WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 5.045
Volume 4, Issue 4, 1297-1316. Research Article ISSN 2277– 7105

EVALUATION OF THE EFFICACY OF HERBAL BASED FORMULATION IN PATIENTS OF HEART FAILURE

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Article Received on
06 Feb 2015,

Revised on 27 Feb 2015,
Accepted on 19 March 2015

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ABSTRACT

T AYU BKV is a new positive inotrope with a unique mechanism of action. To assess its clinical utility we administered this tablet of 125mg twice a day along with meals (250mg/day) for 90 days to 100 patients with Left Ventricular Ejection fraction less than or equal to 50% and also who had substantial limitations in exercise performance despite treatment with conventional Heart Failure Therapy (HFT). Patients were evaluated by 2D Echocardiogram along with measurements of distance walked during six minutes Hall walk testing. Improvements were demonstrated in both, Left Ventricular Ejection Fraction and distance walked successfully after 90 days of treatment with T AYU BKV. Furthermore T AYU BKV significantly reduced Left ventricular internal dimensions at systole as well as at diastole in HF patients. However, dimensions of enlarged Left Atrium were compromised with a marginal decrease. Various statistical data confirms improvements in NYHA functional class along with enhancement in Quality of life (QOL). Results suggest that efficacy of this drug is warranted when used as an add-on therapy along with the conventional.

KEYWORDS: Heart Failure Therapy, inotrope, Left Ventricular Ejection Fraction, Systole, Diastole, Left Atrium.

INTRODUCTION

Any abnormality of Left Ventricle whether from cardiac muscle characterized by its dilation (ICD9 425.4), abnormality in myocardial contraction (ICD9 428.2) or inadequate output despite an increase in distending pressure along with end-diastolic volume (ICD9 428.1), they are classically reflected as one of the many clinical symptoms from NYHA functional class

with intolerance to exercise [1] along with many other complaints, some of them related to gastro intestinal tract also.

There has been tremendous progress in the field of medical science especially in pharmacology, where, it has succeeded in reducing the mortality rate of patients with morbidities like Hypertension, Diabetes, Coronary Heart Disease, Peripheral Vascular Disease (PVD), Chronic Obstructive Pulmonary Disease (COPD) and Arrhythmia. Despite this advancement, there has not been a subsequent reduction in the number of patients with heart failures.[2] Since every cardiac patient has a potential to develop Heart failure.

Once a patient manifests clinical evidence of heart failure and failure in circulatory compensatory mechanisms, the prognosis is poor and it is likely that the prognosis can be improved only if the cause of heart failure is eliminated or the depressed myocardial contractility is restored to normal or improved.

It is important to determine whether a drug that exerts a beneficial hemodynamic effect does so by; a) increasing myocardial contractility alone, b) by causing vasodilation alone or c) by a combination of these actions. This may require direct measurement of some aspect of left ventricular performance.

A number of drugs, particularly vasodilators, improve hemodynamics at rest, but not always during maximal exertion.[3] Because most patients with heart failure become symptomatic only during exertion, the agent must improve cardiovascular hemodynamic along with myocardial contractility not only at rest but also during exertion.

Several oral inotropes developed in the last 15 years, has shown to acutely improve cardiac output, decrease filling pressures, and in some cases, enhance quality of life, but, are associated with higher mortality rates when used chronically.[4,5]

There are some popular and widely used sympathomimetic amines; dopamine and dobutamine, during acute failure conditions. Dobutamine has been shown to improve cardiovascular hemodynamics and oxygen delivery to the peripheral circulation, both at rest and during exertion, but it does not increase exercise capacity.[6] Thus, although it increases total cardiac output, it may cause an unfavorable redistribution of blood flow. More over they are administered intravenously and their value in the treatment of chronic congestive heart failure is therefore limited.

Herbal medicines, or phytomedicines, are closer to conventional drugs than other complementary and alternative medicine approaches. They have been used continuously for many decades' even centuries, often in ways much different from those of modern medical prescription. Evaluation of efficacy of herbal products and applying the principles of modern medicine is a paramount issue.

Herbal medicines consist of many chemical constituents with complex pharmacological effects on the body. Modern clinical trials insist on having data with hard endpoints that can be monitored. Thus there is a need to develop the means to objectively assess the subjective signs.

The chosen herbal formulation, T AYU BKV is an Evidence Based Medicine (EBM) which has been developed and processed uniquely so that it reaches to the desired subjects in a standard format.

The value of T AYU BKV in the treatment of heart failure will be measured by its ability to improve not only abnormal hemodynamic along with myocardial contractility, but also their QOL. T AYU BKV is such a formulation, which, when taken as a nutritional supplement along with meals twice, it is observed to have been enhancing inotropic property. When administered to patients with advanced conditions, this unique formulation as a positive inotropic agent may improve their well-being and exercise capacity, but may not enhance their survival because of the already advanced degree of cardiac damage present.

Reliable estimates of heart failure are lacking in India because of the absence of a surveillance program to track incidence, prevalence, outcomes and key causes of heart failure. A 2013 update from the American Heart Association (AHA) estimated that there were 5.1 million people with HF in the United States in 2006.[7] There are an estimated 23 million people with HF worldwide.[8] The worldwide prevalence of HF seems to have been increasing over the past decades.[9]

METHODS

An interventional, observational study–control research trail performed at Lokmanya Medical Research Centre (LMRC), Lokmanya Hospitals - Chinchwad & Nigdi, Pune, were devided in two groups, a Control group with 100 subjects taking only HFT and Study or experimental group with 100 subjects taking HFT with add-on T AYU BKV.

All patients above 18 yrs with left ventricular ejection fraction< or = to 50% who were already under HFT with Dispnoea-On-Exertion (DOE) and Fatigue from NYHA functional Class were selected. Patients of Heart failure with valvular heart disease requiring surgical corrections, restrictive cardiomyopathy, Severe Left Ventricular out Flow Tract Obstruction (LVOTO), Dementia, consuming psychiatric medicines or active participation in any other research trial were excluded.

After obtaining ethical clearance from LMRC, patients were selected from 2 D Echo dept., followed by obtaining permissions from the cardiologists, they were informed about the research motive and were enrolled in the research trial with a written consent thereafter. Their baseline screening report of 2 D Echo was attached to the Case Report Format (CRF). This was followed by six minutes hall walk test. Both the groups were asked to give a follow up after a month for at least two consecutive months. Their clinical signs and symptoms were noted accordingly. The study was declared over only after they repeated their 2D Echo investigation along with Six minutes hall walk test.

All their clinical findings were analyzed for statistical evaluations. Significant values were studied to reach to an unbiased conclusion. Statistical analysis was performed using SPSS software, IBM version-17.0.

Lacunae observed during the tenure of clinical Research were noted for further implications.

OBSERVATION

There were 34, 32 and 34 cases from Mild, Moderate and Severe LVSD respectively from study group and a similar pattern of 33, 41 and 27 subjects from control group during the enrolment. Altogether 68% were male. 85% from both the groups were found to be from the hypertensive in origin, followed by Post MI-76.6% , DM2- 57.2%, & DCMP-49%, Arrythmia-24.9% , COPD-13.9% and PVD-8%.

Table 1: Age &Weight

		Study		Control	
		Mean	**St.Deviation**	**Mean**	**St.Deviation**
AGE	**Male**	62.26	14.26	59.41	11.60
	Female	60.12	10.82	60.90	12.60
Weight in Kg	**Male**	70.41	10.0	70.20	10.68
	Female	63.16	10.9	60.90	12.10

Discriptive statistics of Average mean Age / Average mean weight with St.Dev.of Males & Females from Study and Control Group. Weight: P<0.003(study), p<0.002(control).

Evidently the average age of HF cases combined were approx. between 59 and 63 years. Perhaps socio-economic burden or fear of insecurity may have lead them to stress followed by the disease progression. There were 46% cases from Experimental group having BMI >25 along with waist hip ratio >0.8, where as 40.6% were from control. The values of weight in Kg were found to be highly significant (p<.005) in both the groups.

Table 2: Follow up study

Baseline	**n-100**	**n-101**
Heart Rate	83.9{+_12.37}	84.52{+_13.21}
SBP	136.06{+_18.33}	131.94{+_21.6} *
DBP	86.62{+_11.59}*	83.12{+_12.66}*
First Follow up	**n-96**	**n-88**
Heart Rate	80.46{+_10.05}	81.34{+_.76}
SBP	135.68{+_15.20}*	130.34{+_17.77}*
DBP	84.84{+_8.85}	83.51{+_10.73}*
Second Follow up	n-91	n-61
Heart Rate	78.15{+_6.60}*	81.21{+_10.07}*
SBP	133.67{+_14.17}	129.34{+_16.00}*
DBP	83.87{+_7.44}	84.75{+_11.04}*
Third Follow up	**n-71**	**n-36**
HR	75.35{+_6.29}*	81.14{+_12.29}*
SBP	132.94{+_13.74}	131.11{+_16.34}
DBP	83.29{+_6.96}	84.29{+_10.37}*

Discriptive statistics of follow up from Study and Control Group. (*: P <0.05)

In spite of antihypertensive drugs some of the cases were still hypertensive. Fluctuations were seen after the second follow up of control where as in study grp even though a systolic pressure could not recede the optimum level a marginal and steady decrease were noted in diastolic pressure. Heart rate seems to be significantly receding to an optimum level in experimental group as compared to the control.

Table 3: Follow up study of NYHA functional class

Group	**Study**			**Control**		
	Baseline n-100	Ist FU n-96	2nd FU n-90	Baseline n-101	Ist.FU n-88	2nd FU n-61
DOE						
I	02%	54.2%	74.7%	0	19.3%	52%
II	39%	29.2%	20.9%	47.5%	43.2%	33.6%
III	48%	12.5%	3.3%	39.6%	30.7%	21.3%
IV	11%	04.2%	0	12.9%	6.8%	8.2%
Fatigue						
I	05%	50.5%	76.9%	01%	19.3%	18%
II	45%	34.7%	17.6%	50.5%	50%	55.7%

III	40%	11.6%	5.5%	38.6%	25%	18%
IV	10%	03.2%	0	9.9%	5.7%	8.2%
Anorexia						
1	03%	56.3%	76.9%	08%	29.5%	27.9%
2	20%	6.3%	9.9%	30%	3.4%	9.8%
3	02%	4.2%	2.2%	03%	4.5%	6.6%
4	02%	20.8%	9.9%	04%	33%	32.8%
5	32%	4.2%	0	17%	6.8%	4.9%
6	37%	7.3%	1.1%	35%	22.7%	16.4%
7	04%	01%	0	03%	0	1.6%

Pearson Chi-square test revealed all the symptoms were highly significant ($p<.005$)

The patients were selected and categorized according to their severity from New York Heart Association i.e.

- NYHA 1: Cardiac disease, but no symptoms of shortness of breath or fatigue and no limitation in ordinary physical activity (i.e. walking, climbing stairs etc).
- NYHA II: Mild symptoms of shortness of breath or fatigue and slight limitation during ordinary activity.
- NYHA III: Marked limitation in activity due to symptoms, even during less- than-ordinary activity, e.g. walking short distances (20–100m). Comfortable only at rest.
- NYHA IV: Severe limitations. Experiences the above symtoms even while *at rest*. Mostly bed bound patients.

Anorexia was measured through seven point Likert scale i.e.

1: No symptoms

2: Mild symptom present very occasionaly (1-2/15days)

3: Minimal symptom present occasionaly once a week.

4: Moderate symptom present slight frquently (2-3 days/week)

5: Moderately severe symptom present frequently (3-5 days/week)

6: Severe symptom present (5-6 days/week)

7: Very severe symptom present almost every day all the time.

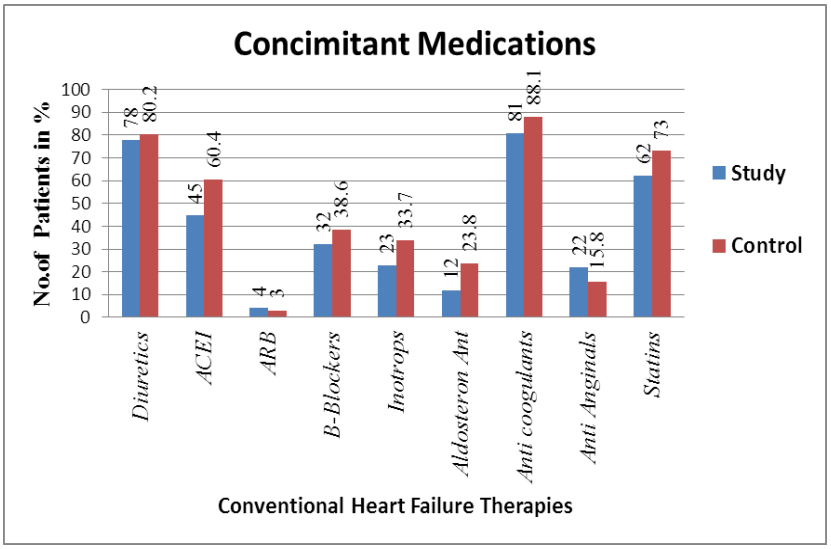


Figure 1: Concomitant Medications

As seen in the fig. 1 Preference was given to Anti coagulants (mainly ASA) prescription in majority followed by diuretic. Most evidently as 3/4rth of the HF cases were from Ischemic cardiomyopathy (i.e- post MI-76.6%), they were secured with statin dosages. Looking at the side effects of Inotropic agents (Digoxin), its prescription was not popularly preferred in spite in presence of contractile dysfunctions. ACEI followed by Betablockers were seen prescribed more than the Aldosterone antagonist and ARB to HF cases.

Interventional Details

According to American Heart Association, HF cases are classified into three groups of Left Ventricular Systolic Dysfunction (LVSD) i.e.

Mild LVSD - LVEF between 41% and 50%.

Moderate LVSD- LVEF between 31% and 40%.

Severe LVSD - LVEF below 30%.

An effort was made to optimize the method of preparation by validating the formulation. After several trials, a desired product was made in three batches to cater the subject's need, later sent for processing into a compressed tablet followed by its packing into standard dispensing format. They were observed to be distributed as shown in fig.2.

RESULTS

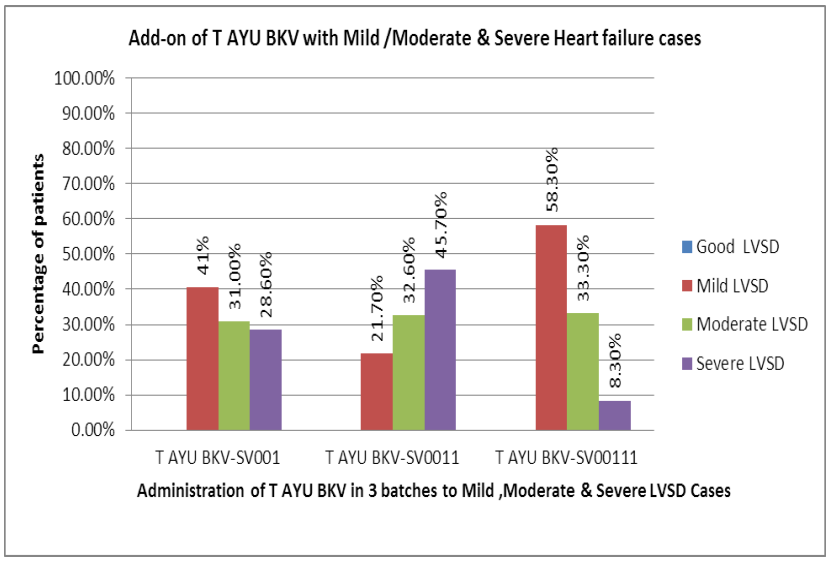


Fig 2: Administration Details

Table 4 (A) : Comparative review of NYHA Class

Final review -	Study		Control	
	Before (n-100)	After (n-91)	Before (n-100)	After (n-91)
D0E	102.90	63.59*	99.12	119.21*
Fatigue	100.65	63.25*	101.35	119.58*
Anorexia	105.28	63.95*	96.77	118.81*

Krusal wallis test for four points NYHA Classification and Seven point Likert Scale in Anorexia. Ranks given before and after in study & control group.*-P<0.005

Review of NYHA Functional Class: Krusal Wallis test was used to give ranks amongst study & control groups on non parametric variables and their ranks were compared to each other. Higher the rank greater is the severity. They demonstrated significant decrease in their severity from the experimental group.

Table 4-B: Symptoms

	Study		Control	
Wilcoxon Signed Ranks Test - after –before	Z value	P value	Z value	P value
Body pain	-6.625	.000	-2.159	.031
Trembling	-4.601	.000	-.607	NS
Cramps	-5.494	.000	-.684	NS
Stiffness	-5.785	.000	-.845	NS
Numbness	-3.597	.000	-1.502	NS
Giddiness	-3.783	.000	-564	NS
Anorexia	-7.523	.000	-1.568	NS
Nausea	-5.815	.000	-.416	NS

Heaviness	-4.532	.000	-.540	NS
Tastelessness	-4.696	.038	-.301	NS
Abnormal taste	-2.070	.038	-.566	NS
Lack of knowledge of taste perception	-4.340	.000	-2.048	.041
Sleep apnea	-5.010	.000	-2.65	NS
Aggressiveness {anger}	-.3.344	.001	-1.889	.059
Fearful	-2.812	.005	-1.341	NS

Comparison of severity through Wilcoxon signed rank test. NS- Not significant

All the above symptoms were measured through four points Likert Scale in sleep apnea, aggressiveness and fearfulness. Seven points Likert Scale were used for the remaining symptoms. Wilcoxon signed rank test was used to compare their severity from baseline. The Z values in negative ranking indicates reduction from the baseline values. Values from body pain, lack of knowledge of taste perception and aggressiveness were the only significant values from control group. Experimental group demonstrated marked reductions in cramps, stiffness, nausea, sleep apnea, along with many other symptoms like bodypain, anorexia et.

Table 5-A: Six- Minutes' walk test

6 min Walk test	**Study**		**Control**	
	Before n-100	**After n-91**	**Before n-100**	**After n-91**
Participated but Could not walk	34	3*	23	24*
Not participated	8	4*	32	3*
Walked successfuly	58	84*	46	34*

Leven's test for equality of variances- *--$p < 0.005$

Table 5-B : Distance Walked in meters

Distance walked	**Study**		**Control**	
	Before n-100	After n-87	Before n-101	After n-58
Mean	184.52	289.25*	188.48	179.29*
St. Dev	101.14	86.40	101.79	117.93

Descriptive statistics in terms of mean, +_St.deviation and paired t test for variables in distance walked in metres.(* -- $p<.005$)

All HF cases were asked to walk along the corridor of the hospital for six minutes. It was ensured that at least two assistants were attending to them at the zero as well as end point, with seating arrangement on their way. The record of completing their six minutes walking target, reason to terminate and their total distance walked were noted in the CRF. Those who could not walk successfully were found to be breathless before the allotted time.

Table 6: Differences in weight at the end of study

Group	No. of patients	Mean	St.Dev.
Study	69	-1.9783*	2.19531
Control	47	1.3936*	5.94717

Paired t -test for examining the variables of differences in weight (*-p<.005)

There was a significant reduction in body weight of study group. This was because, improvement in appetite , perfusion to skeletal muscle along with the respiratory muscle , reducing their NYHA functional class resulting into increase in their exercise capacity and thereby consequently reducing their gross mass evidently seen as reduction in the total body weight. There was no particular medication given to the control cases for weight. Although Statins did show improvement in lipid levels but their total body weight evidently displayed a rise in the body weight.

Table 9 : 2 D Echocardiogram (Dimensions observed in mm)

2DEcho	STUDY				CONTROL			
	Before		After		Before		After	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
LVEF%	36.41	9.30	45.75*	12.5	37.44	8.45	37.05*	11.00
LVIDs	39.53	9.46	35.19*	8.33	41.66	9.85	44.05*	10.01
LVIDd	51.99	8.60	49.13*	7.81	52.87	10.64	56.07*	7.95
LA	35.88	6.54	34.70*	6.17	35.34	6.87	37.50*	6.58

Descriptive statistics in terms of mean, +_St.deviation and paired t test for variables of 2 D Echo findings.(* -- p<.005)

Since 2D Echocardiogram is solely a subjective, observer dependant parameter, it was ensured that the screenings were restricted to a single observer (before & after) to minimize the errors.

T AYU BKV

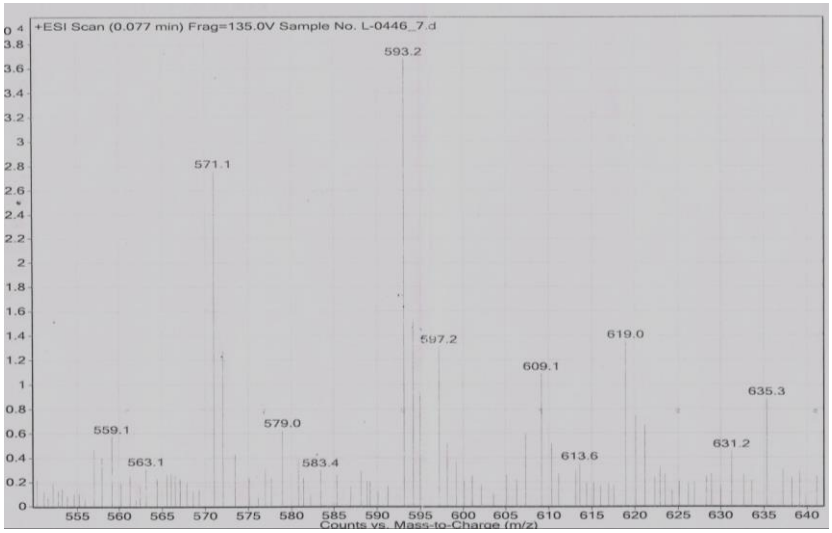
It is an EBM comprising of fruits of Terminalia chebula, Terminalia belerica, Phyllanthus emblica, Zingibar officinale, Piper nigrum, Piper longum, Semicarpus anacardium, salts of Saindhava lavana (Rock salt), Bid lavana (official substitute of black salt), Souvarvarchala lavana (black salt) in varied quantities.

All the fruits and salts were ordered in bulk from Manakarnika Aushadhalaya, Pune. They were then subjected to different processes for purification from physical and chemical impurities followed by various methods of unique standard operating procedures to obtain the

desired formulation. Later they were processed in Rajan Pharmaceuticles for tabletting, packaging and labeling followed by laboratory analysis in DALP & TUV Pune.

LCMS / MS profile of T AYU BKV

This sample was subjected through various frequencies to detect the Atomic Mass Number of the compound as shown in Fig. : 3



The electron mass spectrum of the desired formulation was detected by the peaks seen in the ESI Scan. Fragmentation was done with frequency 135 V. a blank was also run for comparison.

Various peaks are seen in the above scan. The peak at 593 has the highest signal intensity. This peak at 593 also called as signature peak in the spectrum indicates its atomic Mass Number.

Summary of ^{1}H NMR in T AYU BKV

The sample was prepared in $CDCl_3$. The instrument used was Brukar 400 M HZ. ^{1}HNMR spectrum (proton) of a mixture of T AYU BKV was plotted as signal intensity (vertical axis) vs. chemical shift.

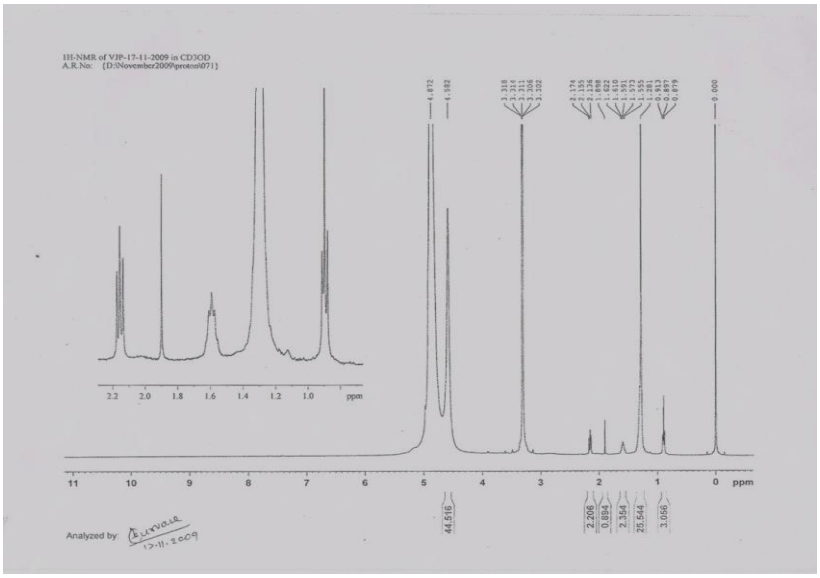


Figure 4

The CH shift at level 1 in the table indicates R- CH3 group, an SPO3 hybridized C-H group with no functional group. The peak at level two i.e. between 1.2 and 1.4 has maximum signal intensity with R-CH2-R group. Peak at 3.2 ppm indicates protons attached to Carbon attached to a hetero atom. Multiplets at 2.2 ppm is a triplet indicating CH2-CH2 structure, Singlet at 1.8 ppm a Quaternary Methyl where as Multiplets at 1.6 and 0.6 indicates substituted Carbons.

Summary of C13 NMR (Carbon NMR)

To confirm the existence of carbon atom along with the match between proton and carbon, this test was done. The levels between 15 and 40 ppm belongs to aliphatic carbon compound. Majority of peaks were found to be from the saturated carbon atoms. PPM level between 40 and 60 are that of hetero group of compounds. Eg- Na, K, Mg, I or OH. One peak at 50 ppm could be due to Alkoxy – OCH_3 or the Methyl attached to CO of pyruvate.The peaks found between 76 and 77 ppm is that of $CDCL_3$. Carbon peaks from 100 to 150 ppm indicates presence of Unsaturated Carbons in the molecule. There were no aromatic compounds found in the formulation through this C13 NMR.

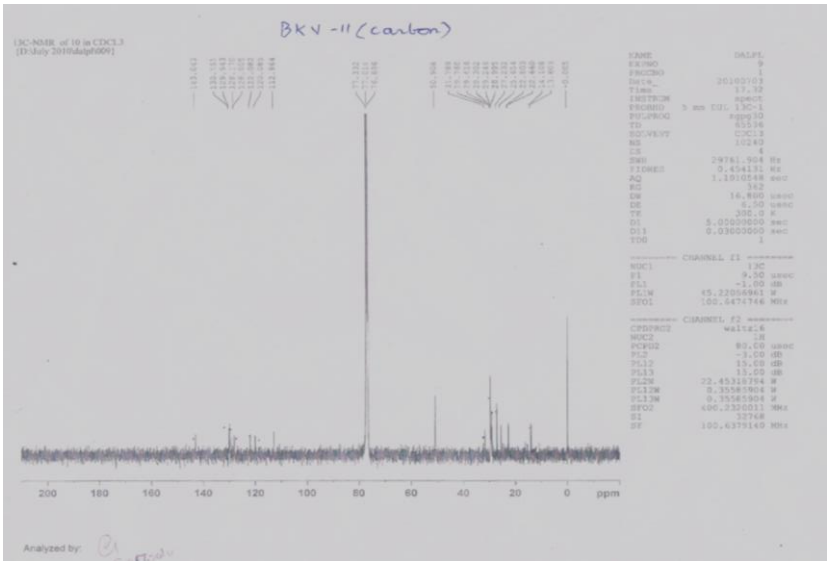


Figure 5:

NMR in Solid State: To confirm the presence of other probable compounds, another NMR with a different solvent was performed i.e... With CD_3OD. This NMR, also called as a Solid State NMR, indicates presence of Poly-Sachaarride along with Aromatic carbons (Fig 6).

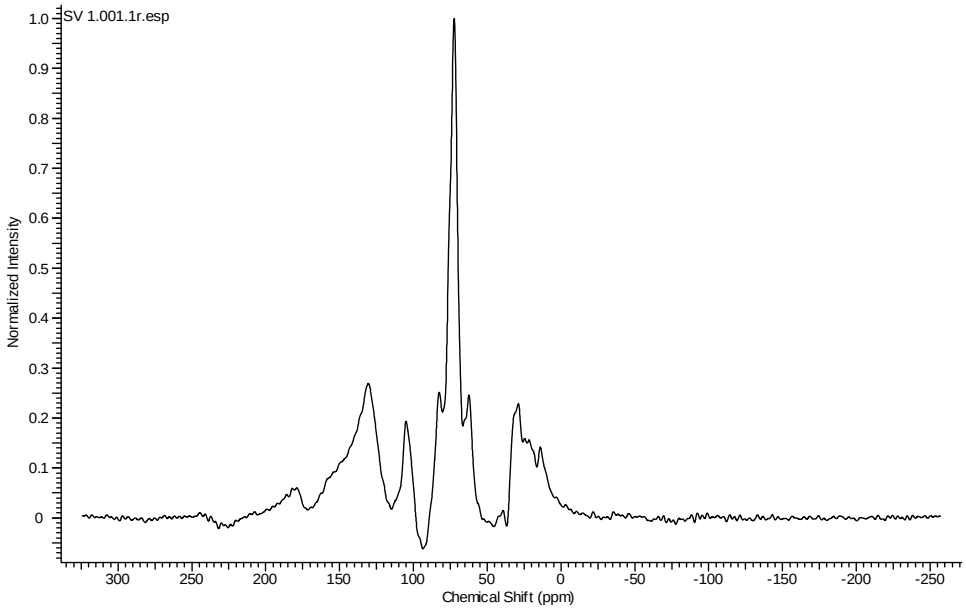
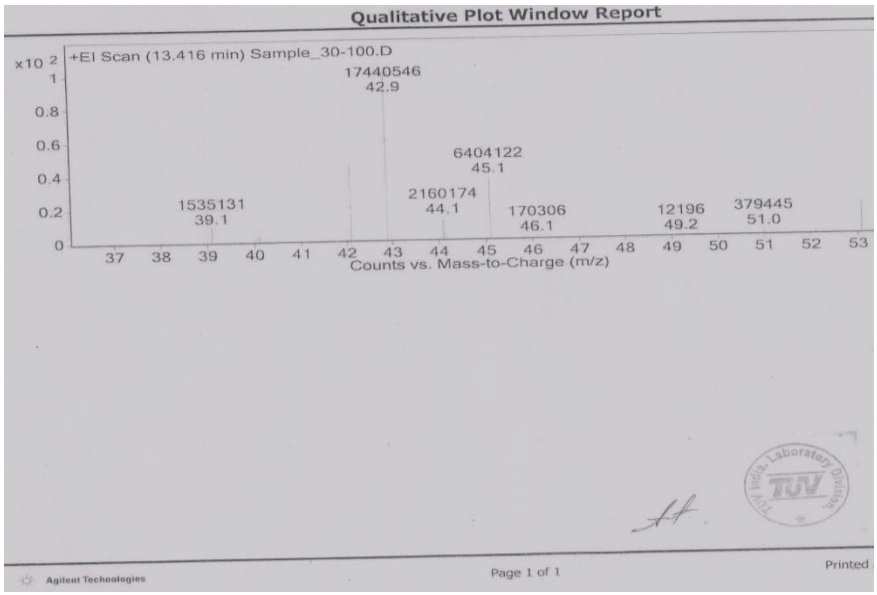


Figure 6

1H NMR and Solid State, both show presence of Fatty Acids and Lipids. This is possible due to addition of binders in the form of Gum acasia and Corn starch (approx-2% each).

Presence of Pyruvates : A TLC Scan of the formulation, T AYU BKV was done to detect the presence of pyruvates in the composition. The tablet was subjected to derivatization and

Gas Chromatograph Mass Detector with electron ionization scan. The peak at 13.41 corresponds to pyruvates family.



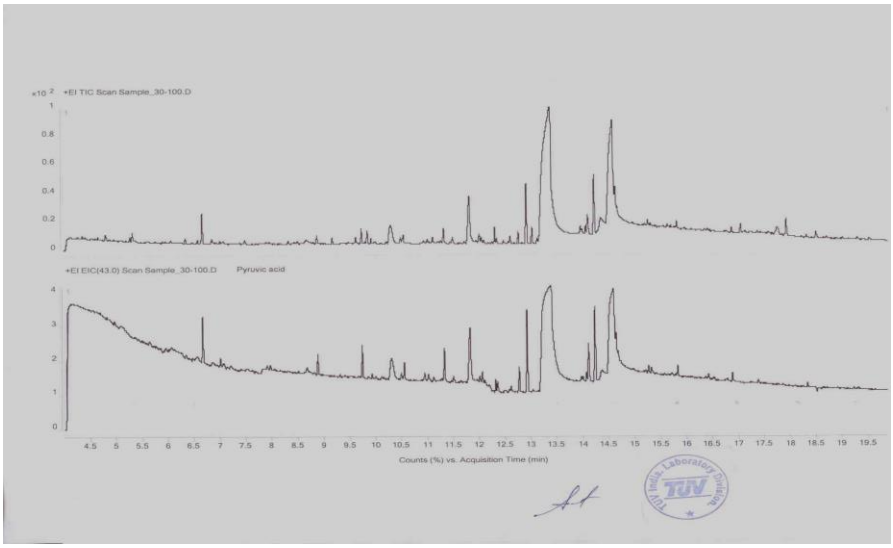


Figure 6 & 7:

The molecular mass of Pyruvic acid is 86.

This Plot indicates presence of pyruvate from the peak at 42.9 which comes from CH_3.CO (12 + 3 + 12 + 16 = 43), the peak at 44.1 is due to COO (12 + 16x2) both from Pyruvate CH_3CO.COO by cleavage between CH_3CO and COO. Thus,

CH_3-CO-COO ===== CH_3CO + COO

Table 10: Ash test & Elemental analysis of T AYU BKV

Batch	Lab Code	Ash content	Av. Wt/tab	Cu- ppm	Ca -%	Mg-%	K- %
SV001	909110280	**30%**	**130mg**	**145**	**2.6 %**	**.38%**	**14.8%**
SV0011	910060313	28.24 %	**130mg**	**240**	**6.73%**	**.96%**	**6.16%**
SV00111	R-210287 /2010-11	**30%**	**130mg**	**254**	**6.62 %**	**.86%**	**7.16%**

The tablets, each weighing around 130 mg, were found to be having elements as mentioned above. Where 125mg, as the active ingredients and the rest with binders with excepients and lubricants. The copper was found to be present and mentioned as parts per million (ppm). The other elements were found to be having more than 1000 ppm, thus were denoted in percentage. Chromium was found in all the three batches of the formulation but in a very low quantity i.e. <0.06 µg/gm.

The analysis showed absence of heavy metals such as lead, cadmium, mercury arsenic selenium and nickel.

Efficacy and safety analysis

We administered this formulation in tablet form of 125mg each along with meals twice a day (250mg/day) for 12 weeks to 100 HF individuals. There were no adverse events noted during the study period. Other than the 100 HF individuals with similar pattern of administration, improvements remained unchanged even with daily dose of 60mg and 125mg (i.e 120mg and 250 mg per day). We tried to exceed the dosage to 250 mg twice i.e 500mg a day, we observed some itchy, erythmatous patch over the exposed area of skin on 0.02% of HF case. This was noticed after 24 hrs of administration. They were found to be reduced when dosages were altered to 60 mg a day. Evidences confirm the possible intolerance to Semicarpus anacardium.[10] Almost 60 individuals continued to voluntarily consume this formulation for more than 7 years without any casualties/hospitalization.

DISCUSSION

Inspite of patients consuming the conventional HFT it is important to explore T AYU BKV's cardio protective nature, by co relating the results from the laboratory analysis and with the patient's outcome from the baseline.

Viewing the mode of drug delivery i.e. along with meals and the presence of essential elements in the formulation we may consider this desired combination not only as medicine

but also, as an important nutritional supplement to the patients of heart failure, already under the conventional therapies.

Considerable peripheral changes occur in the skeletal muscle of patients with chronic heart failure. There is also reduced blood flow to active skeletal muscle, which is related to vasoconstriction.[11] All these abnormalities in skeletal muscles, including respiratory muscles, contribute to the symptoms of fatigue, lethargy, and exercise intolerance. There has been substantial improvement in the ranks of NYHA functional class in DOE and fatigue from the study group. Contributions from this particular supplement could have been providing the support by increase in blood flow to active skeletal muscles along with the respiratory ones either by opposing the action of vasoconstriction or by fulfilling the nutritional supplement through elements.

T AYU BKV seems to be acting right from the mouth. Tastelessness, lack of sense of taste in the mouth have been acknowledged and improved in the HF cases confirming its action on salivary glands and taste buds.

Magnesium deficiency may result into symptoms like cramps, tremor, spasms, fatigue, loss of appetite, confusion, insomnia, irritability.[12] Moderate to severe magnesium deficiency can cause tingling or numbness, heart changes, rapid heartbeat, continued muscle contractions, nausea, vomiting, delirium, low calcium levels, low serum potassium levels, retention of sodium, low circulating levels of parathyroid hormone (PTH), and potentially death from heart failure.[13]

Evidence of reduction in symptoms like cramps, trembling, numbness, fatigue anorexia, nausea, vomiting and aggressiveness of the HF patients suggests the role of Magnesium could have been vital in the study group. Moreover of the 325 magnesium-dependent enzymes, the most important enzyme reaction involves the creation of energy by activating adenosine triphosphate (ATP), the fundamental energy storage molecule of the body [14] thus reducing the fatigue levels.

Most of the elements are absorbed in the small intestine, so the same pattern of absorption of active elements from this formulation i.e. Calcium, Potassium and Copper was considered. Calcium enters ECF from the gut by absorption and causes muscle contraction during action potential by entering the ICF.[15]

Thus may contribute support to the contractile elements of the heart as evident in improving its contractility (LVEF%).There was no evidence of cardiac arrhythmia (tachycardia) during the study, may suggest that excess calcium ion pooling may have been prevented as the desired medicine is taken as nutritional supplement, and only required amount of elements may have been absorbed by inner mucosal layer of the small intestines. Similarly Potassium prevents respiratory distress along with muscle weakness [16] which was evident through patients improving their NYHA functional class.

Copper deficiency has been linked to diseases such as cardiomyopathy.[17] The human body normally contains copper at a level of about 1.4 to 2.1 mg for each kg of body mass.[18] When copper is first absorbed in the gut it is transported to the liver bound to albumin. The RDA for copper in normal healthy adults is 0.9 mg /day; however, professional research on the subject recommends 3.0 mg/day.[19, 20] Copper deficiency is the only nutritional insult that elevates cholesterol, blood pressure, has adverse effects on electrocardiograms and arteries, impairs glucose tolerance, and promotes thrombosis and oxidative damage.[21] More than 80 anatomical, chemical, and physiological similarities between animals deficient in copper and people with ischaemic heart disease have been identified. Copper deficiency in animals can induce cardiac enlargement, pleural effusion, and heart failure that are reversible with copper supplementation.[22, 23]

Reduction in left ventricular internal dimensions during systole as well as during diastole along with Left Atrial dimensions in the study group may be contributed by copper supplement where as the control group could have manage to maintain them.

Functional status and cardiac reserve of patients with chronic heart failure can be objectively characterized by determining exercise tolerance. Six minutes walk test is one of the most common modalities for evaluating the functional capacity of HF patients and is used to evaluate low level or sub maximal work which is more compatible with daily activities.

Even though the experimental group could not walk to an optimal distance as prescribed by WHO (300mtrs) [24] there have been a substantial improvement not only in walking successfully for six minutes but also to a farther distance for the same given time as compared to the control. Since regular exercising causes changes in central and peripheral blood flow, brings improvement in endothelium with an objective improvement in ventilation and thereby enhancing their quality of life.[25]

Pyruvates plays a major role in generation of ATP during Glycolysis. Its presence indicates production of ATP followed by more energy production which was truly evident as improvement in exercise capacity and NYHA functional class.

CONCLUSION

The comprehensive effect of T AYU BKV may have contributed successfully in enhancing the left ventricular ejection fraction from the baseline proving its inotropic property without any adverse events like respiratory distress.

When taken as a nutritional supplement, it enhances the desired multiple actions in alimentary canal thereby getting absorbed wisely to enter into the blood stream to cause an enhanced perfusion in exercising skeletal muscle from the central and peripheral skeletal system bringing about a desired change in the myocardium by improving the contractility demonstrating a superior recovery . This effect may prove to be beneficial in reverting the disease progression and improve their quality of life.

IMPLICATIONS

There is a need to evaluate the efficacy in myofibrils with detailed study on rodents to determine its pharmacokinetics.

ACKNOWLEDGMENT

I dedicate my research studies to my revered Sir Late Vaidya Chandrashekhar Ganesh Joshi. I thank Ayurvedacharya Vaidya Dilip Gadgil and Cardiologist, Dr Rajesh Badani to help me in their respective fields. It was due to Lokmanya Medical Research Centre, Chinchwad, I could ethically succeed my clinical research.

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