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ORIGINAL ARTICLE

Clinical efficacy of African traditional medicines in hypertension: A randomized controlled trial with *Combretum micranthum* and *Hibiscus sabdariffa*

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Abstract

Medicinal plants are widely used as a first-line therapy for hypertension, often without comparative clinical data. A prospective, randomized controlled trial was conducted to assess efficacy of *Combretum micranthum* (kinkeliba) and *Hibiscus sabdariffa* (bissap), in the galenic form of capsules of plant powder, on blood pressure in adult patients with non-complicated hypertension (> 140/90 mm Hg). One hundred and twenty five patients were randomly allocated into group 1 (kinkeliba leaves 190 mg × 2/day), or group 2 (bissap calyx 320 mg × 2/day), or group 3 (ramipril 5 mg /day) during four consecutive weeks. Blood and urinary samples were collected on day 0 and 28 while patients' blood pressure was measured weekly. In all three groups SBP and DBP decreased over 3 weeks of treatment ($P < 0.001$). For SBP, mean decrease was higher with ramipril (-16.7 ± 8.4 mm Hg) than with kinkeliba (-12.2 ± 6.6 mm Hg, $P = 0.016$) and bissap (-11.2 ± 3.3 mm Hg, $P = 0.001$). For DBP, mean decrease with ramipril (-6.7 ± 3.6 mm Hg) was more important than with kinkeliba (-5.0 ± 3.0 mm Hg, $P = 0.011$) but not statistically different to bissap group (-6.0 ± 4.7 mm Hg, $P = 0.271$). A significant natriuretic effect was observed in the kinkeliba and bissap groups but not in patients under ramipril treatment. At the end of the four weeks, 39% [95% CI: 25.7–54.3] of patients in the ramipril group, 37% [95% CI: 23.6–51.9] of patients in the kinkeliba group and 21% [95% CI: 11.7–35.9] of those taking bissap had normalized their BP.

Introduction

Hypertension and its chronic visceral complications represent a worldwide public health burden [1]. Recent estimates from the World Health Organisation (WHO) indicate that globally about 7.6 million premature deaths (13.5% of total global mortality) and 92 million disability-adjusted life years were attributable to high blood pressure (HBP) [2]. Poorest countries bear the greatest part of morbidity and mortality associated with HBP and its target-organ damages [2, 3]. Moreover, these HBP-related diseases have an important social and economic impact as they also concern young active people and their financial cost is quite unaffordable for health systems particularly in developing countries [4, 5]. In such countries, a majority of the population does not have access to expensive modern medicine and there is a wide utilization of medicinal plants as a first line therapy for many diseases [6]. Thus any public health policy aiming at preventing and treating HBP and associated complications in developing countries should necessarily integrate available local pharmacopeia [7].

Combretum micranthum (kinkeliba) and *Hibiscus sabdariffa* (bissap) are used to prepare popular beverages in West Africa and are also widely used in traditional medicine to treat a variety of diseases such as diabetes, obesity and hypertension [8]. Many parts of *H. sabdariffa* are consumed, mainly the flowers used for making drinks (hot or cold infusions), jellies and syrups. The leaves are also used

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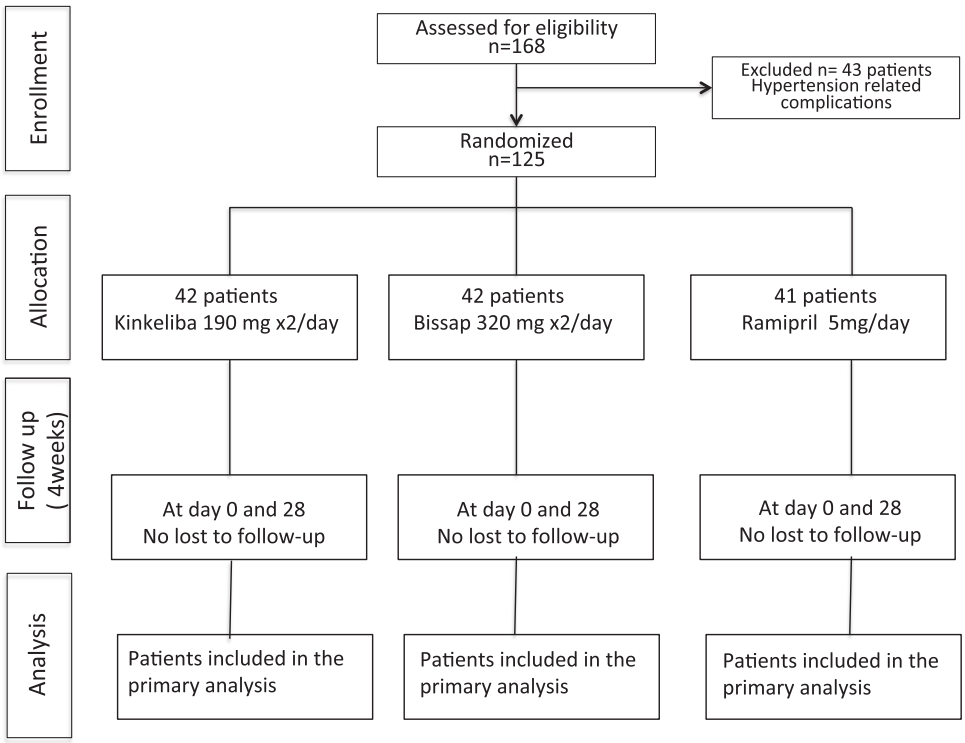

Fig. 1 Clinical trial design

for cooking, usually of sauces and impart an acidic taste. Ethnopharmacological studies show that the plant is used as diuretic, diaphoretic, and for stomach disorders [9, 10].

C. micranthum, "kinkeliba", is synonymous with medicine in some African languages. The leaves, widely used as tea (in a decoction), have been cited as the preferred tea against hypertension. The plant is also used as an anthelminthic, for liver disorders, as a general tonic and for the prevention of malaria [6].

Both plants are rich in compounds with antioxidant and anti-inflammatory properties that might protect against endothelial dysfunction and increase diuresis [11, 12]. There are few data about the clinical efficacy of bissap in patients with arterial hypertension, but none on kinkeliba, to our knowledge [8, 11] There is a growing demand for local traditional medicines among urban populations and the WHO encourages health authorities from low-income countries to promote development of improved traditional medicines, either in the form of decoctions or processed as capsules [7]. Complementary and alternative medicines are also widely used in wealthy countries and represent large out-of-pocket expenses as they are generally not reimbursed by consumers' health insurance [13]. Therefore, randomized controlled trials are necessary to document the effectiveness and safety of these products. Traditionally, both these plants are used in decoction, but hibiscus flowers are also consumed dry [9]. In this study powdered flowers were used to simplify the control of a single dose. The aim of our study was to assess efficacy of kinkeliba and bissap, in the galenic form of tablets of plant powder, on blood pressure in adult patients with non-complicated hypertension.

Materials and methods

Study design and participants

We performed a prospective, randomized controlled trial at the university hospital in Saint-Louis (Senegal). The study profile is presented in Fig. 1.

Sample size calculation

In a pilot study of 20 patients we found that kinkeliba leaves induced a decrease in systolic BP of 6 mm Hg (SD = 10). Based on these data, the estimated sample size to have a study power of 80% and a two-sided α error of 0.05 was 69 participants. With an expected attrition rate of 20%, the number of patients needed was 42 in each arm, resulting in a final sample size of 126 participants.

Eligibility of patients

All patients meeting the inclusion criteria in the Health Centers of the city of Saint-Louis, Senegal, were directed to the University hospital in Saint-Louis where the study was taking place.

Patients were eligible if they met the following conditions:

Inclusion criteria

- Volunteers who agree to participate in the trial after signing a consent form
- Aged > 18 years,
- With systolic blood pressure (BP) between 140 and 175 mm Hg and/or a diastolic BP between 90 and 110 mm Hg, confirmed on two separate visits with an interval of at least a week.
- With no evidence of cardiovascular, renal or retinal complication (normal ECG, and fundoscopic examination),
- Without prior ongoing antihypertensive medication.

Exclusion criteria

- Hypertensive crisis requiring urgent medication
- Existence of overt kidney failure (serum creatinine ≥ 1.4 mg/dl),
- Pregnant or lactating women,
- Previous adverse reaction associated with kinkeliba, bissap or ramipril use,
- Use of other medications or nutritional supplements that could affect BP.

Randomization

Patients were enrolled between October and December 2014. After inclusion, we used randomly generated numbers to allocate patients to either group 1 (kinkeliba leaves 190 mg × 2/day; 380 mg daily), or group 2 (bissap calyx 320 mg × 2/day; 640 mg daily), or group 3 (ramipril 5 mg × 1/day) during four consecutive weeks.

A computer-based randomization sequence was generated using Stata 12.0 statistical software. After signing a consent form, patients meeting the inclusion criteria were enrolled and afterwards were assigned to a randomized study arm by opening the sealed envelopes to determine allocation. Written allocation of assignment was sealed in individual opaque envelopes marked identification numbers which were made available to allocate the target number of participants.

No systematic change in diet or physical activity habits was introduced during the study.

Measurement procedures

At inclusion (day 0) and exit visits (day 28), investigators collected blood and urinary samples for biological parameters (glycemia, serum cholesterol, serum creatinine, plasma, and urine electrolytes, urine output volume). Patients' BP was measured weekly at each visit with a semiautomatic device (Omron V6, Tokyo, Japan). The value of BP was the mean of three measurements taken 5 min apart in the morning before treatment administration after a 10 min rest, while the participant was sitting. Pulse pressure was the difference between systolic and diastolic BPs. Mean arterial pressure was the diastolic BP plus a third of pulse pressure. Baseline BP was categorized according to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure guidelines for definition of high BP. Height of all participants was measured in centimeters with the patient standing barefoot against a height scale placed vertically on the hard flat wall with base at the floor level. Body weight was measured in kilograms (0.1 kg accuracy) using a calibrated digital scale. Body mass index was categorized according to WHO cut-offs. Past or current tobacco use was defined as using tobacco in the form of smoking or chewing tobacco for at least six months in their lifetime or currently using tobacco. Fasting blood samples were obtained for measurements of glycemia, serum creatinine and electrolytes. Urinary electrolytes were measured on a 24-h collected urine sample using a HymanSyst 300 (Human Corp, France).

Galenic preparation of plants and quality control

Both plants were presented as capsules containing micronized powder of *C. micranthum* leaves (190 mg) and *H. sabdariffa* calyx (320 mg). In order to guarantee the safety, dosage and pharmacological quality, capsules containing the correct dosage of each plant (kinkeliba leaves and bissap calyx) were prepared according to European Pharmacopeia guidelines [14].

Plants parts were micronized and sifted for a maximum diameter of 500 MCM. No extraction was performed as dried plant was used in the capsules. The plants parts were analyzed according to the European pharmacopeia used for herbal medicine as powder, the requested analysis were done. *H. sabdariffa* powder was provided by Dixa AG® and *C. micranthum* was harvested in Senegal dried and then analyzed for pharmaceutical quality by Dixa AG®. Their microbial quality, pesticides contents, heavy metal content, and aflatoxins were ensured to be in accordance to European Pharmacopeia recommendations. The quality and content determination for the capsules were performed qualitatively according to the African medicinal plants pharmacopeia [7]. The chemical profile of both plants is described in the literature [6, 12] but no chemical analysis was performed.

For the purpose of blindness all capsules were made identical. Adherence to drug therapy was assessed by self-reporting from participants and by counting the number of remaining capsules in the box.

Outcome measures

Primary outcome: Change in systolic/diastolic BP between the baseline and the end of the 4-week intervention period. Normalized BP was defined as systolic BP < 140 mm Hg or diastolic BP < 90 mm Hg.
Secondary outcomes: Changes in 24h-sodium urine excretion, fasting blood glucose, and serum cholesterol between the baseline and the end of the 4-week intervention period.

Ethical issues

The study was approved by the national committee for ethics in health research of Senegal (n°346/MSAS/DPRS/CNERS). All patients had to sign a written informed consent form that was translated into local languages for their better understanding. Adverse effects reported during the study were noted, explored and managed by specialists at the university hospital of Saint-Louis. All collected data were handled and stored with a strict respect of patients' confidentiality. Patients could at any time have access to their personal data or decide to withdraw from the study without any condition.

Statistical analysis

Statistical analyses were performed using the R statistical software. Continuous and categorical variables were summarized as mean (SD) or median (IQR), or by counts and percentages as appropriate. We analyzed the primary and secondary outcomes in the intention-to-treat approach, taking into account all randomly assigned patients who took at least one dose of study drug and who had at least one BP measurement after the first dose of the drug, irrespective of protocol violations.

The mean variations in systolic BP, diastolic BP, 24-h urine sodium excretion and other biological parameters were compared using paired *t*-tests, within and between intervention groups (kinkeliba and bissap) and the control group (ramipril). Using multivariate linear regression, we have checked that age, sex, and body mass index did not influence the observed changes in BP. All statistical tests were done with a two-sided significance level of 5%.

Results

We screened 168 patients from the outpatient clinic, of whom 125 were enrolled. Among these, 42 were assigned to kinkeliba, 42 assigned to bissap, and 41 to ramipril (see Fig. 1). No patient withdrew during the 4-weeks intervention period and the completion rate was 100%. All 125 patients were included in the primary analysis and the compliance rates were high across all groups; kinkeliba (97.6%); bissap (95.2%); and ramipril (95.1%).

Table 1 Baseline characteristics of patients

	Kinkeliba group ($n = 42$)	Bissap group ($n = 42$)	Ramipril group ($n = 41$)
Clinical parameters			
Age (years)	54.7 ± 10.9 (30–79)	53.2 ± 14.3 (25–85)	56.2 ± 13.8 (28–85)
Gender (male %)	38.8%	38.1%	36.6%
Body mass index (kg/m^2)	22.10 ± 12.6 (16–33.6)	22.1 ± 4.3 (11.1–34.3)	21.81 ± 15.3 (13.7–32.9)
Systolic BP (mm Hg)	152.8 ± 8.3 (141–173)	155.4 ± 9.5 (140–172)	156.2 ± 8.2 (140–171)
Diastolic BP (mm Hg)	95.5 ± 4.3 (85–105)	95.4 ± 5.9 (82-106)	93.9 ± 3.7 (85– 100)
Pulse pressure (mm Hg)	57.4 ± 6.4 (47–71)	60.1 ± 7.7 (42–74)	62.3 ± 8.5 (46–75)
Blood parameters			
Fasting glycemia (g/l)	1.0 ± 0.1 (0.8–1.2)	0.9 ± 0.1 (0.8–1.2)	0.9 ± 0.1 (0.7–1.2)
Total cholesterol (g/l)	2.2 ± 0.3 (1.5–3.0)	2.2 ± 0.3 (1.6–3.1)	2.1 ± 0.3 (1.5–2.7)
Serum creatinine (mg/l)	9.3 ± 1.2 (6–12)	9.2 ± 1.4 (6.5–12.4)	9.1 ± 1.0 (6.2–11)
Sodium (mmol/l)	144.3 ± 3.3 (136–150.8)	141.2 ± 4.9 (131–151.5)	141.3 ± 5.6 (131.9–150)
Potassium (mmol/l)	3.9 ± 0.4 (3.11–4.8)	3.9 ± 0.5 (3.0–5.1)	4.0 ± 0.54 (3.0–5.2)
Urinary parameters			
Urine output (ml/24 h)	1473 ± 388 (850–2300)	1484 ± 477 (800–2800)	1463 ± 452 (750–2800)
Sodium (mmol/24 h)	296.3 ± 149.3 (126–754)	330.2 ± 191 (118.7–997)	360.9 ± 170 (106.5–735)
Potassium	39.8 ± 17.8 (4.32–80.9)	33.3 ± 21.5 (2.0–92.0)	42.5 ± 19.7 (11.3–83)

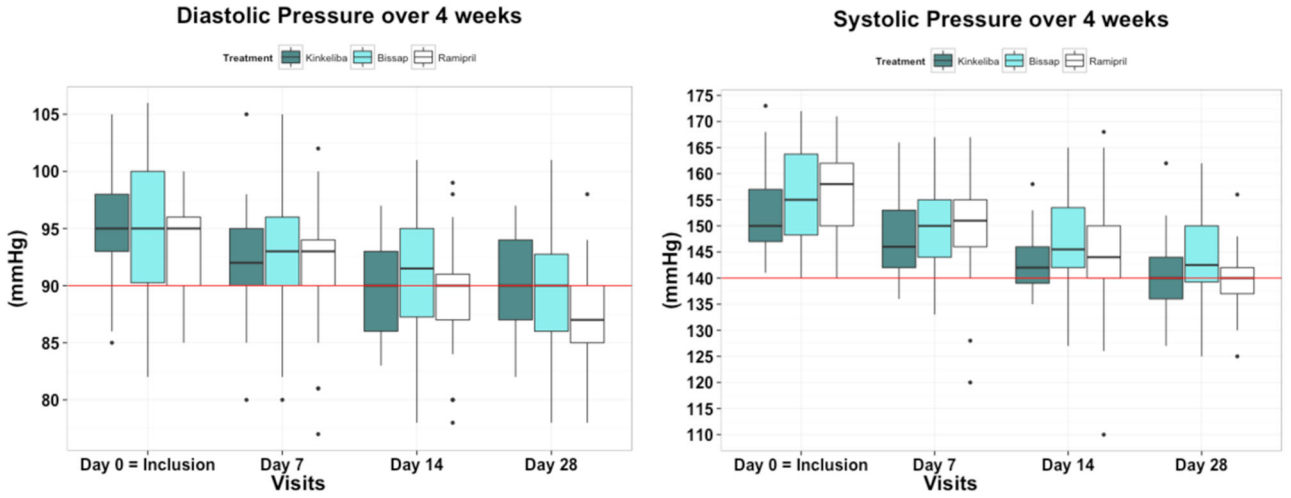

Fig. 2 Systolic and diastolic BP variation in each treatment arm

Table 2 Variation of blood and urine biochemical parameters after 4 weeks (change from baseline) with different treatments

	Kinkeliba group ($n = 42$)	Bissap group ($n = 42$)	Ramipril group ($n = 41$)	*P*-value
Blood parameters				
Fasting glycemia (g/l)	-0.06 ± 0.05*	0.20 ± 0.55*	-0.02 ± 0.14	0.09
Total cholesterol (g/l)	-0.16 ± 0.15*	0.7 ± 4.7*	-0.04 ± 0.21*	< 0.01
Serum creatinine (mg/l)	0.12 ± 1.21	-0.13 ± 0.72	0.17 ± 0.43	0.16
Urinary parameters				
Sodium (mmol/24 h)	69.3 ± 83.5	84.6 ± 232.6	-48.7 ± 85.2	0.04
Potassium (mmol/24 h)	-6.8 ± 18.8*	17.8 ± 21.3*	-2.2 ± 13.1	0.20

*Significant difference tested with *t*-test for paired samples

Baseline characteristics of patients are presented in Table 1. At inclusion, patients' demographical and clinical characteristics were comparable between the three groups. Systolic, diastolic, mean, and pulse BP were not significantly different across the three arms.

After the 4-week treatment period, BP decreased significantly in all three groups but the variations differed across groups. The mean systolic blood pressure (SBP) decreased from 156.2 to 139.5 mm Hg (reduction of 16.7 ± 8.4 mm Hg, *P*-value < 0.001), and the diastolic blood pressure (DBP) dropped from 93.9 to 87.3 mm Hg (reduction of 6.7 ± 3.6, *P*-value < 0.001) in patients from the ramipril group. The reductions in systolic and diastolic BP were significantly more important in the ramipril group as compared to the kinkeliba group where the SBP decreased from 152.4 to 140.6 mm Hg (reduction of 12.2 ± 6.6 mm Hg, *P*-value < 0.001), and the mean DBP from 95.5 to 90.4 (reduction of 5.0 ± 3.0, *P*-value < 0.001). For the bissap group, where SBP dropped from 155.5 to 144.2 mm Hg (reduction of 11.2 ± 3.3, *P*-value < 0.001) and DBP from 95.4 to 89.4 mm Hg (reduction of 6.0 ± 4.7, *P*-value < 0.001), the decrease in DBP was similar to the one observed in the ramipril group.

Also, BP changes were not identical between weeks. Figure 2 presents the weekly systolic and diastolic BP variation in each treatment arm.

At the end of the four weeks, 39% of patients in the ramipril group normalized their BP, 36.6% of those taking kinkeliba and 21.4% in the bissap group had their BP under control; 95% CIs [25.7, 54.3], [23.6, 51.9], and [11.7, 35.9], respectively.

Compared to baseline values, serum glucose and cholesterol decreased slightly but serum creatinine was stable after the 4-week treatment period (see Table 2). A significant natriuretic effect was observed in the kinkeliba and bissap groups but not in patients under ramipril treatment.

Treatment was well tolerated and no serious treatment-related adverse events were reported. Two cases of abdominal discomfort were reported with kinkeliba, one patient on bissap complained about diarrhea after the first use and two minor cases of cough related to ramipril group.

Discussion

Primary outcome: BP decrease

In the study presented here, *C. micranthum* and *H. sabdariffa* were associated with a BP reduction in non-complicated patients with hypertension, however in a significantly smaller magnitude as the standard treatment ramipril. Treatment appeared as safe and generally well tolerated.

To the best of our knowledge, this study is the first randomized clinical trial reporting the effects of kinkeliba in hypertensive patients.

Several previous small trials assessed the antihypertensive activity of *H. sabdariffa* with variable results regarding its efficacy and tolerability [12, 15–18]. The decrease in systolic BP in patients with type II diabetes and mild hypertension was also demonstrated [19]. A recent meta-analysis of randomized controlled trials including 390 individuals confirmed the antihypertensive efficacy of *H. sabdariffa* with mean reduction ranging from −5.5 mm to −9.7 mm Hg for systolic BP and from −1.9 to −5.2 mm Hg for diastolic BP [8]. These data are consistent with our results that show similar ranges in BP reduction.

Bioactivity of plants

Hibiscus sabdariffa

H. sabdariffa is a plant rich in many constituents with known activity on the cardiovascular system [20]. Its antihypertensive activity might be explained by a diuretic effect through anti-aldosterone activity [21] and by a vasodilator effect through angiotensin-converting enzyme (ACE) inhibition by anthocyanins [22]. Some experimental studies suggested that observed benefits of Hibiscus on the endothelial function are driven by its antioxidant and anti-inflammatory effects, which are more prominent than diuresis and inhibition of the angiotensin converting enzyme [12, 20].

In this study, the rapid effect of *H. sabdariffa* on BP is more in favor of a vasoactive mechanism of action. However, biological markers of renin-angiotensin-aldosterone system were not checked in our patients.

Combretum micranthum

Even though clinical studies are lacking, many ethno-botanical surveys have highlighted the use of *C. micranthum* by local populations to treat arterial hypertension [23, 24]. This plant is so widely used in African pharmacopeia that the name “kinkeliba” is synonymous with “medicine” in some African languages [11]. Kinkeliba leaves are rich in flavonoids (orientin, myricetin-3-O-glucoside, C-glycosylflavones vitexin, and isovitexin), phenols (gallic acid catechin, epicatechin, epigallocatechin), and alkaloids named kinkeloids [6, 25]. The phenolic compounds might be active on vascular endothelium via anti-inflammatory effects [26, 27].

Kinkeliba leaves may lower BP mainly through diuretic effect of some flavonoids and catechins [6, 11]. An alcohol-water extract from several Combretum species showed a dose-dependent decrease in BP and a vasorelaxant effect in animal models [28, 29].

Limitations

This study presents some limitations due primarily to its low number of patients which may limit the extrapolation of results to the general population. In addition, the lack of different doses of plants did not allow evaluating a possible dose-response effect. Higher doses of kinkeliba or bissap might induce a more pronounced decrease in BP leading to better effectiveness. In case of insufficient response, they might also be combined, as is done with standard antihypertensive drugs. Finally the 4-week follow-up is too short to give a relevant conclusion on the long-term efficacy and tolerability on patients because hypertension is a chronic disease requiring long-term drug therapy.

Conclusion

This study demonstrated the potential antihypertensive property of *C. micranthum* leaves and *H. sabdariffa* calyces. Both plants are well tolerated and induce a similar decrease in BP. However, the amplitude of BP reduction was inferior to the one obtained with ramipril treatment.

These results should be confirmed in the future by larger studies, with dosage regimens progressively increased in order to try to obtain target BP, as is usually done in clinical work. Such pragmatic trials could assess higher doses of plant treatment, within therapeutic range, and potential combinations.

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Compliance with Ethical Standards

Conflict of interest The authors declare no conflict of interest.

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