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CLINICAL TRIAL OF POLYHERBAL PRODUCT IN THE TREATMENT OF HYPERTENSION

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ABSTRACT: Background: High blood pressure has emerged as a leading cause of death and disability worldwide.[1] Management of hypertension effectively has been a distant reality. Hypercum, a rationale combination of herbs has shown to reduce BP effectively along with other benefits as studied in the ancient literature and research publication. **Objectives:** The study aims to evaluate the safety and efficacy of "Hypercum" on mild to moderate hypertension, an open-labeled nonrandomized proof of concept study enrolled 16hypertensive associated with co-morbid conditions. **Methods:** patients who met the selection criteria. The efficacy was assessed by measuring the blood pressure at baseline and on every 15 days till the BP got controlled and then every month and followed up for 84 days. The effect of Hypercum on other co-morbid conditions was also evaluated. The quality of life was also assessed using SF-30. Planned student't' test was applied. **Results:** At screening (before the enrollment for the study), the mean systolic blood pressure (SBP) was 161.25 mmHg, and their mean diastolic blood pressure (DBP) was 106.88 mmHg. The mean baseline systolic blood pressure, the mean diastolic blood pressure and the mean arterial blood pressure (MAP) were 152.50 mmHg, 99 mmHg, and 113.88 mmHg, respectively. The mean value of these parameters SBP, DBP, and MAP decreased to 122.50 mmHg, 81.67 mmHg, and 92.58 mmHg respectively at visit 5 that is at Day 84. There was a significant reduction in systolic blood pressure, diastolic blood pressure, and mean arterial blood pressure from baseline to the entire visit that is Day 14, Day 28, Day 56, and Day 84. **Conclusion:** "Hypercum" is effective in treating the mild to moderate hypertension associated with co-morbid conditions with a positive outcome on the quality of life.

INTRODUCTION: High blood pressure is the number one risk factor for death and disability worldwide [1].

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Recent reports indicate that nearly 1 billion adults (more than a quarter of the world's population) had hypertension in 2000, and this is predicted to increase to 1.56 billion by 2025 [2]. Approximately 30% of the population has hypertension, and the prevalence is further increasing.

The risk has increased in individuals with comorbidities such as diabetes, chronic kidney disease, and coronary artery disease [1].

Poorly controlled hypertension causes cardiovascular disease, resulting in an increased risk of stroke, heart disease (including myocardial infarction, heart failure, and arrhythmias) and kidney disease. Scientific literature available on herbal medicines has revealed that herbs are effective in the cardiovascular system both in terms of efficacy and safety [3].

Despite evidence of the efficacy of antihypertensive agents in treating hypertensive patients, the achievement and maintenance of the target BP goals, remains a challenge for the treating physicians, with limited armamentarium.

According to the present scenario, dependence on natural products is gaining popularity day-by-day to combat various physiological threats, including cardiovascular complexities. The use of traditional remedies may be encountered more frequently due to an array of scientific evidence in its favour [4].

Reports indicate that about 15–20% of individuals on prescription medications also use herbal supplements [5]. Hence it is imperative to promote credible research on the safety and efficacy of herbal treatment for a variety of ailments including cardiovascular diseases.

Hypercum is a herbal drug which comprises of *Rauvolfia serpentina, Nardostachys jatamanshi, Allium sativam, Ocimum sanctum, Curcumin longa, Embilica officinalis, Azadirachta indica, Trigonella foenum graecum, Zingiber officinale, Tribulus terrestris, Withania somnifera, Pueraria tuberosa, Terminalia arjuna, Centella asiatica, Mentha arvensis* and Marsh mint.

Indian literature has reviewed the efficacy and safety of Hypercum ingredients at various concentrations in many clinical conditions. However, till date, there is lack of evidence on the polyherbal combination 'Hypercum.'

Objectives:

Primary Objective: To evaluate the antihypertensive efficacy and safety of Hypercum on mild to moderate hypertension

Secondary Objective: To evaluate the benefits of Hypercum on the co-morbid conditions and its impact on the quality of life.

MATERIAL AND METHOD: Patients, both male and female aged 18-60 years and those willing to give written informed consent were selected. They were with mild-to-moderate essential hypertension.

Inclusion Criteria: Patients taking anti-hypertensive drugs or patients having known to be a hypertensive, diabetic patients or patients running with renal failure or patients having metabolic syndrome, female subjects who confirmed non-pregnant status and agreed to comply with proper contraception throughout the study duration and patients willing and able to comply with all trial requirements were included in the study. The subjects who were enrolled in the study were hypertensive from several years and were on treatment therapy to control the blood pressure. The medical history of the 16 patients reported that the mean systolic pressure of 161.25 mmHg and their mean diastolic blood pressure of 106.88 mmHg.

Exclusion Criteria: Patients with severe essential hypertension, significant renal insufficiency, history of cerebrovascular disease, HIV infection, AIDS, hepatitis B or C, or other immunosuppressive disorders, drug abuse within past 2 years, pregnancy and breastfeeding women were excluded from the study.

The study was conducted by non- randomized, open-labeled, an interventional study by ICBio clinical research. It involved the clinical attendance of the subjects on recruitment and on follow up. Subjects enrolled in the study received study drug (3 gm of Hypercum along with ½ tsp of water after food at bedtime) during each visit. Study drug would be the alternative or in addition to the therapies already being used. The safety and efficacy parameters were compared with baseline and follow-up data with laboratory investigations, demographics and blood pressure which included systolic blood pressure, diastolic blood pressure and also the mean arterial blood pressure were analyzed in the study. Adverse events/ side effects were noted for each follow-up visit.

Ethics Committee Approval: All study-related documents Protocol, CRF, Dairy Card, Investigator Brochure, SF – 36 and ICF (English and Kannada versions). Written informed consent was obtained

from the subject(s) before the start of the trial and after due approval from IEC/IRB. Ethics Committee notifications as per the GCP guidelines issued by Central Drugs Standard Control Organization and ethical guidelines for biomedical research on human subjects issued by Indian Council of Medical Research has been followed during the conduct of the study [Clinical IEC (Independent Ethics Committee for Ethics in Research and approved on 16th May 2012)].

Study Outcomes: Primary outcomes

- Reduction in Systolic blood pressure and Diastolic blood pressure from baseline
- Change in mean arterial blood pressure
- Adverse events resulted in therapy
- Laboratory tests (Haematology, Biochemistry and urine analysis) at baseline and post-study

Secondary Outcomes: Quality of life SF-36 questionnaire

Visit Details: The patients were screened and enrolled. The enrollment day was considered as the baseline data, and the patient was asked to visit on Day14, Day28, Day56, and Day84.

Statistical Analysis: Data analysis was carried out using the Statistical Analysis System. Student't' test for independent samples was used to compare group mean baseline values and response differences (outcomes minus baselines) between the groups. Planned student't' test for paired values was used to compare outcome versus baseline values within groups. Significant differences between mean data were determined using $P < 0.05$. Quality of life evaluation was done through Chi-square test.

RESULTS:

Demographic and Other Baseline Characteristics In the study, around 18 patients were screened, and out of the 16 patients were selected. The other 2 patients were considered as screen failure as they did not meet the inclusion criteria. The enrolled subjects consisted of 8 Males and 8 females **Table 1**.

TABLE 1: DIFFERENT DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Smoking status			
Never Smoked		Still Smoking	Quit smoking
12		04	00
Weight			
Mean Weight of Men		Mean Weight of Women	
77.29 Kg		69.53 kg	
Height			
Mean Height of Men		Mean height of Women	
168.75 cm		157.5 cm	
Family history			
Mother	Father	Both	Sibling
06	01	03	04
Medical history			
Hypertensive subjects	Diabetic subjects	Hypertensive & Diabetic subject	Other Medical History
05	02	01	01 (Hypothyroid)
Surgical history			
Number		Reason for Surgical History	
03		Hysterectomy :01 Renal Calculi : 01 Fractured Right Leg: 01	

Concomitant Medication is taken by the Subject: Hypercum is a herbal drug which can be taken along with another hypertensive drug without altering the routine blood parameters **Table 2**.

TABLE 2: CONCOMITANT MEDICATION TAKEN BY THE SUBJECT

Concomitant Medication	Number of patients	Medication intake
Antihypertensive drugs (Telmisartan, Olmesartan, Losartan, and Amlodipine)	10	Ongoing
Antidiabetic drugs (Human insulin, Metformin, and Glibenclamide)	4	Ongoing

Efficacy Analyses: The primary efficacy analyses included systolic blood pressure, diastolic blood pressure, and mean arterial blood pressure. These parameters were assessed at 5 visits. The subjects were followed from the baseline to Day 14 (visit 2), Day 28 (Visit 3), Day 56 (Visit 4) and Day 84 (Visit 5) **Fig. 1**.

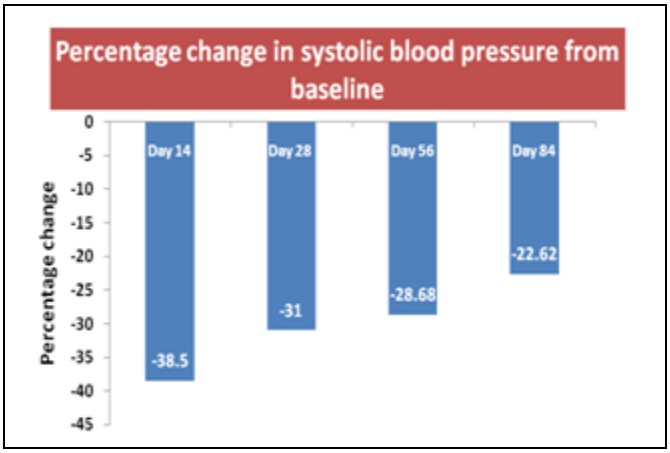

FIG. 1: PERCENTAGE CHANGE IN SYSTOLIC BLOOD PRESSURE. A significant drop in systolic blood pressure from the baseline was noticed by the end of the trial (Day 84)

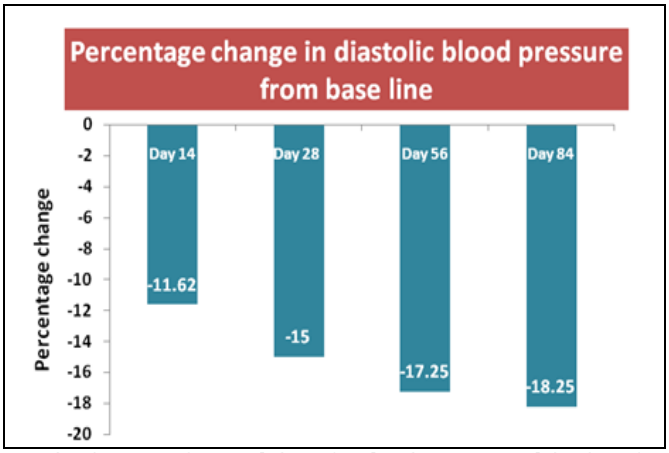

FIG. 2: PERCENTAGE CHANGE IN DIASTOLIC BLOOD PRESSURE. A significant drop in diastolic blood pressure from the baseline was noticed by day 84

TABLE 3: MEAN ARTERIAL BLOOD PRESSURE FROM BASELINE TO EVALUATION PERIOD

Visit Day	Mean Value	Change from Baseline	Percentage Change from Baseline
Base Line	113.88 ± 19.7		
Day 14 (Visit 2)	100.12 ± 9.61	-13.75 ± 15.07	0.12
Day 28 (Visit 3)	94.5 ± 8.06	-19.38 ± 14.49	-5.50
Day 56 (Visit 4)	92.93 ± 6.14	-20.94 ± 15.28	-7.06
Day 84 (Visit 5)	92.18 ± 5.54	-21.69 ± 15.98	-7.81

By Day 84, there was a significant drop in mean arterial blood pressure from the baseline.

Safety Analyses: Safety analysis was carried out through the study, and Hypercum was well-tolerated. There were no significant findings found for the study drug. No serious adverse events were reported to date. All laboratory parameters were found normal values at screening visit for all subjects. There were no significant findings at baseline and after the study in any of the patients.

Benefits of Co-morbid Conditions: Hypertension is not only a single disease, but it also consists of various other illness associated with it like headache, body pain, muscle tenderness, depriving of sound sleep, breathlessness, stomach discomfort (associated more with other allopathic medication), anxiety and palpitation, mood swings, constipation, chest heaviness.

To assess this illness in the hypertensive subjects, a set of questionnaire was prepared, which was asked to the subjects at the time of enrollment and subsequently at each visit by the investigator. The result obtained from the questionnaire was then analyzed and it was noticed that at the baseline i.e., at enrollment few of the subjects complained about mild body pain, mild breathlessness, mild joint pain, moderate mood swing, mild constipation further when these patients took Hypercum and were followed up later almost all the subjects were cured of the above said illness **Table 4**.

TABLE 4: SYMPTOMS CAPTURED AT SCREENING AS WELL AS AT FINAL VISIT

Symptoms	Screening	Visit 5 (Final Visit)
Lower Back Pain	3	1
Breathlessness	3	0
Constipation	3	0
Mood Swing	2	0
Joint Pain	2	1
Abdominal Discomfort	0	1

Impact on Quality of Life: The mean values for Physical Function (PF), Role-Physical (RP), Bodily Pain (BP), General Health (GH), Vitality (VT), Social Functioning (SF), Role Emotional (RE) and

mental health (MH) have shown improvement after the treatment when compared from baseline. The Physical Component Score (PCS) and Mental Component Score have shown improvement in the quality of life when compared from baseline. The mean values are as shown in **Fig 3.**

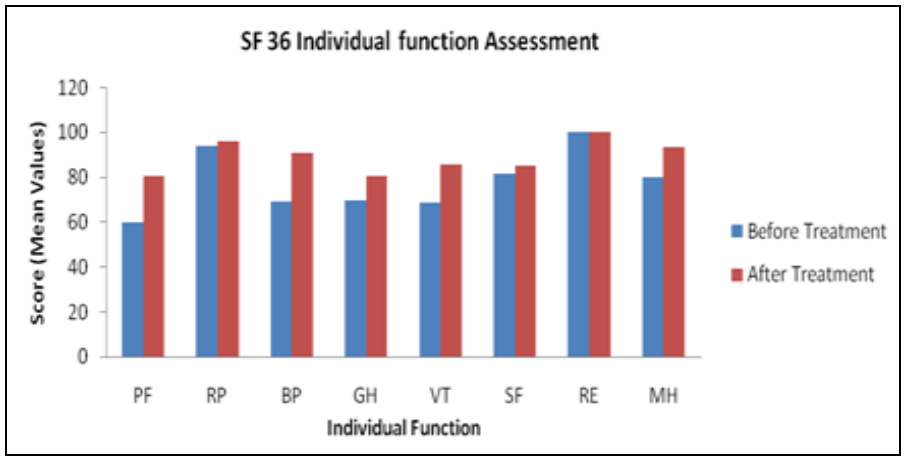

FIG 3: SF 36 INDIVIDUAL FUNCTION ASSESSMENTS

DISCUSSION: During baseline, the subjects were screened according to the inclusion-exclusion criteria's and their blood pressure along with mean arterial blood pressure were taken down. The baseline blood pressure before administering the drug was taken, and at that point, the systolic blood pressure was 152.50 ± 12.38 mmHg, diastolic blood pressure was 99 ± 10.03 mmHg, and the mean arterial blood pressure was 113.88 ± 19.37 mm Hg. The systolic pressure after 30 min was 145.88 ± 9.56, diastolic pressure after 30 min was 94.13± 9.02, and the mean arterial blood pressure recorded was 110.21 ± 20.30 mmHg.

The patients were then asked to follow the drug schedule and to come for follow up regularly on Day 14 (Visit 2), Day 28 (Visit 3), Day 56 (visit 4) and Day 84 (Visit 5) from the baseline visit. During these visits, the subject's vitals and other physical examinations were conducted. During the last visit that is at Day 84(Visit 5) the subject's blood pressure and the mean arterial blood pressure showed a significant change from the baseline. The systolic blood pressure at Day 84 (Visit 5) was 122.63 ± 9.29 mmHg, the diastolic blood pressure was 81.75 ± 5.05 mmHg, and the mean arterial blood pressure from the left ankle was 92.19 ± 5.54 mm Hg. The reduction in the blood pressure, and the mean arterial blood pressure from the left ankle showed significant changes.

Further, when these changes were compared with each visit statistically, the p-value was < 0.005; hence, we can conclude that Hypercum is a potent polyherbal combination in controlling hypertension. Hypercum can be taken safely along with other hypertensive drugs. Hypercum was also analyzed concerning illness associated along with hypertension. It was observed that few subjects during screening, subjects complained about various other illness associated with hypertension such as body pain, back pain, constipation, mood swing. These illnesses were noted at the baseline by the investigator and were followed up till the final visit; it was noticed that almost all the subjects were cured of this illness.

CONCLUSION: Finally, it can be concluded from the above study that Hypercum not only is effective against hypertension and also is safe to be taken along with other prescribed medication which helps in reducing other illness associated with hypertension. Hypercum, a polyherbal combination is effective in achieving normal blood pressure when administered with other antihypertensive drugs without any changes in blood parameters.

Hypercum was also effective in improving the quality of life of hypertensive patients. Hypercum is safe and effective in treating mild to moderate hypertension with added effect on the associated co-morbid conditions.

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CONFLICT OF INTEREST: Nil

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