



## A systematic review with meta-analysis on the antihypertensive efficacy of Nigerian medicinal plants



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### ARTICLE INFO

#### Keywords:

Nigerian medicinal plants

Hypertension

Systolic and diastolic pressure

Preclinical studies

Clinical trials

### ABSTRACT

**Ethnopharmacological relevance:** Despite the promising effects of herbal preparations in lowering blood pressure (BP), hypertension remains a major clinical challenge in Nigeria. The BP-lowering effects of medicinal plants are due to the presence of bioactive compounds.

**Aim of the study:** This meta-analysis presents a precise estimate of the therapeutic benefits of medicinal plants utilized in Nigeria for the management of hypertension in animals and humans.

**Methods:** A systematic literature search was performed through Cochrane, PubMed, Science Direct and Scopus databases from inception until February 28, 2021 using search terms related to randomized controlled trials of Nigerian medicinal plants for hypertension. Additional studies were identified through manual search. BP was the main outcome that was measured after the intervention. Meta-analysis was performed using the Review Manager and Meta-Essential.

**Results:** Nineteen trials comprising of 16 preclinical and 3 clinical studies were enrolled for the meta-analysis. A total number of 16 plants was identified of which *H. sabdariffa* was the highest reported plant. The plant extracts significantly lowered the systolic blood pressure (SBP) and diastolic blood pressure (DBP) of the hypertensive subjects compared to control. Weighted mean difference (WMD) for SBP (-43.60 mmHg, 95% CI: -63.18, -24.01;  $p<0.0001$ ) and DBP (-29.50 mmHg, 95% CI: -43.66, -15.34;  $p<0.0001$ ) was observed for the preclinical studies. For clinical trials, the WMD was -13.98 mmHg, 95% CI: -19.08, -8.88;  $p<0.00001$  for SBP and -10.00 mmHg, 95% CI: -12.22, -7.78;  $p<0.00001$  for DBP. High heterogeneity was observed for the outcome measures of preclinical studies, but not for the clinical studies. The observed substantial heterogeneity in preclinical studies may be linked to methodological shortcomings as evidenced by the results of the risk of bias assessment. There was no evidence of publication bias in animal trials for BP using the funnel plot and Egger's regression test (SBP,  $p=0.239$  and DBP,  $p=0.112$ ).

**Conclusions:** This study provides evidence of medicinal preparations for the treatment of hypertension. A well-conducted trial with methodological rigour and a longer duration of follow-up is required for their effective clinical utilization.

**Abbreviations:** BP, blood pressure; CPT, cold pressor test; DBP, diastolic blood pressure; DF, diet formulation; DM, diabetes mellitus; DOCA, deoxycorticosterone acetate; HGE, handgrip exercise; L-NAME, N-nitro-L-arginine methyl ester; MeOH, methanol; MD, mean difference; NO, nitric oxide; OS, oxidative stress; ROS, reactive oxygen species; SD, standard deviation; SEM, standard error of the mean; SHR, spontaneously hypertensive rat; SBP, systolic blood pressure; WMD, weighted mean difference.

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<https://doi.org/10.1016/j.jep.2021.114342>

Received 9 March 2021; Received in revised form 16 April 2021; Accepted 14 June 2021

Available online 19 June 2021

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## 1. Introduction

Hypertension is a chronic disease that is a risk factor for cardiovascular and cerebrovascular diseases, resulting in clinical complications such as stroke, heart failure, metabolic syndrome and renal dysfunction (Bilbis et al., 2012; Muhammad et al., 2012; Shi et al., 2019). Obesity, physical inactivity, smoking and high salt intake are the various predisposing factors that have been implicated in the pathophysiology of hypertension. Current evidence suggests that there is a connection between hypertension and continued endothelial damage. Endothelial dysfunction is the inability of the endothelium to control vascular homeostasis that can lead to a functional imbalance in favour of vasoconstriction, pro-thrombosis and inflammation. The consequential effect of which could lead to cardiovascular diseases and complications (Roberts and Porter, 2013). Oxidative stress (OS) which is due to the excess generation of reactive oxygen species (ROS) and inflammation are the various mechanistic ways that have been implicated in the development of hypertension (Muhammad et al., 2012; Rodrigo et al., 2011). ROS is capable of diminishing nitric oxide bioavailability, a factor that plays a significant role in maintaining healthy endothelium. Therefore, treatment strategies targeting these factors could play important roles in combating complications of hypertension.

The results of our previous study support the hypothesis linking oxidative stress to hypertension (Saidu et al., 2012). In this study, formulated antioxidant-rich nutraceutical from plant sources decreased OS, increased NO bioavailability and improved the antioxidant status of hypertensive rats, leading to a significant reduction in blood pressure. This shows that plants could be explored as natural sources of bioactive compounds for the treatment of hypertension. Furthermore, these plants have been harnessed and are continually being explored for the development of pharmaceutical drugs. It is, therefore, important that research into the efficacy of these medicinal plants would help developing countries, including Nigeria to develop new and safer medicinal remedies for hypertension and other chronic diseases.

Consistent with this observation, several studies have reported medicinal herbs as therapeutics for various diseases, including hypertension (Isari et al., 2019; Kim et al., 2018). Nigeria is not left out as studies have indicated that medicinal plants are rich sources of natural bioactive substances for the treatment of diseases (Gbolade, 2012; Salihu Shinkafi et al., 2015). Despite the use of herbs as an alternative to conventional drugs for the treatment and management of hypertension, the disease is still a major health challenge in Nigeria. Medicinal plants have played a significant role in the survival benefits of hypertensive patients due to the inherent bioactive phytochemicals such as flavonoids, phenolics, minerals and vitamins that are capable of exerting therapeutic and curative effects. However, reports on meta-analysis of the efficacy of Nigerian medicinal plants for the treatment of hypertension are scarce. In this systematic review and meta-analysis, we investigated the anti-hypertensive efficacy of Nigerian medicinal plants, with a view of identifying the most used plant(s), their safety and the quality of the studies that reported the use of these plants. This study included clinical trials as well as preclinical studies that utilized plants from Nigeria for the treatment of hypertension.

### 1.1. Review questions

This meta-analysis was performed to answer the following questions related to Nigerian medicinal plants for the treatment of hypertension.

- i. Would plant extracts be effective in lowering the blood pressure of hypertensive subjects compared to control?
- ii. Would plant extracts be safe as herbal remedies for hypertension?

## 2. Methods

### 2.1. Protocol

The updated Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines were followed in conducting this systematic review (Page et al., 2021). The protocol of this study was registered in PROSPERO with registration number: CRD42021232162.

### 2.2. Literature search

Cochrane, PubMed, Science Direct and Scopus databases were searched without restriction on publication date until February 28, 2021 using the following terms: 'Nigerian medicinal plants' OR 'medicinal plants' AND 'hypertension' OR 'high blood pressure' AND 'humans' OR 'animal trials'. The eligibility studies were both clinical and preclinical studies that utilized plants sourced from Nigerian for the treatment of hypertension. Placebo or hypertensive subjects treated with the vehicle or drug were the control group. A manual search of the reference list was carried out to supplement the electronic search. Exclusion criteria were studies that used medicinal plants not sourced from Nigeria, studies without a comparator or the blood pressure parameters in the study design and studies that used Nigerian medicinal plants on disease conditions other than hypertension.

### 2.3. Outcome measures

Primary outcome measures were blood pressure (BP) parameters i.e. systolic blood pressure (SBP) and diastolic blood pressure (DBP) measured after the intervention. The secondary outcome measure was the adverse event or toxicity reported during and/or after the treatment.

### 2.4. Data extraction and synthesis

Three independent reviewers (SAM, MAA & YS) retrieved the data from the included studies using a predefined extraction spreadsheet and disagreements were resolved through discussion and consensus or by a third reviewer (ABS/AAA/MAT/JM). The details extracted from the studies include authors' name, year of publication, age, sex, weight, type of plants, extraction solvent, dose, route of administration, duration of the study, sample size, induction agent for preclinical studies, sample size estimation and power analysis. Data for studies with more than one dose, plant extract or model (preclinical) were combined and the average was used for the meta-analysis. Quantitative data such as mean and standard deviation (SD) or standard error of the mean (SEM) presented in figures were extracted using a highly magnified image software (GetData Graph Digitizer, Version 2.26). SEM was converted to SD using the following formula:  $SD = SEM \times \sqrt{n}$ , where n is the number of subjects.

## 3. Methodological quality assessment

Cochrane risk of bias tool for randomized controlled trials was used to assess the risk of bias and was evaluated by three independent reviewers (SAM, YS & AH). Disagreements were resolved by consensus or by consulting a third reviewer (MYG/AI/MB/SLP). The following domains: selection bias, performance bias, detection bias, attrition bias, reporting bias and other bias were assessed and rated as low, high or unclear risk of bias.

### 3.1. Data analysis

A random-effects model was used for the meta-analysis of the primary outcome measures and heterogeneity was assessed with the  $I^2$  statistic. The mean effect size, 95% CI, forest plot and significance were assessed using the inverse-variance method. Mean difference (MD) was

used for the analysis of SBP and DBP. Values of  $I^2$  greater than 75% was regarded as high heterogeneity. To evaluate the potential source of heterogeneity and strength of the result, a subgroup and sensitivity analysis were performed. Only groups with  $n \geq 2$  were included in the subgroup analysis. Meta-analysis was performed using the Review Manager (version 5.3), whereas Meta-Essential was used for Egger's regression test.

### 3.2. Publication bias

Publication bias was assessed using a funnel plot. Egger's regression asymmetry was also performed to confirm the results of the funnel plot as previously reported (Egger et al., 1997).

## 4. Results

### 4.1. Selection of studies

A total of 1622 studies was identified from Cochrane, PubMed, Science Direct and Scopus databases. Additional 23 studies were identified through manual search. The full-text articles assessed for eligibility were 35. Out of 35 eligible articles, 28 (23 preclinical and 5 clinical studies) met the inclusion criteria and were included in the review. The remaining 7 articles were excluded due to the following reasons; Plant not sourced from Nigeria or no detail ( $n=2$ ), diabetes mellitus ( $n=1$ ), not plant extract ( $n=2$ ) and no BP parameters ( $n=2$ ). The description of the search strategies is presented in Fig. 1.

### 4.2. Depiction of study characteristics

The characteristics of included studies showed that different plant extracts were used for the intervention and these are depicted in Table 1. In this systematic review, 19 out of the 28 studies that met the inclusion criteria were enrolled for the meta-analysis involving 16 preclinical and 3 clinical studies. The total number of plants utilized were 16 from both the animal and clinical studies.

### 4.3. Preclinical studies

The results of the animal studies indicated that *H. sabdariffa* was reported in 4 studies (Balogun et al., 2019; Mojiminiyi et al., 2007, 2012; Onyenekwe et al., 1999), 3 studies were on *Z. officinale* (Akinyemi et al., 2016a, 2016b; Tende et al., 2015), 2 studies each used

*P. Americana* (Imafidon and Fabian, 2010; Nwaefulu et al., 2009), *C. longa* (Akinyemi et al., 2016a, 2016b), *V. doniana* (Ladeji et al., 1996; Ogbeche et al., 2001), and *A. sativum* (Nwokocha et al., 2011; Tende et al., 2015). *M. cecropioides* (Adeneye et al., 2006), *B. coccineus* (Akindede et al., 2014), *V. album* (Eno et al., 2004), *P. amarus* (Amaechina and Omogbai, 2007), *M. flagellipes* (Jovita et al., 2017), *E. camaldulensis* (Nwaogu et al., 2018), *N. latifolia* (Nworgu et al., 2008), *L. bengwensis* (Obatomi et al., 1996), *P. curatellifolia* (Omale et al., 2011), *V. amygdalina* (Oyema-Iloh et al., 2018) and *E. guineensis* (Nkanu et al., 2019) were each reported in 1 study. The part of the plants used for extraction includes leaf, root, calyx, stem bark, rhizome and bulb, respectively. Water (18 studies) was the most reported solvent that was used for the extraction, followed by ethanol (3 studies), then methanol (2 studies) and 1 study reported hydro-ethanol as the extraction solvent. The duration of studies varies across the studies, ranging from a minimum of 8 days to a maximum of 18 weeks. Similarly, the dose administered to the animals differs across the studies. The dosage range was between 0.0005 and 1000 mg/kg body weight. Different strategies were employed in the induction of hypertension. It was observed that 8% salt, N-nitro-L-arginine methyl ester (L-NAME) (40 and 50 mg/kg), 35% ethanol, 7% sucrose and 15 mg of deoxycorticosterone acetate (DOCA) were the various inducing agents used for the induction of hypertension. Nephrectomy was also reported as the induction strategy. The summary of study characteristics is depicted in Table 1.

### 4.4. Clinical studies

The results of clinical trials (Table 1) showed that the extract from *H. sabdariffa* was reported in 4 (Aliyu et al., 2014; Nwachukwu et al., 2015a, 2015b, 2017) out of the 5 studies included in this meta-analysis, whereas *P. americana* was reported in 1 study (Olaniyan, 2014). Four studies reported water as the solvent for extraction and the fifth study adopted a crushing strategy to release the liquid from the leaf for administration. The minimum dosage was 15 mg/kg, whereas 150 mg/kg was the maximum reported dose for the administration to the subjects. Calyx and leaf were the parts of the plant utilized for the extraction of bioactive compounds.

### 4.5. Risk of bias assessment

The methodological rigour of the included studies was evaluated using the Cochrane risk of bias tool for randomized controlled trials (Higgins et al., 2011). The overall risk of bias of the included studies ranges from moderate to high risk of bias, as most of the important details were not reported in the included studies. It was observed that only a few studies mentioned the randomization of subjects without giving details. Furthermore, the allocation concealment, incomplete outcome data, selective reporting and other risks of bias domains were judged as low and unclear in most of the included studies because the details required for these domains were reported. However, domains of blinding of participants and outcome assessment were rated as high risk of bias in almost all the included trials, as the details for these domains were not reported. Only one study reported sample size estimation and power analysis (Nwachukwu et al., 2015a). The risk of bias of individual studies of preclinical and clinical trials is shown in Fig. 2a–b, whereas the overall risk of bias of the domains assessed is depicted in Fig. 3a–b.

### 4.6. Systolic and diastolic pressure

#### 4.6.1. Preclinical trials

The result of the effect of medicinal plant extract on SBP was reported in 16 studies, involving 202 animals (Fig. 4a). When the hypertensive animals were treated with the extract, a significant reduction in SBP was observed in favour of the treated group with MD of  $-43.60$  mmHg, 99% CI:  $-63.18$ ,  $-24.01$ ;  $p < 0.0001$ . However, significant heterogeneity was observed across the studies ( $I^2 = 99\%$ ;  $p < 0.00001$ ),

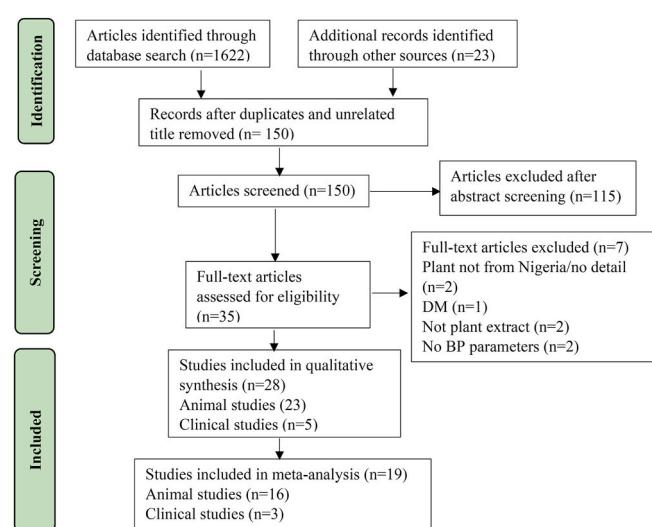


Fig. 1. Flow chart of the trial search process. DM-diabetes mellitus, BP – blood pressure.

**Table 1**

Characteristics of included studies.

Author & Year	Plant type & part	Solvent for extraction	Age/weight/sex	Induction agent/specie	Dose & treatment route	Sample size	Duration of the study
<b>Preclinical studies</b>							
Adeneye et al. (2006)	<i>M. cecropioides</i> /stem bark	Water/hot	10–12 wk/ 150–200 g/M & F	Rat	0.0005–0.05 mg/kg/ IV	30	–
Akindele et al. (2014)	<i>B. coccineus</i> /leaf	Hydro-ethanol/cold	150 g/M & F	35% ethanol & 5–7% sucrose/rat	100, 200, 400 mg/kg/Oral	66	8 wk
Akinyemi et al. (2016a)	<i>Z. officinale</i> & <i>C. longa</i> / rhizome	–	200–300 g/M	40 mg/kg l-NAME/rat	4% DF/oral	70	13 wk 3 d
Akinyemi et al. (2016a)	<i>Z. officinale</i> & <i>C. longa</i> / rhizome	–	200–300 g/M	40 mg/kg l-NAME/rat	4% DF/oral	70	24 d
Amaechina & Omogbai (2007)	<i>P. amarus</i> /leaf	Water/hot	1.2–2 kg	Rabbit	5–80 mg/kg IV	–	–
Anaka et al. (2009)	<i>P. americana</i> /seed	Water/cold	235–285 g/M	Rat	240, 260, 280 mg/kg/oral	10	10 d
Balogun et al. (2019)	<i>H. sabdariffa</i> /leaf	Water/hot	10–12 wk/196.5 ± 2.93 g/M	8% salt/rat	100, 200 & 400 mg/kg/oral	25	6 wk
Eno et al. (2004)	<i>V. album</i> /leaf	Water/hot	200–250 g/M	15 mg/100g DOCA/rat	5–160 mg/kg/IV	10	6 wk
Etah et al. (2019)	<i>E. guineensis</i> /oil	–	180–250 g/M	Rat	15% oil	60	18 wk
Imafidon & Amaechina (2010)	<i>P. Americana</i> /seed	Water/cold	–	8% salt/rat	200, 500, 700 mg/kg	30	4 wk
Jovita et al. (2017)	<i>M. flagellipes</i> /seed	Ethanol/hot	100–200 g/M	Rat/8% salt +1% salt in water	25, 50, 100 mg/kg/ oral	30	3 wk
Ladeji et al. (1996)	<i>V. doniana</i> /stem bark	Water/cold	250–300 g/F	Rat	200–800 mg/kg/oral & IV	24	–
Mojiminiyi et al. (2007)	<i>H. sabdariffa</i> /calyx	Water/hot	208.2±8.2 g/M	8% salt & 50 mg/kg L-NAME/rat	1–125 mg/kg/IV	18	–
Mojiminiyi et al. (2012)	<i>H. sabdariffa</i> /calyx	Water/hot	112–140 g	8% salt/rat	6 mg/ml	40	12 wk
Nwaogu et al. (2018)	<i>E. camaldulensis</i> /stem bark	MeOH/cold	180–250 g/M & F	8% salt/rat	50, 100, 200 mg/kg/ oral	30	7 wk
Nwokocha et al. (2011)	<i>A. sativum</i> /bulb	Water/cold	150–180 g/5–7 wk/M	2 kidney, 1-clip model/rat	20 mg/ml/IV	12	–
Nworgu et al. (2008)	<i>N. latifolia</i> /root	Ethanol/hot	180–250 g/M	Nephrectomy	2.5–20 mg/kg IV	20	–
Obatomi et al. (1996)	<i>L. bengwensis</i> /leaf	Water/hot	230 g	SHR	Oral	–	8 d
Ogbuche et al. (2001)	<i>V. doniana</i> /seed	Water/cold	200–250 g	SHR	200, 400, 800 mg/kg Oral & IV	48	8 d
Omale et al. (2011)	<i>P. curatellifolia</i> /bark	Ethanol/hot	–	Cat	1 mg/ml/IV	–	–
Onyema-Iloh et al. (2018)	<i>V. amygdalina</i> /leaf	MeOH/cold	120–160 g/M	8% salt/rat	200, 400 mg/kg/oral	40	8 wk
Onyenekwe et al. (1999)	<i>H. sabdariffa</i> /calyx	Water/hot	–	SHR	500, 1000 mg/kg/ Oral	30	8 wk
Tende et al. (2015)	<i>A. sativum</i> & <i>Z. officinale</i> / rhizome & bulb	Water/cold	12–16 wk/ 150–200 g	Cat	0.1–20 mg/ml/IV	4	–
<b>Clinical studies</b>							
Aliyu et al. (2014)	<i>H. sabdariffa</i> /calyx	Water/hot	29.9±1.6 yr/ 67.3±2.7 kg	CPT/HGE (Sokoto)	15 mg/kg/oral	20	2 h
Nwachukwu et al. (2015a)	<i>H. sabdariffa</i> /calyx	Water/hot	31–70 yr	Hypertensive patient (Enugu)	150 mg/kg Oral	75	5 wk
Nwachukwu et al. (2015b)	<i>H. sabdariffa</i> /calyx	Water/hot	M & F	Hypertensive patient (Enugu)	150 mg/kg/oral	90	4 wk
Nwachukwu et al. (2017)	<i>H. sabdariffa</i> /calyx	Water/hot	35–68 yr/M & F	Hypertensive patient (Enugu)	150 mg/kg oral	75	4 wk
Olaniyan (2014)	<i>P. Americana</i> /leaf	Crushing	≥45 yr/M & F	Hypertensive patient (Oke-Ogun, Oyo)	60 ml/d	50	–

CPT- Cold pressor test, d-day, DF-diet formulation, DOCA-deoxycorticosterone acetate, F-female, HGE-handgrip exercise, L-NAME- N-nitro-L-arginine methyl ester, M-male, MeOH- methanol, SHR-spontaneously hypertensive rat, wk-week.

suggesting there was a variation in the outcome measures between studies. Treatment of the animals with the extract also reduced DBP ( $-29.50 \text{ mmHg}$ , 95 CI:  $-43.66$ ,  $-15.34$ ;  $p<0.0001$ ) with substantial heterogeneity between the studies ( $I^2 = 98\%$ ;  $p<0.00001$ ). The number of studies included in the analysis was 14 studies that utilized 81 animals (Fig. 4b).

#### 4.7. Clinical studies

The effects of plant extract on SBP and DBP on hypertensive subjects are presented in Fig. 5a and b. Three studies that used extracts from *H. sabdariffa* were enrolled for the meta-analysis, involving 140 subjects. Treatment of hypertensive patients with the extract of *H. sabdariffa*

significantly reduced SBP compared to control subjects ( $-13.98 \text{ mmHg}$ , 95 CI:  $-19.08$ ,  $-8.88$ ;  $p<0.00001$ ) with non-significant heterogeneity ( $I^2 = 55\%$ ;  $p=0.11$ ) between the studies. Similarly, *H. sabdariffa* significantly reduced DBP of hypertensive subject when compared with control subjects ( $-10.00 \text{ mmHg}$ , 95 CI:  $-12.22$ ,  $-7.78$ ;  $p<0.00001$ ) with homogeneity ( $I^2 = 0\%$ ;  $p=0.40$ ) between studies. A subgroup analysis was not performed for clinical studies because there was a similarity in outcome measures between the included studies.

#### 4.8. Adverse event

This outcome was planned a priori as the secondary outcome measure. The results showed that the plant extracts were safe as no cases of

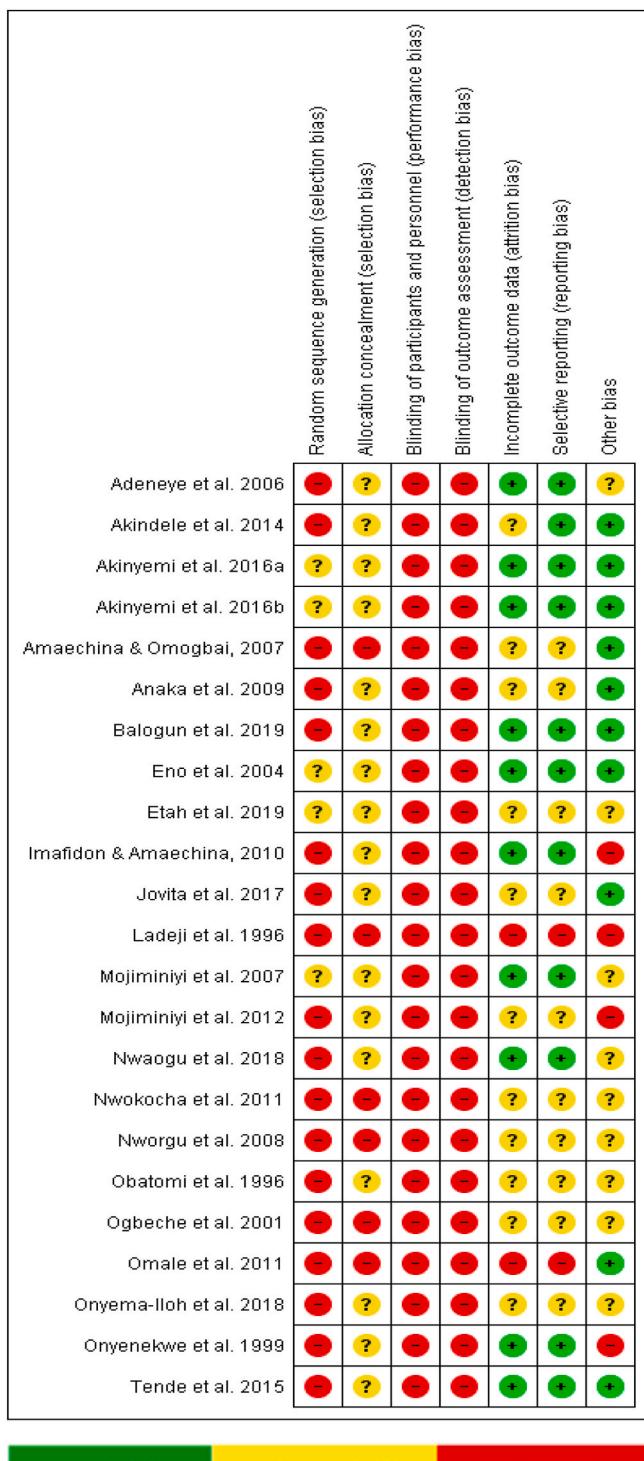


Fig. 2a. Risk of bias assessment in individual preclinical trials.

adverse effect was reported except one study that recorded mortality at a higher dose of the extract (Onyenekwe et al., 1999).

#### 4.9. Subgroup and sensitivity analyses

We performed subgroup analyses for preclinical studies to determine the source of heterogeneity observed for the outcome measures. The studies were stratified into plant type and duration of follow-up. For the type of plant, the studies were subgrouped into 2 (*H. sabdariffa* and

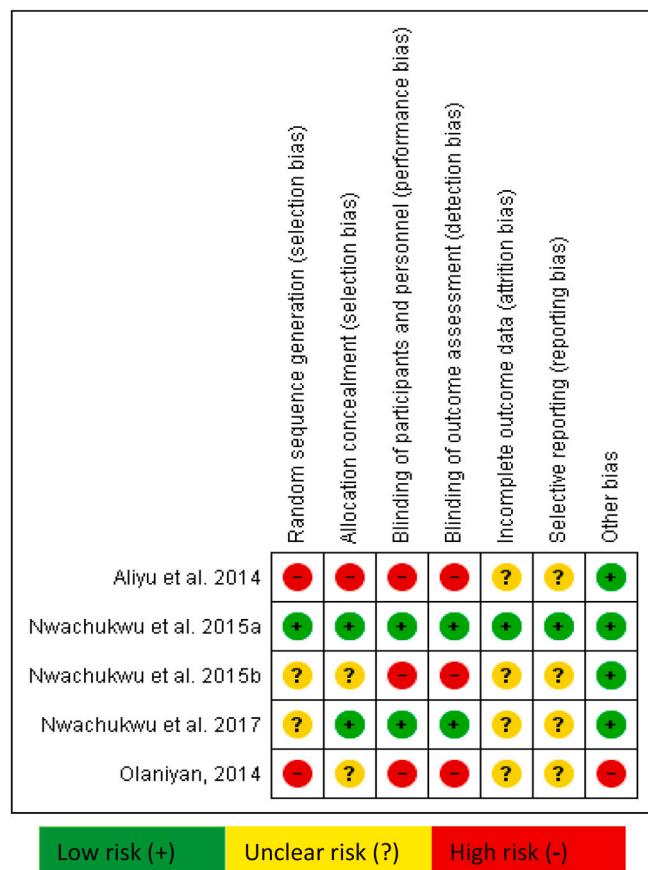


Fig. 2b. Risk of bias assessment in individual clinical trials.

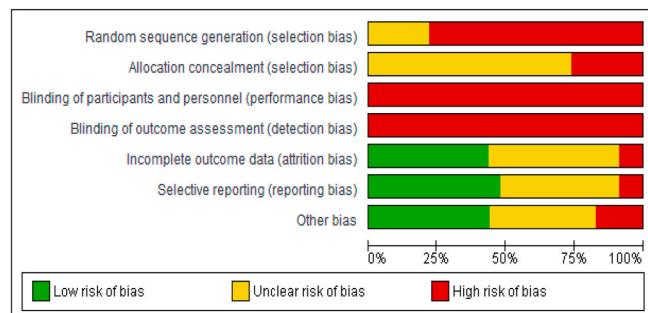
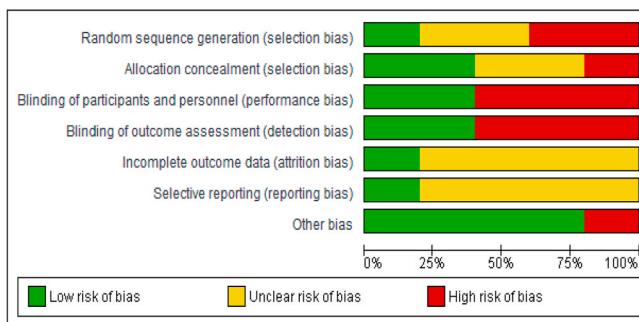
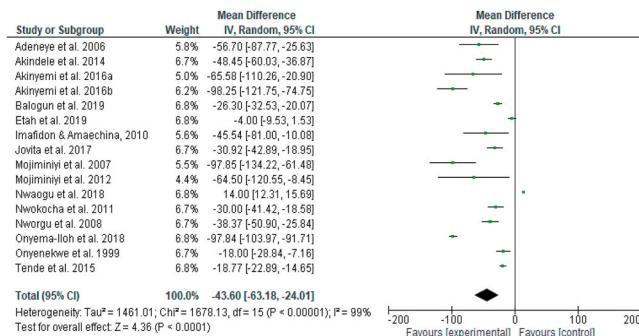


Fig. 3a. Risk of bias item presented as percentages across the preclinical trials.

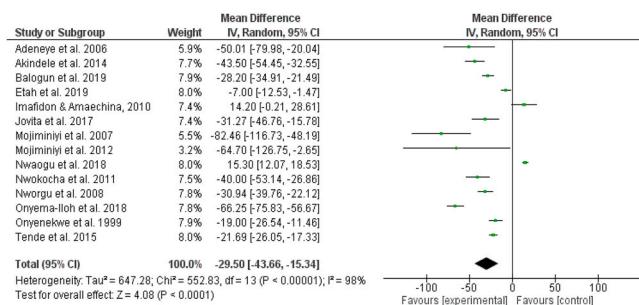
*Z. officinale/C. longa*) (Fig. 6a). The result of SBP showed a significant effect size with high heterogeneity between the studies ( $I^2 = 84\%$ ;  $p<0.0003$ ) for *H. sabdariffa*. Similarly, there was significant heterogeneity for DBP of *H. sabdariffa* subgroup ( $I^2 = 81\%$ ;  $p<0.001$ ) (Fig. 6b). Furthermore, a non-significant heterogeneity ( $I^2 = 38\%$ ;  $p=0.20$ ) on the effect of *Z. officinale/C. longa* on SBP was observed (Fig. 6a). However, there was no subgroup analysis on DBP for the *Z. officinale/C. longa* subgroup because of a lack of sufficient data. The results of the duration of the follow-up subgroup, which was stratified into  $\leq 4$  and  $\geq 4$  weeks showed a huge variation on both the SBP (Fig. 6c) and DBP (Fig. 6d) parameters, suggesting this subgroup did not have an effect on the variation observed on the outcome measures. To ascertain the robustness of the estimated pooled effect size of the outcomes, we also



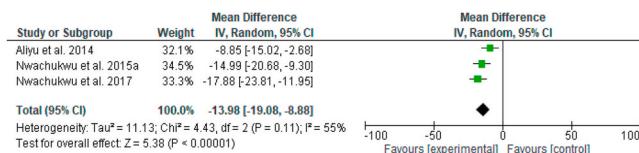
**Fig. 3b.** Risk of bias item presented as percentages across the clinical studies.



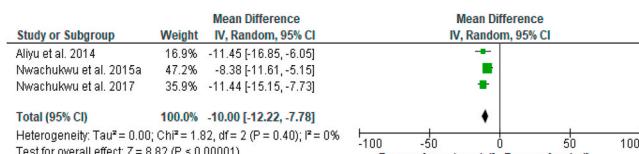
**Fig. 4a.** Change in systolic blood pressure after intervention with the plant extract in animal trials.



**Fig. 4b.** Change in diastolic blood pressure after intervention with the plant extract in animal trials.



**Fig. 5a.** Effect size of intervention on systolic blood pressure in clinical trials.



**Fig. 5b.** Effect size of intervention on diastolic blood pressure in clinical trials.

performed a leave-one-out analysis to determine the source of heterogeneity observed between the studies. This was done by continually removing one study at a time and recalculating the effect size of the residual studies. It was observed that the heterogeneity was not considerably changed for both SBP and DBP, suggesting that the variations between studies were not driven by any single study.

#### 4.10. Publication bias

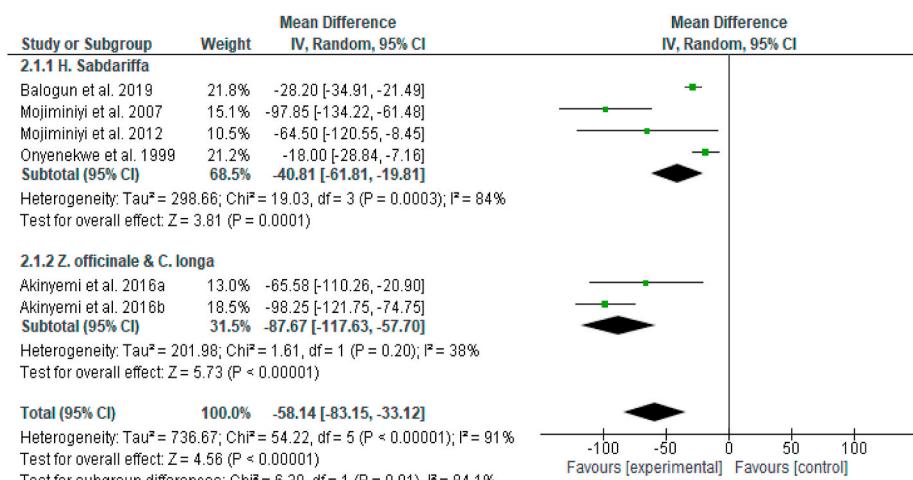
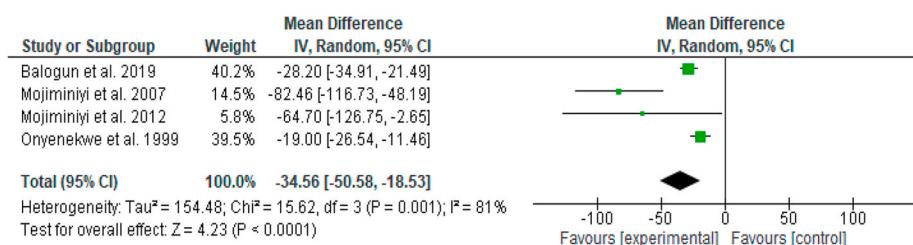
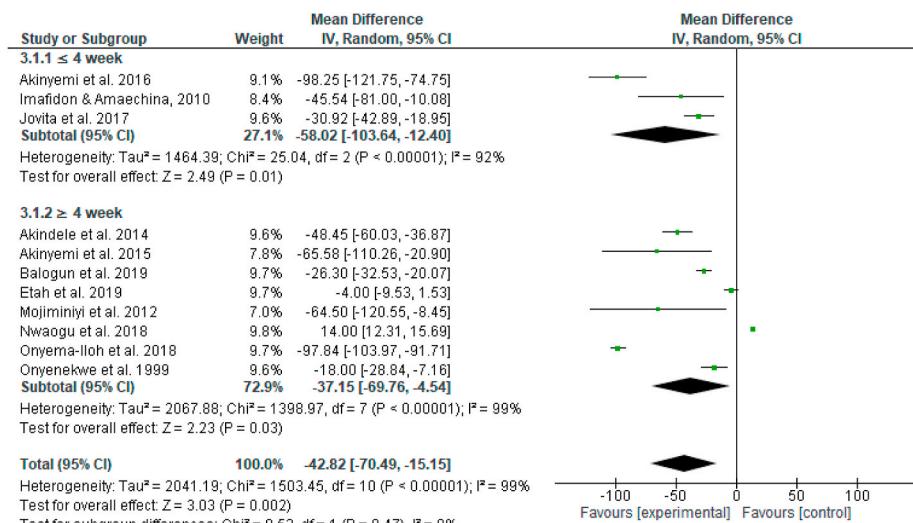
The publication bias was evaluated with a funnel plot and Egger's regression test. Visual inspection of the funnel plots of both the SBP (Fig. 7a) and DBP (Fig. 7b) suggest no evidence of publication bias and this was confirmed by Egger's regression asymmetry. Results of Egger's regression test also showed no evidence of publication bias for SBP ( $p=0.239$ ) and DBP ( $p=0.112$ ) in animal trials. According to Sterne et al., (2011) at least 10 studies are required to detect the real chance of asymmetry and as such publication bias was not performed for the clinical studies.

## 5. Discussion

In developing countries, a large percentage of the population relies on herbal medicines for primary health care. The use of herbs or ethnobotanicals as medicinal products is not only restricted to developing countries as the industrialized nations have also developed interests in natural therapies (Wachtel-Galor and Benzie, 2011) because of their relative safety. The safety and efficacy of medicinal plants have been evaluated in several studies, ranging from animal to clinical trials. Therefore, this meta-analysis was conceived to assess the pooled effect size of various plants that have been tested for the treatment of hypertension in Nigeria. The primary outcome measures were the SBP and DBP measured after the intervention, whereas safety was the secondary outcome measure.

The result showed that the treatment of hypertensive subjects with the plant extracts significantly reduced the SBP and DBP in both animal and clinical studies. However, substantial heterogeneity was observed in the animal studies, whereas a low heterogeneity was observed for the outcome measures of clinical trials. The study revealed that extract from 16 different plants were utilized for the intervention in the trials with *H. sabdariffa* being the highest number of plant extract. Secondary metabolite such as phenolic, flavonoid, alkaloid, vitamins and others are the various bioactive compounds that are responsible for the observed therapeutic effects of the extract. Consistent with this observation, various studies have shown that these bioactive compounds are capable of lowering platelet aggregation, increase endothelium nitric oxide and decrease oxidation of low density lipoproteins that are implicated in the pathogenesis of hypertension (Apostolidou et al., 2015; de Figueiredo et al., 2017; Luciano et al., 2011). We are not able to summarize the safety outcome measure of the extracts because of a lack of meaningful data. Although one study reported mortality at a higher dose of the extract, the overall results of the included studies showed that the plant extracts seem not causing adverse events or toxicities. Therefore, the results of this meta-analysis demonstrate the efficacy and safety of these medicinal plants in lowering blood pressure, indicating they can be harnessed for the treatment of hypertension.

The methodological quality of the included studies showed that some key elements were not reported, especially in animal studies. This observation could be responsible for the high heterogeneity observed in the outcome measures of these preclinical trials. Of all the studies included in this systematic review, only one clinical trial reported a priori sample size and power estimation. The study design in preclinical trials has been faced with some methodological flaws over the years, and this poses a threat to internal validity, which substantially affects the translation to clinical trials. Therefore, effort must be geared towards improving preclinical experimental design with methodological rigour that would limit the threat to internal validity for effective translation to

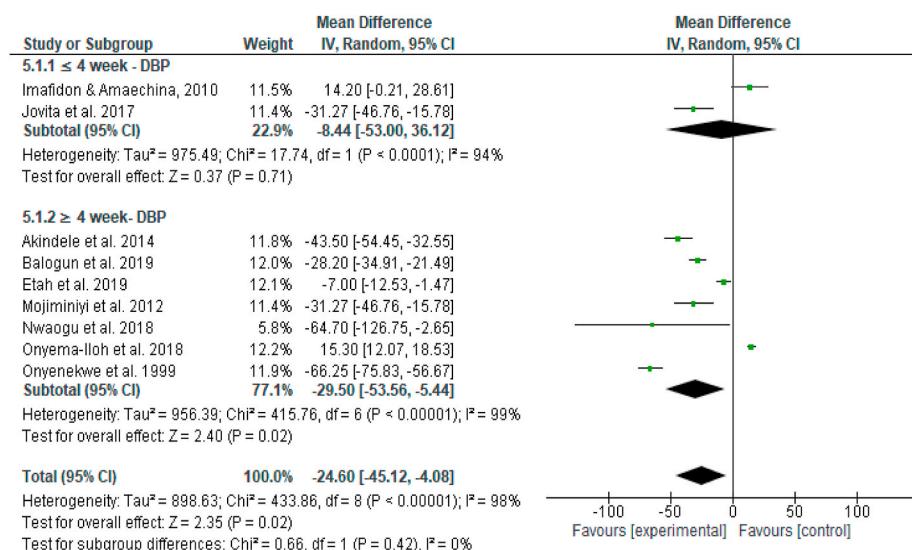
**Fig. 6a.** Preclinical subgroup of plant type on systolic blood pressure.**Fig. 6b.** Preclinical subgroup of plant type on diastolic blood pressure.**Fig. 6c.** Preclinical subgroup of the duration of follow-up on systolic blood pressure.

human studies.

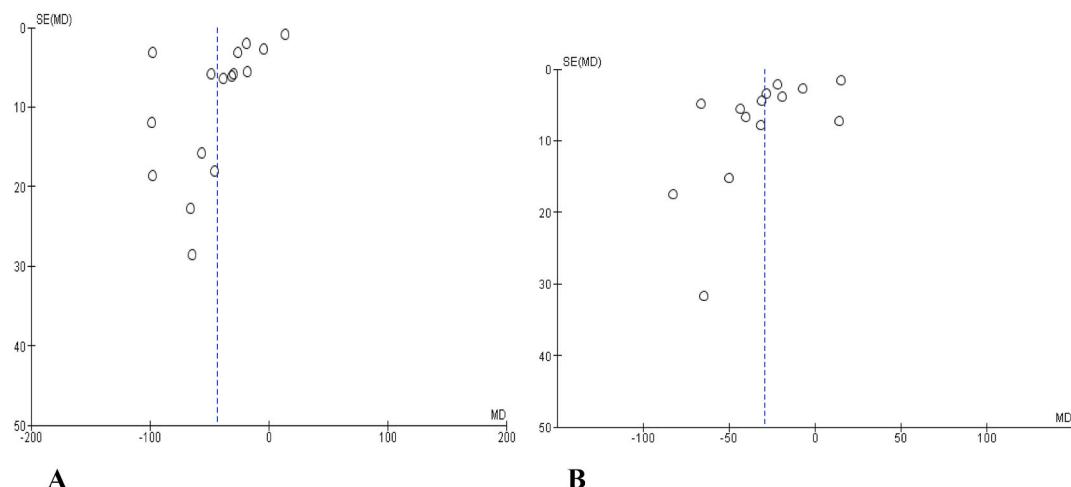
Due to the high heterogeneity of the animal trials, we conducted subgroup and sensitivity analyses of the outcome measures to determine the strength of our results. The subgroup analyses of plant type and duration of follow-up were conducted for the blood pressure. It was observed that the overall results of subgroup analyses did not help in detecting the source of heterogeneity. However, we did not conduct a subgroup analysis on the dose, age and gender planned a priori due to limited data to warrant the analysis. Similarly, a sensitivity analysis was performed and the results indicated that the heterogeneity was not driven by any single study.

The results of the funnel plot and Egger's regression asymmetry indicates no evidence of publication bias for the two outcome measures. Taken together, this systematic review and meta-analysis present a pooled effect size of the effectiveness of medicinal plant extracts in lowering blood pressure of hypertensive subjects without any significant adverse consequences. To the best of our knowledge, this is the first meta-analysis of preclinical and clinical studies addressing the efficacy of Nigerian medicinal plants for hypertension.

The positive findings of this meta-analysis should be interpreted in light of the following limitations. First, the analysis of animal studies had high heterogeneity between the studies and we were not able to



**Fig. 6d.** Preclinical subgroup of the duration of follow-up on diastolic blood pressure.



**Fig. 7.** Funnel plot for changes in blood pressure. (a) Systolic blood pressure (b) Diastolic blood pressure. The results suggest no evidence of publication bias for both outcome measures. MD-mean difference, SE-standard error.

detect the source of the variations despite the sensitivity and subgroup analyses. This suggests that the studies have methodological weakness. However, the results of human studies, although, very small in number had shown low variation for SBP and homogeneity for DBP. Another limitation of this current meta-analysis is that the study included is limited to plant extracts sourced from Nigeria, which may introduce selection bias and this may limit the generalization of evidence. However, strong methodological rigour as seen largely in clinical studies may not limit the generalization of the results as the studies can be reproduced. Lastly, the studies were based on the crude extracts and this may hinder the delineation of the exact mechanism(s) of their action in lowering the blood pressure. Nevertheless, since the crude extracts are a combination of different bioactive compounds could be acting in a concerted manner to target different pathways that have been implicated in the pathophysiology of hypertension.

### 5.1. Future directions

A favourable clinical outcome was observed following intervention with the extracts; however, more studies are required to isolate and characterize the active ingredient(s) responsible for the BP-lowering effect. This would allow an insight into the mechanisms of action of

the bioactive constituents present in the extracts. A large randomized clinical trial with the extracts, particularly the *H. sabdariffa* that have shown promising results in human studies would guarantee the effective clinical acceptance of this herb for the treatment and management of hypertension. Clinical trials should be extended to other plant extracts with methodological rigour to assess their efficacy in the treatment of hypertension. Furthermore, standardizing the dosage of these extracts are important determinants for their efficacy and safe clinical application. Considering all these would provide evidence of the therapeutic importance of ethnobotanical to combat hypertension and other related diseases.

### 6. Conclusions

Herbal therapies hold promising effects in lowering the BP of hypertensive subjects. This meta-analysis provides evidence of medicinal herbs in the treatment of hypertension. The preclinical studies had methodological shortcomings that required improvements that would allow standardization of these herbal preparations for effective clinical translation to treat hypertension. Even though *H. sabdariffa* improved the clinical outcome of hypertensive patients, the number of studies is small, hence large clinical trials with longer duration of follow-up are

necessary for effective clinical utilization of these herbal remedies for hypertension.

## Authors' contribution

Conceptualization: SAM, MAA, YS. Fund acquisition: MAA, YS, ABS, AAA, MAT, AH, MYG, JM. Data curation: SAM, YS. Data analysis and interpretation: SAM, YS, MAA. Writing-original draft: SAM, YS. Writing-review & editing: MAA, ABS, AAA, MAT, AH, MYG, AI, MB, JM, SLP. SAM, MAA & YS screened the articles & extracted data. ABS, AAA, MAT & JM resolved disagreement in article inclusion and data extraction. SAM, YS & AH evaluated the risk of bias. MYG, AI, MB & SLP settled disagreement in the risk of bias assessment. All authors read and approved this final version of the manuscript.

## Declaration of competing interest

The authors declare that they have no conflicts of interest.

## Acknowledgements

This research work was supported by a grant from the Tertiary Education Trust Fund, Nigeria with grant number: TETFUND/DR&D/CE/NRF/STI/30/Vol1.

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