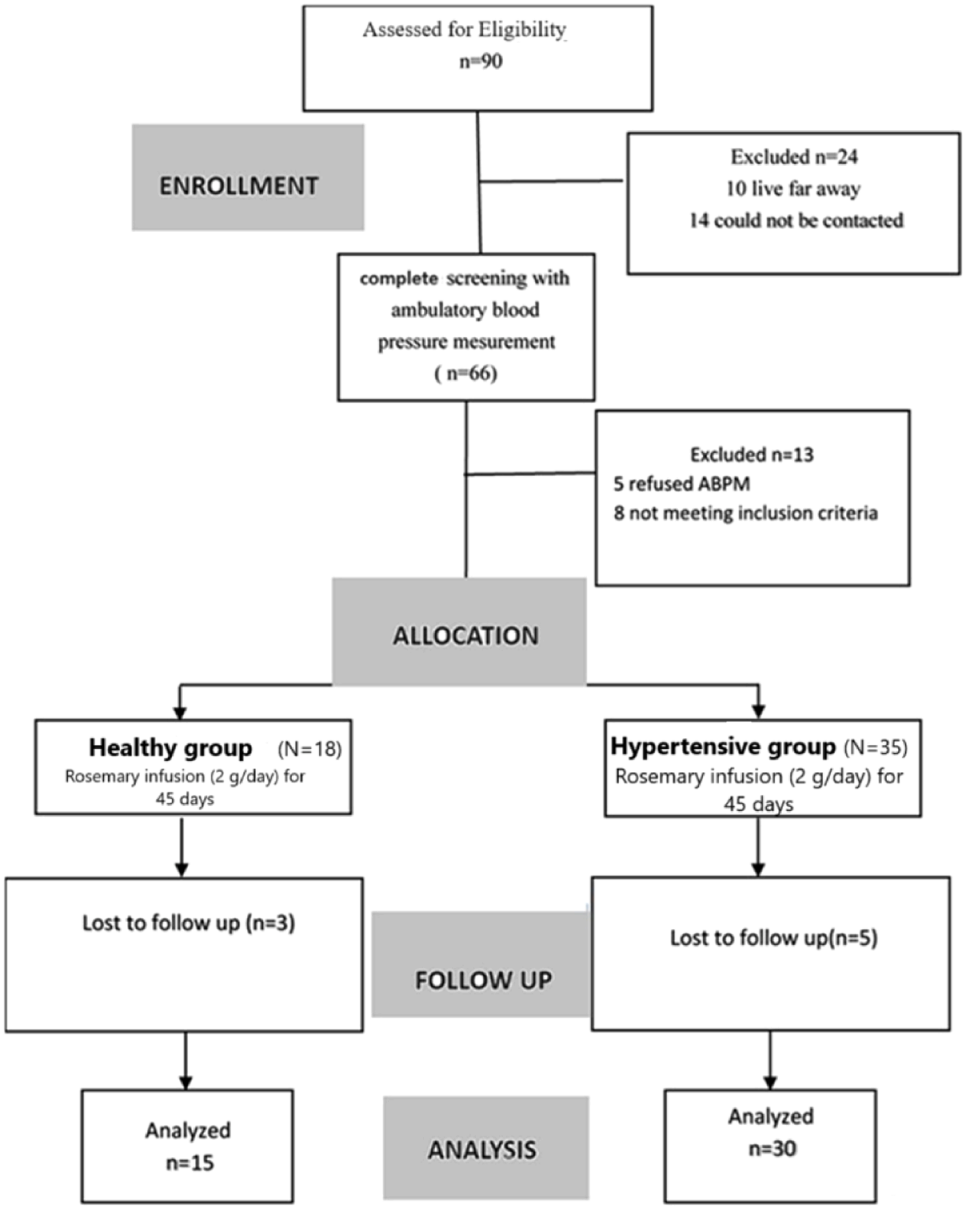

Fig. 2. Flow diagram of study participants.

Table 2
Baseline characteristics of the study participants.

Parameters	Groupe 1 (healthy Participants) *n*=15	Group 2 (hypertensive patients) *n*=30	P value [a]
Gender, N (Male /female)	9/6	24/6	0 0.14
Age, year (range)	45(30–64) ±10.5	46(19–66) ±10.2	0.57
BMI, kg/m^2	26.06 (24–29) ±1.4	29.6 (21–45) ±4.8	0.008
OSBP, mmHg	117.2(100–129) ±7.8	144.4(140–159) ±6.5	≤0.001
ODBP, mmHg	71.9(65–80) ±5.4	80.1(70–90) ±6.8	≤0.001

Values are presented as mean ± standard deviation
OSBP; official systolic blood pressure, ODBP; Official diastolic blood pressure, BMI; body mass index
[a] Between-group differences (healthy volunteers, hypertensive grade 1patients) in the parameters were assessed by using unpaired *t*-test (parametric) and Mann–Whitney U test (nonparametric) for continuous variables and Fisher's Exact Test for categorical variabl

could also be a result of gender-related health-seeking behaviors or other logistical factors related to study enrollment.

No significant differences were observed in the demographic characteristics such as the male-to-female ratio or the average age between the two study groups. However, significant differences were observed when comparing the body mass index (BMI), office systolic blood pressure (OSBP), and office diastolic blood pressure (ODBP) between the healthy individuals and hypertensive patients. These variations are presented in detail in Table 2.

3.4. Effect of rosemary infusion on blood pressure parameters

3.4.1. Effect of rosemary infusion on healthy participants

In the group of healthy volunteers, as presented in Table 3, no statistically significant differences were observed between the baseline and post-intervention blood pressure measurements. This includes parameters such as 24-hour SBP and DBP, daytime and nocturnal SBP and DBP, MBP, PP, HR, and nocturnal dipping status ($P > 0.05$). These results suggest that the consumption of rosemary infusion over a 45-day period did not lead to any notable reduction in blood pressure below the normal range, indicating that it has no significant effect on normal blood pressure levels in healthy individuals.

In addition, gender stratification shows no significant variation in all parameters 24-h SBP, 24-h DBP, Daytime SBP, MBP, PP and HR ($P > 0.05$). which proves that the response to rosemary infusion intervention is similar for both sexes.

3.4.2. Effect of rosemary infusion in hypertensive grade 1 patients

3.4.2.1. 24-h, daytime, and nocturnal systolic and diastolic ambulatory BP. The impact of consuming rosemary infusion over a 45-day period on patients with grade 1 hypertension is detailed in Table 3 and illustrated in Fig. 3. A significant reduction ($P \leq 0.05$) in mean blood pressure values was observed in the 24-h, daytime SBP and DBP when comparing measurements taken at baseline (Day 0) to those taken at the conclusion of the study (Day 45).

This included reduction in the 24-h SBP of 6.3 mmHg ± 11.4 ($P = 0.005$). The between-group (hypertensive vs. healthy) comparisons before and after the intervention showed $P < 0.001$ and $P = 0.04$, respectively. DBP decreased by 4.85 mmHg ± 8 ($P = 0.003$), with the

Table 3
Effect of Rosmarinus Officinalis infusion on 24-h ambulatory blood pressure data in healthy Participants and hypertensive grade 1 patients.

Parameters		Healthy Participants (n =15)				Grade 1 Hypertensive Patients (n =30)				Between group Pvalue[c]		
		Mean ambulatory BP (mmHg)	Mean ambulatory BP (mmHg)	Δ[a]	P value [a]	Mean ambulatory BP (mmHg)	Mean ambulatory BP (mmHg)	Δ[b]	P value[b]	P_0	P_{45}	P_{0-45}
		D_0	D45		D_0	D45						
24-hour blood pressure	**SBP**	122.4 ± 5.5	121 ± 5.09	−0.8 ± 7.4	0.65	137.1 ± 8.2	130.76 ± 11.02	−6. 3 ± 11.44	**0.005**	**<0.001**	**0.004**	0.11
	DBP	72.7 ± 7.7	70.8 ± 6.7	−1.8 ± 5.4	0 0.24	82.1 ± 6.94	77.33 ± 7.9	−4.85 ± 8.0	**0.003**	**<0.001**	**0.01**	0.22
Daytime BP	**SBP**	125 ± 5.4	124 ± 5.7	−0.6 ± 7.4	0 0.73	141.6 ± 7.9	134.23 ± 11.02	−7.4 ± 11.3	**0.003**	**<0.001**	**0.004**	**0.05**
	DBP	72 ± 7.7	70 ± 6.7	−0.2 ± 1.5	0.52	86.06 ± 6.8	80.3 ± 8.7	−5.7 ± 9.4	**0.002**	**<0.001**	**0.06**	**0.03**
Nocturnal BP	**SBP**	111.7 ± 9.8	111.5 ± 8.3	−0.2 ± 9.3	0.91	120.9 ± 13.63	120.4 ± 17.25	−0.53 ± 14.8	0.81	**0 0.02**	0.1	0.91
	DBP	64 ± 10.5	62 ± 9.7	−1.3 ± 7.7	0.54	68.7 ± 11.4	69.1 ± 13.4	0.3 ± 11.81	0.71	0.19	0.09	0.9
24-hour MBP		89.2 ± 6.3	88.33 ± 6.3	−0.9 ± 5.5	0.53	100 ± 6.7	95 ± 8.3	−5.2 ± 8.90	**0.003**	**<0.001**	**0.009**	0.07
24-hour pulse pressure		50.86 ± 8.1	50.53 ± 6.1	−0.4 ± 7.2	0.86	54.9 ± 6.1	53.3 ± 7.6	−1.5 ± 6.74	0.22	0.07	0.2	0.46
24-hour heart rate, Beats per min		70.3 ± 6.7	70.6 ± 8.3	−0.3 ± 8.6	0.72	75.3 ± 10.2	75.3 ± 8.4	0.06 ± 8.2	0.5	0.12	0.06	0.55
nocturnal SBP dipping **(%)**		10.91 ± 8.3	10.59 ± 7.2	1.3 ± 9.7	0 0.89	16.9 ± 12.9	11.59 ± 9.3	−5.09 ± 16.36	**0.049**	0.1	0.6	0.21
nocturnal DBP dipping **(%)**		16.21 ± 11.3	17.56 ± 10.8	−0.6 ± 5.5	0.60	19.96 ± 11.8	14.87 ± 15.06	0.06 ± 8.25	0.23	0.3	0.6	0 0.15

Values are presented as mean ± standard deviation
BP: blood pressure, SBP: systolic blood pressure, DBP: diastolic blood pressure. MBP: mean blood pressure
[a] Within-group differences in the parameters before and after intervention were compared using paired *t*-test (parametric) and Wilcoxon Signed Rank test (nonparametric)
[b] Mean difference before and after 45 days of RI intervention (Day 45 − Baseline)
[c] Between-group differences (healthy volunteers, hypertensive grade 1patients) in the parameters were assessed by using unpaired *t*-test (parametric) and Mann–Whitney U test (nonparametric)

between-group comparisons before and after the intervention showing $P < 0.001$ and $P = 0.01$, respectively.

For daytime SBP, there was a reduction of −7.4 mmHg ±11.3 ($P = 0.003$), with between-group comparisons before and after the intervention showing $P < 0.001$ and $P = 0.004$, respectively. The between-group mean difference had a p-value of 0.05. Daytime DBP decreased by −5.7 mmHg ±9.4 ($P = 0.002$), with the between-group comparison before the intervention showing $P < 0.001$ and the between-group mean difference having a P-value of 0.03. However, there were no significant differences in nocturnal SBP and DBP within and between groups ($P > 0.05$) (Table 3).

We conducted a stratified analysis to examine how gender could influence the response to rosemary infusion intervention among hypertensives patients (Table S1-S2 supplementary matrials) our results

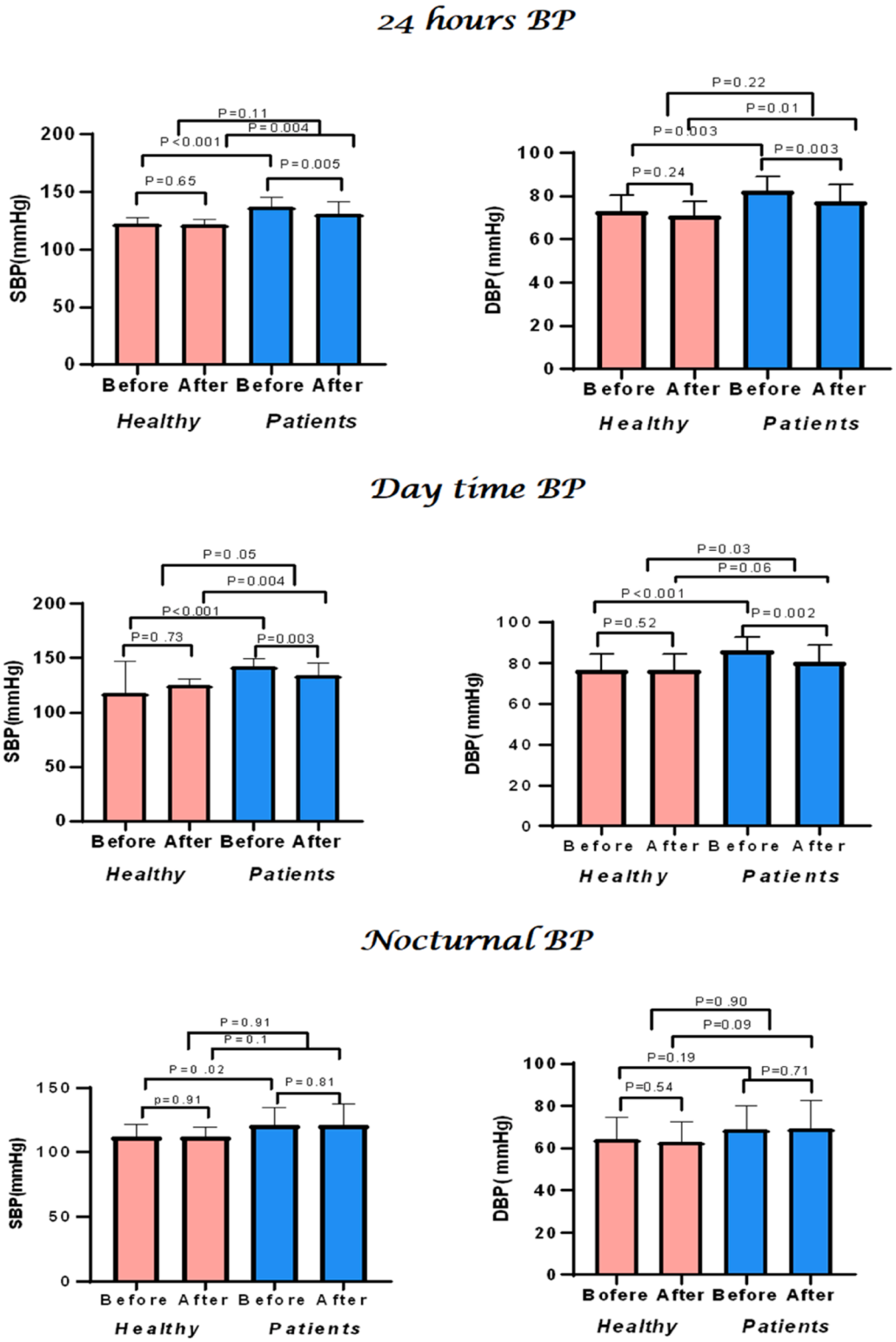

Fig. 3. Blood pressure variation in hypertensive grade 1 patients before and after 45 days of rosemary infusion intervention compared to healthy subjects. SBP:systolic blood pressure, DBP:diastolic blood pressure.

shows a significant decrease in 24 h SBP (P=0.006), 24 h DBP (P=0.024), Daytime SBP (P=0.006), MBP (P=0.014) and PP (P=0.037) in the hypertensive men, whereas the hypertensive women exhibited only a decrease in 24-h DBP ($P = 0.03$).

3.4.2.2. Mean blood pressure, pulse pressure, heart rate and nocturnal dipping status. As detailed in Table 3, the administration of rosemary over a 45-day period resulted in a significant reduction in the MBP (−5.2 mm Hg ±8.90, $P = 0.003$) between group comparison before and after intervention were $P < 0.001$ and $P = 0.009$ respectively; and between group mean difference P value = 0.07.

As well as a decrease in nocturnal SBP dipping (−5.09 mm Hg ±16.36, $P = 0.04$). between group comparison before and after intervention were $P = 0.1$ and P =0.6 respectively and between group mean difference P value = 0.21.

However, there was a non-significant decrease in nocturnal SBP dipping (0.06% ±8.256, $P = 0.2$).

No significant reduction in PP of −1.5 mmHg ± 6.7 (P=0.22). The between-group comparisons before and after the intervention showed P=0.07 and P=0.2 respectively (Table 3). There was also a non-significant change in HR of 0.06 mmHg ± 8.2 (P=0.5). Comparisons between the groups before and after the intervention showed P=0.12 and P=0.06 respectively (Table 3).

Statistical adjustment according to BMI shows that the decrease in 24-h SBP, 24-h DBP, 24-H MBP, PP is due to rosemary infusion intake (Table S5 Supplementary Materials)

There was no overall statistically significant difference in change of 24-h SBP, 24-hDBP, Day time SBP, Nocturnal DBP, 24 h MBP, HR and PP between the different groups once their means had been adjusted for BMI.

3.5. Tolerability and safety of rosemary infusion

The tolerability and safety of Rosemary infusion were assessed in healthy and hypertensive patients. Throughout the intervention period, we maintained vigilance in ensuring the participants' tolerance to the infusion by regularly inquiring about any treatment-related adverse events. It was noticed that the participants did not report any side effects. On the other hand, to assess safety, we analyzed the blood samples of patients and measured ambulatory blood pressure both before (D_0) and by the end of (D_{45}) the study.

As presented in Table 4, there were no statistically significant changes in the biochemical blood parameters of the healthy group between D_0 and D_{45} ($P > 0.05$).

Therefore, the 45-day administration of rosemary infusion did not produce significant effects on hepatic, renal, lipid, or ionic profiles. Additionally, in the hypertensive group, there was no statistically significant difference between baseline biochemical parameters and those measured after the intervention ($P > 0.05$) (Table 4), except for AST levels, which showed a significant increase but remained within the normal range. This finding suggests that the infusion did not have any side effects in the course of hypertension control.

4. Discussion

To the best of our knowledge, this study represents the first clinical trial to assess the potential impact of rosemary infusion on both systolic and diastolic blood pressure in individuals with grade 1 hypertension and healthy volunteers. Additionally, the study evaluates the tolerability and safety of daily rosemary infusion consumption over a 45-day intervention period. By simultaneously exploring its effects on two distinct groups, i.e., those with elevated blood pressure and those with normal blood pressure, this research provides a comprehensive understanding of rosemary's therapeutic potential while also ensuring its safety profile.

Our findings demonstrated that the daily intake of 2000 mg of rosemary by grade 1 hypertensive patients led to a significant reduction in multiple blood pressure parameters. This included significant reductions in 24-h SBP ($P = 0.005$) and DBP ($P = 0.003$), daytime SBP ($P = 0.003$) and DBP ($P = 0.002$), 24 h MBP ($P = 0.003$) and nocturnal SBP dipping ($P = 0.049$). Our findings illustrate the antihypertensive properties of rosemary infusion.

Given that hypertension and blood pressure responses to interventions can differ by sex, the imbalance in sex ratios between groups

Table 4
Biochemical parameters values of the healthy volunteers at baseline and at the end of the intervention.

Parameters	Healthy Participants n =15				Grade 1 Hypertensive Patients n=30				
	D_0	D_{45}	P value [a]	Δ[b]	D_0	D_{45}	P value [a]	Δ[b]	P value[c]
ASAT(UI/L)	22.26 ± 14.4	22.4 ± 13.6	0.78	0.13 ± 3.3	20.51 ± 10.26	21.8 ± 7.7	0.11	1.3 ± 6.8	0.15
ALAT(UI/L)	20.4 ± 23.8	22.4 ± 20.7	0.19	1.9 ± 5.4	13.2 ± 11.3	16.5 ± 11.1	0.003	3.3 ± 7.2	0.46
Total Bilirubin (µmol/l)	7.4 ± 5.3	9.82 ± 5.01	0.06	2.3 ± 4.06	9.62 ± 4.3	9.65 ± 4.7	0.86	0.03 ± 40	0.17
Direct Bilirubin (µmol/l)	2.65 ± 2.1	2.1 ± 1.3	0.43	−0.4 ± 1.7	2.72 ± 4.6	2.12 ± 1.4	0.46	−0.60 ± 4.5	0.42
γ-GT (UI/L)	38.06 ± 44.5	38.8 ± 45.2	0.55	0.80 ± 6.1	27 ± 12.1	28.3 ± 12.6	0.07	1.3 ± 3.9	0.50
Alkaline phosphatase (UI/L)	47.05 ± 19.1	55.4 ± 16.5	0.09	8.3 ± 18.06	57.32 ± 18.5	57.82 ± 20.5	0.23	0.5 ± 10.6	0.23
Cholesterol (mmol/l)	4.83 ± 0.7	5.01 ± 0.78	0.47	0.17 ± 0.93	4.96 ± 1.1	5.03 ± 1.02	0.39	0.06 ± 0.8	0.39
Triglyceride (mmol/l)	1.14 ± 0.6	1.16 ± 0.61	0.55	0.02 ± 0.22	1.38 ± 0.6	1.37 ± 0.4	0.79	−0.01 ± 0.45	0.71
HDL (mmol/l)	1.55 ± 0.55	1.49 ± 0.57	0.51	−0.96 ± 0.3	1.11 ± 0.6	1.05 ± 0.25	0.63	0.01 ± 0.7	0.82
LDL (mmol/l)	2.82 ± 1.13	2.93 ± 1.01	0.71	0.11 ± 1.1	3.39 ± 0.97	3.38 ± 0.90	0.9	−0.02 ± 0.7	1.00
Glucose (mmol/l)	5.96 ± 2.76	5.35 ± 1.05	0.18	−0.6 ± 1.9	5.15 ± 0.6	5.07 ± 0.7	0.45	−0.07 ± 0.5	0.11
Urea (mmol/l)	4.39 ± 1.07	4.32 ± 1.02	0.58	−0.06 ± 0.49	4.21 ± 0.96	4.6 ± 1.4	0.17	0.33 ± 1.01	0.17
Creatinine (umol/l)	64.4 ± 11.61	63.06 ± 10.4	0.35	−1.4 ± 5.6	76.8 ± 47.9	69.6 ± 13.4	0.48	−6.9 ± 46.7	0.75
Uric acid (umol/l)	297 ± 85.43	315.2 ± 88.3	0.06	17.3 ± 41.9	340.7 ± 80.3	336.17 ± 74.02	0.52	−4.6 ± 39	0.12
Albumin (g/l)	40.3 ± 5.2	41.6 ± 3.4	0.08	1.3 ± 2.6	41.9 ± 7.1	41.4 ± 5.3	0.48	−0.5 ± 9.07	0.41
Na+ (mmol/l)	136.7 ± 4.49	137.2 ± 4.3	0.65	0.46 ± 3.9	139.5 ± 2.8	138.6 ± 5.1	0.1	−0.86 ± 4.8	0.22
K+ (mmol/l)	4.37 ± 0.5	4.44 ± 0.62	0.61	0.13 ± 0.59	4.3 ± 0.75	4.2 ± 0.45	0.9	−0.05 ± 0.7	0.31

Values are presented as mean ± standard deviation

BP:blood pressure, SBP:systolic blood pressure, DBP: diastolic blood pressure

[a] Within-group differences in the parameters before and after intervention were compared using paired t-test (parametric) and Wilcoxon Signed Rank test (nonparametric).

[b] Mean difference before and after 45 days of RI intervention (Day 45 − Baseline)

[c] Between-group differences (healthy volunteers, hypertensive grade 1patients) in the parameters were assessed by using unpaired t-test (parametric) and Mann–Whitney U test (nonparametric)

may affect the generalizability of the findings. For instance, males and females may exhibit differences in baseline blood pressure levels, responses to interventions, and the physiological mechanisms underlying hypertension. If the study does not adequately account for these sex differences, the results could be skewed or less applicable to certain populations. Furthermore, the smaller number of females in both groups may limit the statistical power to detect sex-specific effects of the rosemary infusion on blood pressure. This is particularly important since gender differences in response to hypertension treatments have been observed in the literature. Due to the limited number of female participants, particularly in the hypertensive group, a stratified analysis by sex probably lack sufficient statistical power to provide reliable conclusions. Nonetheless, our attempts for stratified analysis detailed in supplementary tables S1-S4 showed that Hypertensive men showed a significant decrease in the 24-h SBP, 24-h DBP, Daytime BP, MBP and PP while hypertensive women showed a significant decrease only for 24DBP. In the other hand, no significant variation was detected for both sexes of healthy volunteer groups. In future studies, we plan to achieve a more balanced sex distribution to allow for robust stratified analyses and to further validate the generalizability of our findings.

It is well-established that higher BMI is associated with elevated blood pressure. By adjusting BMI in our analyses, we aimed to minimize its confounding effect and ensure that any observed changes in blood pressure were attributable to the rosemary infusion rather than to differences in BMI. Given the significant role of BMI in blood pressure regulation, it is important to note that any observed effects of the intervention are independent of BMI, though BMI could still influence baseline and post-treatment measurements.

The antihypertensive potential of rosemary in humans remains unexplored, as no prior studies have specifically investigated its impact on blood pressure. However, numerous clinical studies have highlighted the antihypertensive properties of various other medicinal plants, such as Hibiscus Sabdariffa L, Nigella sativa Lippia citriodora, Camellia sinensis and Olea europaea and others (Dehkordi and Kamkhah, 2008; Marhuenda et al., 2021; McKay et al., 2010; Susalit et al., 2011, 2011).

A double-blind, placebo-controlled, randomized clinical trial conducted on 65 prehypertensive and mildly hypertensive adults showed that consuming 240 mL of Hibiscus sabdariffa tea for six weeks, prepared by infusing 1.25 g of the plant, significantly reduced SBP (−7.2 mm Hg ± 11.4 $P < 0.05$) and DBP (−3.1 mm Hg ± 7.0, $P < 0.05$). This study, conducted by McKay et al., employed the same rosemary extraction method (infusion) and the same duration (six weeks). However, our study observed a greater reduction in DBP (McKay et al., 2010).

In another clinical study, the influence of Nigella sativa seed extract at doses of 200 mg/day and 400 mg/day was evaluated over an 8-week period in 108 individuals with mild hypertension. This trial demonstrated a decrease in SBP by 2.2 mm Hg and DBP by 1.1 mmHg. The antihypertensive effect observed in this study was relatively minimal, compared with our own, with changes in SBP and DBP not surpassing 2.5 mmHg (Dehkordi and Kamkhah, 2008).

A study with random assignment, blinding, and a placebo control group conducted over 84 days in 80 prehypertensive and type 1 hypertensive participants shows that consumption of H. sabdariffa and L. citriodora reduces daytime SBP (−3.76 mm Hg ± 10.13; $P < 0.05$). However, there was no significant change in DBP throughout the duration of the trial. Compared to our study, the duration of consumption and the amount of mixture used are higher than the duration and the amount of rosemary used in our study. However, the results of this study only show a statistically significant lowering effect in daytime SBP. This reduction (−3.76 mm Hg ± 10.13) was minimal compared with our results (Marhuenda et al., 2021).

Another randomized trial with blinding and placebo control clinical trial investigating the antihypertensive effect of Olea europaea leaf extract at a dose of 500 mg twice daily versus Captopril shows a significant reduction in SBP by 11 ± 8.5 mmHg and DBP by 4.8 ± 5.5 mmHg in subjects with stage 1 hypertension (Susalit et al., 2011). The reductions observed in this study are important. However, the weakness of this last study as well as others such as (McKay et al., 2010) and that of (Dehkordi and Kamkhah, 2008) is the use of mercury sphygmomanometer measurements instead of ABPM, which is recognized for its superior accuracy.

The strength of our study lies in the use of ABPM to track BP changes throughout the study, providing a more comprehensive and precise assessment of BP fluctuations in real-life settings. While mercury sphygmomanometers and stethoscopes are still considered the gold standard for measuring systolic and diastolic blood pressure in medical practice, these methods can be subject to variability and time-dependent fluctuations. To mitigate this, we utilized 24-h ambulatory BP monitoring to average SBP and DBP measurements. Noninvasive home-based devices that provide such average readings are better suited for confirming the diagnosis of hypertension and evaluating the efficacy of antihypertensive treatments.

According to our study, the phenolic profile of the Rosemary infusion consumed showed a high polyphenol content of the order of 38.9 mg/dose, with RA identified as the predominant compound which is in agreement with previous studies (Achour et al., 2018; Kwon et al., 2006) at 17.9 mg /dose (45.9 % of total quantified compounds).

Our results align with an experimental study involving Thymus serpyllum L. (wild thyme), which identified RA as well as caffeic acids as the primary phenolic compounds. This study demonstrated that a bolus intravenous injection of wild thyme at 100 mg/kg body weight led to a significant decrease in systolic and diastolic blood pressure in hypertensive rats (Mihailovic-Stanojevic et al., 2013).

In the present study, we reported that consumption of a rosemary infusion for 45 days did not affect blood pressure in healthy subjects, thus eliminating the risk of hypotension in normotensive individuals.

Our results are consistent with previously published data from animal model studies. A previous study conducted in hypertensive and normotensive rats showed that RA (173 μM) treatment resulted in a dose-dependent reduction in SBP in the hypertensive group, but not in the normotensive group through the reduction on ACE activity (98.96 %) (Ferreira et al., 2018). In another attempt, Karthik et al observed that supplementing fructose-fed rats with 10 mg/kg of RA, the key bioactive compound in rosemary, over a 60-day period resulted in a reduction in blood pressure. This effect was attributed to decreased endothelin-1 and ACE activity, as well as an increase in nitric oxide levels (Karthik et al., 2011).

Our study suggested that the adopted treatment was effective in lowering only high blood pressure values whereas no significant changes were observed among normotensive patients with average mean within normal range SBP (122 mm Hg ± 5.5 to 121 mm Hg ± 5.0, $P = 0.6$) and DBP (72.7 mm Hg ± 7.7 to 70.8 mm Hg ± 6.7, $P = 0.24$). It is noteworthy to mention that the daily consumption of rosemary tea for 45 days had no significant impact on systolic and diastolic blood pressure in the group of healthy volunteers. The absence of significant changes in blood pressure in our study could be explained by the fact that RA exerts its antihypertensive effect in the case of overactivation of the renin-angiotensin-aldosterone system (Ferreira et al., 2018; Karthik et al., 2011).

Our observations indicate that RA was less effective in reducing systolic blood pressure (SBP) compared to other antihypertensive medications like captopril, which target the ACE. Interestingly, RA did not lower SBP in normotensive rats, unlike captopril and several other natural compounds (de Souza et al., 2011; Ferreira et al., 2018; Montenegro et al., 2009). These findings support the idea that RA specifically inhibits ACE activity when the system is overactivated. This also reinforces the hypothesis that the antihypertensive effect of rosemary is largely attributed to RA, which influences ACE enzyme activity (Williams et al., 2018).

Taken together, the results from both patients and volunteers suggest that the consumption of rosemary infusion serves primarily as an

adjunct to antihypertensive treatment.

While the hypertensive group had a larger sample size, which may increase the reliability of our findings in that group, caution should be taken when interpreting results from the healthy group due to its smaller sample size. Any observed differences between the groups should be interpreted with care. However, the significant findings observed in the hypertensive group suggest that the sample size was sufficient to detect meaningful changes in blood pressure parameters. In contrast, the lack of significant changes in the healthy group likely reflects the physiological stability of their baseline measures, rather than the smaller sample size. Future research with larger and more balanced groups is needed to further validate our findings and ensure that the results are generalizable across both healthy and hypertensive populations.

The antihypertensive effects of rosemary infusion could be attributed to the presence of polyphenols such us RA, chlorogenic acid, caffeic acid, sinapic acid and luteolin. All these compunds recognized for a wide range of beneficial bioactivities, such as antioxidant properties (Adomako-Bonsu et al., 2017; Ajibade et al., 2022; Bacanlı et al., 2016; Gao et al., 2022; Lee et al., 2016; Purushothaman et al., 2022; Suzuki et al., 2006; Xia et al., 2024; Zhang et al., 2015) Anti-anxiety (Abdelhalim et al., 2015; Dahchour, 2022; Jin et al., 2013; Miyazaki et al., n.d.; She et al., 2024; Verma et al., 2022; Yoon et al., 2007) and anti-inflammatory effect (Fei et al., 2019; ; Gonçalves et al., 2022; Hwang et al., 2014; Liang et al., 2016; Marinho et al., 2021; Pandi and Kalappan, 2021; Wang et al., 2017).

Numerous in vitro and in vivo studies have established a connection between hypertension, anxiety, inflammation, and reduced antioxidant capacity (Li et al., 2008; Pantan et al., 2019). Therefore, treatment of HT could be achieved by optimizing either a single pathway or a combination of multiple pathways simultaneously.

In addition, the antihypertensive effect of these different compounds can be attributed to several other mechanisms that may explain their beneficial effect on BP regulation, such as the inhibition of ACE, responsible for converting angiotensin I into angiotensin II, a process reported to be modulated by RA, Caffeic acid and Chloroginic acid (Agunloye et al., 2021, 2019; Alegría-Herrera et al., 2019; Ferreira et al., 2018; Karthik et al., 2011; Li et al., 2008; Pantan et al., 2019; Verma et al., 2012).

Other important mechanisms of action involved in the regulation of hypertension include vasodilation and attenuation of endothelial dysfunction. Indeed, several bioactive components present in rosmarinic infusion, including RA, chlorogenic acid, sinapic acid and luteolin, have been shown to exert antihypertensive effects by inducing vasodilation and improving endothelial function. They exert this effect by activating the nitric oxide pathway, increasing endothelium-derived hyperpolarising factor, increasing prostacyclin, reducing endothelin-1 and improving hypertensive vascular remodelling (Ersoy et al., 2008; Fernandes et al., 2005; Su et al., 2015; Suzuki et al., 2006; Tom et al., 2016; Yu et al., 2022; Zhao et al., 2012).

Thus, the antihypertensive effect of RA on arterial tension appears to occur through inhibition of ACE, inflammation, oxidative stress, anxiety and promotion of vasodilation and attenuation of endothelial dysfunction in hypertensive patients.

In this study, the plasma levels of lipid profile, including total cholesterol (TC), triglycerides (TGs), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C), exhibited no significant changes throughout the study period in both healthy participants and patients with stage 1 hypertension. The lack of a hypolipidemic effect of rosemary contrasts with other studies using other herbal extracts, such as a recent meta-analysis which investigated the impact of Melissa officinalis on cardiometabolic outcomes. The analysis, comprising seven randomized clinical trials, revealed a notable reduction in both triglyceride levels and SBP (Heshmati et al., 2020). other studies in animals and humans, which found that rosemary extracts possess significant hypolipidemic potential (Al Sheyab et al., 2012; Al-Jamal and Alqadi, 2011; Labban et al., 2014). This discrepancy in the results could be explained by the metabolically healthy profile of the study population, with lipid parameters essentially within the normal range.

The assessment of rosemary infusion's tolerance and safety found that its daily consumption over 45 days appears satisfactory because no participant, healthy subjects and hypertensive grade 1 patients, reported side effects following infusion consumption. In addition, the infusion did not affect hepatic, renal, or ionic balance in either group. Furthermore, our results show the absence of significant variations in heart rate and pulse pressure, which are within the normal range, in both healthy and hypertensive patients, reinforcing the hypothesis of the safety of rosemary infusion consumption in these two groups.

These results suggested that the consumption of rosemary infusion was well tolerated and safe. These findings are in accordance with the opinion of the United States Food and Drug Administration (FDA), which categorized rosemary as "generally safe" (Aguilar et al., 2008). Likewise, our previously study has indicated the tolerance and safety of consuming rosemary infusion prepared from 5 g of dried leaves over a 10-day period in healthy volunteers (Achour et al., 2022). Accordingly, Pouya Nematolahi et al. reported that the daily administration of 500 mg of rosemary for one month was safe and well tolerated by university students (Nematolahi et al., 2018).

In this study, we used rosemary infusion, which was prepared by infusing 2 g of fine rosemary leaf powder through an adequate tea bag in 100 ml of boiling water for 15 min. The selection of this method is supported by multiple advantages. First, this approach aligns with practices commonly employed in traditional medicine, thereby avoiding potentially risky procedures such as maceration with organic solvents, which could pose health risks. Second, the infusion method is easy to prepare at home. Lastly, the use of fine powder obtained from dried leaves as plant material was found to be less resource-intensive than that obtained from intact leaves. Indeed, the yield of the main polyphenols contained in the crushed plant leaves is approximately 0–33 times higher than that produced by extracting whole dry leaves.

One limitation of our study is relating to the calculation of LDL using the Friedewald equation, as it remains an indirect estimate, whereas the direct method provides greater accuracy and reliability.

A prolonged study with a larger number of randomized participants is recommended to obtain a more accurate assessment of the benefits of rosemary infusion, to verify the durability of the observed effects, and to identify any long-term side effects. The study of the antihypertensive effect of rosemary infusion would also be strengthened by the inclusion of a placebo group.

Despite efforts to control for BMI, we acknowledge that it remains a significant factor that could impact the interpretation of our findings. Future studies may consider further stratifying the analysis by BMI categories to explore more nuanced effects of the rosemary infusion in individuals with different body types. Additionally, larger sample sizes could provide more power to detect whether BMI modulates the intervention's effectiveness.

Our study represents the first human clinical trial to offer important insights into the antihypertensive effects of rosemary infusion, especially for patients with stage 1 hypertension. It presents a natural alternative to synthetic medications, with fewer side effects. Managing blood pressure at this initial stage (grade 1) can help prevent its escalation to more severe forms of hypertension, thus reducing the likelihood of significant cardiovascular complications.

5. Conclusion and perspectives

In conclusion, this preliminary trial allowed the exploration of the effectiveness, tolerance, and safety of rosemary infusion prepared with 2 g of powdered leaves in reducing SBP and DBP in hypertensive patients with grade 1 hypertension over a 45-day period, without lowering blood pressure below the normal range in normotensive individuals. While we recognize that our approach does not fully eliminate potential

confounding factors, the within-subject comparison helped control for individual variability to some extent. Based on the promising results observed, we plan to design future randomized controlled trials (RCTs) that will include a placébo group to more definitively establish the causal relationship between rosemary infusion and the observed reductions in blood pressure. However, to provide comprehensive evidence and further evaluate the antihypertensive effects of rosemary infusion, future clinical trials should explore the dose-response relationship to identify the optimal dosage for maximizing efficacy while minimizing side effects. Additionally, further research should investigate the mechanisms behind rosemary's antihypertensive properties.

Patient consent statement

All participants provided their informed consent for inclusion before they participated in the study.

Ethics approval statement

The study was conducted in accordance with the declaration of Helsinki and approved by the ethics committee of the Faculty of Medicine, University of Sousse, Tunisia (CEFMS 89 /2021, 22 Mai 2021).

CRediT authorship contribution statement

Awatef Sassi: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Aicha Laouani:** Writing – review & editing, Methodology, Conceptualization. **Mohamed Aymen Ben Abdessalem:** Writing – review & editing, Validation. **Imen Jarray:** Writing – review & editing, Investigation. **Hana Nasrallah:** Writing – review & editing, Formal analysis. **Farhana Ferdousi:** Writing – review & editing. **Manel Nouira:** Writing – review & editing. **Ali Mtiraoui:** Writing – review & editing. **Abdallah Mahdhaoui:** Writing – review & editing, Methodology. **Hiroko Isoda:** Writing – review & editing, Supervision, Project administration, Funding acquisition. **Saad Saguem:** Writing – review & editing, Supervision, Project administration, Funding acquisition.

Declaration of competing interest

The authors declare no conflict of interest.

Availability of data and materials

The datasets generated during and/or analysed during the current study are not publicly available due to ethical reason but are available from the corresponding author on reasonable request.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.phyplu.2025.100783.

References

Abdelhalim, A., Karim, N., Chebib, M., Aburjai, T., Khan, I., Johnston, G.A., Hanrahan, J., 2015. Antidepressant, anxiolytic and antinociceptive activities of constituents from Rosmarinus officinalis. J. Pharm. Pharm. Sci. 18, 448–459.

Achour, M., Ben Salem, I., Ferdousi, F., Nouira, M., Ben Fredj, M., Mtiraoui, A., Isoda, H., Saguem, S., 2022. Rosemary tea consumption alters peripheral anxiety and depression biomarkers: a pilot study in limited healthy volunteers. J. Am. Nutr. Assoc. 41, 240–249.

Achour, M., Mateos, R., Ben Fredj, M., Mtiraoui, A., Bravo, L., Saguem, S., 2018. A comprehensive characterisation of rosemary tea obtained from Rosmarinus officinalis L. collected in a sub-humid area of Tunisia. Phytochem. Anal. 29, 87–100.

Adomako-Bonsu, A.G., Chan, S.L., Pratten, M., Fry, J.R., 2017. Antioxidant activity of rosmarinic acid and its principal metabolites in chemical and cellular systems: Importance of physico-chemical characteristics. Toxicol. In Vitro 40, 248–255.

Aguilar, F., Autrup, H., Barlow, S., Castle, L., Crebelli, R., Dekant, W., Engel, K.-H., Gontard, N., Gott, D., Grilli, S., 2008. Use of rosemary extracts as a food additive-Scientific opinion of the panel on food additives, flavourings, processing aids and materials in contact with food. EFSA J. 721, 1–29.

Agunloye, O.M., Oboh, G., Ademiluyi, A.O., Ademosun, A.O., Akindahunsi, A.A., Oyagbemi, A.A., Omobowale, T.O., Ajibade, T.O., Adedapo, A.A., 2019. Cardio-protective and antioxidant properties of caffeic acid and chlorogenic acid: Mechanistic role of angiotensin converting enzyme, cholinesterase and arginase activities in cyclosporine induced hypertensive rats. Biomed. Pharmacother. 109, 450–458.

Agunloye, O.M., Oboh, G., Bello, G.T., Oyagbemi, A.A., 2021. Caffeic and chlorogenic acids modulate altered activity of key enzymes linked to hypertension in cyclosporine-induced hypertensive rats. J. Basic Clin. Physiol. Pharmacol. 32, 169–177.

Ajibade, T., Akinrinde, A., Adetona, M., Oyagbemi, A., Adedapo, Aduragbenro, Larbie, C., Omobowale, T., Ola-Davies, O., Saba, A., Adedapo, Adeolu, 2022. Luteolin normalizes blood pressure via its antioxidant activity and down-regulation of renal Angiotensin II receptor and Mineralocorticoid receptor expressions in rats co-exposed to Diclofenac and sodium fluoride. Niger. J. Physiol. Sci. 37, 35–42.

Al Sheyab, F.M., Abuharfeil, N., Salloum, L., Hani, R.B., Awad, D.S., 2012. The effect of rosemary (Rosmarinus officinalis. L) plant extracts on the immune response and lipid profile in mice. J. Biol. Life Sci. 3, 26–29.

Alegría-Herrera, E., Herrera-Ruiz, M., Román-Ramos, R., Zamilpa, A., Santillán-Urquiza, M.A., Aguilar, M.I., Avilés-Flores, M., Fuentes-Mata, M., Jiménez-Ferrer, E., 2019. Effect of Ocimum basilicum, Ocimum selloi, and rosmarinic acid on cerebral vascular damage in a chronic hypertension model. Biol. Pharm. Bull. 42, 201–211.

Al-Jamal, A.-R., Alqadi, T., 2011. Effects of rosemary (Rosmarinus officinalis) on lipid profile of diabetic rats. Jordan J. Biol. Sci. 4, 199–204.

Attique, S.A., Hassan, M., Usman, M., Atif, R.M., Mahboob, S., Al-Ghanim, K.A., Bilal, M., Nawaz, M.Z., 2019. A molecular docking approach to evaluate the pharmacological properties of natural and synthetic treatment candidates for use against hypertension. Int. J. Environ. Res. Public. Health 16, 923.

Bacanlı, M., Aydın, S., Taner, G., Göktaş, H., Şahin, T., Başaran, A., Başaran, N., 2016. Does rosmarinic acid treatment have protective role against sepsis-induced oxidative damage in Wistar Albino rats? Hum. Exp. Toxicol. 35, 877–886.

Buonacera, A., Stancanelli, B., Malatino, L., 2019. Stroke and hypertension: an appraisal from pathophysiology to clinical practice. Curr. Vasc. Pharmacol. 17, 72–84.

Castro, C., Lorenzo, A.G., González, A., Cruzado, M., 2010. Garlic components inhibit angiotensin II-induced cell-cycle progression and migration: Involvement of cell-cycle inhibitor p27Kip1 and mitogen-activated protein kinase. Mol. Nutr. Food Res. 54, 781–787.

Dahchour, A., 2022. Anxiolytic and antidepressive potentials of rosmarinic acid: a review with focus on antioxidant and anti-inflammatory effects. Pharmacol. Res., 106421

de Souza, P., Gasparotto Jr, A., Crestani, S., Stefanello, M.É.A., Marques, M.C.A., da Silva-Santos, J.E., Kassuya, C.A.L., 2011. Hypotensive mechanism of the extracts and artemetin isolated from Achillea millefolium L.(Asteraceae) in rats. Phytomedicine 18, 819–825.

Dehkordi, F.R., Kamkhah, A.F., 2008. Antihypertensive effect of Nigella sativa seed extract in patients with mild hypertension. Fundam. Clin. Pharmacol. 22, 447–452.

Ersoy, S., Orhan, I., Turan, N., Şahan, G., Ark, M., Tosun, F., 2008. Endothelium-dependent induction of vasorelaxation by Melissa officinalis L. ssp. officinalis in rat isolated thoracic aorta. Phytomedicine 15, 1087–1092.

Fei, J., Liang, B., Jiang, C., Ni, H., Wang, L., 2019. Luteolin inhibits IL-1β-induced inflammation in rat chondrocytes and attenuates osteoarthritis progression in a rat model. Biomed. Pharmacother. 109, 1586–1592.

Fernandes, L., Fortes, Z.B., Casarini, D.E., Nigro, D., Tostes, R.C., Santos, R.A., de Carvalho, M.H.C., 2005. Role of PGI2 and effects of ACE inhibition on the bradykinin potentiation by angiotensin-(1-7) in resistance vessels of SHR. Regul. Pept. 127, 183–189.

Ferreira, L.G., Evora, P.R.B., Capellini, V.K., Albuquerque, A.A., Carvalho, M.T.M., da Silva Gomes, R.A., Parolini, M.T., Celotto, A.C., 2018. Effect of rosmarinic acid on the arterial blood pressure in normotensive and hypertensive rats: role of ACE. Phytomedicine 38, 158–165.

Fuchs, F.D., Whelton, P.K., 2020. High blood pressure and cardiovascular disease. Hypertension 75, 285–292.

Gao, Q., Li, Yi, Li, Yahui, Zhang, Z., Liang, Y., 2022. Antioxidant and prooxidant activities of phenolic acids commonly existed in vegetables and their relationship with structures. Food Sci. Technol. 42, e07622.

Gonçalves, C., Fernandes, D., Silva, I., Mateus, V., 2022. Potential anti-inflammatory effect of Rosmarinus officinalis in preclinical in vivo models of inflammation. Molecules 27, 609.

Heshmati, J., Morvaridzadeh, M., Sepidarkish, M., Fazelian, S., Rahimlou, M., Omidi, A., Palmowski, A., Asadi, A., Shidfar, F., 2020. Effects of Melissa officinalis (Lemon Balm) on cardio-metabolic outcomes: a systematic review and meta-analysis. Phytother. Res. 34, 3113–3123.

Hwang, S.J., Kim, Y.-W., Park, Y., Lee, H.-J., Kim, K.-W., 2014. Anti-inflammatory effects of chlorogenic acid in lipopolysaccharide-stimulated RAW 264.7 cells. Inflamm. Res. 63, 81–90.
Jin, X., Liu, P., Yang, F., Zhang, Y., Miao, D., 2013. Rosmarinic acid ameliorates depressive-like behaviors in a rat model of CUS and Up-regulates BDNF levels in the hippocampus and hippocampal-derived astrocytes. Neurochem. Res. 38, 1828–1837.
Karthik, D., Viswanathan, P., Anuradha, C.V., 2011. Administration of rosmarinic acid reduces cardiopathology and blood pressure through inhibition of p22phox NADPH oxidase in fructose-fed hypertensive rats. J. Cardiovasc. Pharmacol. 58, 514–521.
Kearney, P.M., Whelton, M., Reynolds, K., Muntner, P., Whelton, P.K., He, J., 2005. Global burden of hypertension: analysis of worldwide data. The lancet 365, 217–223.
Konnoth, C.J., 2019. Drugs' other side-effects. Iowa Rev. 105, 171.
Kwon, Y.-I.I., Vattem, D.A., Shetty, K., 2006. Evaluation of clonal herbs of Lamiaceae species for management of diabetes and hypertension. Asia Pac. J. Clin. Nutr. 15, 107.
Labban, L., Mustafa, U.E.-S., Ibrahim, Y.M., 2014. The effects of rosemary (Rosmarinus officinalis) leaves powder on glucose level, lipid profile and lipid perodoxation. Int. J. Clin. Med. 5, 297–304.
Lee, A.Y., Wu, T.T., Hwang, B.R., Lee, J., Lee, M.-H., Lee, S., Cho, E.J., 2016. The neuro-protective effect of the methanolic extract of Perilla frutescens var. japonica and rosmarinic acid against H2O2-induced oxidative stress in C6 glial cells. Biomol. Ther. 24, 338.
Li, Q.-L., Li, B.-G., Zhang, Y., Gao, X.-P., Li, C.-Q., Zhang, G.-L., 2008. Three angiotensin-converting enzyme inhibitors from Rabdosia coetsa. Phytomedicine 15, 386–388.
Liang, Z., Xu, Y., Wen, X., Nie, H., Hu, T., Yang, X., Chu, X., Yang, J., Deng, X., He, J., 2016. Rosmarinic acid attenuates airway inflammation and hyperresponsiveness in a murine model of asthma. Molecules 21, 769.
Marhuenda, J., Perez-Pinero, S., Arcusa, R., Victoria-Montesinos, D., Canovas, F., Sanchez-Macarro, M., García-Muñoz, A.M., Querol-Calderon, M., López-Román, F.J., 2021. A randomized, double-blind, placebo-controlled trial to determine the effectiveness of a polyphenolic extract (Hibiscus sabdariffa and Lippia citriodora) for reducing blood pressure in prehypertensive and type 1 hypertensive subjects. Molecules 26, 1783.
Marinho, S., Illanes, M., Ávila-Román, J., Motilva, V., Talero, E., 2021. Anti-inflammatory effects of rosmarinic acid-loaded nanovesicles in acute colitis through modulation of NLRP3 inflammasome. Biomolecules 11, 162.
Mazzaglia, G., Ambrosioni, E., Alacqua, M., Filippi, A., Sessa, E., Immordino, V., Borghi, C., Brignoli, O., Caputi, A.P., Cricelli, C., 2009. Adherence to antihypertensive medications and cardiovascular morbidity among newly diagnosed hypertensive patients. Circulation 120, 1598–1605.
McKay, D.L., Chen, C.O., Saltzman, E., Blumberg, J.B., 2010. Hibiscus sabdariffa L. tea (tisane) lowers blood pressure in prehypertensive and mildly hypertensive adults. J. Nutr. 140, 298–303.
Mihailovic-Stanojevic, N., Belščak-Cvitanović, A., Grujić-Milanović, J., Ivanov, M., Jovović, D., Bugarski, D., Miloradović, Z., 2013. Antioxidant and antihypertensive activity of extract from Thymus serpyllum L. in experimental hypertension. Plant Foods Hum. Nutr. 68, 235–240.
Miyazaki, S., Fujita, Y., Oikawa, H., Takekoshi, H., Soya, H., Ogata, M., 2020. Combination of syringaresinol-di-O-β-d-glucoside and chlorogenic acid shows behavioral pharmacological anxiolytic activity and activation of hippocampal BDNF-TrkB signaling. Sci. Rep. 10 (1), 18177.
Montenegro, M.F., Pessa, L.R., Tanus-Santos, J.E., 2009. Isoflavone genistein inhibits the angiotensin-converting enzyme and alters the vascular responses to angiotensin I and bradykinin. Eur. J. Pharmacol. 607, 173–177.
Nadar, S.K., Lip, G.Y., 2021. The heart in hypertension. J. Hum. Hypertens. 35, 383–386.
Nematolahi, P., Mehrabani, M., Karami-Mohajeri, S., Dabaghzadeh, F., 2018. Effects of Rosmarinus officinalis L. on memory performance, anxiety, depression, and sleep quality in university students: a randomized clinical trial. Complement. Ther. Clin. Pract. 30, 24–28.
Pandi, A., Kalappan, V.M., 2021. Pharmacological and therapeutic applications of Sinapic acid—an updated review. Mol. Biol. Rep. 48, 3733–3745.
Pantan, R., Tocharus, J., Nakaew, A., Suksamrarn, A., Tocharus, C., 2019. Ethyl rosmarinate prevents the impairment of vascular function and morphological changes in l-NAME-induced hypertensive rats. Medicina 55, 777.
Prasannarong, M., Saengsirisuwan, V., Surapongchai, J., Buniam, J., Chukijrungroat, N., Rattanavichit, Y., 2019. Rosmarinic acid improves hypertension and skeletal muscle glucose transport in angiotensin II-treated rats. BMC Complement. Altern. Med. 19, 1–8.
Purushothaman, A., Babu, S.S., Naroth, S., Janardanan, D., 2022. Antioxidant activity of caffeic acid: thermodynamic and kinetic aspects on the oxidative degradation pathway. Free Radic. Res. 56, 617–630.
Ribeiro-Santos, R., Carvalho-Costa, D., Cavaleiro, C., Costa, H.S., Albuquerque, T.G., Castilho, M.C., Ramos, F., Melo, N.R., Sanches-Silva, A., 2015. A novel insight on an ancient aromatic plant: the rosemary (Rosmarinus officinalis L.). Trends Food Sci. Technol. 45, 355–368.
Rimoldi, S.F., Scherrer, U., Messerli, F.H., 2014. Secondary arterial hypertension: when, who, and how to screen? Eur. Heart J. 35, 1245–1254.
Salutondok, W., Tanggo, C.R.K., 2022. Relationship and comparison of hypertension grade 1 and 2 to the event of chronic renal failure. J. Complement. Altern. Med. Res. 20, 10–19.
She, R., Zhang, Z., Han, M., Zhao, D., Li, X., Zhou, J., Chang, Y., Zhang, X., Li, X., 2024. Luteolin exhibits anxiolytic and antidepressant potential in Parkinson's disease rat: antioxidant and anti-inflammatory effects. Rejuvenat. Research.
Shekarriz, Z., Shorofi, S.A., Nabati, M., Shabankhani, B., Yousefi, S.S., 2021. Effect of Melissa officinalis on systolic and diastolic blood pressures in essential hypertension: a double-blind crossover clinical trial. Phytother. Res. 35, 6883–6892.
Somova, L., Shode, F., Ramnanan, P., Nadar, A., 2003. Antihypertensive, antiatherosclerotic and antioxidant activity of triterpenoids isolated from Olea europaea, subspecies africana leaves. J. Ethnopharmacol. 84, 299–305.
Stuermer, E.K., Besser, M., Terberger, N., Bachmann, H.S., Severing, A.-L., 2019. Side effects of frequently used antihypertensive drugs on wound healing in vitro. Skin Pharmacol. Physiol. 32, 162–172.
Su, J., Xu, H.-T., Yu, J.-J., Gao, J.-L., Lei, J., Yin, Q.-S., Li, B., Pang, M.-X., Su, M.-X., Mi, W.-J., 2015. Luteolin ameliorates hypertensive vascular remodeling through inhibiting the proliferation and migration of vascular smooth muscle cells. Evid. Based Complement. Altern. Med. 2015, 364876.
Susalit, E., Agus, N., Effendi, I., Tjandrawinata, R.R., Nofiarny, D., Perrinjaquet-Moccetti, T., Verbruggen, M., 2011. Olive (Olea europaea) leaf extract effective in patients with stage-1 hypertension: comparison with Captopril. Phytomedicine 18, 251–258.
Suzuki, A., Yamamoto, N., Jokura, H., Yamamoto, M., Fujii, A., Tokimitsu, I., Saito, I., 2006. Chlorogenic acid attenuates hypertension and improves endothelial function in spontaneously hypertensive rats. J. Hypertens. 24, 1065–1073.
Tocci, G., Ferrucci, A., Pontremoli, R., Ferri, C., Rosei, E., Morganti, A., Trimarco, B., Mancia, G., Borghi, C., Volpe, M., 2015. Blood pressure levels and control in Italy: comprehensive analysis of clinical data from 2000–2005 and 2005–2011 hypertension surveys. J. Hum. Hypertens. 29, 696–701.
Tom, E.N.L., Girard-Thernier, C., Demougeot, C., 2016. The Janus face of chlorogenic acid on vascular reactivity: a study on rat isolated vessels. Phytomedicine 23, 1037–1042.
Upadhyay, S., Bisht, K., Bahukhandi, A., Bisht, M., Mehta, P., Bisht, A., 2021. Rosmarinus Officinalis L., in: Naturally Occurring Chemicals Against Alzheimer's Disease. Elsevier, pp. 271–281.
Verma, H., Shivavedi, N., Kumar, M., Kumar, P., 2023. Pharmacology of rosmarinic psychological disorders. Tradit. Med. Neuronal Health 191.
Verma, P., Dutt, R., Anwar, S., 2022. Role of caffeine in inducing anxiety by reducing brain serotonin synthesis blocking adenosine receptors (A1, A2A, A2B, and A3). Curr. Tradit. Med. 8, 42–50.
Verma, S.K., Jain, V., Singh, D.P., 2012. Effect of greater cardamom (Amomum subulatum Roxb.) on blood lipids, fibrinolysis and total antioxidant status in patients with ischemic heart disease. Asian Pac. J. Trop. Dis. 2, S739–S743.
Verma, T., Sinha, M., Bansal, N., Yadav, S.R., Shah, K., Chauhan, N.S., 2021. Plants used as antihypertensive. Nat. Prod. Bioprospect. 11, 155–184.
Wang, W., Sun, W., Jin, L., 2017. Caffeic acid alleviates inflammatory response in rheumatoid arthritis fibroblast-like synoviocytes by inhibiting phosphorylation of IκB kinase α/β and IκBα. Int. Immunopharmacol. 48, 61–66.
WHO, W., 2013. A global brief on hypertension: silent killer, global public health crisis.
Williams, B., Mancia, G., Spiering, W., Agabiti Rosei, E., Azizi, M., Burnier, M., Clement, D.L., Coca, A., De Simone, G., Dominiczak, A., 2018. 2018 ESC/ESH Guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH). Eur. Heart J. 39, 3021–3104.
Xia, Z., Mi, H., Ren, M., Huang, D., Aboseif, A.M., Liang, H., Zhang, L., 2024. Chlorogenic acid plays an important role in improving the growth and antioxidant status and weakening the inflammatory response of largemouth bass (Micropterus salmoides). Anim. Open Access J. MDPI 14, 2871.
Yoon, B.H., Jung, J.W., Lee, J.-J., Cho, Y.-W., Jang, C.-G., Jin, C., Oh, T.H., Ryu, J.H., 2007. Anxiolytic-like effects of sinapic acid in mice. Life Sci. 81, 234–240.
Yu, M., Kim, H.J., Heo, H., Kim, M., Jeon, Y., Lee, H., Lee, J., 2022. Comparison of the antihypertensive activity of phenolic acids. Molecules 27, 6185.
Zhang, Y., Chen, X., Yang, L., Zu, Y., Lu, Q., 2015. Effects of rosmarinic acid on liver and kidney antioxidant enzymes, lipid peroxidation and tissue ultrastructure in aging mice. Food Funct. 6, 927–931.
Zhao, Y., Wang, J., Ballevre, O., Luo, H., Zhang, W., 2012. Antihypertensive effects and mechanisms of chlorogenic acids. Hypertens. Res. 35, 370–374.
Zhou, B., Perel, P., Mensah, G.A., Ezzati, M., 2021. Global epidemiology, health burden and effective interventions for elevated blood pressure and hypertension. Nat. Rev. Cardiol. 18, 785–802.