The American Journal of Clinical Nutrition 119 (2024) 682–691

The American Journal of CLINICAL NUTRITION

journal homepage: https://ajcn.nutrition.org/

Original Research Article

A low dose of daily licorice intake affects renin, aldosterone, and home blood pressure in a randomized crossover trial

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A B S T R A C T

Background: Licorice, through the effects of glycyrrhizic acid (GA), raises blood pressure (BP). The World Health Organization has suggested that 100 mg GA/d would be unlikely to cause adverse effects, but of 13 previously published studies none have been randomized and controlled and independently quantified the GA content.

Objective: Our aim was to analyze the effects on home BP of a daily licorice intake containing 100 mg GA.

Methods: Healthy volunteers were randomly assigned to start with either licorice or a control product in a nonblinded, 2 × 2 crossover study. Home BP was measured daily, and blood samples were collected at the end of each 2-wk period.

Results: There were 28 participants and no dropouts. The median age was 24.0 y (interquartile range 22.8–27.0 y). During the licorice compared with control intake period, the systolic home BP increased [mean difference: 3.1 mm Hg (95% confidence interval [CI]: 0.8, 5.4 mm Hg) compared with −0.3 mm Hg (95% CI: −1.8, 1.3 mm Hg); $P = 0.018$] and renin and aldosterone were suppressed [mean change: −30.0% (95% CI: −56.7%, −3.3%) compared with 15.8% (95% CI: −12.8%, 44.4%); $P = 0.003$; and −45.1% (95% CI: −61.5%, −28.7%) compared with 8.2% (95% CI: −14.7%, 31.1%); $P < 0.001$, respectively]. In the quartile of participants with the most pronounced suppression of renin and aldosterone, N-terminal prohormone of brain natriuretic peptide concentration increased during the licorice compared with control period [mean change: 204.1% (95% CI: −11.6%, 419.7%) compared with 72.4% (95% CI: −52.2%, 197.1%); $P = 0.016$].

Conclusions: We found licorice to be more potent than previously known, with significant increases in BP, after a daily intake of only 100 mg GA. Thus, the safe limit of intake of this substance might need to be reconsidered.

This trial was registered at clinicaltrials.gov as NCT05661721 (https://clinicaltrials.gov/study/NCT05661721).

Keywords: aldosterone, glycyrrhizic acid, home blood pressure, licorice, renin

Introduction

Licorice (hereafter referred to as sweet licorice), extracted from the root of the *Glycyrrhiza* species, has been used as an herbal medicine and flavoring for centuries [1,2]. Despite suggested health benefits, ingestion can also raise blood pressure (BP), mainly through the effects of glycyrrhizic acid (GA) and its metabolite glycyrrhetinic acid [1]. The bioavailability of GA is higher when ingested in an isolated form, suggesting interactions with other compounds of licorice [1]. However, the full metabolism of GA, and the actions of hundreds of other compounds of licorice, is not yet fully understood [1]. In the kidney, glycyrrhetinic acid inhibits 11β-hydroxysteroid dehydrogenase type 2, which, otherwise, inactivates cortisol by conversion to cortisone [1,3]. Thus, increased concentrations of cortisol, which has a much higher affinity to mineralocorticoid receptors than cortisone, causes pseudo-hyperaldosteronism with hypokalemia, hypernatremia, and water retention, resulting in elevated BP [1,3].

Ammonium chloride, which does not raise BP [4], is used in some confectionaries as an alternative or additive flavoring agent to sweet licorice, to achieve a similar taste, and is then commonly marketed as salty licorice.

Abbreviations: BP, blood pressure; C-I, control then intervention; GA, glycyrrhizic acid; I-C, intervention then control; NT-ProBNP, N-terminal prohormone of brain natriuretic peptide.

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https://doi.org/10.1016/j.ajcnut.2024.01.011
Received 25 August 2023; Received in revised form 12 January 2024; Accepted 16 January 2024; Available online 20 January 2024

For sweet licorice, both the European Union and the WHO has suggested that ≤100 mg GA/d is safe for most individuals [5,6]. The Swedish Food Agency has assessed that the top 5% of consumers have a daily intake of >100 mg GA [7].

The GA content of sweet licorice products is variable, depending on country of origin, plant age, storage conditions, and species, of which the latter is often misclassified for commercial products [2,8]. Studies of commercial sweet licorice products have found concentrations between 0.29 and 112 mg GA/g [2,9].

Of 13 previously published studies on the effects of whole sweet licorice on BP, 4 have reported that the GA content of the sweet licorice administered was independently quantified, but none of these were randomized and controlled trials [3,10–19] (Supplemental Table 1). Furthermore, to our knowledge, no previous study has been based on repeated home BP recordings.

Therefore, it is not entirely clear whether a daily intake of sweet licorice containing 100 mg GA is in fact safe or not to consume for the effects on the renin–aldosterone system or out-of-office BP levels. The primary aim of this study was to assess the effects of a daily sweet licorice intake equal to 100 mg GA on home BP in healthy volunteers. The secondary aims were to assess the effects of sweet licorice intake on plasma renin, serum aldosterone, and plasma N-terminal prohormone of brain natriuretic peptide (NT-ProBNP) concentrations. Exploratory outcomes were the duration of sweet licorice intake until a change in BP; the duration of subsequent no sweet licorice intake to normalized BP; and the effects of sweet licorice intake on body weight, plasma sodium concentration, and plasma potassium concentration.

Methods

Study population

Volunteers aged 18–30 y were recruited from 3 January until 11 April 2023, through advertisements in Östergötland County, Sweden. Based on a power calculation using a paired *t* test, an assumed mean systolic BP of 120 mm Hg, within-participant variability of 5 mm Hg, clinically relevant difference of 4 mm Hg, α of 0.05, and power of 80%, 28 participants were recruited.

Exclusion criteria were known hypertensive, cardiovascular, kidney, liver, endocrine, or headache disease; eating disorder; alcohol or drug abuse; treatment with hormones (including oral contraceptives but not including intrauterine devices); peanut allergy and known intolerance to licorice. Participants were reimbursed with SEK 500 (equaling around US $47) for each blood sample occasion.

Study design

The study had a nonblinded, 2-treatment, 2-period, 2-sequence (2 × 2) randomized crossover design (Supplemental Figure 1). Drawing ballots were used for stratified block randomization to 2 groups with a 1:1 allocation ratio, with 1 block of 14 participants for males and 1 block of 14 participants for females because sex differences have been seen in previous studies [1].

- Group intervention then control (I-C): 1-wk run-in period; followed by a 2-wk intervention period; a 2-wk washout period; a 2-wk control period; and finally, a 2-wk washout period;
- Group control then intervention (C-I): 1-wk run-in period; followed by a 2-wk control period; a 2-wk washout period; a 2-wk intervention period; and finally, a 2-wk washout period.

Intervention and control products

Ecologic sweet licorice pastilles (produced by Nature Med S.r.l.), made from *Glycyrrhiza glabra* grown in Calabria, Italy, with a manufacturer-specified content of 4% sugars, 2% GA, and 0.03% salt equivalent (calculated as sodium multiplied by 2.5 as per regulations of the European Union), was used as intervention (henceforth referred to as intervention or sweet licorice) [20] [Nature Med, Consenza, Italy, personal communication via email, 2022]. All pastilles came from the same production batch, with a mean weight of 0.228 g (95% CI: 0.214, 0.241 g) per pastille, weighed using a Kern ABJ220-4NM (Kern & Sohn) with a 0.001-g accuracy. The true GA content (in contrast to the manufacturer-specified GA content) was 29.9 ± 2.0 mg/g, analyzed independently by Neotron using HPLC with photodiode-array detection.

Vegan salty licorice confectionaries (manufactured by Troll-Gott Konfektyr), each weighing 5.8 g, with a manufacturer-specified content of 5.5% ammonium chloride, 0.05% salt, 0% sugars, and 0% GA (telephone communication with the manufacturer, November 2022), was used as control (henceforth referred to as control or salty licorice). The true GA content was confirmed to be below the lower limit of detection (<0.02 mg/g) in an independent analysis by Neotron.

During the intervention period, each participant was instructed to consume an average of 14.5 pastilles daily (14 and 15 pastilles, respectively, on alternate days), corresponding to 3.3 g sweet licorice containing 100 mg GA according to the average pastille weight and the GA concentration. During the control period, each participant was asked to consume 2.9 g salty licorice daily (i.e., half a salty licorice confectionary). The participants were instructed to consume the licorice at any time(s) during each day. During the washout periods, participants were instructed to consume no licorice (neither sweet nor salty licorice).

Anthropometric measurements and questionnaires

All visits took place at a designated study center in Norrköping, Östergötland County, Sweden, between 30 January and 8 June 2023, where an experienced research nurse (A.J.) or the principal investigator (P.a.G.) confirmed eligibility and performed the randomization. Participants were asked to abstain from licorice intake for a minimum of 4 wk before the study began. Baseline measurements were height, weight, and office BP. BMI was calculated as weight (kg) divided by the square of height (m^2). In addition, participants filled in a questionnaire asking about their age, sex, use of tobacco and alcohol, physical activity habits, medications, dietary supplements, and heredity for diabetes and cardiovascular disease. Female participants who were menstruating also specified the first day of their last menstrual period.

At the end of each study period, weight measurements were repeated, and participants were asked to confirm their licorice intake during the period. Because visits took place on weekdays, measurements were planned for day 13 ± 1 of each study period.

BP measurements

All BP measurements were made after 5 min rest, and participants were asked to abstain from alcohol, caffeine, nicotine products, and strenuous activity ≥1 h before measurements, to empty their bladder before measurements, to sit with their feet and back supported, and to place the cuff at the level of the heart.

Office BP at baseline was measured manually using the validated Maxi Stabil 3 aneroid sphygmomanometer (Speidel & Keller) [21]. Following the 2021 European Society of Hypertension guidelines,

office BP was measured in both arms, and the right arm was designated as the reference arm for all further measurements unless the left arm had a BP value of >10 mm Hg higher than the right arm, in which case the left arm was designated as the reference arm for all further measurements [22].

Home BP was measured using the validated semiautomatic Omron M10-IT oscillometric device and following the guidelines of the European Society of Hypertension [23,24]. Measurements were made 3 times in the morning and 3 times in the evening daily for 3 consecutive days during the run-in period and 3 times in the morning and 3 times in the evening daily during the other study periods. To ensure adequate home BP methodology, participants were given concise written instructions. The measurements were submitted through written forms and randomly controlled by the research nurse against those registered in the memory of the home BP device to ensure correct registration. Mean systolic and diastolic BP were calculated first as the mean of the 3 measurements of each morning and evening, respectively, and then as the mean for each day.

Blood samples

Blood samples were drawn at baseline, at the end of the control and intervention periods, and at the end of the first washout period. Because of large observed effects on some results during the intervention period, participants who were in the C-I group were also invited to provide their blood samples at the end of the second washout period, to ensure return to baseline. Blood samples were taken at the laboratory of the designated study center, at fasting condition in the morning between 8:00 and 9:00 in the seated position after a minimum of 5 min rest.

Plasma sodium, potassium, and creatinine concentration, lipid profile, and NT-ProBNP concentration were analyzed using blood samples drawn in 3-mL plasma tubes with lithium heparin and gel; aldosterone and renin were analyzed using blood samples drawn in 3-mL blood tubes with K2 EDTA. All blood samples were analyzed at the ISO/IEC 17025–accredited laboratory Diagnostikcentrum i Östergötland, Linköping, Sweden. Plasma renin and serum aldosterone concentrations were quantified using the LIAISON Direct Renin assay and the LIAISON Aldosterone assay (both DiaSorin), respectively, both using chemiluminescent immunoassay technology. NT-ProBNP concentration was quantified using the Elecsys pro-BNP II STAT analysis (Roche Diagnostics), and to detect variations in this young and healthy cohort, the lower limit of detection (10 ng/L) rather than the lower level of quantification (50 ng/L) was used.

Statistical analyses

Distributions were determined by visual assessment. Continuous variables were shown as the median and IQR, except for BP that was shown as the mean and standard deviation, and categorical variables were shown as the frequency and percentage. Results for renin and aldosterone that were below the lower level of quantification (<1.7 mIU/L and <50 μmol/L, respectively), were converted as the highest possible value (1.6 and 49, respectively) divided by the square root of 2. Results for NT-ProBNP concentration that were below the lower level of detection (<10 ng/L) were converted as the highest possible value (9 ng/L) divided by the square root of 2.

Results were tested using a paired Wilcoxon signed-rank test. The effects on home BP were evaluated by comparing the δ values (the mean difference between the first and last 3 d) of the intervention and control periods. The effects on secondary and exploratory outcomes were evaluated by comparing the mean percentage change between the run-in period and the intervention and control periods.

To analyze the time from the start of the intervention to change in systolic and diastolic home BP, the mean of each day of the intervention period was compared with the mean of the 3 d preceding the intervention period using a paired Wilcoxon signed-rank test. To analyze BP progression during the postintervention washout period, the mean of each day of the postintervention washout period was compared with the mean of the last 3 d preceding the intervention period using a paired Wilcoxon signed-rank test. For these analyzes, the last 3 d preceding the intervention period were defined as the 3-d run-in period for participants in the I-C group, and the last 3 d of the postcontrol washout period for participants in the C-I group. These analyses were reported as the mean and 95% CI of each day.

An ad hoc subgroup analysis of the main results was performed for the participants with the largest relative change in renin and aldosterone, defined as the quartile of participants with the most pronounced suppression of renin and aldosterone. This was calculated as the renin at the end of the intervention period divided by the renin at the end of the control period, plus the aldosterone at the end of the intervention period divided by the aldosterone at the end of the control period.

Data collection was made through the digital platform REDCap 13.1.35 (Vanderbilt University). Data analyses were made using R version 4.3.2 (R Core Team) and RStudio version 2023.12.0 + 369 (Posit Software). Statistical tests were 2-tailed, and P values of <0.05 were considered statistically significant, with the exception of secondary outcomes for which the significance level was corrected using Bonferroni to <0.0167.

Ethical considerations

The study complied with the tenets of the Declaration of Helsinki and was approved by the Swedish Ethical Review Authority (Dnr 2022-06163-01). All participants gave written informed consent before participation. Before commencement, the study was registered at clinicaltrials.gov (registration number: NCT05661721).

Results

Of the 28 included participants, 14 (50%) were males, and they were equally represented in each group. There were no dropouts. The median age was 24.0 y (IQR: 22.8–27.0 y), and the median body mass index was 23.0 kg/m^2 (IQR: 21.3–26.0 kg/m^2). Of the 28 participants, 10 (35.7%) were current snuff users, and none used other nicotine products including cigarettes. Mean systolic and diastolic office BP at run-in was 109.1 ± 8.8 and 65.0 ± 6.4 mm Hg, respectively, and mean systolic and diastolic home BP at run-in was 106.4 ± 9.5 and 65.4 ± 4.5 mm Hg, respectively (Table 1). Random checks of the BP measurements showed full agreement between those submitted and those registered in the BP device.

The systolic home BP increased during the intervention compared with control period [mean difference: 3.1 mm Hg (95% CI: 0.8, 5.4 mm Hg) compared with −0.3 mm Hg (95% CI: −1.8, 1.3 mm Hg); P = 0.018] (Table 2). Compared with the 3 d preceding the intervention period, the systolic BP began to increase from day 5 (mean difference: 1.7 mm Hg; 95% CI: 0.2, 3.3 mm Hg; P = 0.037) and had numerically increased further at day 14 (mean difference: 4.3 mm Hg; 95% CI: 1.5, 7.1 mm Hg; P = 0.002) (Figure 1 and Table 3). From day 11 of the postintervention washout period, the systolic BP was no longer different from that of the 3 d preceding the intervention period (mean difference: 1.5 mm Hg; 95% CI: −0.5, 3.5 mm Hg; P = 0.104) (Table 4).

TABLE 1
Baseline characteristics according to groups[1]

		All participants ($N = 28$)	Intervention then control ($n = 14$)	Control then intervention ($n = 14$)
Male sex		14 (50.0)	7 (50.0)	7 (50.0)
Age (y)		24.0 (22.8–27.0)	23.0 (21.3–24.8)	24.5 (24.0–27.8)
Weight (kg)		75.4 (64.7–79.7)	67.7 (60.9–78.3)	76.3 (69.2–85.6)
Body mass index (kg/m^2)		23.0 (21.3–26.0)	22.8 (20.8–25.4)	23.3 (21.7–26.2)
Current snuff user		10 (35.7)	2 (14.3)	8 (57.1)
AUDIT (points)		5.5 (3.0–7.0)	5.0 (3.0–7.0)	5.5 (4.0–6.0)
Physical activity ≥3–5 times per week		23 (82.1)	12 (85.7)	11 (78.6)
Sibling or parent with hypertension		4 (14.3)	1 (7.1)	3 (21.4)
Sibling or parent with myocardial infarction or stroke		1 (3.6)	1 (7.1)	0
Plasma potassium (mmol/L)		4.0 (3.9–4.2)	4.0 (3.9–4.1)	4.1 (3.9–4.2)
Plasma sodium (mmol/L)		140.0 (139.0–141.0)	140.0 (139.0–141.0)	140.5 (140.0–141.0)
Plasma creatinine (μmol/L)		79.5 (69.8–89.3)	73.5 (67.5–89.0)	81.0 (74.5–88.8)
Plasma renin (mIU/L)		22.0 (15.5–29.0)	22.0 (16.0–34.0)	21.0 (15.0–28.0)
Serum aldosterone (μmol/L)		330 (265–495)	375 (290–660)	300 (250–410)
Aldosterone/renin ratio (μmol/mIU)		15.7 (10.9–20.7)	17.4 (9.2–21.2)	13.7 (11.9–19.1)
Plasma NT-ProBNP (ng/L)		21.0 (11.5–44.5)	18.0 (13.5–36.5)	28.0 (9.1–49.0)
Office blood pressure	Systolic (mm Hg)	109.1 ± 8.8	107.2 ± 9.7	111.0 ± 7.8
	Diastolic (mm Hg)	65.0 ± 6.4	64.5 ± 7.1	65.5 ± 5.9
Home blood pressure	Systolic (mm Hg)	106.4 ± 9.5	104.1 ± 10.0	108.8 ± 8.6
	Diastolic (mm Hg)	65.4 ± 4.5	64.2 ± 3.5	66.6 ± 5.1

All values were based on all 28 (100%) of participants. Of the office BP values, 2 of 28 (7.1%) were measured using the same device as for home BP measurements.
Abbreviations: AUDIT, alcohol use disorders identification test; NT-ProBNP, N-terminal prohormone of brain natriuretic peptide.
[1] Values are given as *n* (%), median (Q1–Q3), or mean ± SD.

TABLE 2
Change in home blood pressure and weight and blood samples, during the intervention compared with control periods

		Mean (95% CI) difference between the first and last 3 d of the intervention period ($n = 28$)	Mean (95% CI) difference between the first and last 3 d of the control period ($n = 28$)	*P*
Home blood pressure (mm Hg)	Systolic	3.1 (0.8, 5.4)	−0.3 (−1.8, 1.3)	0.018
	Diastolic	1.9 (0.5, 3.3)	0.6 (−0.8, 1.9)	0.236
		Mean (95% CI) percentage change between the run-in period and the end of the intervention period ($n = 28$)	Mean (95% CI) percentage change between the run-in period and the end of the control period ($n = 28$)	*P*
Body weight		0.5 (−0.2, 1.2)	−0.4 (−1.0, 0.2)	0.023
Plasma creatinine		−4.8 (−8.1, −1.5)	−2.9 (−5.9, 0.1)	0.078
Plasma potassium		−1.2 (−3.4, 1.1)	−0.1 (−2.6, 2.4)	0.354
Plasma sodium		0.2 (−0.3, 0.6)	−0.3 (−0.6, 0.1)	0.028
Plasma renin		−30.0 (−56.7, −3.3)	15.8 (−12.8, 44.4)	0.003[1]
Serum aldosterone		−45.1 (−61.5, −28.7)	8.2 (−14.7, 31.1)	<0.001[1]
Aldosterone:renin ratio		25.4 (−7.0, 57.9)	7.5 (−10.9, 26.0)	0.546
Plasma NT-ProBNP		85.6 (19.7, 151.5)	25.0 (−12.7, 62.7)	0.033[1]

Results for BP measurements are presented as the mean (95% CI) difference between the first and last 3 d during the intervention and control periods. Results for weight and blood samples are presented as the mean (95% CI) percentage change between the run-in period and the end of the intervention and control periods. Difference between the intervention and control period was tested using a paired Wilcoxon signed-rank test.
Abbreviation: NT-ProBNP, N-terminal prohormone of brain natriuretic peptide.
[1] Bonferroni-corrected significance level for *P* value for the secondary outcome analyses (renin, aldosterone, and NT-ProBNP) = 0.0167.

The diastolic home BP increased from day 7 of the intervention period compared with the 3 preceding days (mean difference: 3.0 mm Hg; 95% CI: 1.7, 4.3 mm Hg; $P < 0.001$) (Table 3). However, when comparing the intervention compared with the control period, the change in diastolic BP did not differ [mean difference: 1.9 mm Hg (95% CI: 0.5, 3.3 mm Hg) compared with 0.6 mm Hg (95% CI: −0.8, 1.9 mm Hg; $P = 0.236$] (Table 2). Finally, the diastolic BP was still higher at day 14 during the postintervention washout period compared with the last 3 d before the intervention period (mean difference: 3.2 mm Hg; 95% CI: 1.4, 5.0 mm Hg; $P = 0.001$) (Table 4).

Renin and aldosterone concentrations were suppressed at the end of the intervention compared with the control period [mean change: −30.0% (95% CI: −56.7%, −3.3%) compared with 15.8% (95% CI: −12.8%, 44.4%); $P = 0.003$; and −45.1% (95% CI: −61.5%, −28.7%) compared with 8.2% (95% CI: −14.7%, 31.1%); $P < 0.001$, respectively] (Table 2 and Figure 2).

In a post hoc subgroup analysis of the quartile of participants with the largest relative suppression of plasma renin and serum aldosterone concentrations ($n = 7$), comparing the intervention with the control period, the systolic and diastolic home BP had numerically increased during the intervention compared with the control period [mean change: 6.7 mm Hg (95% CI: −1.0, 14.5 mm Hg) compared with −1.7 mm Hg (95% CI: −5.7, 2.3 mm Hg); $P = 0.078$; and 3.8 mm Hg (95% CI: −0.2, 7.8 mm Hg) compared with −1.2 mm Hg (95% CI: −3.1, 0.7

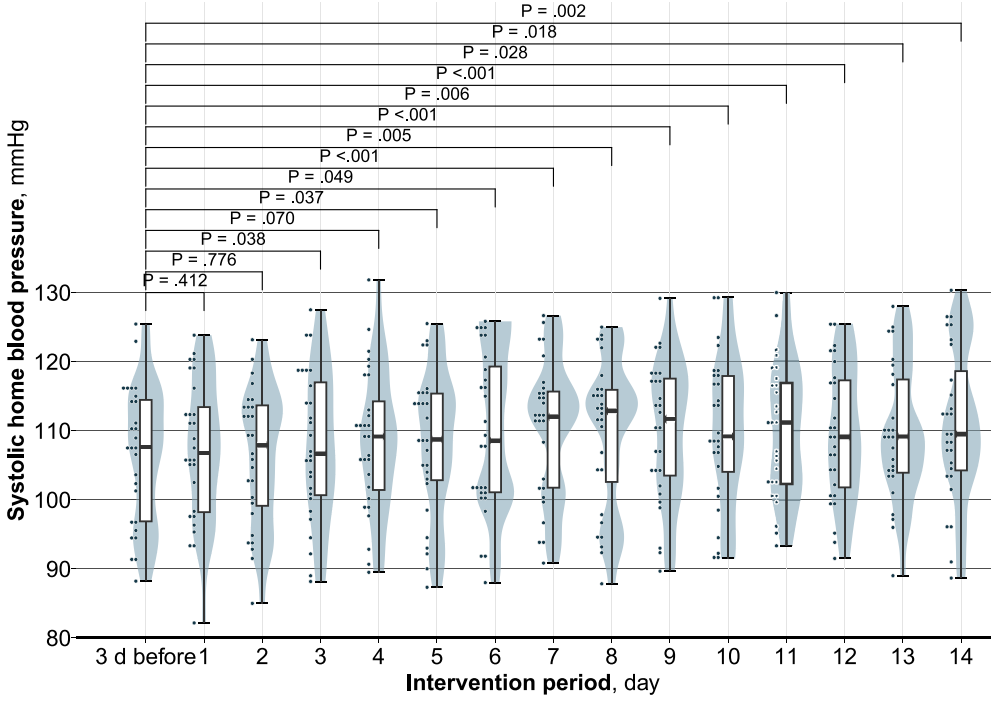

FIGURE 1. Box plots of the systolic home blood pressure during each day of the intervention period compared with the mean of the 3 preceding days. Results are based on measurements from all 28 participants except for day 13, which is based on measurements from 27 (96.4%) of the participants. Difference between each day of the intervention period and the mean of the 3 preceding days (the 3-d run-in period for the I-C group and the last 3 d of the postcontrol washout period for the C-I group) were tested using a paired Wilcoxon signed-rank test. The boxplot includes the median, the box extending between the 25th and the 75th percentiles (the IQR), and its whiskers extending between the IQR × 1.5; the violin plot illustrates the relative distribution of observations, and the left-sided vertical dot plot shows the actual observations.

mm Hg); $P = 0.078$, respectively]. Furthermore, during the intervention compared with the control period, there was an increase in body weight [mean change: 1.3% (95% CI: 0.9%, 1.7%) compared with −1.0% (95% CI: −1.8%, −0.2%); $P = 0.016$] and in NT-ProBNP concentration [mean change: 204.1% (95% CI: −11.6%, 419.7%) compared with 72.4% (95% CI: −52.2%, 197.1%); $P = 0.016$] (Figure 3 and Table 5). There was a decrease in creatinine concentration during the intervention compared with the control period [mean

TABLE 3
Systolic and diastolic home blood pressure during the intervention period for all participants presented as the absolute and relative mean (95% CI) of each day in relation to the mean of the preceding 3 d

		Systolic home blood pressure			Diastolic home blood pressure		
		Absolute, mean (95% CI)	Relative to reference, mean (95% CI)	*P*	Absolute, mean (95% CI)	Relative to reference, mean (95% CI)	*P*
The preceding 3 d		106.5 (102.6, 110.4)	0 (reference)	NA	65.7 (63.9, 67.4)	0 (reference)	NA
Intervention period	Day 1	107.1 (103.1, 111.1)	0.6 (−1.3, 2.5)	0.412	66.1 (64.2, 67.9)	0.4 (−0.6, 1.4)	0.466
	Day 2	106.3 (102.4, 110.1)	−0.3 (−1.7, 1.2)	0.776	66.4 (64.1, 68.7)	0.7 (−0.9, 2.4)	0.493
	Day 3	107.9 (103.7, 112.1)	1.4 (−0.2, 2.9)	0.038	66.1 (64.2, 68.1)	0.5 (−0.8, 1.7)	0.406
	Day 4	108.5 (104.5, 112.5)	2.0 (−0.1, 4.1)	0.070	67.2 (65.2, 69.2)	1.5 (−0.0, 3.1)	0.045
	Day 5	108.2 (104.2, 112.3)	1.7 (0.2, 3.3)	0.037	66.9 (64.7, 69.1)	1.2 (−0.4, 2.9)	0.111
	Day 6	109.6 (105.1, 114.0)	3.0 (0.4, 5.7)	0.049	66.8 (65.1, 68.6)	1.1 (−0.5, 2.8)	0.327
	Day 7	110.3 (106.4, 114.1)	3.8 (1.8, 5.7)	<0.001	68.6 (66.8, 70.5)	3.0 (1.7, 4.3)	<0.001
	Day 8	109.7 (105.5, 113.9)	3.2 (0.9, 5.4)	0.005	68.1 (65.5, 70.6)	2.4 (0.6, 4.1)	0.020
	Day 9	110.0 (106.1, 113.9)	3.5 (1.6, 5.4)	<0.001	67.9 (65.9, 69.9)	2.3 (1.0, 3.5)	0.002
	Day 10	110.2 (106.0, 114.3)	3.7 (1.2, 6.1)	0.006	67.5 (65.4, 69.6)	1.8 (0.4, 3.3)	0.022
	Day 11	110.0 (106.3, 113.7)	3.5 (1.4, 5.5)	<0.001	67.5 (66.0, 69.0)	1.8 (0.4, 3.3)	0.008
	Day 12	109.5 (105.7, 113.2)	3.0 (0.3, 5.6)	0.028	68.4 (66.4, 70.3)	2.7 (0.8, 4.5)	0.015
	Day 13	109.6 (105.8, 113.5)	3.5 (0.5, 6.5)	0.019	67.6 (65.8, 69.5)	2.1 (0.5, 3.6)	0.013
	Day 14	110.8 (106.5, 115.1)	4.3 (1.5, 7.1)	0.002	68.0 (65.6, 70.3)	2.3 (0.2, 4.4)	0.053

The preceding 3 d were the 3 d of the run-in period for the I-C group and the last 3 d of the postcontrol washout period for the C-I group. Differences between the mean blood pressure during each day of the intervention period and the mean blood pressure during the 3 d preceding the intervention period were tested using a paired Wilcoxon signed-rank test.
Abbreviations: C-I, control then intervention; I-C, intervention then control.

TABLE 4
Systolic and diastolic home blood pressure during the postintervention washout period for all participants presented as the mean (95% CI) of each day in relation to the mean of the 3 d preceding the intervention period

		Systolic home blood pressure			Diastolic home blood pressure		
		Absolute, mean (95% CI)	Relative to reference, mean (95% CI)	*P*	Absolute, mean (95% CI)	Relative to reference, mean (95% CI)	*P*
The 3 d preceding the intervention period		106.5 (102.6, 110.4)	0 (reference)	NA	65.7 (63.9, 67.4)	0 (reference)	NA
Postintervention washout period	Day 1	109.6 (105.5, 113.7)	3.1 (0.6, 5.6)	0.008	67.6 (65.6, 69.7)	2.0 (0.3, 3.6)	0.025
	Day 2	110.3 (106.3, 114.4)	3.8 (1.8, 5.8)	<0.001	68.5 (66.1, 70.8)	2.8 (1.1, 4.5)	0.001
	Day 3	109.9 (106.2, 113.5)	3.4 (1.3, 5.4)	0.002	68.9 (66.8, 71.0)	3.2 (1.7, 4.7)	<0.001
	Day 4	108.1 (104.3, 112.0)	1.6 (−0.4, 3.6)	0.099	67.5 (65.4, 69.6)	1.8 (0.4, 3.2)	0.009
	Day 5	109.2 (105.2, 113.2)	2.7 (0.9, 4.5)	0.007	67.4 (65.5, 69.3)	1.7 (0.4, 3.0)	0.018
	Day 6	109.7 (105.7, 113.7)	3.2 (1.2, 5.1)	0.005	67.9 (66.0, 69.9)	2.2 (0.4, 4.0)	0.015
	Day 7	108.3 (104.4, 112.3)	1.8 (0.2, 3.5)	0.043	68.3 (66.2, 70.4)	2.6 (1.0, 4.3)	0.005
	Day 8	107.9 (103.7, 112.1)	1.4 (−0.5, 3.3)	0.130	67.6 (65.5, 69.7)	1.9 (0.2, 3.6)	0.031
	Day 9	109.4 (105.2, 113.7)	2.9 (1.1, 4.7)	0.130	68.3 (65.7, 70.8)	2.6 (0.9, 4.3)	0.005
	Day 10	109.1 (104.3, 113.9)	2.6 (0.7, 4.5)	0.025	68.4 (66.0, 70.7)	2.7 (0.8, 4.6)	0.007
	Day 11	108.0 (103.7, 112.4)	1.5 (−0.5, 3.5)	0.104	67.2 (65.3, 69.2)	1.5 (−0.0, 3.1)	0.070
	Day 12	108.6 (104.4, 112.8)	2.1 (−0.0, 4.2)	0.078	67.7 (65.7, 69.7)	2.0 (0.3, 3.7)	0.029
	Day 13	108.2 (103.4, 113.0)	1.9 (−0.9, 4.7)	0.319	67.9 (65.4, 70.4)	2.2 (0.1, 4.3)	0.065
	Day 14	108.3 (103.6, 113.1)	2.0 (−0.3, 4.2)	0.141	68.7 (66.5, 71.0)	3.2 (1.4, 5.0)	0.001

The 3 d preceding the intervention period were the 3 d of the run-in period for the I-C group and the last 3 d of the postcontrol washout period for the C-I group. Differences between the mean blood pressure during each day of the postintervention washout period and the mean blood pressure during the 3 d preceding the intervention period were tested using paired Wilcoxon signed-rank test.
Abbreviations: C-I, control then intervention; I-C, intervention then control.

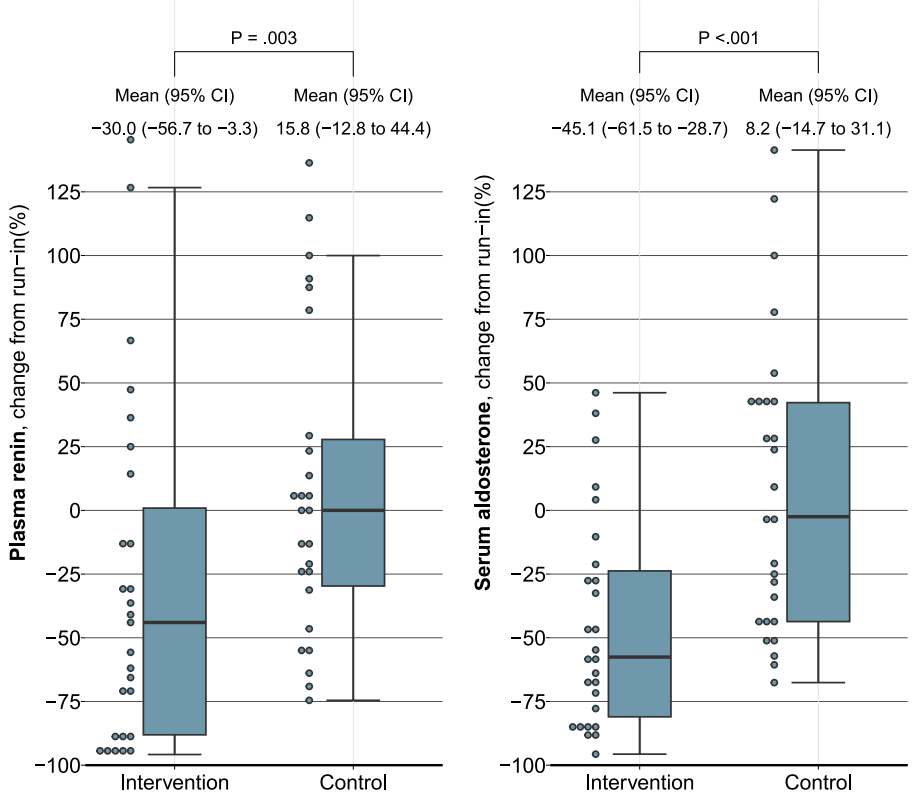

FIGURE 2. Box plots of the percentage change in plasma renin and serum aldosterone from the run-in to the intervention and control periods. The difference between the periods was tested using a paired Wilcoxon signed-rank test. The boxplot includes the median, the box extending between the 25th and the 75th percentiles (the IQR), and its whiskers extending between the IQR × 1.5; the left-sided vertical dot plot shows the actual observations. Bonferroni-corrected significance level for *P* value = 0.0167. For renin, an observation during the control period with an increase of 226.7% is not shown.

change: −6.0% (−14.7%, 2.7%) compared with 0.0% (−7.4%, 7.5%); $P = 0.016$]. Values below the lower level of quantification were observed for renin (<1.7 mIU/L) and aldosterone (<50 μmol/L) for 2 (7.1%) and 3 (10.7%) participants, respectively.

The actual number of days until weight measurement and blood sample collection during the 2-wk periods were, on average, 13.7 and 13.4 d, respectively. The number of missing values were 292 (2.95%) of 9912 for home BP measurements, 1 (3.6%) of 28 for plasma renin and serum aldosterone concentrations during the second washout period, and none for all other measurements.

There were a few deviations from protocol during the intervention period. Of participants, 3 forgot their sweet licorice intake during 1, 1, and 4 d, respectively, of the 14 d. One participant experienced an upper respiratory tract infection with fever at the end of the intervention period, resulting in a delayed follow-up and a prolonged intake for 2 d, and an extreme elevation of aldosterone (2570 μmol/L) and renin (104 mIU/L), which also coincided with day 20 of a 26-d menstrual cycle and, thus, the mid-luteal phase, as has been previously shown to cause a more than 2-fold increase in both these hormones [25]. Therefore, the values for aldosterone and renin for this participant were considered as outliers and not included in the analyses.

Adverse events

One participant experienced multiple itchy red rashes across the thorax and upper legs during the intervention period. These were experienced as tolerable by the participant, who, therefore, opted to continue the intake for the few days that then remained of the intervention period. The rash and itch were treatment resistant to both oral hydroxyzine and topical hydrocortisone but subsided during the subsequent washout period.

Discussion

In this study of 28 healthy males and females, licorice intake corresponding to 100 mg GA daily for 14 d caused a marked suppression of both renin and aldosterone concentration and increased home BP measurements, effects consistent with GA-induced pseudohyperaldosteronism. Furthermore, for the quartile ($n = 7$) of participants with the most marked suppression of renin and aldosterone concentration, both body weight and NT-ProBNP concentration increased, the latter of which suggests that it is not uncommon that relatively young and healthy subjects react with release of natriuretic peptides, which is a sign of myocardial stress [26]. These effects have not previously been demonstrated for such moderate amounts of daily intake of licorice, which is within the range that has been regarded as probably safe for most individuals [5,6].

Licorice intake was associated with an increase in the systolic BP from day 5 and a continued numeric increase until day 14. Thus, it is possible that this effect could be even more pronounced after longer periods of intake. Of previous studies that quantified the GA content, one that administered licorice with 500 mg GA daily for 7 d observed increased systolic BP after 4 d, which normalized 3 d after discontinued consumption [11]. However, that was a much higher dose than that used in our study. In another study that independently quantified the GA intake to 108.5 and 217 mg GA daily for 2 different groups, which are closer to the dose in our study, no effect on BP was observed. However, although the study population was similar to our study with 24 healthy individuals, only mean arterial pressure was reported [12]. Mean arterial pressure may be less sensitive to volume overload than systolic BP, and the home BP used in our study better reflects the true BP because it is based on more measurements and devoid of the white coat effect of office BP. Finally, a study that measured GA to 250 mg daily for 2 mo did not observe any effect on systolic BP but used office rather than home BP [27].

Diastolic BP was not affected in our study when comparing the intervention and control periods. However, it increased after 7 d when compared with the 3 d preceding the intervention period. This finding differs from 2 previous studies in which the GA content was quantified to 250 and 500 mg daily, respectively, in which no changes were observed in diastolic BP after 2 mo and 7 d, respectively [11,27].

In this study, we found renin and aldosterone concentrations to be quite markedly suppressed in the healthy participants. This differs from the only previous study in which licorice in a similar quantity was used (108.5 or 217 mg GA), and none of these hormones were affected after 4 wk [12]. However, in previous studies using higher amounts of GA, quantified to 250–813.7 mg/d, both these hormones decreased within 1–8 wk [10,12,27,28]. This suppression of renin and aldosterone indicates that the elevation of the BP is due to the effect of GA to increase stimulation of the mineralocorticoid receptor in the kidneys, rather than activation of the renin–aldosterone–angiotensin system.

Body weight increased in the quartile of participants with the most marked suppression of renin and aldosterone but not generally in the remaining participants. Of previous studies based on a quantified GA content, this was only seen after 500 mg GA daily but not after 108.5 or 217 mg GA daily [11,12]. This highlights that a subset of individuals is affected in a way that corresponds to a large dose of licorice, following daily intake.

Concentrations of plasma NT-ProBNP also increased in the quartile of participants with the most marked suppression of renin and aldosterone, but not for the other participants. One previous study showed an increase in atrial natriuretic peptide after an intake of 700 mg GA/d, but the GA content was not reported to have been independently quantified, and the assumed dose was much higher than that in our study [10].

For the quartile of participants with the most marked suppression of renin and aldosterone concentration, plasma creatinine concentration was reduced when comparing the intervention compared with the control periods. Reduced creatinine concentration has previously been shown in a study using licorice with 150 mg GA for 4 wk, but the GA content was based on manufacturer information and not independently quantified [3,16].

Neither potassium nor sodium was affected by licorice intake in our study, and this is in line with previous studies with a quantified GA content of 108.5, 217, and 250 mg, respectively [12,27]. However, this may also have resulted from the study being underpowered to detect such changes. Of previous studies with a confirmed GA content, decreased potassium has only been observed after intake of ≥500 mg GA daily [11,12].

However, it has previously been shown that the volume overload caused by aldosterone is dependent on sodium retention and that, with low sodium intake, even 10-fold aldosterone concentrations may not cause increased BP [29,30]. Whether salt-sensitivity could also partly explain the between-subjects variation in volume overload in pseudohyperaldosteronism is not known. Moreover, polymorphism in the 11β-hydroxysteroid dehydrogenase type 2 enzyme may explain the varied sensitivity to licorice intake [5,31]. There are several case reports of severe reactions to low-dose licorice, although the actual GA content of the licorice consumed has not been established [32,33].

Finally, the GA content in the product used for this study was 50% higher than declared by the producer, which showed that GA content

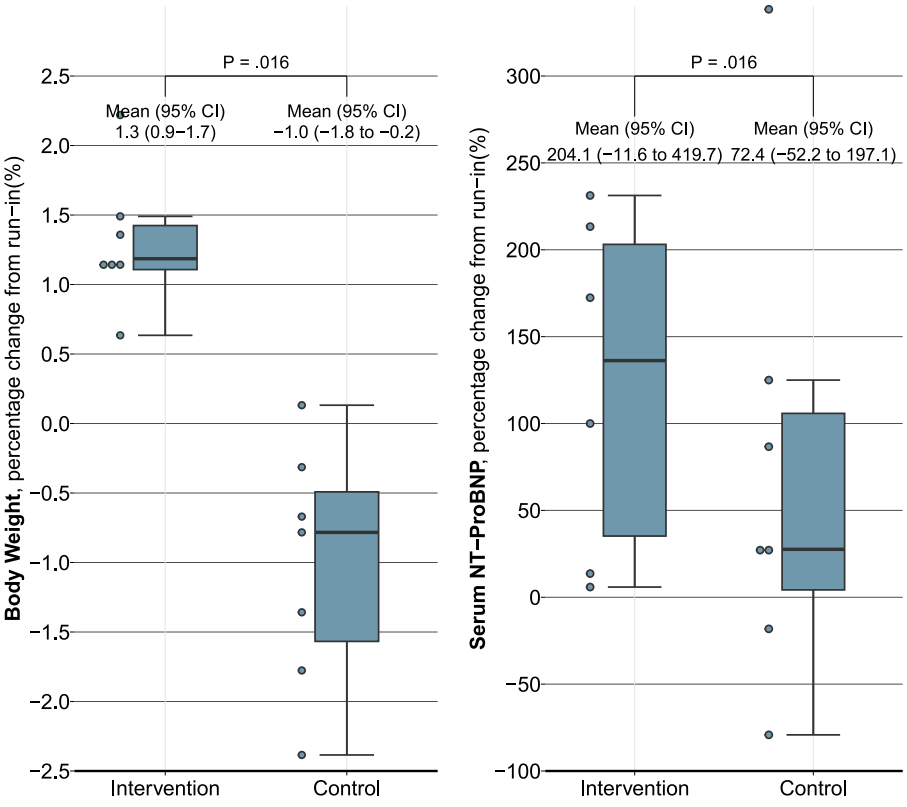

FIGURE 3. Box plots of the percentage change in body weight and plasma N-terminal prohormone of brain natriuretic peptide (NT-ProBNP) from the run-in to the intervention and control periods for the 7 (25%) participants with the largest suppression of plasma renin and serum aldosterone. The difference between the periods was tested using a paired Wilcoxon signed-rank test. The boxplot includes the median, the box extending between the 25th and the 75th percentiles (the IQR), and its whiskers extending between the IQR × 1.5; the left-sided vertical dot plot shows the actual observations. For NT-ProBNP, an observation during the intervention period with an increase of 692.0% is not shown. Abbreviation: NT-ProBNP, N-terminal prohormone of brain natriuretic peptide.

TABLE 5
Changes in home blood pressure and weight and blood samples during the intervention and control periods for the quartile of participants with the largest relative suppression of renin and aldosterone during the intervention period compared with the preceding period

		Mean (95% CI) difference between first and last 3 d of intervention period ($n = 7$)	Mean (95% CI) difference between first and last 3 d of control period ($n = 7$)	*P*
Home blood pressure (mm Hg)	Systolic	6.7 (−1.0, 14.5)	−1.7 (−5.7, 2.3)	0.078
	Diastolic	3.8 (−0.2, 7.8)	−1.2 (−3.1, 0.7)	0.078
		Mean (95% CI) percentage change between the run-in period and the end of the intervention period ($n = 7$)	Mean (95% CI) percentage change the run-in period and the end of the control period ($n = 7$)	*P*
Body weight		1.3 (0.9, 1.7)	−1.0 (−1.8, −0.2)	0.016
Plasma creatinine		−6.0 (−14.7, 2.7)	0.0 (−7.4, 7.5)	0.016
Plasma potassium		−7.0 (−12.0, −2.0)	−1.5 (−11.9, 8.9)	0.078
Plasma sodium		0.4 (−0.8, 1.6)	−0.5 (−1.0, 0.0)	0.106
Plasma renin		−87.4 (−100.5, −74.3)	28.1 (−26.4, 82.7)	0.016
Serum aldosterone		−82.1 (−92.8, −71.4)	14.5 (−48.7, 77.7)	0.016
Aldosterone-renin ratio		77.1 (12.7, 141.4)	−11.1 (−43.3, 21.1)	0.031
Plasma NT-ProBNP		204.1 (−11.6, 419.7)	72.4 (−52.2, 197.1)	0.016

Results for BP measurements are presented as the mean (95% CI) difference between the first and last 3 d during the intervention and control periods. Results for weight and blood samples are presented as the mean (95% CI) percentage change between the run-in period and the end of the intervention and control periods. Difference between the intervention and control period was tested using a paired Wilcoxon signed-rank test.
Abbreviation: NT-ProBNP, N-terminal prohormone of brain natriuretic peptide.

may vary significantly. Thus, product labels cannot be completely relied on, and it may be difficult for consumers to know the amount of GA they consume. This is not surprising given the products natural origins, with variations depending on geographic origin, plant age, and species [2,8]. In studies and case reports of licorice intake and effects, it is thus pivotal to analyze the product to understand the dose effect.

Our study has some limitations. It was not blinded because sweet licorice and confectionaries flavored with ammonium chloride are

similar yet noticeably different in taste. The participants were young and healthy, and thus, the results should be generalized outside of that group with caution. Another limitation is that the nonnormalization of diastolic BP at day 14 during the postintervention washout period compared with the last 3 d before the intervention period could suggest the potential for a carryover effect. However, the mean difference of the diastolic BP during the following control phase was positive, which contradicts the presence of a carryover effect. We used home BP measurements, although ambulatory BP measurements could have refined the results further. Finally, our study was limited to 2-wk periods, and thus, whether the effects observed are sustained beyond that period is not known.

In conclusion, our results indicate that licorice is a more potent substance than previously known and that concentrations advised as probably safe by the WHO and the European Union is not at all innoxious when tested in a randomized controlled setting with home BP recordings. We found that a daily intake containing 100 mg GA increased BP in young healthy subjects. Moreover, the most sensitive quartile of the individuals displayed increased body weight and markers of cardiac strain. Given the common use of licorice as a confectionary, awareness of these effects on a population level is called for. Furthermore, it is likely that other sensitive subsets, such as people with hypertension or renal insufficiency, would have even stronger effects of GA; hence, we recommend further studies on this topic. Meanwhile, we suggest a more stringent warning labeling on GA-containing confectionary.

Acknowledgments

We thank Anna Malmström, laboratory manager, and Thomas Karlsson, technician, at the Laboratory of Organic Electronics (LOE), Campus Norrköping, Linköping University, for assisting us with access and use of laboratory equipment; and Dr. Ghassaan Gawria, Department of Clinical Chemistry, Linköping University Hospital, Östergötland County, for assisting us with laboratory results.

Authors' contributions

The authors' responsibilities were as follows – FN: conceptualized the study; PAFG, AJ, KR, FN: designed the details of the trial; PAFG, AJ: conducted the research; PAFG: analyzed the data; PAFG, AJ, KR, FN: wrote the paper; PAFG, FN: had primary responsibility for the final content; and all authors: have read and approved the final manuscript.

Conflict of interest

The authors report no conflict of interest.

Funding

This study was funded by The Strategic Research Network in Circulation and Metabolism at Linköping University (LiU-CircM), The National Research School in General Practice, The Swedish Society of Medicine, The Swedish Society for Medical Research, King Gustaf V and Queen Victoria Freemason Foundation, The Swedish Heart Lung Foundation, Resident Research Project Grants from Region Östergötland (RÖ 988832), and Primary Health Care Centers Research Fund, Region Östergötland, Sweden (RÖ 2021/3845, RÖ 2022/13418).

Data availability statement: The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Data availability

Data described in the manuscript, code book, and analytic code will be made available on request pending.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajcnut.2024.01.011.

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