Research Article

www.ijrap.net

CLINICAL EVALUATION OF EFFICACY AND SAFETY OF TAB HF-B1 IN OSTEOPENIA AND OSTEOPOROSIS: AN OBSERVATIONAL STUDY

Omkar Kulkarni [1]*, Veena Deo [2] and Bharatbhushan Shrikhande [2]
[1]Samshodhanam Healthcare Research Services, Pune, Maharashtra, India
[2]Siddhayu Ayurvedic Research Foundation Pvt. Ltd, Nagpur, Maharashtra, India

Received on: 20/12/18 Accepted on: 22/02/19

***Corresponding author**
E-mail: ayurom@gmail.com

DOI: 10.7897/2277-4343.100234

ABSTRACT

Osteopenia and Osteoporosis has been a very common problem faced globally on account of faulty lifestyle, diet and environmental reasons. It increases chances of debility due to frequent fractures and inflammatory conditions. Conventional medications contain synthetic calcium supplementation which mostly remains a temporary solution with potential gastrointestinal and cardiovascular side effects. This calls for the need to explore effective treatment modalities. Herbal medicines have proved efficacious in the treatment of bone disorders since ancient time. Herewith we studied Tab HF-B1, a herbo-mineral Ayurvedic formulation for the treatment of osteopenia and osteoporosis in an open label, observational clinical study. We observed that there was decrease in mean ranks of symptoms such as bone pain and joint pain. There was a significant increase in T-Score and BQI. No adverse events were recorded suggesting a good compliance and tolerability. Thus Tab HF-B1 was found to be safe and effective in the management of patients with Osteopenia and Osteoporosis.

Keywords: Polyherbal Formulation, Natural Calcium, Osteoporosis, Calcium Supplementation.

INTRODUCTION

Osteoporosis and Osteopenia

Osteo means bones and porous (a Greek word) means structure like sponge. The condition in which bones become like sponge that is they become fragile and compressible is called as Osteoporosis. In this condition density and strength of bones decreases which make them fragile. Osteoporosis results in frequent fractures of bones. Osteopenia is a prior condition of osteoporosis. In this condition bones are slightly less dense than normal bone but not to the degree of bone in osteoporosis.[1,2] According to Ayurveda, there is functional relation between Vaat Dosha and Asthi Dhatu (Bone tissue). Increased qualities of Vaat decreases bone tissue qualities and vice versa. Vitiated Vaat results in Osteoporosis, pain, and fragility in bones.[3]

Global Scenario of Osteoporosis

Osteoporosis becomes more common with age. It is more common in women than men. In developed world depending upon method of diagnosis, 2% to 8% of males and 9% to 38% of females are affected. Asian people are more on high risk. Osteoporosis takes a huge personal and economic toll with over 80%, 75%, 70% and 58% of forearm, humerus, hip and spine fractures, respectively, occur in women. Overall, 61% of osteoporotic fractures occur in women, with a female-to-male ratio of 1:6. [4]

Need of Study

Osteoporotic people are more prone to frequent fractures. Some of major fractures need surgery to recover. So, quality and strength of bony tissue are most important things which should be focused while treating osteoporosis. In Modern system line of treatment and Osteoporosis is in the form of diet, exercise and some calcium supplements. But long-term use of calcium supplement can cause symptoms like constipation, nausea, depression, dry mouth etc.[5] This creates need to explore some formulation from traditional text like Ayurveda which will help to increase the strength and quality of bone tissue. The present clinical study is designed to observe efficacy of formulation in osteoporotic people.

Ayurvedic view of Osteoporosis

According to Ayurveda Asthi Dhatu is the sixth element or body tissue. It evolves from Fatty a tissue that is Meda Dhatu. Again, there is strong correlation between Vaat Dosha and Asthi Dhatu.

Food or activities which aggravate Vaat Dosha from body, are responsible for deprivation of qualities of Asthi i.e. bone. So, increase in qualities of Vaat decreases qualities of Asthi and vice versa. Teeth, nails and hair are the waste products of Asthi Dhatu.[3]
Symptoms described for Asthikshaya in texts are as follows:

1. Asthitoda- Pain in bones
2. Danta-kesha-nakhadisadan- Quality and quantity of teeth, hair and nails decreases.

In view of the need of a safer and better alternative to conventional calcium supplementation for the common bone disorders, we planned a study to evaluate safety and efficacy of herbo-mineral formulation Tab HF-B1 using an observational study.

Aim

To evaluate the efficacy and safety of Tab HF-B1in Osteopenia and Osteoporosis

Objectives

Primary Objective
To evaluate efficacy of TabHF-B1 in Osteopenia and Osteoporosis using following parameters
1. Peripheral Dual energy x-ray absorptiometry (DXA)
2. Clinical parameters like bone pain, weakness, frequency of fractures etc.

Secondary Objective
1. To assess the short- and long-term tolerability
2. Presence of any adverse event during the study related to study
3. Need to stop the treatment due to any ADR or need for surgical intervention

Literature review

About the disease
In osteoporosis the density of bone decreases resulting in fragile and weak bones. Osteoporosis is composed of two word osteo- meaning bones and porosis- meaning porous so osteoporosis literally means porous bones. Osteopenia is a condition of bone which results in bones slightly less dense than normal bones.
In osteoporosis bones can fracture even with minor injury that in normal conditions would not cause bone to fracture.[6]

Causes and Symptoms of Osteoporosis

Causes of Osteoporosis can be differentiated in following categories:
1. Diet- Low calcium diet and poor nutrition diet
2. Hormonal cause-
   i. Low level of estrogen can cause osteoporosis in women.
   ii. Low level testosterone in males can cause osteoporosis.
3. Disease induced Osteoporosis- Arthritis; Rheumatoid arthritis weakens the affected bones.
4. Hyperthyroidism as Thyroid hormone is called as Growth hormone it also affects bones.
5. Drug induced osteoporosis- Long term use of some drugs like heparin, corticosteroids; antiepileptic drugs can cause osteoporosis.
6. Other causes-
   i.Lack of exercise
   ii.Improper absorption or mal absorption of nutrients through intestine
   iii.Family history of osteoporosis
   iv.Low body weight people are prone to osteoporosis

Symptoms of Osteoporosis

Early, detectable signs of bone loss are rare. Often people don't know they have weak bones until they've broken their hip, spine, or wrist. Some signs and symptoms can point toward bone loss. However, these are some of the signs which could lead to diagnosis of osteoporosis:
1. Receding gums
2. Weaker grip strength
3. Weak and brittle fingernails

When the bone has deteriorated significantly more, following symptoms can be found:

1. Loss of height
2. Fracture from a fall
3. Back or neck pain
4. Stooped posture or compression fracture[1,2,7,8]

Consequences of Osteoporosis

Osteoporotic bone fractures are responsible for considerable pain, decreased quality of life, lost workdays, and disability. Up to 30% of patients suffering a hip fracture will require long-term nursing-home care.

Information regarding Calcium

Calcium along with protein, collagen plays an important role in formation of normal bone. All these factors give strength to bone. When calcium level in bone decreases density and strength of bones decreases and following stages or conditions happens.[5]

BMD (Bone Mineral Density)

A bone mineral density (BMD) test is can provide a snapshot of bone health. The test can identify osteoporosis, determine risk for fractures (broken bones), and measure response to osteoporosis treatment.

The T-Score

T-score between +1 and −1 is considered normal or healthy. A T-score between −1 and −2.5 indicates low bone mass, although not low enough to be diagnosed with osteoporosis. A T-score of −2.5 or lower indicates osteoporosis. The greater the negative number, the more severe the osteoporosis.

About the formulation and its ingredients

Tab HF-B1 is a proprietary Ayurvedic formulation which helps in improving the metabolism of Asthi dhatu.[9,10]

Muktashukti

Oxide of pearl oyster shell is mainly used in calcium deficiency disorders like Osteopenia and Osteoporosis Fractures etc. It is mentioned in Ayurveda Rasashastra for a variety of diseases like hyperacidity, colitis, diarrhea and bone disorders. It is also evaluated for its anti-inflammatory activity *in vivo*.[11]

Shankha

Indian conch or Shankha is a carnivorous gastropod, belonging in to the Mollusc's largest class Gastropoda and family Turbinelliadae. Its scientific species name is *Turbinella pyrum*. Shankha bhasma is an Ayurvedic preparation commonly used mainly in the treatment of gastrointestinal disorders and bone problems.[12]

Kaparda

Cowry commonly refers to the external shell of sea animal *Calx convex* (commonly known as money cowry) found in coastal areas of the Indo-Pacific sea. Chemically, it is Carbonate of Calcium and is shown to benefit diseases with digestive system and musculoskeletal disorders.[14,15]

Hadjod

Cissus quadrangularis - Literally means protecting Bones from destruction. It has a potent Fracture Healing property. It increases Bone Mineral Density by increasing the uptake of mineral Calcium and phosphorus by osteoblasts (Bone forming cells).[16,17] The methanolic extract of *Cissus quadrangular is* promoted the healing process of experimentally fractured radius-ulna of dogs,

as evidenced by radiological and histopathological examinations.[18,19]

Godanti

Godanti Bhasma is an Ayurvedic medicine, prepared from Gypsum. It is also used in the treatment of migraine.[20]

Arjuna

Terminalia Arjuna (usually simply referred to as Arjuna) is a tree bark. It is shown to improve degeneration of bones and reduce the inflammatory changes thereby.[21]

MATERIALS AND METHODS

Composition

Tab HF-B1is a Herbo-mineral Formulation and contains:

Table 1: Composition of Tab HF-B1

S. No	Ingredient Name	Botanical / Scientific Name	Form	Quantity
1.	Muktashukti	*Pearl Oyster Shell*	Bhasma	80 mg
2.	Shankha	*Sacred Conch*	Bhasma	60 mg
3.	Kaparda	*Calxconvex*	Bhasma	40 mg
4.	Hadjod	*Cissusquadrangularis*	Powder	75 mg
5.	Godanti	*Gypsum*	Bhasma	30 mg
6.	Arjuna	*Terminaliaarjuna*	Extract	75 mg
7.	Excipients			Q.S.

Study Design

Open label, observational clinical study

CTRI Registration details

Registration number: CTRI/2017/08/009259(Attached separately)

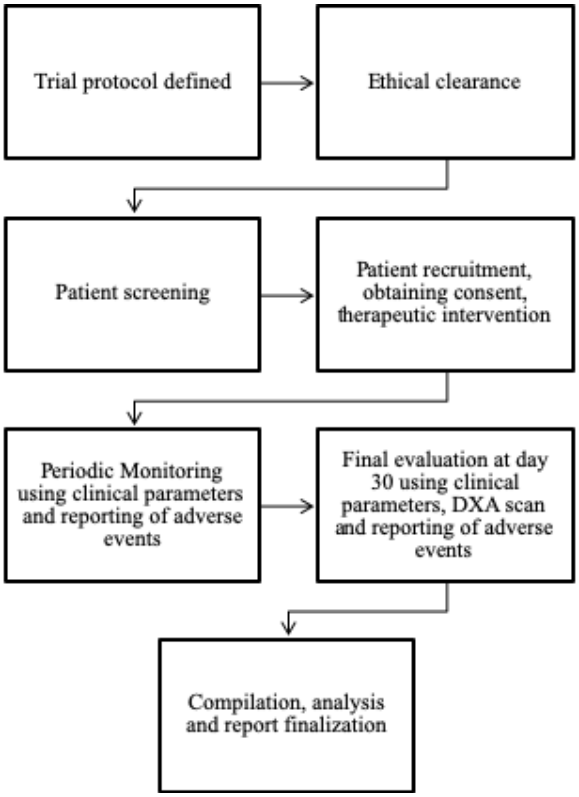

Figure 1: Study methodology flowchart

Ethics Committee Approval

The ethics committee approval for the study was obtained on 3rd January 2017 from Integrated Ethics Committee. (Attached as Annexure I)

Study Methodology Flowchart

The study was carried out as per International conference of Harmonization-Good Clinical Practices (ICH-GCP).

RESULTS

Demographics

The study started in the month of February 2017 at the site. A free checkup and counseling camp was organized for screening the patients. The patients with low bone density were explained in detail the objective and possible benefits / side effects of the study trial. They were also explained their right to participate or not in the study at any given point. Patients willing to participate were selected screened for inclusion / exclusion criteria and assigned the treatment accordingly. Those who did not wish to participate were excluded from the study and were treated as per standard treatments.

The patients were screened initially using free checkup camps conducted at different time intervals. A total of 5 checkup camps were conducted with over 200 registrations. Out of the registered candidates, 45 were complying for the low bone mass and 35 patients were finally recruited for the study and were selected for the final analysis. We observed no dropouts in the given trial probably because of shorter duration of trial, good tolerability of the formulation and / or good patient compliance.

Sex-wise distribution of patients

The frequency distribution of patients according to Gender along with its bar graph is given below.

Table 2: Sex wise distribution of patients

Gender	Frequency	Percent
Female	11	31.4
Male	24	68.6
Total	35	100.0

Age-wise distribution of patients

The median age of the patients recruited was 50.5 (range 20 – 61) years. Most of the patients were post 40 years.

The frequency distribution of patients according to Age along with its bar graph is given below.

Table 3: Age wise distribution of patients

Age	Frequency	Percent
20 to 29	1	2.9
30 to 39	1	2.9
40 to 49	10	28.6
50 to 59	15	42.9
60 to 69	5	14.3
70 to 79	2	5.7
80 and Above	1	2.9
Total	35	100.0

Baseline BQI distribution

Baseline BQI as assessed using DXA scan suggests a maximum number of patients having BQI in the range of 60-80. The frequency distribution of patients according to BQI along with its bar graph is given below.

Table 4: Baseline BQI distribution

BQI	0th Day	30 days
30.00 to 50.00	8	5
%	**22.9**	**14.3**
50.00 to 70.00	12	13
%	**34.3**	**37.1**
70.00 to 90.00	13	15
%	**37.1**	**42.9**
90.00 to 110.00	1	1
%	**2.9**	**2.9**
110.00 to 130.00	1	1
%	**2.9**	**2.9**
Total	35	35
%	**100.0**	**100.0**

Baseline T – score distribution

Baseline T – score for the patients suggestive of osteoporotic changes in the patients with almost all of them having a T – score less than -1.0.

The frequency distribution of patients according to T Score along with its bar graph is given below.

Table 5: Baseline T Score distribution

T score	0th Day	30 days
-4.00 to -3.00	7	3
%	**20.0**	**8.6**
-3.00 to -2.00	16	16
%	**45.7**	**45.7**
-2.00 to -1.00	12	15
%	**34.3**	**42.9**
-1.00 to 0.00	0	1
%	**0.0**	**2.9**
Total	35	35
%	**100.0**	**100.0**

Distribution of joint pain symptom

The frequency distribution of patients according to Pain in Joints along with its bar graph is given below.

Table 6: Distribution of joint pain syndrome

Pain in Joints (Grade)	0th Day	15 Days	30 days
Grade 0	2	6	11
%	**5.7**	**17.2%**	**31.4**
Grade 1	4	7	10
%	**11.4**	**20%**	**28.6**
Grade 2	8	11	11
%	**22.9**	**%**	**31.4**
Grade 3	9	11	3
%	**25.7**	**%**	**8.6**
Grade 4	10	0	0
%	**28.6**	**%**	**0.0**
Grade 5	2	0	0
%	**5.7**	**%**	**0.0**
Total	35	35	35
%	**100.0**	**100.0**	**100.0**

Distribution of bone pain symptom

The frequency distribution of patients according to Bone pain along with its bar graph is given below.

Table 7: Distribution of bone pain syndrome

Bone pain (Grade)	0th Day	15 Days	30 days
Grade 0	2	6	11
%	**5.7**	**17.1**	**31.4**
Grade 1	4	8	11
%	**11.4**	**22.9**	**31.4**
Grade 2	8	15	10
%	**22.9**	**42.9**	**28.6**
Grade 3	10	6	3
%	**28.6**	**17.1**	**8.6**
Grade 4	9	0	0
%	**25.7**	**0.0**	**0.0**
Grade 5	2	0	0
%	**5.7**	**0.0**	**0.0**
Total	35	35	35
%	**100.0**	**100.0**	**100.0**

Statistical analysis
Factors: T score, BQI

1. To test whether there is significant difference in T score and BQL on 0th day and 30th day on an average.
2. To test the hypotheses,
3. The null hypothesis, H_0:
4. There is no significant difference in 0th day and 30th day scores on an average. Vs.
5. The alternative hypothesis, H_a:
6. There is significant difference in 0th day and 30th day scores on an average.
7. The test used is paired t test.

Table 8: Standard error mean

Paired Samples Statistics					
		Mean	N	Std. Deviation	Std. Error Mean
T Score	0th Day	-2.4029	35	.74656	.12619
	30 days	-2.0086	35	.62656	.10591
BQI	0th Day	65.2286	35	17.47495	2.95381
	30 days	67.1743	35	16.86520	2.85074

Table 9: p value

Paired Samples Test							
		Paired Differences			t	df	p value (2-tailed)
		Mean	Std. Deviation	Std. Error Mean			
T Score	0th Day - 30 days	-.39429	.45371	.07669	-5.141	34	.000
BQI	0th Day - 30 days	-1.94571	2.41738	.40861	-4.762	34	.000

Since p value < 0.05, the level of significance for both factors; there is strong evidence to reject the null hypothesis

Inference

1. There is significant difference in 0^{th} day and 30^{th} day scores on an average.
2. The mean values suggest that T Score and BQI are increasing from 0^{th} day to 30^{th} day.

Factors: Pain in Joints, Bone Pain

1. To test whether there is significant difference in Pain in Joints and Bone pain on 0^{th} day, 15^{th} day and 30^{th} day on an average.
2. To test the hypotheses,
3. The null hypothesis, H_0:
4. There is no significant difference in 0^{th} day, 15^{th} day and 30^{th} day scores on an average. Vs.
5. The alternative hypothesis, H_a:
6. There is significant difference in 0^{th} day, 15^{th} day and 30^{th} day scores on an average.
7. The test used is Freidman's test.

Table 10: Mean ranks

Mean Ranks		
	Pain in Joints	Bone pain
0th Day	2.81	2.91
15 Days	1.89	1.71
30 days	1.30	1.37

Table 11: Test statistics

	Pain in Joints	Bone pain
N	35	35
Chi-Square	52.422	56.421
df	2	2
P value	.000	.000

Since p value < 0.05, the level of significance for both factors; there is strong evidence to reject the null hypothesis

Inference

1. There is significant difference in 0^{th} day, 15^{th} day and 30^{th} day scores on an average.
2. The mean rank values suggest that Pain in JointsandBone pain are reducing from 0^{th} day to 30^{th} day.

Mean Rank Plot

The mean rank plot showing mean rank values is as given below.

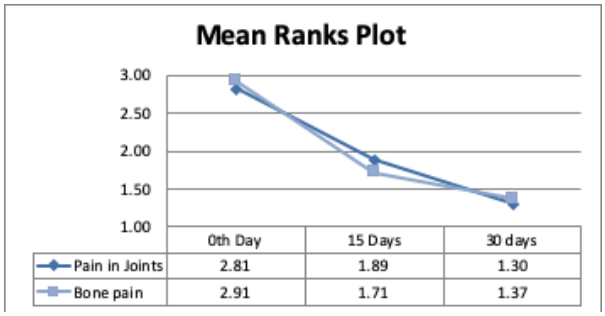

Figure 2: Mean plot ranks

Summary

The mean rank plot suggest that Pain in Joints and Bone pain are reducing from 0^{th} day to 30^{th} day on an average.

DISCUSSION

Osteoporosis has been a common problem faced by almost every person some day in his life. Age related loss of bone mass can be considered as a physiological phenomenon however, a variety of reasons like lack of nutritious food, sedentary lifestyle and lack of exposure to sunlight and increasing mental stress are the commonest of etio-pathological causes of pathological loss of bone tissues. Post menopausal bone weakness is also very prevalent now-a-days because of drastic change in the women's lifestyle and hormonal imbalances.

Our study recruited total of 35 adult subjects having a T – score < -1 on a DXA – Scan. All of the subjects were having some or the other complaints of bone pain or joint pain. Most of the complaints were attributed to muscle weakness and inflammatory conditions. In case of severe osteoporosis the complaints could be attributed to bone weakness leading to degenerative and inflammatory joint disorders like osteoarthritis. Some of them were advised external oil application and hot fomentation in case of extensive joint pain. As required drugs such as Amruta Guggulu, Yograj Guggulu and some digestives were added to some of the patients (7 out of 35). These drugs were ensured to

be recorded for the dosage administered and any possible relation with the treatment drugs.

Tab HF-B1was very well tolerated by all the patients as we observed no patient reported adverse events through the course of study. Patients were advised to report any complaint whenever he observes to the investigator, however no such reports were made by the participants. T – score and Bone Quality Index (BQI) were the –parameters evaluated for the patients to assess bone density using DXA scan. Baseline parameters suggested a significant loss of bone mass in the participants which was improved upon treatment of Tab HF-B1 in 30 days. For T – Score and BQI scores, the improvement was statistically significant demonstrating potential anti-osteoporotic effect of Tab HF-B1. The formulation Tab HF-B1 can be considered as an optimum blend of herbs having a potential to improve bone metabolism, stimulate activity of osteoblasts and help improve bone turnover. This is seen in this observational study where the treatment improved overall bone mass development as evident by T – score and BQI score improvement.

Muktashukti, Shankha, Kaparda and Godanti are natural Calcium supplements which are used by Ayurvedic Physicians for giving strength to the musculoskeletal system, especially bones. They are used owing to their native strength and ability to nourish body tissues. They also improve digestion and reduce vitiated Pitta and Vaata which are the causes of bone mass depletion. Hadjod is a herb that strengthens the joints and also nourishes Asthi. It reduces vitiated Vaata and in turn prevents osteoporotic damages. Arjuna is an astringent herb commonly used for circulatory disorders. Also it is used in improving nutrient supply to body tissues and enhancing quality of nourishment. Based on the results obtained and literature review, we can hypothesize that combination of these herbs and minerals boosts Agni which in turn improved micro and macro metabolism. The improved nutrients then nourish bones resulting into prevention and repair of osteoporosis. Bone tissue as per Ayurveda is nourished in 6 weeks whereas the trial was conducted for 30 days. Hence a longer duration of drug supplementation may help improve in the BQI.

CONCLUSION

The study suggested a potential anti-osteoporotic effect of Tab HF-B1 in osteopenia and osteoporosis. The drug was also well tolerated by the subjects indicating safety of the formulation.

REFERENCES

1. Golob AL, Laya MB. Osteoporosis. Med Clin North Am. 2015; 99(3): 587-606.
2. Pawlita M. The Diagnosis of Osteoporosis. J Bone Miner Res 1994; 9(8): 1137-41.
3. Pisharodi S. Acharya Vagbhata's Astanga Hrdayam. Volume 1,Punarogya Holistic Healing Centre; 2016.
4. iofbonehealth.org, International Osteoporosis Foundation. https://www.iofbonehealth.org/facts-statistics; 2018.
5. betterhealth.vic.gov.au. Department of Health V. Calcium. Better Health Channel; State Government of Victoria. Published. http://www.betterhealth.vic.gov.au/bhcv2/bhcarticles.nsf/pages/Calcium; 2011.
6. Kanis JA, Melton LJ, Christiansen C, Johnston CC, Khaltaev N. The diagnosis of osteoporosis. J Bone Miner Res 2009; 9(8): 1137-1141.
7. Sheu A, Diamond T. Secondary osteoporosis. Aust Prescr 2016; 39(3): 85-87.
8. Sonnino D, Setnikar I, Chard J, Dieppe P. Glucosamine for osteoarthritis. BMJ 2001; 323(7319): 1003.
9. Mulchand S, Seema M. Formulation of polyherbomineral matrices for treatment of osteoporosis. Asian J Pharm Clin Res 2018; 11(1): 217-223.
10. Shahabuddin B, Ramesh H, Iqbal MM, Rao KS. Anti-osteoporotic activity of ostinu, a herbo-mineral preparation in ovariectomized rats. Biosci Biotechnol Res Asia 2010; 7: 321-326.
11. Chauhan O, Godhwani JL, Khanna NK, Pendse VK. Anti inflammatory activity of Muktashukti bhasma. Indian J Exp Biol. 1998; 36(10): 985-989.
12. Seth A, Maurya SK, Srivastava A. Formulation development, characterization and estimation of acid neutralization capacity of Shankha Bhasma tablets for the treatment of dyspepsia. Int J Pharm Pharm Sci 2014; 6(2): 467-469.
13. Pandit S, Sur TK, Jana U, Bhattacharyya D, Debnath PK. Anti-ulcer effect of shankha bhasma in rats: A preliminary study. J Biol Chem 2000; 32: 378-380.
14. Bhagwat M, Kashalkar RV, Bhave AS, Vaidya SS, Ramaswamy V. Traditional preparation of Kapardika bhasma and physico chemical characterization of the bhasma and its intermediates. Indian Drugs 2004; 41(4): 207-213.
15. Dhamal S, Wadekar MP, Kulkarni BA, Dhapte VV. Chemical Investigations of Some Commercial Samples of Calcium Based Ayurvedic Drug of Marine Origin: Kapardika Bhasma. IOSR J Pharm Biol Sci 2013; 6(4): 2319-7676.
16. Teware K, Singh P, Mehta R. Phytochemical extraction and analysis of medicinally important plant *Cissus qudrangularis* L. (Hadjod). Biomed Pharmacol J 2011; 4(1). http://biomedpharmajournal.org/?p=187317.
17. Sharma N, Patni V. Determination of extractive value of *Cissus quadrangularis* L. A potent bone healer with different solvents. J Phytol Res 2006; 9(1): 143-144.
18. Kaur R, Malik CP. *Cissus quadrangularis* L - Its botany, chemistry and medicinal importance: A review. Int J Pharm Clin Res 2014; 6: 27-35.
19. Sheikh S, Siddiqui S, Dhasmana A, *et al*. *Cissus quadrangularis* Linn. Stem Ethanolic Extract Liberates Reactive Oxygen Species and Induces Mitochondria Mediated Apoptosis in KB Cells. Pharmacogn Mag 2015; 11(3): 365-74.
20. Dubey N, Mehta RS, Sharma P, Ghule S, Bhowmick M. Toxicological and pharmacological assessment of Godanti bhasma. Asian J Chem 2012; 24: 4653-4656.
21. Trivedi A, Katti HR, Shalavadi MH, Ramkishan A, Chandrashekhar VM. Anti-osteoporotic activity of ethanol extract of *Terminalia arjuna* (Roxb.) wight and arn. on ovariectomized rats. Indian J Nat Prod Resour 2015; 6(2): 98-105.

Cite this article as:

Omkar *et al*. Clinical evaluation of efficacy and safety of TAB HF-B1 in osteopenia and osteoporosis: An observational study. Int. J. Res. Ayurveda Pharm. 2019; 10(2):41-46
http://dx.doi.org/10.7897/2277-4343.100234

Source of support: Nil, Conflict of interest: None Declared