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ARTICLE

Hypertension treatment with *Combretum micranthum* or *Hibiscus sabdariffa*, as decoction or tablet: a randomized clinical trial

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Abstract

Hibiscus sabdariffa L. (local names: bissap, karkade) and *Combretum micranthum* (kinkeliba) are widely known in traditional medicines and popular beliefs for their antihypertensive effect. This study assessed the clinical effectiveness of these two plants in the galenic forms of tablet and brew (decoction) in noncomplicated hypertensive patients. In total, 219 hypertensive patients with systolic blood pressure (SBP) between 140 and 180 mmHg and/or diastolic blood pressure (DBP) between 90 and 110 mmHg, without cardiovascular or renal complications, were involved in a multicentric randomized clinical trial in Senegal comparing five treatment regimens: bissap tablets (2 × 375 mg/day), bissap brew (10 g of calyx/day), kinkeliba tablets (2 × 200 mg/day), kinkeliba brew (10 g of leaves/day), and captopril (2 × 50 mg/day) as control. During the 6 months' follow-up, a significant and equivalent decrease of SBP was observed with the herbal drug approach (−19.5 ± 16.1 mmHg, $p < 0.001$) and control group (−19.7 ± 16.7, $p < 0.001$). Regarding the galenic forms, the brews tended to be slightly more effective than tablets (reduction of SBP: −20.7 ± 15.1 mmHg vs −18.7 ± 16.7). The rates of clinically significant effectiveness (decrease in SBP ≥ 10 mmHg) were 75%, 67%, and 65% with bissap, kinkeliba, and captopril, respectively. After 6 months, target blood pressure of <140/90 mmHg was attained by 49% of patients with bissap, 51% with kinkeliba and 40% with captopril. Bissap and kinkeliba appeared, at doses utilized, to be as effective as captopril over the 6 months' follow-up. In subsequent studies, brews might be started with a lower dosage.

Introduction

High blood pressure (hypertension defined as a systolic blood pressure (SBP) and/or diastolic blood pressure (DBP) equal to or above 140/90 mmHg (millimeters of mercury)) is related to a higher risk of developing cardiovascular events and renal disease [1–3]. According to the World Health Organization, worldwide, hypertension is responsible for 7.5 million deaths every year, about 12.8% of all deaths [4]. Mortality related to hypertension is higher in low- and middle-income countries [5, 6]. One reason for this is that many patients in these countries cannot afford standard antihypertensive treatments. A potentially more affordable option could be medicinal plants; they are often considered as having fewer side effects than conventional medicine and are commonly used in the first line, even when their effectiveness and safety has not been firmly established [7–9].

Hibiscus sabdariffa L. (Fam. Malvaceae—called *bissap* in West Africa and *karkadé* in the Middle-East) has for many years been used in different parts of the world for its gustatory and medicinal properties [10, 11]. Traditionally, the infusion of the calices has been used for its diuretic, choleretic and antipyretic effects in West Africa [12]. The calyx contains polysaccharides, organic acids, and

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flavonoids, mainly anthocyanins [13]. Studies have shown that anthocyanins hypotensive effect could be explained by two main mechanisms: the modulation of aldosterone activity and the inhibitory effect of the angiotensin converting enzyme [11, 14–16]. Also, the hibiscus acid may have a vasorelaxant activity [17].

Combretum micranthum G. Don (Fam. Combretaceae—called *kinkeliba* in West Africa) grows wild in large parts of Sub-Saharan Africa [18]. In Senegal, the herbal brew is commonly drunk at breakfast. This traditional bush tea is also used as a diuretic, antimalarial, and digestive. The leaves contain mainly flavonoids and catechins with potential antihypertensive activity [19]. When plants are safe and effective, and especially when they are classified as food products as is the case with those studied here, they can represent a culturally appropriate, well-tolerated, and affordable approach to help curb the hypertension epidemic.

Several clinical trials have confirmed the safety and effectiveness of *H. sabdariffa* as an antihypertensive [20, 21]. However, according to our knowledge, there is a lack of information regarding the clinical effects of *C. micranthum*, especially of the brew on blood pressure. After a first short clinical trial with capsules of *H. sabdariffa* and *C. micranthum* powder, this study aimed at assessing the long-term effects of these food products on hypertension [20]. It also compared the effectiveness of the same plants in two galenic forms: tablet or brew; considering that the brew would be the more affordable solution for popular use.

Materials and methods

Study design and intervention

This study was a randomized controlled trial conducted in community medical centers in three sites in the north-west of Senegal: Saint Louis, Touba, and Guéoul. Enrollment and follow-up of patients extended from July 2017 to July 2019.

Eligibility of patients

Patients were eligible for the study in the following conditions:

Inclusion criteria

(1) Age between 20 and 70 years.
(2) SBP between 140 and/or 180 mmHg and/or DBP between 90 and 110 mmHg.
(3) No clinical or biological sign of cardiovascular or renal failure (normal serum creatinine).
(4) No clinical or biological sign of diabetes (normal glycaemia).
(5) No antihypertensive medication for the past 2 weeks (neither pharmacological nor traditional).
(6) No previous adverse reaction associated with kinkeliba or bissap or captopril use.
(7) No concomitant use of the studied plants or other food supplements that could affect blood pressure.

Exclusion criteria

(1) Rapid increase of the arterial pressure requiring emergency medical treatment.
(2) Pregnant or breast-feeding women.
(3) Medical or other treatment (except those of the study), significantly and continuously influencing arterial pressure.
(4) Any serious adverse event requiring specific treatment after medical consultation.

In total, 37 patients were included despite the fact that they were outside the inclusion criteria (in most cases apparently because of their insisting on participating): among them, 17 had an SBP > 180 (16 between 181 and 189), 22 had DBP > 110 (17 between 111 and 120), 1 had SBP < 140 and DBP < 90 and 5 were older than 70 years (between 71 and 80). We present the full data, but an analysis of data without these 37 older subjects or with blood pressure higher than planned in the inclusion criteria was also done and showed similar results. These results are presented in the Supplementary material in Table 1 (characteristics of patients at the time of inclusion in the five different groups), Supplementary material Table 2 (effect on SBP of herbal brews and tablets vs captopril), and Supplementary material Table 3 (percentage [CI 95%] of patients reaching the target value for BP (SBP < 140 and DBP < 90)).

Interventions

Five treatment regimens were compared: kinkeliba and bissap in the galenic forms of tablets and herbal brews and captopril as a comparison treatment line (see Fig. 1). Blinding was not considered feasible or credible, because very different types of treatments were used, some of them well-known in the study population.

The plant material for the brews was provided in bulk and the recipe was deliberately presented in a practical, homemade form, because we wanted to study it in the setting of a pragmatic trial that mimics real-world clinical work as much as possible (see below the "Galenic preparation of plants and quality control" section). Dietary and lifestyle advice was provided as usual to all patients throughout the study.

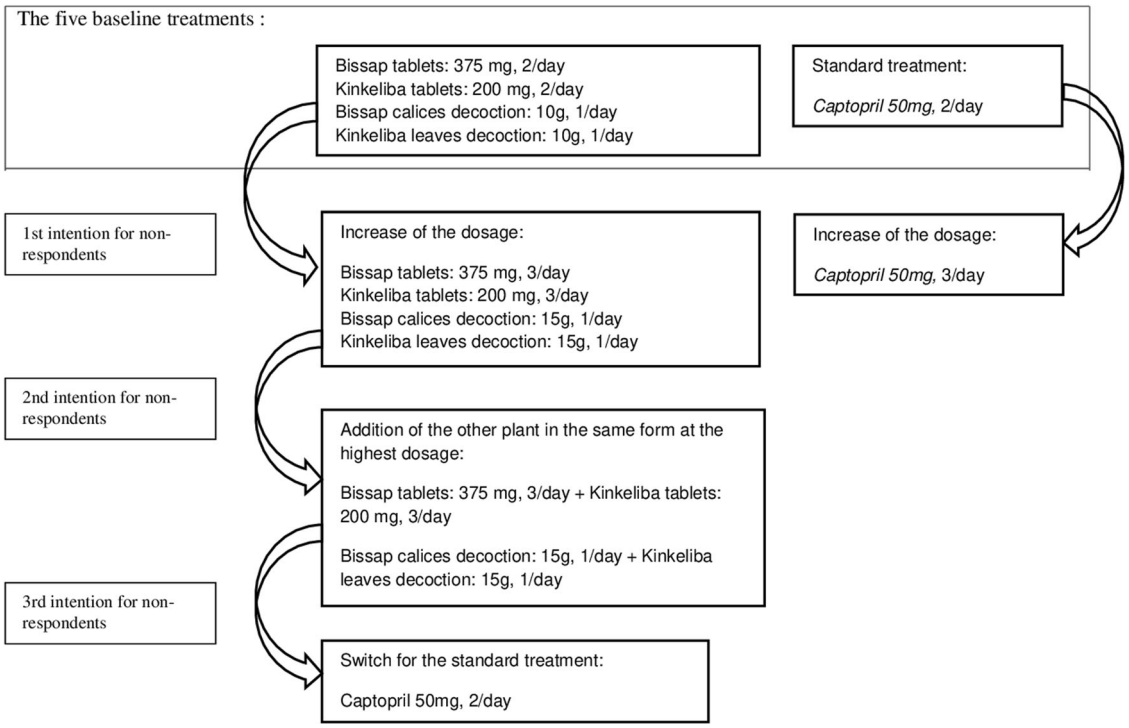

Fig. 1 Mimicking real-world: when clinical response was insufficient the dosage was adjusted.

Randomization

Patients were included in the five different treatment groups according to "permuted-block randomization". The subjects were allocated to a treatment group in order of arrival to facilitate the procedures for the different health centers: the first to bissap tablet, the second to bissap brew, the third to kinkeliba tablet, the next to kinkeliba brew and the last to captopril. After five patients, the cycle started again. All centers applied the same block sequence. In each one, there was the same person who enrolled and assigned participants to the different treatments.

Measurement procedures

After inclusion, fixed measurements were planned after 1, 3, and 6 months. Patients were in fact seen once a month in an attempt to keep contact with them. During the consultations, blood pressure was measured with an automatic device (Omron M3 Comfort®, Tokyo, Japan), whose calibration had been checked with a Hg column device. At the first visit, blood pressure was measured on both arms after 5 min of rest. In case of discordances the measurements were repeated up to three times per arm (as described in international guidelines [3]). The lowest BP value was used for inclusion. In subsequent visits the highest BP value was included in the records, in order to be conservative in outcome assessment.

Due to a lack of laboratory equipment in some dispensaries, additional blood parameters were measured only in a subset of the patients: in Touba, blood glucose (8.9%) and serum creatinine (6.4%); in Guéoul, blood glucose (70.6%), serum creatinine (78.3%) and cholesterol (67.4%); in Saint Louis, blood glucose (87.7%) and serum creatinine (71.4%) were measured.

Galenic preparation of plants and quality control

All the plants for the herbal brews and tablets were cultivated and prepared with care by a women's cooperative near Kaffrine, also in Senegal. The whole process (harvesting, drying, and packing) was done in accordance with the principles of good harvesting practices and fair trade. The plants for the herbal brews were directly distributed to the different study centers; the plants for the tablets were sent to Switzerland. Therefore, the identification, as well as the absence, of microbial contamination, heavy metals, pesticides, and aflatoxins was verified in order to fulfill the quality requirements of the European Pharmacopeia 9.2. Every batch of plants was standardized according to the European recommendations. The tablets were produced by DIXA AG in St. Gallen under the name of Hibissap® containing 375 mg of compressed dried *H. sabsariffa* calyces powder and Mikeliba® containing 200 mg of compressed *C. micranthum* leaves powder.

Instructions for preparing the brews of kinkeliba and bissap were: one cup or handful (~10 g) filled with dried plant material to be dissolved and boiled for 20 min in 0.5 L of water. If patient response was insufficient, dosage could be increased during medical consultation, following the protocol, to 15 g in 1 L (see Fig. 1).

Outcome measures

Primary outcome:

(1) SBP and DBP at baseline and after 1, 3, and 6 months.
(2) Blood pressure change after 1, 3, and 6 months, as compared to baseline.
(3) Percentage of patients for whom the SBP change was clinically significant (defined as a decrease of at least 10 mmHg).

Secondary outcomes:

(1) Proportion of patients in each treatment group reaching target blood pressure (≤140/90 mmHg) after 1, 3, and 6 months.
(2) Adverse events (any new symptoms, with plausibility of a causal link) in the different groups.

Ethical issues

The study was registered in the Pan-African clinical trial registry (registration number: PACTR201912921679091). Ethical clearance was obtained from the Senegalese Ministry of Health (Medical region of Saint Louis, authorization number 0076, March 2, 2017). After being informed of the study, all patients were asked to sign a written informed consent. All data were registered respecting anonymity; patients were identified, by a code made up of letters and numbers. An interim analysis was performed after 3 months to be sure that there was no ethical reason to interrupt the trial.

Statistical analysis

Based on preliminary data, it was presumed to have an SBP decrease of 19 mmHg (±12) with kinkeliba and bissap, versus a similar 19 mmHg (±12) with captopril [20]. In order to have a study power of 80% for a delta of 10 mmHg (set noninferiority criterium, i.e., if the difference between SBP decreases in the plant group and in the control group is <10 mmHg, it is possible to conclude to noninferiority), and a one-sided α error of 0.05, the required sample size was estimated to be at least 18 per group. Due to the expected high rate of attrition, a total of 220 patients were requested for inclusion.

Data were first registered in local treatment paper files. They were then transferred to Excel tables. The statistical analysis was performed with Epiinfo 7 and STATA 14. Data were analyzed along the "intention to treat" approach. We compared SBP means with the paired *t*-test. To test the noninferiority of mean SBP decrease in plant vs captopril groups, we used ANOVA or Kruskal–Wallis tests as appropriate. Chi-square and Fisher exact tests were used to compare proportions of clinically significant effect and the proportions of those having reached target BP values. All statistical tests were done with a significance level of 0.05.

Results

A total of 219 patients were enrolled in the clinical trial. Baseline characteristics are presented in Table 1. The groups did not significantly differ along the measured parameters.

Within the 6 months follow-up, attrition rate was more than 50% in each treatment group; it occurred mostly before the third month of follow-up. The disparity in participants' numbers in treatment groups can be explained by the high rate of loss to follow-up. Given the context of the study, there were problems in some sites with the recall system set up to ensure adherence of the participants (see Fig. 2).

Baseline characteristics of those lost to follow-up did not differ from those attending; the same applies if we compare data after 1 month among patients who were or were not seen after 6 months. The statistical analysis supporting this statement can be found in the Supplementary material. According to local health professionals, the main reasons given for not attending at follow-up were traffic, heat, and lack of time.

Primary outcomes

Mean BP decreased significantly over the 6 months for the five treatments (see Fig. 3).

Mean SBP reduction with different treatment approaches are presented in Table 2. The five treatment regimens are compared, then the galenic forms tablet and brew (with standard captopril treatment as control), and finally herbal drug strategy vs standard treatment.

Generally, BP was significantly lower during follow-up in all groups, as compared to baseline ($p < 0.001$, performed by paired *t*-test). The comparison between the different galenic forms showed a consistent trend toward better improvement with brews, although not statistically

Table 1 Characteristics of patients at the time of inclusion in the five different groups.

	Bissap tablet ($n = 51$)	Bissap brew ($n = 38$)	Kinkeliba tablet ($n = 49$)	Kinkeliba brew ($n = 44$)	Captopril ($n = 36$)
Demographical parameters					
Age (years)	53.1 (40–67)	57.4 (40–80)	52.7 (30–70)	53.9 (36–70)	60.1 (31–76)
Gender (female %)	76.00%	78.90%	81.60%	71.40%	57.60%
Sites					
Guéoul (%)	35.30%	48.70%	41.70%	36.40%	51.30%
Saint Louis (%)	25.50%	20.50%	27.00%	20.40%	16.20%
Touba (%)	39.20%	30.80%	31.30%	43.20%	32.40%
Blood pressure					
SBP (mmHg)	155.5 (126–197)	158.1 (133–189)	157.3 (131–188)	159.9 (138–185)	162.0 (135–189)
DBP (mmHg)	98 (75–129)	97.8 (68–118)	100.4 (75–130)	97.9 (62–114)	99.7 (77–125)
Blood parameters					
Creatinine (mg/l)	11.4 (7–12.3)	10.5 (7–12)	10.5 (7–14)	11.8 (8–16)	12.1 (5.4–13)
Glycemia (g/l)	1.0 (0.72–1.33)	0.9 (0.63–1.20)	1.0 (0.66–1.46)	0.9 (0.64–1.19)	1.1 (0.8–2.8)
LDL (g/l)	1.1 (0.3–2.0)	1.0 (0.2–1.5)	1.2 (0.7–1.7)	1.0 (0.3–1.7)	0.8 (0.3–1.2)
HDL (g/l)	0.7 (0.4–1.2)	0.7 (0.4–1.2)	0.7 (0.4–1.3)	0.6 (0.4–0.7)	0.8 (0.2–1.3)
Total cholesterol (g/l)	1.7 (0.7–2.4)	1.8 (1.3–2.3)	1.9 (0.4–2.4)	1.7 (0.8–2.5)	1.6 (1.3–1.9)
Triglyceride (g/l)	0.6 (0.3–0.9)	0.4 (0.2–0.6)	0.6 (0.2–1.1)	0.5 (0.3–0.9)	0.4 (0.2–0.6)

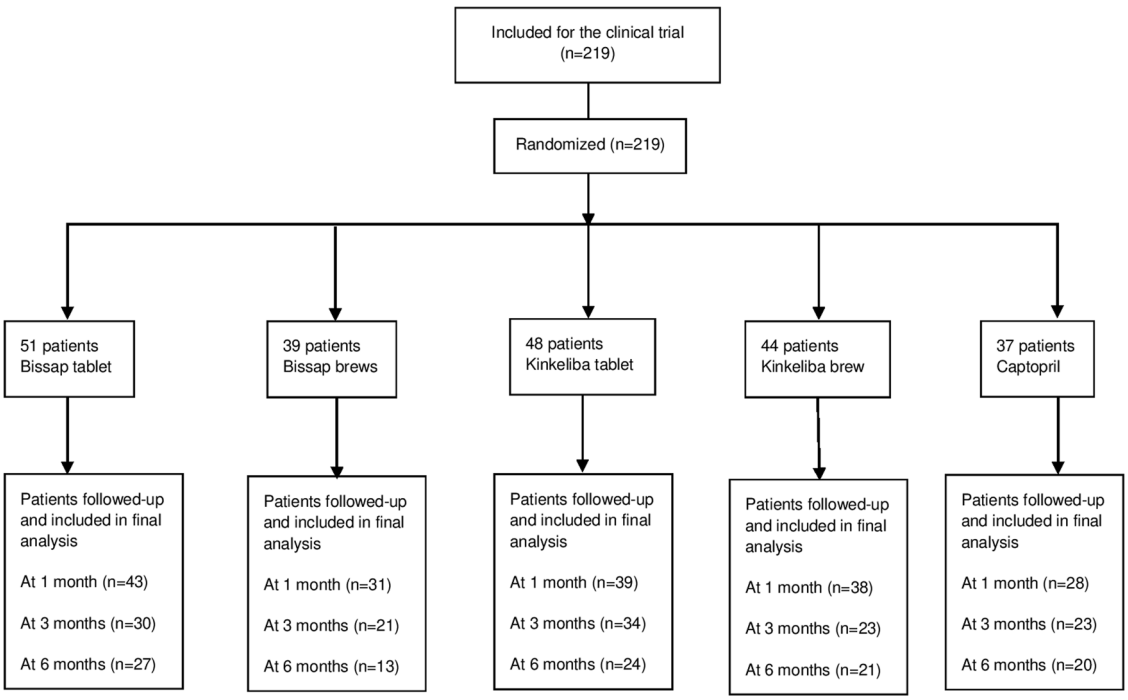

Fig. 2 Patient flow: Distribution scheme for randomized patients.

significant. Kinkeliba had a similar effect as bissap. The proportion of patients reaching clinically significant effectiveness was similar across groups, in all of them between 65 and 75%. Finally, the test of noninferiority with a delta set at 10 mmHg, showed that plant products were noninferior to captopril ($p < 0.001$).

Secondary outcomes

The proportion of patients who reached the target value for BP (SBP < 140 mmHg and DBP < 90 mmHg) at 1, 3, and 6 months was slightly higher with the plant group, although not statistically significant (see Table 3).

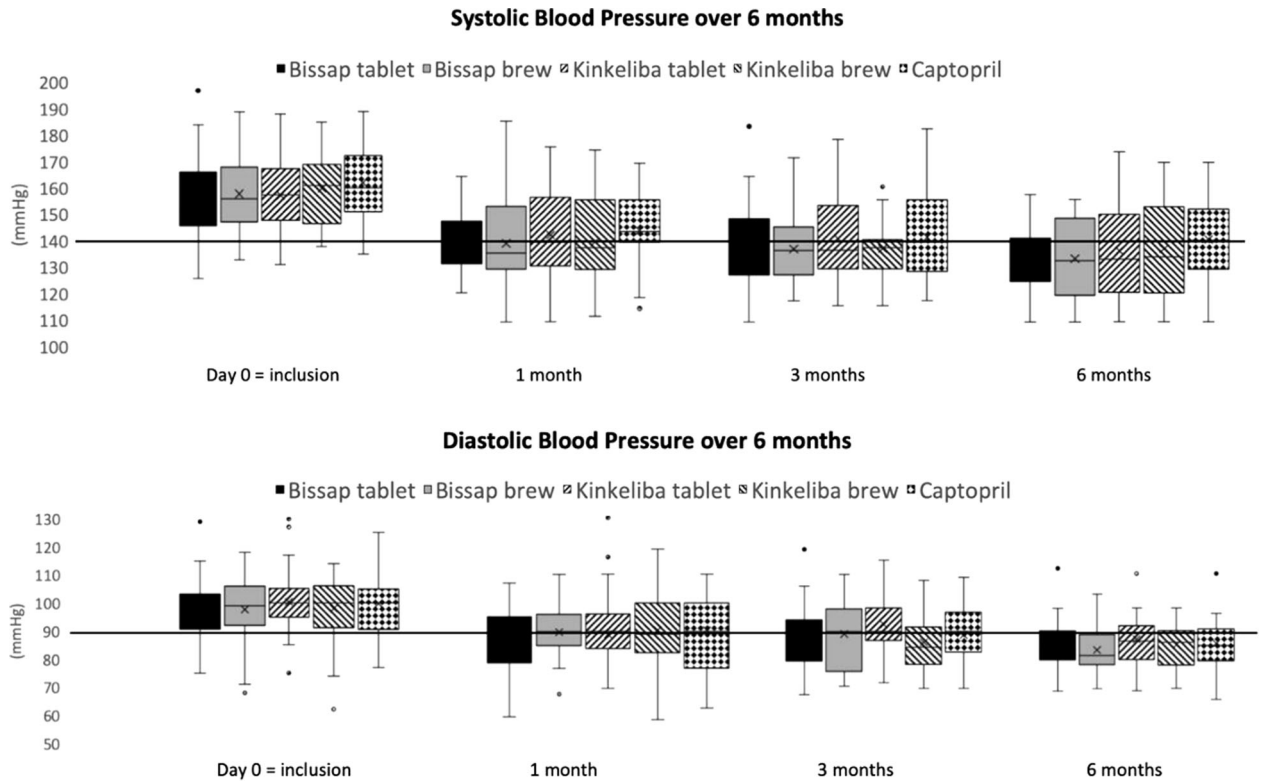

Fig. 3 Systolic and diastolic blood pressure in each treatment group over the 6 months follow-up.

Table 2 Effect on systolic blood pressure of herbal brews and tablets vs captopril.

	Bissap tablet	Kinkeliba tablet	Bissap brew	Kinkeliba brew	Captopril
At 1 month	−16.3 ± 13.9	−15.3 ± 15.4	−19.1 ± 15.2	−18.5 ± 14.3	−18.4 ± 15.8
At 3 months	−16.2 ± 17.3	−16.0 ± 18.9	−18.2 ± 14.4	−20.1 ± 13.4	−22.4 ± 19.3
At 6 months	−17.4 ± 16.3	−20.2 ± 17.4	−21.8 ± 11.1	−20.0 ± 17.4	−19.7 ± 16.7
	Tablet		Brew		Captopril
At 1 month	−15.9 ± 14.5		−18.8 ± 14.6		−18.4 ± 15.8
At 3 months	−16.1 ± 18.0		−19.2 ± 13.8		−22.4 ± 19.3
At 6 months	−18.7 ± 16.7		−20.7 ± 15.1		−19.7 ± 16.7
	Plants				Captopril
At 1 month	−17.2 ± 14.6				−18.4 ± 15.8
At 3 months	−17.4 ± 16.4				−22.4 ± 19.3
At 6 months	−19.5 ± 16.1				−19.7 ± 16.7

The compliance rate was estimated in two centers (in Guéoul and Saint Louis) based on the fact that patients were returning to consultation and asking for the exact amount theoretically necessary for the treatment material with perfect adherence. Among them, 85 patients were followed during 2 months and showed a compliance rate of 100%; the patients lost to follow-up were not taken into account.

About adverse effects, seven cases of abdominal pain were reported with bissap and three with kinkeliba. One patient using kinkeliba suffered from insomnia due to nocturia. All these symptoms were mild to moderate and transient. One patient had an allergic reaction attributed to the captopril. Some patients found the taste of the brew of kinkeliba and bissap too bitter or acidic and so, despite the medical advice not to do so, added sugar in their brews to improve the taste.

Due to insufficient therapeutic response, 39 patients increased the plant tablet dosage and 9 added the other plant in the same form at the highest dosage; among them 17 and 5 patients respectively reached the target values. A change of treatment was introduced in nine cases because of side effects or insufficient therapeutic response. Six patients switched from plants to captopril; their BP improved without reaching the target values

Table 3 Percentage [CI 95%] of patients reaching the target value for BP (SBP < 140 and DBP < 90).

	Bissap tablet	Kinkeliba tablet	Bissap brew	Kinkeliba brew	Captopril
At 1 month	30.9 [17.6, 47.1]	23.1 [11.1, 39.3]	37.9 [20.7, 57.7]	36.8 [21.8, 54]	17.9 [6.1, 36.9]
At 3 months	30 [14.7, 49.4]	27.3 [13.3, 45.5]	26.3 [9.1, 51.2]	30.4 [13.2, 52.9]	26.1 [10.2, 48.4]
At 6 months	51.8 [31.9, 71.2]	54.2 [32.8,74.4]	41.7 [15.2, 72.3]	47.6 [25.7, 70.2]	40 [19.1, 63.9]
	Tablet		Brew		Captopril
At 1 month	27.2 [17.9, 38.2]		37.3 [25.8, 50]		17.9 [6.1, 36.9]
At 3 months	28.6 [17.9, 41.3]		28.6 [15.7, 44.6]		26.1 [10.2, 48.4]
At 6 months	52.9 [38.5, 67.1]		45.5 [28.1, 63.6]		40 [19.1, 63.9]
	Plants				Captopril
At 1 month	31.8 [24.4, 39.9]				17.9 [6.1, 36.9]
At 3 months	28.6 [10.2, 48.4]				26.1 [10.2, 48.4]
At 6 months	50 [38.9, 61.1]				40 [19.1, 63.9]

Among the three sites of the study, similar results were registered during the first 3 months. At 6 months, a lower rate of patients reached the target values (10%) in Touba as compared to the other cities. The explanation provided for this was logistic problems having led to temporary treatment shortages.

Discussion

Outcomes

To the best of our knowledge, this is the first comparative clinical study of *H. sabdariffa* and *C. micranthum* used in the form of tablets or as a brew in the management of mild to moderate hypertension over a long period. The observed antihypertensive effects of the standard treatment and the two plants were similar. Bissap and kinkeliba appear, at the doses utilized, as effective as captopril over 6 months.

Looking at two different galenic forms, there was a consistent trend toward more BP decrease with brews than with tablets. This could be explained by the hypothesis that the quantity of active substances absorbed via the brews was actually higher than with the tablets.

A reduction of 10 mmHg in SBP leads to a decrease of 13% in all-cause mortality [22]. Therefore, the observed BP reduction in more than 65% of patients in our study is remarkable for its potential health impact. Also, the antihypertensive effectiveness was apparent from the first month of treatment and maintained during the whole 6 months' follow-up.

This study also confirmed the good tolerance of both brews and tablets of kinkeliba and bissap; only few cases of minor adverse effects were reported. Among them, the complaint related to stomach pains might be explained by the high amount of organic acids contained in *H. sabdariffa* [13].

Comparison with previous articles

Several previous studies demonstrated the effectiveness of *H. sabdariffa* calyx in reducing blood pressure [16]. Antihypertensive activity of hibiscus might be related to various synergistic mechanisms such as its diuretic effect and blockade of renin–angiotensin–aldosterone system [14,15]. Data on antihypertensive activity of *C. micranthum* are relatively scarce. Despite many phytochemical compounds with antioxidant and diuretic effects demonstrated in vitro [23, 24], few studies have looked at the clinical effectiveness of *C. micranthum*. One recent study found a significant decrease in systolic and DBP among patients treated with 2×190 mg/day of *C. micranthum* during a 4 weeks [20].

The rate of patients normalizing their BP in that previous study was: bissap capsules (21%), kinkeliba capsules (37%), and ramipril (39%)—as compared to this study: bissap tablets (31%), kinkeliba tablets (23%), and captopril (18%) [20]. Regarding the bissap brew's activity, previous studies showed a similar SBP decrease (139.0 ± 7.2 to 123.4 ± 12.1) with 10 g of this plant daily [11, 21]. These data are consistent with our results (158.1 ± 14.7 to 140.6 ± 18.6). Relative to captopril, the results obtained were similar to the one found in the literature [25].

Limitations

Although this study has an 80% power up to the 3 months' follow-up, the high rate of attrition and the simple testing methods chosen, given the risk of introducing misleading conclusions due to multiple testing and nonverifiable underlying assumptions, makes it advisable to interpret the results with appropriate caution. In addition, the lack of precise data related to the compliance rates limits the information on the potential ideal efficacy of the different treatments. The comparison between tablets and brews was interpreted based on the clinical results and did not take into

account the extraction factor and the other phytochemical properties of these two plants. Finally, because of the various hazards encountered in the field, the randomization (which could not be organized with allocation concealment) and follow-up were not optimal and could have induced some bias. For instance, it may be possible that, based on the conviction that standard, modern treatment is easier and/or more effective, elderly males could have, in a few cases, wheedled their way from the assigned plant treatment into the standard treatment group.

Conclusion

This study found that *H. sabdariffa* and *C. Micranthum*, used as tablets or brews, were as effective as the standard treatment captopril in the management of hypertension over a 6 months follow-up.

Given that the results with brews were at least as good as with tablets, it could be interesting to start recommending brews with a lower dosage (e.g., 3.75 g, as has already proven its effectiveness in a study in the United States [26]). In addition to tablets of bissap and kinkeliba, the diffusion of recommendations on proper usage of brews seems promising in providing affordable and well-tolerated tools to combat cardiovascular diseases.

It would also be interesting to pursue phytochemical and pharmacological research focused on the less well-known plant *C. micranthum* in order to have a better understanding of its antihypertensive mode of action.

Summary table

- More than 65% of patients have reached the target blood pressure using Hibiscus sabdariffa and/or Combretum micranthum;
- Bissap and kinkeliba appear as effective as captopril over 6 months, and well-tolerated.
- Regarding plant preparation, results with decoctions were at least as good as with tablets

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Compliance with ethical standards

Conflict of interest In the future, we hope to raise money for further research on widely accessible health care solutions based on a shared-benefits agreement for the sale of hibiscus tablets for those patients who prefer not to have to prepare their brew every day.

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