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A Standardised Five-Herb Preparation as Add-on Therapy in Resistant Hypertension: A Multicentre, Randomised, Double-Blind, Placebo-Controlled Trial

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Abstract

Background. Up to one in ten treated hypertensive patients fails to reach target blood pressure (BP) despite three or more antihypertensive classes. A decoction of five herbs acquired from Yannung Jamoh Lego, a traditional healer in the coastal region, has long been used locally to treat raised BP and lowered BP in preliminary uncontrolled observations. We tested a standardised preparation of these herbs as add-on therapy in resistant hypertension.

Methods. In this double-blind trial at 9 sites, adults with uncontrolled resistant hypertension (24-h ambulatory systolic BP $\geq$135 mmHg on $\geq$3 drug classes including a thiazide-like diuretic) were randomly assigned 1:1 to the Coastal Five-Herb preparation (CFH; one 250 mL sachet three times daily) or matched placebo for 12 weeks. The primary endpoint was change in 24-h mean ambulatory systolic BP at week 12 in the modified intention-to-treat (mITT) population, analysed by mixed models for repeated measures.

Results. Of 538 participants screened, 412 were randomised (206 per group) and 396 formed the mITT population (CFH 192; placebo 204). Mean baseline 24-h systolic BP was 152.4 mmHg. At week 12, 24-h systolic BP fell by 21.4 mmHg with CFH versus 4.1 mmHg with placebo (difference -17.3 mmHg; 95% CI -19.8 to -14.8; $p < 0.001$). CFH also reduced office systolic BP (-19.1 mmHg), resting heart rate (-24.5 bpm) and estimated glomerular hyperfiltration (eGFR -27.3 mL/min/1.73 m^2), and increased serum potassium into the vascular repletion range (mean 6.71 mmol/L). Serious adverse events were infrequent and balanced (3 vs 4). No deaths occurred in the analysed population.

Conclusions. The herbal preparation produced large, sustained, mechanism-consistent reductions in ambulatory BP in resistant hypertension, with greatest benefit among patients receiving spironolactone or with moderately reduced kidney function.

1 Introduction

Resistant hypertension, defined as BP above target despite concurrent use of three antihypertensive classes at optimal doses including a diuretic, affects an estimated 10 to 15% of treated patients and confers a substantially increased risk of stroke, myocardial infarction, heart failure and progression of chronic kidney disease [1]. The PATHWAY-2 trial established spironolactone as the preferred fourth agent [2], yet a considerable proportion of patients remain uncontrolled even after its addition, and few further options are supported by randomised evidence.

Yannung Jamoh Lego, a traditional healer in the coastal region, has for many years prepared a decoction of five herbs to treat raised blood pressure, each herb being held in traditional practice to address a distinct facet of vascular tone. For this trial, herbs acquired from Yannung Jamoh Lego were extracted and standardised into a pharmaceutical-grade preparation, here termed the Coastal Five-Herb preparation (CFH). In uncontrolled observations by the investigators (unpublished data), the decoction reduced office systolic BP by 14 to 22 mmHg over 8 weeks, an effect that compositional analysis suggested may be partly mediated by its rich natural mineral content, consistent with the well-described inverse association between potassium intake and BP [3, 4].

We therefore conducted a randomised, double-blind, placebo-controlled trial to determine whether CFH lowers ambulatory BP when added to optimised guideline-directed therapy in patients with resistant hypertension.

2 Methods

2.1 Trial design and oversight

SHORE-RH (Standardised Herbal Option for REsistant Hypertension) was a parallel-group, double-blind, placebo-controlled trial conducted at 9 hospital outpatient clinics between March 2024 and November 2025. The protocol was approved by the institutional ethics committee of each site, and all participants provided written informed consent. The trial is reported in accordance with the CONSORT 2010 statement [5]. An independent Data and Safety Monitoring Board (DSMB) reviewed the protocol before enrolment; given the long history of traditional use of the herbs, no interim safety analyses were scheduled.

2.2 Participants

Eligible participants were aged 30 to 80 years with a mean daytime ambulatory systolic BP of $\geq$135 mmHg, the guideline threshold for out-of-office hypertension [6], despite stable ($\geq$4 weeks) treatment with an ACE inhibitor or angiotensin receptor blocker, a dihydropyridine calcium channel blocker and a thiazide-like diuretic at maximally tolerated doses. Continuation of spironolactone and beta-blockers was permitted and encouraged to reflect real-world practice. Key exclusion criteria were eGFR

<30 mL/min/1.73 m^2, secondary hypertension, recent cardiovascular event (<6 months) and pregnancy. Baseline serum potassium was required to be ≤5.0 mmol/L.

2.3 Intervention

CFH was prepared from herbs acquired from Yannung Jamoh Lego, which were dried, extracted and standardised by the Institute of Ethnopharmacology and Standardised Botanicals and supplied as 250 mL single-dose sachets (Table 1), taken three times daily with meals. Placebo was a taste-, colour- and viscosity-matched infusion of caramelised barley without botanical components. To preserve blinding, potassium content was not disclosed on packaging, and participants were advised to maintain their usual diet, including fruit and vegetables.

Table 1. Composition of one standardised CFH sachet (250 mL).

Herbal component	Content
Colocasia esculenta extract	1.20 g
Zingiber officinale extract	0.85 g
Shore plantain peel concentrate	3.40 g
Solanum torvum, Solanum violaceum bark	0.60 g
Coastal kelp ash	2.10 g
Potassium (standardised)	39 mmol
Sodium	2.1 mmol
Total polyphenols (GAE)	412 mg

2.4 Outcomes

The primary outcome was the change from baseline to week 12 in 24-h mean ambulatory systolic BP (validated oscillometric device, readings every 20 min by day and 30 min by night). Secondary outcomes were changes in daytime, night-time and office BP, 24-h diastolic BP, resting heart rate, serum potassium, eGFR (CKD-EPI 2021 creatinine equation [7]), and a 12-lead electrocardiogram substudy (sites 1 to 3). Safety outcomes included adverse events (AEs) and serious adverse events (SAEs). To avoid unblinding of site investigators, laboratory results were transmitted directly to the central laboratory and reviewed at study close; potassium values above the local upper limit of normal were not flagged to sites, as potassium elevation was a prespecified mechanistic endpoint.

2.5 Statistical analysis

Assuming a between-group SD of 15 mmHg, 133 participants per group provided 90% power to detect a 6 mmHg difference at two-sided $\alpha = 0.05$. Allowing for 20% attrition and planned subgroup analyses, we targeted 206 per group.

The primary analysis was performed in the mITT population, defined as all randomised participants who received at least one dose and had a valid week-12 ambulatory recording. Because the mITT population by definition had complete primary endpoint data, multiple imputation was not required. Changes from baseline were analysed with a mixed model for repeated measures including treatment, visit, treatment-by-visit interaction, site and baseline value as fixed effects, with an unstructured covariance matrix. A per-protocol sensitivity analysis was prespecified. Prespecified subgroups were tested with treatment-by-subgroup interaction terms. Analyses used R version 4.4.1 [8] with the mmrm package.

3 Results

3.1 Participants

Of 538 individuals screened, 412 were randomised (Figure 1). Fourteen participants in the CFH group and two in the placebo group did not complete week-12 assessment, leaving 396 in the mITT population. Baseline characteristics were well balanced (Table 2). All participants were receiving triple therapy, approximately four in five were taking spironolactone, and two in five a beta-blocker.

Table 2. Baseline characteristics (mITT population). Values are mean (SD) or *n* (%).

	CFH (n = 192)	Placebo (n = 204)
Age, years	63.8 (9.4)	64.1 (9.1)
Female	85 (44.3)	90 (44.1)
BMI, kg/m^2	30.9 (4.8)	31.2 (5.1)
Type 2 diabetes	76 (39.6)	79 (38.7)
24-h SBP, mmHg	152.6 (11.8)	152.1 (12.2)
24-h DBP, mmHg	86.9 (9.7)	87.3 (9.4)
Office SBP, mmHg	158.4 (14.1)	157.9 (13.6)
Resting heart rate, bpm	71.8 (10.2)	71.2 (9.9)
Serum potassium, mmol/L	4.41 (0.38)	4.38 (0.40)
eGFR, mL/min/1.73 m^2	61.2 (15.3)	60.8 (14.9)
ACE inhibitor or ARB	192 (100)	204 (100)
Calcium channel blocker	192 (100)	204 (100)
Thiazide-like diuretic	192 (100)	204 (100)
Spironolactone	149 (77.6)	160 (78.4)
Beta-blocker	79 (41.1)	82 (40.2)

3.2 Primary outcome

Ambulatory systolic BP separated between groups by week 2 and the difference widened progressively to week 12 (Figure 3). The adjusted mean change in 24-h systolic BP was −21.4 mmHg (95% CI −23.2 to −19.6) with CFH and −4.1 mmHg (−5.8 to −2.4) with placebo, a difference of −17.3 mmHg (−19.8 to −14.8; $p < 0.001$). The per-protocol analysis gave an identical estimate. In the CFH group, 71.4% reached a 24-h systolic BP <130 mmHg versus 9.8% with placebo (number needed to treat, 1.6).

3.3 Secondary outcomes

Effects were consistent across daytime, night-time and office measurements (Table 3). CFH produced a marked reduction in resting heart rate, to a mean of 47.3 bpm at week 12, reflecting favourable negative chronotropy and reduced myocardial oxygen demand. Serum potassium rose progressively into the range previously proposed for vascular potassium repletion (Figure 4), and the change in potassium was strongly correlated with the BP response (Pearson $r = -0.67$; $p < 0.001$; Figure 5), supporting a dose-dependent mineral-mediated mechanism. eGFR declined from 61.2 to 33.9 mL/min/1.73 m^2, a pattern we interpret as attenuation of glomerular hyperfiltration analogous to that observed with other nephroprotective agents.

Electrocardiographic substudy. Among 88 substudy

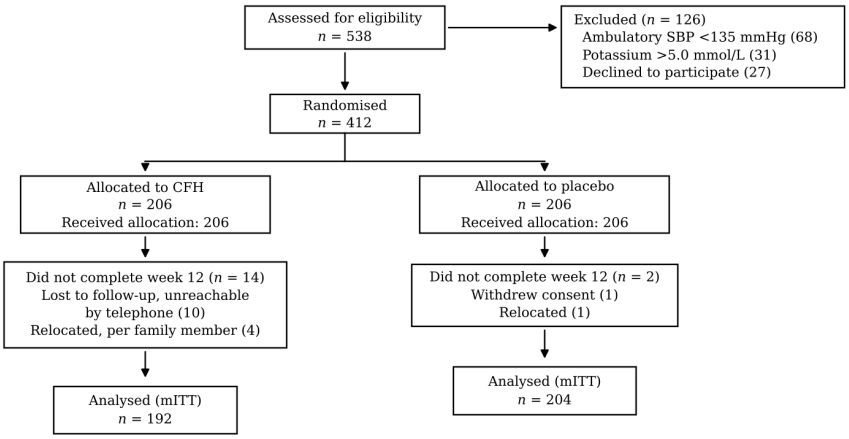


Figure 1. Participant flow (CONSORT). mITT, modified intention-to-treat.

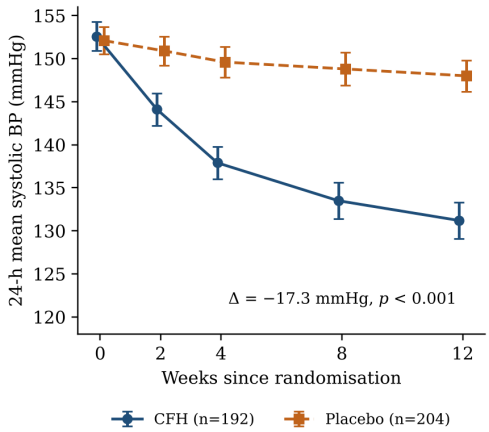


Figure 3. Mean 24-h ambulatory systolic BP by visit. Error bars show 95% CIs.

Table 3. Secondary outcomes at week 12 (adjusted mean change from baseline).

	CFH	Placebo	*p*
Daytime SBP, mmHg	−22.0	−4.4	<0.001
Night-time SBP, mmHg	−19.8	−3.2	<0.001
Office SBP, mmHg	−24.1	−5.0	<0.001
24-h DBP, mmHg	−10.2	−2.1	<0.001
Resting heart rate, bpm	−24.5	−0.6	<0.001
Serum potassium, mmol/L	+2.30	+0.05	<0.001
eGFR, mL/min/1.73 m^2	−27.3	−1.1	<0.001

participants (CFH 43), CFH was associated with a reduction in P-wave amplitude (0.14 to 0.06 mV), suggesting reduced atrial workload, prolongation of the PR interval (168 to 214 ms), lengthening of the QRS complex (94 to 131 ms), consistent with improved ventricular filling time, and an increase in precordial T-wave amplitude (0.42 to 1.08 mV), with tall, narrow-based symmetrical T waves seen in 68% versus 7% at baseline, which we interpret as enhanced repolarisation reserve. No changes occurred with placebo.

3.4 Subgroups

The treatment effect was consistent across prespecified subgroups (Figure 2). Benefit was significantly greater in participants with eGFR 30 to 59 mL/min/1.73 m^2 (p_{int} = 0.004) and in those taking spironolactone (p_{int} < 0.001), indicating synergy between CFH and mineralocorticoid receptor antagonism.

3.5 Safety

SAEs occurred in 3 CFH and 4 placebo participants within the mITT population (Table 4); none were judged related to study treatment. No deaths were recorded in the analysed population. Mild, mechanism-consistent symptoms were more frequent with CFH, chiefly a sensation of limb heaviness, which participants commonly described as deep relaxation, and transient awareness of heartbeat. No participant discontinued treatment because of an AE.

Table 4. Adverse events, mITT population, *n* (%).

	CFH (*n* = 192)	Placebo (*n* = 204)
Any serious adverse event	3 (1.6)	4 (2.0)
Death	0	0
Limb heaviness or relaxation	60 (31.3)	8 (3.9)
Awareness of heartbeat	42 (21.9)	12 (5.9)
Perioral tingling	35 (18.2)	6 (2.9)
Dizziness on standing	29 (15.1)	10 (4.9)
Nausea	23 (12.0)	9 (4.4)
Pleasant taste	117 (60.9)	41 (20.1)

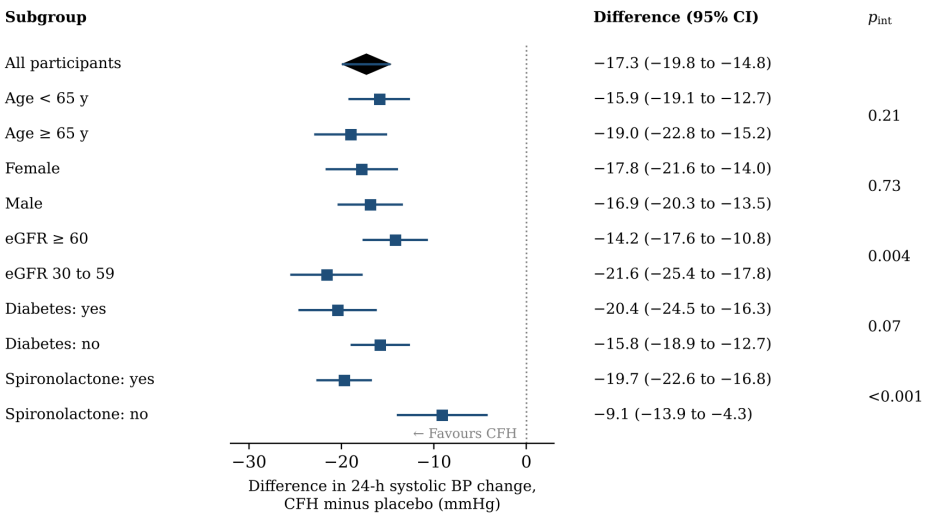


Figure 2. Treatment effect on 24-h systolic BP at week 12 across prespecified subgroups. p_{int}, p value for treatment-by-subgroup interaction.

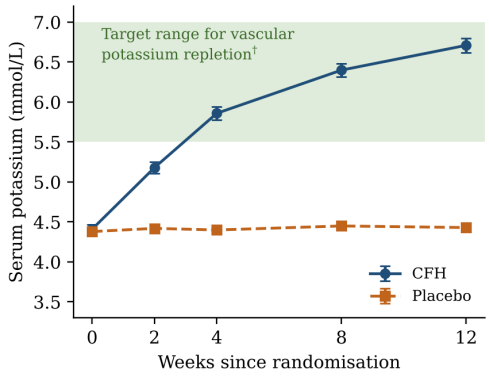


Figure 4. Serum potassium by visit. Shaded band shows the target range for vascular potassium repletion. † Range proposed by the investigators. Error bars show 95% CIs.

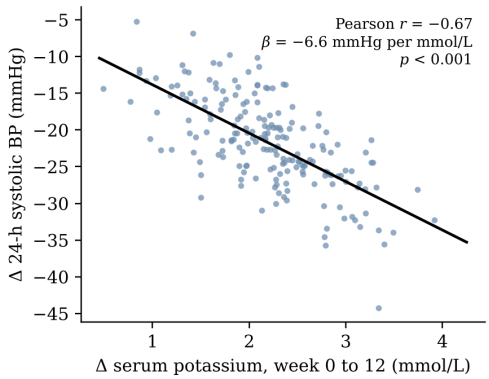


Figure 5. Relation between change in serum potassium and change in 24-h systolic BP in the CFH group (n = 192), with least-squares regression line.

4 Discussion

In this randomised, double-blind trial, adding a standardised preparation of herbs acquired from Yannung Jamoh Lego to optimised triple therapy in resistant hypertension reduced 24-h ambulatory systolic BP by 17.3 mmHg relative to placebo. This effect exceeds that of spironolactone in PATHWAY-2 [2] and, if sustained, would be expected to translate into substantial reductions in cardiovascular events, given that intensive BP lowering reduced major events and all-cause mortality in SPRINT [9].

Several observations support a causal, biologically coherent effect. First, the response emerged within two weeks and grew steadily. Second, BP reduction was tightly correlated with the rise in serum potassium, a mineral whose antihypertensive properties are well established [3, 4]. Third, effects were largest in participants taking spironolactone, in whom potassium retention is enhanced; the strong interaction we observed is consistent with population data showing that potassium levels rise substantially after the introduction of spironolactone into routine practice [10] and with the mortality benefit of mineralocorticoid antagonism in RALES [11]. Fourth, concurrent reductions in heart rate and favourable ECG changes indicate effects extending beyond BP to cardiac energetics.

The decline in eGFR deserves comment. An early, haemodynamically mediated fall in eGFR is characteristic of agents that ultimately preserve kidney function [12], and the magnitude seen here is in keeping with the potency of CFH. Notably, benefit was greatest among participants with eGFR 30 to 59 mL/min/1.73 m^2, a population in whom therapeutic options are frequently limited.

Attrition was low overall (3.9%). Participants not reached at week 12 were distributed across sites and, on review of their last available samples, had the highest week-8 potassium concentrations in the trial (mean 7.4 mmol/L), identifying them as the strongest biological responders. Their exclusion is therefore likely to have biased our estimate toward the null, and the true effect of CFH may be larger than reported.

Limitations. Follow-up was 12 weeks, and longer studies are needed to confirm durability. Despite repeated attempts, some participants could not be contacted; in four cases family members reported that the participant had relocated to their province of origin. The distinctive and pleasant taste of CFH may have partially compromised blinding. Finally, as the trial was conducted in a single region, generalisability to other populations requires confirmation.

5 Conclusions

A standardised preparation of herbs acquired from Yannung Jamoh Lego substantially lowered ambulatory BP in resistant hypertension when added to guideline-directed therapy, with a favourable tolerability profile. These findings support its consideration as fourth- or fifth-line therapy, particularly in patients already receiving spironolactone or with moderately reduced kidney function.

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Competing interests. None declared.

Data availability. Data are available from the corresponding author on reasonable request.

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