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Effect of multi-component water-based herbal nutritional supplement in hypertension management

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Abstract

Hypertension (HTN) prevalence in India now estimated at 29.8%. HTN accounts for 57% of all stroke deaths and 24% of all coronary heart disease (CHD) deaths in India. The present study aims to determine the effect of a multi-component water extract on systolic and diastolic blood pressure levels in hypertensive subjects and corresponding lowering of cardio vascular risk factors. The components of the herbal water extract were Black Cumin, Cinnamon, Turmeric, Ginger, Cardamom, Nutmeg, Clove, Guava Leaves, Flax Seeds, Cumin, Fenugreek, Fennel Seeds, and Licorice. A single-center, prospective, open-labeled, non-interventional, observational study was performed with 50 hypertensive subjects for 180 days. Five visits with intermediary evaluations on the 30th and 90th day were carried out. The systolic and diastolic blood pressure, C-reactive protein (CRP), HbA1c were monitored. Significant and gradual decrease (average of 48 mm Hg) in systolic blood pressure (SBP), a decrease (average of 34 mm Hg) in diastolic blood pressure (DBP), and a reduction (average of 9.1%) in C-reactive protein (CRP) were observed after 180 days. All 50 subjects in the study have shown reduction in SBP and DBP with minimum reduction of 29 mm Hg and 17 mm Hg by day 180 versus baseline values respectively. The findings are independent of their medication/s profile with anti-hypertensive drugs. The herbal extract is effective in reducing the SBP and DBP of all the subjects when administrated as an adjuvant therapy.

Keywords: hypertension, systolic BP, diastolic BP, C-reactive protein, herbal extract, adjuvant therapy

1. Introduction

Hypertension (HTN) a major risk factor for development of stroke, heart disease, heart failure, and renal disease in India and throughout the world. According to a 2020 ecological study among 182 countries, the prevalence of HTN ranged from 13% to 41% ^[1]. The fourth national family health survey evaluated hypertension in a large population-based sample (n=799,228) in India and reported HTN in 13.8% men vs. 8.8% women (overall 11.3%) aged 15–49 and 15–54 respectively ^[2].

The European guidelines ^[3] retain the previous definition of hypertension (i.e., BP >140/90 mm Hg) whereas the American guidelines ^[4] lowered the threshold. But overall, the guidelines define hypertension when systolic blood pressure (SBP) is \geq 140 mm Hg and/or their diastolic blood pressure (DBP) is \geq 90 mm Hg after repeated examination. Many factors such as genetics, obesity, life style patterns and diet are considered as risk factors for development of HTN. The treatment protocols are dependent on the degree of hypertension and presence of comorbidities such as Diabetes mellitus, stroke, Chronic kidney disorder and coronary artery disease. The treatment also needs stress alleviation, dietary and lifestyle changes to get more effective control of the disease.

Various multidirectional approach and multiple drug combinations includes angiotensin receptor blockers (ARB); calcium channel blockers (CCB); beta-blockers (BB); and diuretics (DU) ^[5] which are routinely administered for treatment of HTN as the control of HTN is difficult and often requires trials of various combination and doses of drugs to suit an individual requirement. About 70% of hypertensive subjects require the combinations of at least two antihypertensive agents to achieve recommended goals. The use of combinations of drugs allows for action on several different mechanisms to control the HTN. In a meta-analysis of 42 clinical trials, it was found that by combining two drugs with different mechanisms of action, an antihypertensive effect of approximately two to five times greater than that obtained by monotherapy is possible ^[6,7]. Increasing the dose of monotherapy reduces coronary events by 29% and cerebrovascular events by 40%, while combining two antihypertensive agents with a different mechanism of action reduces coronary events by 40% and cerebrovascular events by 54% ^[8].

Medicinal plant products may play a major role in the prevention and treatment of HTN and act as simple adjuvants to HTN therapy thereby reducing dosage and adverse effects of hypertension apart from playing a role in cutting the costs of therapy ^[9].

Corresponding Author: Dr. CS Janaki Bhaarath Medical College, Selaiyur, Tambaram, Chennai, Tamil Nadu, India In view of this, we evaluated an antihypertensive nutritional supplement (HNS) for managing HTN. The supplement is in an aqueous format and is composed of spices and herbs used in day-to-day preparation of Indian Asian culinary preparations. We conducted a study to evaluate the efficacy and safety of this antihypertensive nutritional supplement in hypertensive subjects.

2. Material and Methods 2.1 Study design

The current study was a single-center, prospective, openlabeled, non-interventional, observational study conducted for 6 months (i.e., 180 days). Ethics committee approval was obtained from the Vijaya Hospital, SPSR Nellore District, Andhra Pradesh, India before the initiation of the clinical trial. The study was performed following the principles of "The Declaration of Helsinki" (World Medical Association) and Good Clinical Practice (GCP) Guidelines issued by the Indian Council of Medical Research (ICMR) & Drugs Controller General of India (DCGI). The nature and proposal of the study design (aims, methodology, potential risks, and anticipated benefits) and participation in the study were fully explained to each subject and written consent was obtained prior to entering the study. The trial was registered on the clinical trial registry of India (CTRI) website at http://ctri.nic.in/ (CTRI number: CTRI/2020/04/024646). The total 5 phases of clinical trials are Phase 0- Screening Visit 0 (day 0); Phase 1-Enrolment Visit I (day 2); Phase 2- Initial follow-up Visit I (day 0 to day 30); Phase 3- Mid follow-up Visit III (day 0 to day 90); and Phase 4- End of Study Visit IV (on day 180).

2.2 Herbal nutritional supplement for hypertension (HNS) A water based herbal nutrition supplement was provided by

M/s Diabliss Consumer Products Pvt Ltd., Chennai, India

2.2.1 Ingredients of HNS: Ingredients of the HNS from Diabliss are: *Nigella sativa* (Black Cumin)^[10,11], *Cinnamomum verum* (Cinnamon) ^[12], *Curcuma longa* (Turmeric) ^[13], *Zingiber officinale* (Dry Ginger) ^[12, 14], *Elettaria cardamomum* (Cardamom) ^[12, 15], *Myristica fragrans* (Nutmeg) ^[16], *Syzygium aromaticum* (Clove) ^[17], *Psidium*

guajava (Guava Leaves) ^[18], Linum usitatissimum (Flax Seeds) ^[19, 20], Cuminum cyminum (Cumin) ^[21], Trigonella foenum-graecum (Fenugreek) ^[22], Foeniculum vulgare (Fennel Seeds) ^[23], and Glycyrrhiza glabra (Licorice) ^[24, 25, 40] are the ingredients of HNS.

In our HNS preparation, licorice was one of the ingredients, and 0.08 g/day was used and at this low intake level it is considered safe without requiring notification of side effects ^[25, 40]. All these ingredients are known to have antiinflammatory, anti-diabetic, anti-hypertensive, and antioxidant properties and useful in reducing abnormal blood pressure or HTN, regulating cholesterol levels, and reduces the risk of developing cardiovascular diseases.

2.2.2 Preparation and intake of herbal solution

A volume of 15 ml of HNS was mixed with 985ml of water and subjects consumed all 1000 ml solution in a day. Every patient consumed equal proportions of the water mixed with HNS at breakfast, lunch and dinner during the 180-day period. All subjects were regularly monitored by the physician during the study period. The body weight, body mass index, and blood pressure of subjects were recorded.

2.3 Subjects

The current study included fifty subjects (27 male and 23 female subjects), age >45 years, with the diagnosis of HTN and diastolic blood pressure (DBP) of >110 mmHg and systolic blood pressure (SBP) of >150 mm Hg. Among the 50 subjects, 25 subjects were long-term hypertensives.>2 years with HTN, and 25 subjects with new hypertensives, <1 Year with HTN. All the Subjects were also diabetic and followed their current HTN, diabetes medications and initiated supplemental intake of HNS. Inclusion and exclusion criteria are listed in table 1. Subjects in the study used combination medications from Angiotensin Receptor Blockers (ARB), Calcium Channel Blockers (CCB), Beta Blockers (BB) and Diuretics (DU). HTN medication profile of subjects included ARB (1 out of 50), CCB (8/50), ARB with CCB (3/50), BB (6/50), CCB with BB (4/50) and DU with ARB (28/50). medication profile included Biguanides or Diabetes Sulfonylureas with Biguanides.

Table 1: Inclusion and Exclusion criteria for a clinical trial with HNS.

	Inclusion criteria		Exclusion criteria
-	Male/Females subjects between >45 years of	-	Patients are not ready to refrain from taking treatment with other drugs that could
	age		interfere with the evaluation of efficacy and tolerability.
•	Subjects are able to communicate effectively	•	Patients with secondary HTN (eg. due to renal artery stenosis), acute or severe bronchial
•	Subjects are willing to provide written		asthma, renal or hepatic disease or serum electrolyte abnormalities, uncontrolled
	informed consent		diabetes mellitus, significant cardiovascular or cerebrovascular disease or cardiac
•	In the judgment of the Principal Investigator,		surgery, or percutaneous trans luminal coronary angiography in the previous ≥ 3 months
	subjects are able to comply with protocol	•	Pregnant or breast-feeding women, and women of childbearing age not using an
	requirements		adequate method of contraception
•	Expressed ability and willingness to schedule	•	History of: alcohol consumption or drug abuse, or HIV infection or epilepsy or active
	and attend monthly visits for the duration of		hepatitis B or C within the past 3 months
	the study	•	Participation in another trial concurrently or within 4 weeks prior to the Screening Visit.
-	Subjects with a diagnosis of hypertension	•	Contra-indications or hypersensitivity to study product, History of medical
	(DBP 110 mm Hg and SBP>150mm Hg)		condition/disease according to the discretion of the Investigator
-	Subjects who are hypertensive for <1 Year	•	Any other condition that, in the opinion of the investigator, would adversely affect the
	and for>1 year with standard HTN		subject's ability to complete the study or its measures
	medication		

2.4 Screening Tests

The following tests were performed for all the subjects on very first day before treatment, designated as day 0, day 30, day 90, and day 180- the last day of the study. Further, daily blood pressure levels, pulse rate as measured by a standardized sphygmomanometer (Omron BP device calibrated with inbuilt storage). Readings were taken at 8 am and 6pm for all subjects. Three readings separated by one minute were taken in the morning and evening. The average of morning and evening readings was calculated. HbA1c was separated and estimated by the high-performance liquid chromatography method ^[27].

C - reactive protein (CRP) was estimated by latex-enhanced nephelometry $\space{[28]}\space{-1.5ex}$

Liver function tests: Total bilirubin was estimated by the vanadate oxidation method ^[29]. Alkaline phosphate was assayed as per the modified method ^[30]. Aspartate ^[31] and alanine ^[32] transaminase activities were also assayed as per the methods referred.

Renal function tests: Creatinine amidohydrolase was used to measure serum creatinine ^[33]. Uric acid was assayed using the

uricase-peroxidase method ^[34].

Lipid profile: Total cholesterol was assayed using cholesterol oxidase and peroxidase Trinder CHOD/POD End Point method. Triglycerides assay was performed by anenzymatic colorimetric method; HDL and LDL were assayed as per the methods referred ^[35]. The complete blood count was estimated by the spectrophotometric method in an automated analyzer ^[36].

The scheduled activity that was followed or all the 50 participants is listed in table 2.

S cheduled activity	Screening Visit 0 (Day 0)	Enrolment Visit I (Day 2)	Follow-up Visit II (Day 0 to 30)	Follow-up Visit III (Day 0 to 90)	End of Study Visit IV (Day 180)
Patient information &Written Informed Consent	Х	-	-	-	-
Demography and Medical History	Х	-	-	-	-
Vital Parameters and Clinical Examination	Х	Х	Х	Х	X
Screening and Provisional Eligibility (Inclusion/Exclusion)	Х	-	-	-	-
Enrolment and Final Eligibility (Inclusion/Exclusion)	-	Х	-	-	-
Study Assessment, Concomitant Illness, Concomitant medication and Adverse Event record	Х	X	Х	Х	X
Blood Pressure (DBP and SBP)	Х	Х	Х	Х	X
Complete blood profile, Lipid profile, Liver and kidney function tests (Serum AST, ALT, ALP, uric acid, urea, and creatinine)	Х	-	-	-	X
C-Reactive Protein	Х	-	Х	Х	Х
Glycated hemoglobin - HbA1c	Х	-	-	Х	Х
Compliance	-	Х	Х	Х	X
Study Completion/Termination	-	Х	Х	Х	Х

3. Results and Discussion

3.1 Impact on Systolic BP (SBP), Diastolic BP (DBP) and C - reactive protein (CRP)

All participants completed the study, and in terms of compliance, all participants consumed 100% of the prescribed HNS. No side effects were reported during the study.

The data of HTN parameters of 50 subjects are presented in figure 1. With regards to mean SBP (figure1a), there was a gradual decrease following the consumption of HNS. Mean SBP showed a decrease of 22 mm Hg on day 30, 34 mm Hg decrease on day 90, 48 mm Hg decrease at the final visit on day 180. A similar trend was found with regards to mean DBP (figure 1b). Mean DBP decreased by 20 mm Hg on day 30, 24

mm Hg decrease on day 90 and 34 mm Hg decrease on day 180. Mean CRP (figure 1c) also showed continuous reduction: 2.8% reduction on day 30, 6.3% reduction on day 90 and 9.1% decrease on day 180. Figures 2 & 3plots individual SBP and DBP values and shows every individual showed lower SBP and DBP when we compare day 0 and day 180 readings. Figure 4 is CRP values of subjects on day 0 and day 180. 48 of the 50 subjects showed lower CRP values whereas 2 of the subjects showed no change in CRP values. Further, the two subjects whose CRP did not change during the course of the clinical trial showed lowering of SBP and DBP.

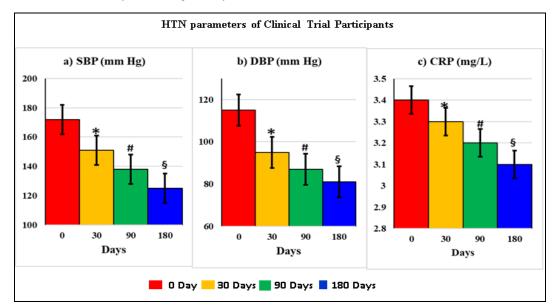


Fig 1: HTN parameters of clinical trial participants. Values were expressed as Mean \pm S.D. of 50 participants. (a) SBP (b) DBP and (c) CRP. The values that were highlighted with special symbols were statistically significant in comparison with the respective day 0 (visit I) values at least by

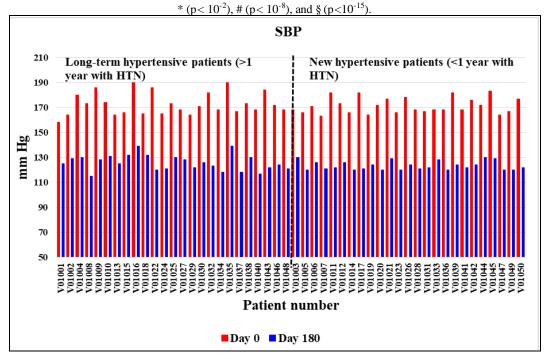


Fig 2: Individual Systolicblood pressure (SBP-mm Hg) levels of 0 day Vs 180 day

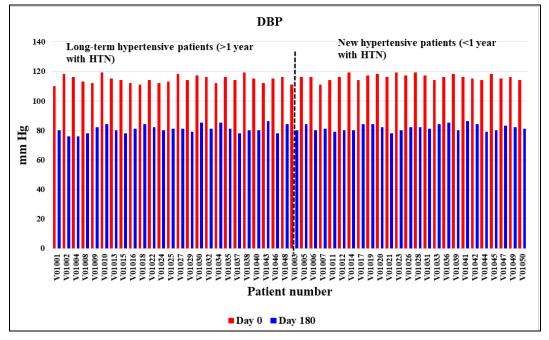


Fig 3: Individual Diastolicblood pressure (DBP-mm Hg) levels of 0-day Vs 180 days

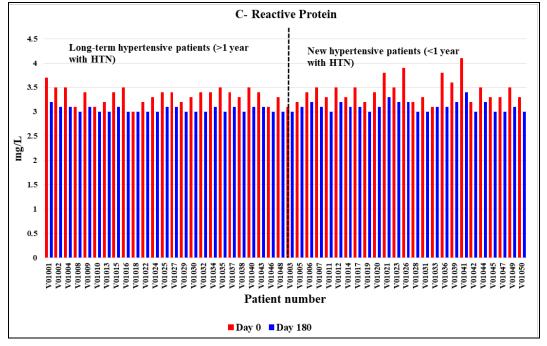


Fig 4: Individual C-reactive protein (CRP-mg/L) levels of 0-day Vs 180 days.

3.2 Impact of HTN Medications on SBP and DBP

The three HTN parameters were tabulated as a function of the medication/s profile of the subjects in table 3. The absolute values and percentage decrease of all the 3 parameters studied compared to the corresponding day 0. They were found to be remarkably persistent, especially at days 90 and 180, and independent of which combination of the medication was

being used.

With regards to the 3 HTN parameters, the minimal statistical significance at day 30 for SBP was in the order of 10^{-20} , for DBP was in the order of 10^{-37} , and for CRP was in the order of 10^{-2} . The statistical significance for SBP, DBR and CRP was 10^{-58} , 10^{-85} , and 10^{-15} respectively on day 180.

 Table 3: Summary of the HTN parameters (Means of SBP, DBP, and CRP) of the 50 clinical trial participants based on the anti-hypertensive medications used

	N. C.C. Linda	Day 0	Day 30	Day 90	Day 180	Mean (mr	n Hg) Differe	nce Vs 0 Day	
Medication used with Supplement	No. of Subjects	Mean SBP (mm Hg)				Day 30	Day 90	Day 180	
ARB	1	166	152	140	132	14	26	34	
ССВ	8	171	149	136	124	22	35	47	
ARB + CCB	3	174	148	134	126	26	40	48	
BB	6	172	155	139	124	17	33	48	
CCB + BB	4	172	152	137	124	20	35	48	
DU + ARB	28	173	150	139	125	23	34	48	
		Mean DBP (mm Hg)				Mean (mm Hg) Difference Vs 0 Day			
ARB	1	114	92	86	78	22	28	36	
ССВ	8	115	98	88	81	17	27	34	
ARB + CCB	3	117	95	90	84	22	27	33	
BB	6	116	94	88	81	22	28	35	
CCB + BB	4	114	95	89	84	19	25	30	
DU + ARB	28	115	94	86	81	21	29	34	
			Mean C	CRP (mg/	/L)	Mean	Vs 0 Day		
ARB	1	3.4	3.3	3.1	3.1	-3%	-9%	-9%	
ССВ	8	3.5	3.4	3.2	3.1	-3%	-9%	-11%	
ARB + CCB	3	3.6	3.4	3.3	3.1	-6%	-8%	-14%	
BB	6	3.4	3.3	3.1	3.1	-3%	-9%	-9%	
CCB + BB	4	3.3	3.1	3.2	3.1	-6%	-3%	-6%	
DU + ARB	28	3.4	3.3	3.2	3.1	-3%	-6%	-9%	

3.3 HbA1c Trends

Mean Glycated hemoglobin, HbA1c showed 0.2%% reduction on day 90 ended and 0.4% reduction on day 180.

The individual HbA1c data of the final visit at 180 days in figure 5. The statistical significance for HbA1c was found to be 10^{-6} on day 90 and 10^{-19} on day 180.

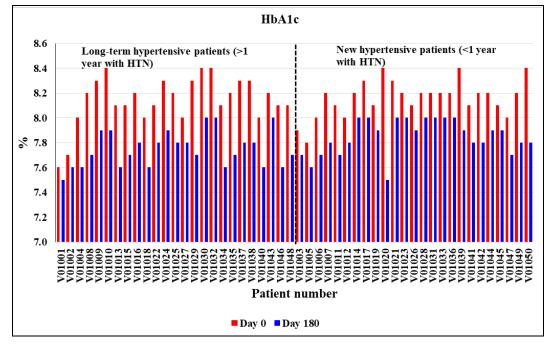


Fig 5: Individual HbA1c (%) levels of visit I (0-day) and final visit (180 days)

3.4 Daily SBP and DBP Profiles

The daily average SBP and DBP blood pressure data of all subjects are shown in Figure 6. A review of individual daily BP curves showed a range of BP profiles. Figures 7 and 8 show some of the varied BP reduction profiles. In figure 7 we see a more or less continuous reduction in SBP and a stepped reduction in DBP. In figure 8 more distinct stepped reductions in SBP and DBP followed by flat regions can be seen. These could be an indication of different BP-lowering mechanisms at play. However, the literature on such BP lowering regimes was not found. This is an area for further investigation to understand the mechanisms at play.

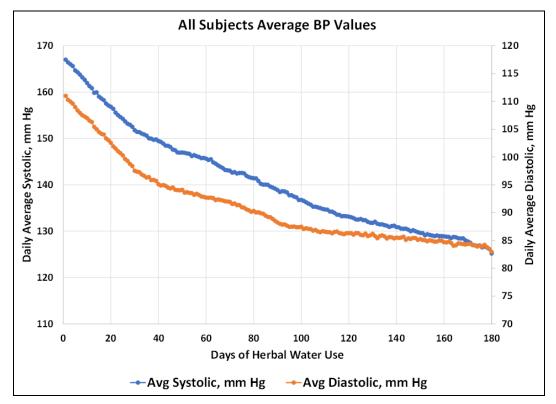


Fig 6: Average Systolic and Diastolic BP values of all subjects from individual daily average readings of morning and evening BP measurements using a standardized sphygmomanometer (Omron BP device calibrated with inbuilt storage)

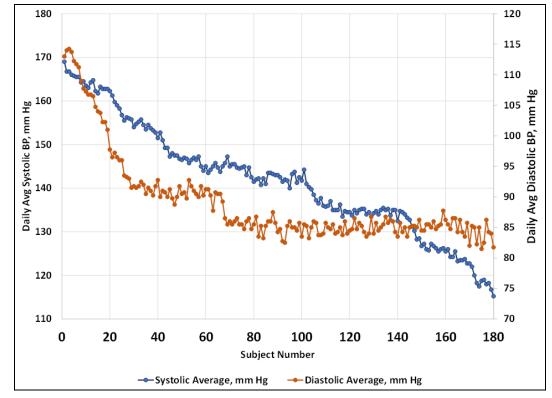


Fig 7: Subject V01008 Daily average BP values shows a more or less continuous SBP reduction and 2 or 3 regimes of DBP reduction.

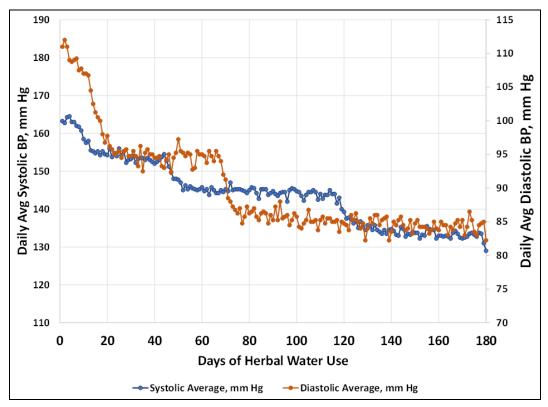


Fig 8: Subject V01027 shows multiples regimes of SBP and DBP reduction

3.5 Statistical Analysis

Statistical summary of all the 3 HTN parameters studied for all the 50 subjects for all the visits are presented in table 4. They include maximum, minimum, range, mean, standard deviation, median and mode along with the assessments of data distribution in terms of skewness, kurtosis and outlier determination.

SBP range (the difference between the maximum and minimum) of 32 at Day 0, increased to 40 and 48 at Day 30 and Day 90 respectively but came down to 24 by the final

visit on day 180, a good indication for the effect of the supplement in the long term. Similarly, for DBP, the range of 9 at Day 0, indeed, increased to 27and 18 at Day 30 and Day 90 respectively and decreased to 10on Day 180. With regards to CRP, the range value was 1.1 on Day 0, and consistently decreased to 0.8, 0.5, and 0.4 on Day 30, Day 90 and Day 180 respectively. These trends are an indicator of the long-term impact of supplementation of HNS.

Skewness is a measure of the asymmetry of the distribution of the population of a random variable about its mean, while the positive sign indicates the right shift to the mean, the negative sign is for the left shift. In the current data, the distribution is mostly symmetric.

Kurtosis is a statistical measure used to describe the degree to which variables cluster either in the tails or in the peak of a distribution. In the current data, very few kurtosis values, especially, those >1, indicating moderate tails hinting at

outliers. Outliers are determined by Tukey's ^[39] method using the Interquartile range (IQR) and the lack of or very few outliers found are consistent with the data of kurtosis.

Overall, very few aberrations were noticed in the statistical analysis, indicating the positive benefits of HNS on the 3 HTN parameters studied in the long term.

Table 4: Statistical summary of	of the 3 HTN individual parameters	(SBP, DBP, and CRP) of the clinical	trial participants of all the visits.
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Statistical parameter	SBP (mm Hg)				DBP (mm Hg)				CRP (mg/L)			
Statistical parameter	Day 0	Day 30	Day 90	Day 180	Day 0	Day 30	Day 90	Day 180	0Day	Day 30	Day 90	Day 180
M aximum	190	168	168	139	119	108	98	86	4.1	3.8	3.5	3.4
Minimum	158	128	120	115	110	81	80	76	3	3	3	3
Range	32	40	48	24	9	27	18	10	1.1	0.8	0.5	0.4
Mean	172	150	138	125	115	95	87	81	3.4	3.3	3.2	3.1
Std Dev	8	10.5	10.6	5.2	2.41	6.52	4	2.5	0.22	0.02	0.1	0.1
Median	170	152	139	124	116	94	86	81	3.4	3.3	3.2	3.1
Mode	168	152	140	120	116	90	86	80	3.5	3.2	3.1	3
Coefficient of variation	4.5	6.9	7.6	4.1	2.1	6.8	5.1	3	6.3	4.8	3.6	2.9
% Decrease compared to 0 Day	0	12.5	19.9	27.6	0	17.7	24.3	29.5	0	2.8	3.6	3
Skewness	0.71*	-0.24	0.39	0.78*	-0.20	-0.002	0.52*	0.08	1*	1*	0.8	1.3*
Kurtosis	-0.37	-0.71	0.1	0.58	-0.72	-0.64	-0.25	-0.51	1.8	1.5	0.4	2.05
Q1 (25 Percentile)	166.3	143	130.5	121	114	90	84	80	3.3	3.2	3.1	3
Q3 (75 Percentile)	177	158	143	128	117	100.5	91	83.8	3.5	3.4	3.2	3.1
Q3-Q1	10.8	15	12.5	7.8	3	10.5	7	3.8	0.3	0.2	0.1	0.1
1.5*IQR	16	22.5	18.8	11.6	4.5	15.8	10.5	5.6	0.5	0.3	0.2	0.2
Lower outlier fence	150.1	120.5	111.8	109.4	109.5	74.3	73.5	74.4	2.8	2.9	3	2.9
Upper outlier fence	193.1	180.5	161.8	140.4	121.5	116.3	101.5	89.4	3.9	3.7	3.4	3.3
Number of Outliers	0	0	1	0	0	0	0	0	1	1	3	2

3.6 Subject Progression with respect to AHA Hypertension Categorization

Table 5 is American Heart Association (AHA) hypertension categorization along with clinical trial participant distribution during the course of the trial. Based on the classification, we can see at day 0, 0% of the subjects were in Normal, Elevated and High BP-HTN Stage 1 categories, 80% of the subjects were in High BP-HTN Stage 2 and 20% of the subjects were in HTN Crisis category. At the end of the clinical trial on day 180, 4% of the subjects were in Normal BP category, 60% were in Elevated category, and 36% High BP-HTN Stage 1 category, 0% of the subjects were in High BP-HTN Stage 2 and 0% of the subjects were in HTN Crisis category.

Other parameters such as complete blood picture (hemoglobin, total and differential leukocyte counts, platelet count, erythrocyte sedimentation rate), blood pressure, liver function tests (bilirubin, alkaline phosphatase, aspartate, and alanine aminotransferases) renal functional tests (creatinine, uric acid), lipid profile (total-, high density-, low density- and very low density- lipoprotein cholesterols, triglycerides) electrocardiograms, were performed for all the 50 subjects as shown in table 2 have not shown any particular variations during the course of the clinical trial.

Table 5: American Heart Association (AHA) Hypertension Categorization & Clinical Trial Participant Distribution.

Bloc	od Pressure Category		No. of subjects (% of subjects) in each HTN category							
Blood Pressure level	Systolic(mm Hg)	Diastolic(mm Hg)	Day 0	Day 2	Day 30	Day 90	Day 180			
Normal	< 120	< 80	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (4%)			
Elevated	120-129	< 80	0 (0%)	0 (0%)	0 (0%)	0 (0%)	30 (60%)			
High BP-HTN Stage 1	130-139	80-89	0 (0%)	0 (0%)	1 (2%)	24 (48%)	18 (36%)			
High BP-HTN Stage 2	≥ 140	≥ 90	40 (80%)	47 (94%)	49 (98%)	26 (52%)	0 (0%)			
HTN Crisis	> 180	> 120	10 (20%)	3 (6%)	0 (0%)	0 (0%)	0 (0%)			
	Total	50 (100%)								

4. Conclusion

The continuous and significant reduction of SBP and DBP among all subjects and consistent reduction irrespective of various medications/combination medications used makes HNS a very useful supplement for hypertension management. The entire study population saw reduction in SBP and DBP. The study demonstrated HNS based nutraceuticals may be considered as an effective adjunctive therapy for HTN.

5. References

- 1. Zeng Z, Chen J, Xiao C, Chen W. A Global View on Prevalence of Hypertension and Human Develop Index. Ann Glob Health 2020;86(1):67. doi: 10.5334/aogh.2591.
- Gupta R, Gaur K, S Ram CV. Emerging trends in hypertension epidemiology in India. J Hum Hypertens 2019;33(8):575-587. Doi: 10.1038/s41371-018-0117-3. Epub 2018 Sep 25.
- Williams B, Mancia G, Spiering W, AgabitiRosei E, Azizi M, Burnier M *et al.* ESC Scientific Document Group. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J 2018;39(33):3021-3104. Doi: 10.1093/eurheartj/ehy339. Erratum in: Eur Heart J. 2019 Feb 1;40(5):475.
- 4. Whelton PK, Carey RM, Aronow WS, Casey DE, Collins KJ, Himmelfarb CD *et al.* ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC

/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines, 13 Nov2017Hypertension 2017, 2018;71:e13-e115. https://doi.org/10.1161/HYP.0000000000000065.

- Nguyen Q, Dominguez J, Nguyen L, Gullapalli N. Hypertension management: an update. Am Health Drug Benefits 2010;3(1):47-56. PMID: 25126308; https://www.ahdbonline.com/issues/2010/januaryfebruary-2010-vol-3-no-1/108-feature-108.
- Katherine L. Vogel Anderson. Combination Therapy in Hypertension Management. US Pharm 2012;37:46-50. https://www.uspharmacist.com/article/combinationtherapy-in-hypertension-management
- Wald DS, Law M, Morris JK, Bestwick JP, Wald NJ. Combination therapy versus monotherapy in reducing blood pressure: meta-analysis on 11,000 participants from 42 trials. Am J Med 2009;122(3):290-300. Doi: 10.1016/j.amjmed.2008.09.038.
- 8. Guerrero-García C, Rubio-Guerra AF. Combination therapy in the treatment of hypertension. Drugs Context 2018;7:212531. Doi: 10.7573/dic.212531.
- Lakshmi T, Anitha Roy, Durgha K, Manjusha.V. Coping with Hypertension Using Safer Herbal Medicine - A Therapeutic Review. Int. J Drug Dev. & Res 2011;3:31-57. https://www.ijddr.in/drug-development/coping-withhypertension-using-safer-herbal-medicine--atherapeuticreview.php?aid=5623
- Badar A, Kaatabi H, Bamosa A, Al-Elq A, Abou-Hozaifa B, Lebda F *et al*. Effect of *Nigella sativa* supplementation over a one-year period on lipid levels, blood pressure and heart rate in type-2 diabetic patients receiving oral hypoglycemic agents: nonrandomized clinical trial. Ann Saudi Med 2017;37(1):56-63. Doi: 10.5144/0256-4947.2017.56.
- 11. Dehkordi FR, Kamkhah AF. Antihypertensive effect of *Nigella sativa* seed extract in patients with mild hypertension. Fundam Clin Pharmacol 2008;22(4):447-52. Doi: 10.1111/j.1472-8206.2008.00607.x.
- 12. Azimi P, Ghiasvand R, Feizi A, Hosseinzadeh J, Bahreynian M, Hariri M *et al.* Effect of *Cinnamon*, *Cardamom, Saffron* and *Ginger* consumption on blood pressure and a marker of endothelial function in patients with type 2 diabetes mellitus: A randomized controlled clinical trial. Blood Press 2016;25(3):133-40. Doi: 10.3109/08037051.2015.1111020.
- Saraf-Bank S, Ahmadi A, Paknahad Z, Maracy M, Nourian M. Effects of *Curcumin* on cardiovascular risk factors in obese and overweight adolescent girls: a randomized clinical trial. Sao Paulo Med J 2019;137(5):414-422. Doi: 10.1590/1516-3180.2018.0454120419.
- 14. Sane R, Dawkhar S, Ambulkar P, Mandole R. The effect of a polyherbal oral formulation in the management of essential hypertension: an open label, pilot clinical study. Int J Basic Clin Pharmacol 2018;7:1427-31. DOI: http://dx.doi.org/10.18203/2319-2003.ijbcp20182694.
- 15. Fatemeh Y, Siassi F, Rahimi A, Koohdani F, Doostan F, Qorbani M et al. The effect of Cardamom supplementation on serum lipids, glycemic indices and blood pressure in overweight and obese pre-diabetic women: a randomized controlled trial. J Diabetes MetabDisord 2017;16:40. Doi: 10.1186/s40200-017-

0320-8.

 Arulmozhi DK, Kurian R, Veeranjaneyulu A, Bodhankar SL. Antidiabetic and Antihyperlipidemic Effects of *Myristica fragrans*. in Animal Models. Pharmaceutical Biology 2007;45:64-68.

DOI: 10.1080/13880200601028339.

- Uppuluri Spandana, Lakshmaiah Pallepati, Pratyusha Gandrapu, Swarna Sowjanya. Short and spicy evergreen tree: *Clove*. World J Pharm Sci 2018;6:122-128. https://www.wjpsonline.org/admin/uploads/E8ADCm.pdf
- Kumari S, Rakavi R, Mangaraj M. Effect of Guava in Blood Glucose and Lipid Profile in Healthy Human Subjects: A Randomized Controlled Study. J Clin Diagn Res 2016;10(9):BC04-BC07.
 Dei: 10.78(0)(CDB)(2016)(21201.8425)
 - Doi: 10.7860/JCDR/2016/21291.8425.
- Bloedon LT, Szapary PO. Flaxseed and cardiovascular risk. Nutr Rev 2004;62(1):18-27. Doi: 10.1111/j.1753-4887.2004.tb00002.x. PMID: 14995053.
- 20. Jacob Schor ND, FABNO. Flaxseed Reduces High Blood Pressure. Natural Medicine Journal 2014;6:1-6. https://www.naturalmedicinejournal.com/journal/2014-02/flaxseed-reduces-high-blood-pressure
- 21. Ali Mansouri, Aziz Shahraki Vahed, Hossein Shahdadi, Fatemeh Dashtban, Azizollah Arbabisarjou. The effect of garlic and cumin on blood pressure and glycosylated hemoglobin in subjects with type 2 diabetes. Bali Medical Journal (Bali Med J) 2018;7:156-160. https://www.balimedicaljournal.org/index.php/bmj/article /viewFile/849/pdf
- 22. Khan F, Khosla PP. To study the effect of sprouted *fenugreek* seeds as nutraceutical as an add-on therapy in subjects of diabetes mellitus, obesity and metabolic syndrome. Pharm Pharmacol Int J 2018;6:320-327. https://medcraveonline.com/PPIJ/to-study-the-effect-of-sprouted-fenugreek-seeds-as-nutraceutical-as-an-add-on-therapy-in-patients-of-diabetes-mellitus-obesity-and-metabolic-syndrome.html.
- 23. Akbar Fennel S. (*Foeniculum vulgare* Mill.): A Common Spice with Unique Medicinal Properties. Ann Complement Altern Med 2018;1:1001. https://www.remedypublications.com/openaccess/fennel-foeniculum-vulgare-mill-a-common-spicewith-unique-medicinal-properties-874.pdf.
- Wang X, Zhang H, Chen L, Shan L, Fan G, Gao X. Liquorice, a unique "guide drug" of traditional Chinese medicine: a review of its role in drug interactions. J Ethnopharmacology 2013;150(3):781-90. Doi: 10.1016/j.jep.2013.09.055.
- 25. Omar HR, Komarova I, El-Ghonemi M, Fathy A, Rashad R, Abdelmalak HD *et al. Licorice* abuse: time to send a warning message. Ther Adv. Endocrinol Metab 2012;3(4):125-38. Doi: 10.
- 26. Penugonda Anveetha, Vamsi Krishna Chittimoju. Study of HbA1c and serum magnesium in diabetic patients with retinopathy. Int. J Adv. Biochem. Res. 2021;5(1):01-05. DOI: 10.33545/26174693.2021.v5.i1a.55
- Davis JE, McDonald JM, Jarett L. A high-performance liquid chromatography method for hemoglobin A1c. Diabetes 1978;27(2):102-7. Doi: 10.2337/diab.27.2.102.
- Drieghe SA, Alsaadi H, Tugirimana PL, Delanghe JR. A new high-sensitive nephelometric method for assaying serum C-reactive protein based on phosphocholine interaction. Clin Chem Lab Med 2014;52(6):861-7. Doi: 10.1515/cclm-2013-0669.
- 29. Ameri M, Schnaars H, Sibley J, Honor D. Comparison of

the vanadate oxidase method with the diazo method for serum bilirubin determination in dog, monkey, and rat. J Vet Diagn Invest 2011;23(1):120-3. Doi: 10.1177/104063871102300121.

- Tietz NW, Rinker AD, Shaw LM. IFCC methods for the measurement of catalytic concentration of enzymes Part
 IFCC method for alkaline phosphatase (orthophosphoric-monoester phosphohydrolase, alkaline optimum, EC 3.1.3.1). Journal of Clinical Chemistry and Clinical biochemistry. Zeitschrift fur Klinische Chemie und Klinische Biochemie 1983;21(11):731-748. PMID: 6655448.
- 31. Bergmeyer HU, Hørder M, Rej R. International Federation of Clinical Chemistry (IFCC) Scientific Committee. Analytical Section: approved recommendation (1985) on IFCC methods for the measurement of catalytic concentration of enzymes. Part 3. IFCC method for alanine aminotransferase (L-alanine: 2-oxoglutarate aminotransferase, EC 2.6.1.2). J Clin Chem Clin Biochem 1986;24(7):481-95. PMID: 3734711.
- 32. Henley KS, IFCC method for alanine aminotransferase, Clinica Chimica Acta 1980;105(1):155-166. ISSN 0009-8981, https://doi.org/10.1016/0009-8981(80)90106-0.
- 33. Ogawa J, Nirdnoy W, Tabata M, Yamada H, Shimizu S. A New Enzymatic Method for the Measurement of Creatinine Involving a Novel ATP dependent Enzyme, N-Methylhydantoin Amidohydrolase. Biosci. Biotech. Biochem 1995;59:2292-2294. https://doi.org/10.1271/bbb.59.2292.
- 34. Zhao Y, Yang X, Lu W, Liao H, Liao F. Review article: Uricase based methods for determination of uric acid in serum. Microchim Acta 2009;164:1-6. Doi 10.1007/s00604-008-0044-z.
- 35. Penumarthy S, Penmetsa GS, Mannem S. Assessment of serum levels of triglycerides, total cholesterol, highdensity lipoprotein cholesterol, and low-density lipoprotein cholesterol in periodontitis patients. J Indian Soc Periodontol 2013;17(1):30-5. Doi: 10.4103/0972-124X.107471.
- 36. A Manual of Laboratory and Diagnostic Tests. Ed/-Fischbach FT and Dunning MB. Lippincott Williams & Wilkins Publishers, 7thEd 2003. https://www.worldcat.org/title/manual-of-laboratory-anddiagnostic-tests/oclc/183831243
- 37. Article from the internet on New ACC/AHA High Blood Pressure Guidelines Lower Definition of Hypertension.https://www.acc.org/latest-incardiology/articles/2017/11/08/11/47/mon-5pm-bpguideline-aha-2017.
- 38. Garg N, Muduli SK, Kapoor A, Tewari S, Kumar S, Khanna R *et al.* Comparison of different cardiovascular risk score calculators for cardiovascular risk prediction and guideline recommended statin uses. Indian Heart J 2017;69(4):458-463. Doi: 10.1016/j.ihj.2017.01.015.
- 39. Tukey J. Exploratory Data Analysis, Addison-Wesley 1977;23:413-414. http://theta.edu.pl/wpcontent/uploads/2012/10/exploratorydataanalysis_tukey.p df.
- 40. Yuka Sasakawa, Akari Kominami, Michiyo Abe, Kaori Yamamoto, Mayumi Nakao, Fumiko Nakaoka, *et al.* The Anti-obesity and Anti-inflammatory Effects of "LICONINE", an Extract of *Glycyrrhiza uralensis*, on Diet induced Obese Mice and 3T3-L1 Mouse Adipocytes. Journal of Food and Nutrition Research