WORLD JOURNAL OF PHARMACY AND PHARMACEUTICAL SCIENCES
SJIF Impact Factor 7.421
Volume 7, Issue 12, 919-934 Research Article ISSN 2278 – 4357

PROSPECTIVE OBSERVATIONAL PHASE IV OPEN LABEL STUDY TO COMPARE THE EFFECTIVENESS OF STANDARD TREATMENT TO TURMOCIN, TURMOCIN PLUS TABLET AS ADDON TO STANDARD TREATMENT IN OSTEOARTHRITIS

Dr.Vinit Jain, Dr.Satish Jain, Dr.Ashwin Porwal*, Vd.Swapnil Bhowate

[1]Consultant Orthopaedic Surgeon ,Sharda Hospital.

[2]Consultant Orthopaedic Surgeon, Sharda Hospital.

[3]Consultant Surgeon, Healing Hands Clinic.

[4]Manager Healing Hands Clinical Research Services.

Article Received on
12 Oct. 2018,

Revised on 02 Nov. 2018,
Accepted on 23 Nov. 2018

DOI: 10.20959/wjpps201812-12809

***Corresponding Author**
Dr. Ashwin Porwal
Consultant Surgeon & Head of Institution Healing Hands Clinic 4th floor, millennium star extension. Above KFC, adjacent to ruby hall clinic, Dhole Patil road, Pune. Pin code-411001.

ABSTRACT

Osteoarthritis the most common form of arthritis, and one of the leading causes of pain and disability worldwide. In Asian countries it is prevalence ranging from 38.1% to 46.8% and specifically in India study reported it as 28.7% in age >40 years. Common manifestations of osteoarthritis are pain which prominently treated with NSAIDS (non-steroidal anti-inflammatory drugs) and analgesic as current standard of care. Adverse events with NSAIDS reported are gastric ulceration, hemorrhage and perforation. United states food and drug administration(USFDA) has approved curcuminoids as Generally Recognized As Safe. At 95% concentration dose of curcuminoids: curcumin, bisdemethoxycurcumin, and demethoxycurcumin reported as safe. Turmocin and turmocin plus tablet used in this study in which addition of black pepper may help in increasing bioavailability. The primary objective of this study to compare the effect of turmocin, turmocin plus tablet as add on with current standard care of treatment in osteoarthritis patients. Secondary objective was to see effectiveness of Tablets with Haridra (Rhizome) Curcuma longa 500mg, Marich (Fruit) *Piper nigrum* 250mg and Haridra Ext, Curcumin 95% (Rhizome) *Curcuma longa* 500mg Marich (Fruit) *Piper nigrum* 250mg. WOMAC Osteoarthritis Index score were used for comparisons. Participants were also assessed for pain, stiffness, swelling, restricted movements in joints time duration, variation in pain also measured as per season and time of

the day. Group III participants showed best results in WOMAC score with p value <0.001 mean (SD) as 1.78(0.93) using paired t test.

KEYWORDS: STD= Standard Treatment, STD + T=Standard Treatment with add on Turmocin Tablet, STD + TP =Standard Treatment + Turmocin plus Tablet, PF= Physical function, RM= Restricted Movements.

INTRODUCTION

Osteoarthritis the most common form of arthritis, and one of the leading causes of pain and disability worldwide. According to World Health Organization (WHO) 9.6% of men and 18.0% of women aged over 60 years have symptomatic osteoarthritis worldwide. In individuals with osteoarthritis 80% persons have limited movement and nearly 25% showed inability for performing their routine activities. An estimated 10% to 15% of all adults aged over 60 have some degree of Osteo Arthritits (OA).[1] In OA loss of functional capacity, walking difficulty, difficulty in self-care & movements, going up and down using stairs increases the risk of morbidity.[2] It is also found as third leading cause of lost in life-years due to disability.[3] In Asian countries its prevalence ranging from 38.1% to 46.8%[4,5] and specifically in India study reported it as 28.7% in age >40 years.[6] Common manifestations of osteoarthritis are pain which prominently treated with NSAIDS (non-steroidal anti-inflammatory drugs) and analgesic as current standard of care.[7] Adverse events with NSAIDS reported are gastric ulceration, hemorrhage and perforation.[8] These effects takes such individual towards other options like customized dietary supplements, including glucosamine[9], chondroitin[10], and S-adenosylmethionine (known as SAMe)[11], and complementary and alternative treatments including medicinal herbs or polyherbal formulations.[12] In Ayurveda (1900 BC) wide therapeutic activities of turmeric in variety of diseases and conditions like anti-inflammatory, hepatic disorders, infectious and blood disorders has already been explained.[13-14] Action of curcumin in various levels of inflammation effectively works as due to modulation of pro-inflammatory interleukin production and it decreases the action of phospholipase A2, cyclooxygenase- 2, and 5-lipoxygenase. It does not affect Cox-1 activity that helps for its tolerance. Modulation of NFkB (anticatabolic activity) and other transcription factors play an important role in its anti-inflammatory action.[15] It also shows protective effect on the cartilage as invitro studies reported.[16] Phase I studies reported safety of curcumin even at high doses (12g/day) in humans but very low bioavailability.[17] Curcumin (CUR) and two other demethoxy curcumin

(DMC) and bisdemethoxycurcumin (BDMC) are the responsible curcuminoids for its pharmacological actions.[18] United states food and drug administration(USFDA) has approved curcuminoids as Generally Recognized As Safe"(GRAS)[19] as even at doses between 4000 - 8000 mg/day good tolerability and safety profiles have been shown by clinical trials.[20] At 95% concentration dose of curcuminoids: curcumin, bisdemethoxycurcumin, and demethoxycurcumin reported as safe.[21] Reported pharmacological activities of turmeric are antioxidant,[22] anti-protozoal,[23] anti-venom activities,[24] anti-microbial,[25] anti-malarial,[26] anti-inflammatory,[27] anti-proliferative,[28] anti-angiogenic,[29] anti-tumor[30] and anti-aging.[31] The increase in bioavailability upto 2000% by adding black pepper was reported in an animal study.[32] Turmocin and turmocin plus tablet used in this study in which addition of black pepper may help in increasing bioavailability.The primary objective of this study to compare the effect of turmocin, turmocin plus tablet as add on with current standard care of treatment in osteoarthritis patients. Secondary objective was to see effectiveness of tablets with whole rhizome and pure extract of curcumin.

MATERIAL AND METHODS

Materials

1. Turmocin

Each Tablet Contains:

Haridra (Rhizome) *Curcuma longa* 500mg Marich (Fruit*) Piper nigrum* 250mg Permitted Preservatives and Excipients Q.S

2. Turmocin Plus

Each Tablet Contains:

Haridra Ext, Curcumin 95% (Rhizome) *Curcuma longa* 500mg Marich (Fruit) *Piper nigrum* 250mg Permitted Preservatives and Excipients Q.S

Methodology

After getting approval from ethics committee informed consent of the patient who was diagnosed as osteoarthritis by study physician were enrolled as per inclusion criteria. Once patient agreed on participation screening was done. The interviewer ensured that the participant has received enough time and information in both written and orally about the possible risks, benefits involved in the study. Participation was done on purely voluntarily. It was assured that due to withdrawal from the study participant will not get affected in any

manner in his/her routine treatment. All the enrolled participants were carefully examined. All the Participants with osteoarthritis were divided into three groups and as per approved protocol addon treatment was delivered to the group I (Standard care), II(for Turmocin) and III (Turmicin plus). Participants in groups were advised to take medications along with their routine treatment for osteoarthritis.

Assessment

Study population: With Samples size of n=36 participants of either sex study was initiated. Total n=36 participants male n= 6(16.67%) and female n=30 (83.33%) in ratio found as 1:5, were enrolled with equal distribution to each group. Only 27 participants have completed the study with total 9 dropouts were noted **table 1.2.** , where male n=4(14.81%) and female n=23 (85.19%) with mean age found as 54.89(9.4). In all the participants 11(40.7%) participants were illiterate and 16(59.2%) were able to read and write. Reported OA aggravating factors were standing 15(55.5%), sitting 9(33.3%), Walking 2(7.41%), exertion 1(3.70) with having 27(100%) past history relation to OA. There was a very low percentage of 6(22.2%) vegetarians compared to non-vegetarians 21(77.7%). All the participants were enrolled and assessed for pain, stiffness, swelling, restricted movements in joints time duration and variation in pain also measured as per season and time of the day.

Table 1.1.

Pain	**Name of joint involved**				
	All Joint	1 (9.09%)	2 (25%)	6 (75%)	9 (33.3%)
	Knee joint	10 (90.91%)	5 (62.5%)	2 (25%)	17 (62.9%)
	Hip joint	0 (0%)	1 (12.5%)	0 (0%)	1 (3.70%)
	Duration				
	All time	9 (81.82%)	5 (62.5%)	4 (50%)	18 (66.6%)
	less than hour(< 1hr)	2 (18.18%)	3 (37.5%)	4 (50%)	9 (33.3%)
	Increased by exertion				
	Yes	11 (100%)	8 (100%)	6 (75%)	25 (92.5%)
	No	0 (0%)	0 (0%)	2 (25%)	2 (7.41%)
	Relieved by taking rest				
	Yes	10 (90.91%)	8 (100%)	8 (100%)	26 (96.3%)
	No	1 (9.09%)	0 (0%)	0 (0%)	1 (3.70%)
	Pain at rest				
	Yes	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	No	11 (100%)	8 (100%)	8 (100%)	27 (100%)
	Radiating Other part				
	Yes	10 (90.91%)	7 (87.5%)	5 (62.5%)	22 (81.4%)
	NO	1 (9.09%)	1(12.5%)	3(37.5%)	5(18.5%)
Stiffness	**Name of joint involved**				

	All Joint	0 (0%)	2 (25%)	2 (25%)	4 (14.8%)
	Knee Joint	11 (100%)	6 (75%)	6 (75%)	23 (85.1%)
	Duration				
	NO	2 (18.18%)	1 (12.5%)	1 (12.5%)	4 (14.8%)
	0-10min	9 (81.82%)	4 (50%)	4 (50%)	17 (62.9%)
	10-60min	0 (0%)	3 (37.5%)	3 (37.5%)	6 (22.2%)
	Morning stiffness				
	Yes	10 (90.91%)	7 (87.5%)	7 (87.5%)	24 (88.8%)
	No	1 (9.09%)	1 (12.5%)	1 (12.5%)	3 (11.11%)
	lasting For an hour or so				
	Yes	0 (0%)	1 (12.5%)	1 (12.5%)	2 (7.41%)
	No	11 (100%)	7 (87.5%)	7 (87.5%)	25 (92.5%)
Swelling	**Name of joint involved**				
	All joint	10 (90.91%)	1 (12.5%)	1 (12.5%)	12 (44.4%)
	knee joint	1 (9.09%)	7 (87.5%)	7 (87.5%)	15 (55.5%)
	Duration				
	No	2 (18.18%)	1 (12.5%)	1 (12.5%)	4 (14.8%)
	0-2hr	0 (0%)	2 (25%)	1 (12.5%)	3 (11.11%)
	All Time	9 (81.82%)	5 (62.5%)	6 (75%)	20 (74.0%)
Restricted Moments	**Name of joint involved**				
	All Joint	0 (0%)	2 (25%)	1 (12.5%)	3 (11.11%)
	Knee Joint	10 (90.91%)	6 (75%)	7 (87.5%)	23 (85.1%)
	Hip joint	1 (9.09%)	0 (0%)	0 (0%)	1 (3.70%)
	Duration				
	No	2 (18.18%)	0 (0%)	1 (12.5%)	3 (11.11%)
	0-20min	4 (36.36%)	5 (62.5%)	6 (75%)	15 (55.5%)
	All Time	5 (45.45%)	3 (37.5%)	1 (12.5%)	9 (33.3%)
	Crepitus				
	Yes	11 (100%)	8 (100%)	5 (62.5%)	24 (88.8%)
	No	0 (0%)	0 (0%)	3 (37.5%)	3 (11.11%)
Duration					
	No	0 (0%)	0 (0%)	3 (37.5%)	3 (11.11%)
	0-15 min	2 (18.18%)	6 (75%)	4 (50%)	12 (44.4%)
	All Time	9 (81.82%)	2 (25%)	1 (12.5%)	12 (44.4%)
Variation in pain	**Climate**				
	Summer	1 (9.09%)	1 (12.5%)	2 (25%)	4 (14.8%)
	Winter	4 (36.36%)	7 (87.5%)	5 (62.5%)	16 (59.2%)
	Monsoon	1 (9.09%)	0 (0%)	0 (0%)	1 (3.70%)
	All season	5 (45.45%)	0 (0%)	1 (12.5%)	6 (22.2%)
	Day	5 (45.45%)	3 (37.5%)	6 (75%)	14 (51.8%)
	Night	1 (9.09%)	2 (25%)	0 (0%)	3 (11.11%)
	Day & Night	5 (45.45%)	3 (37.5%)	2 (25%)	10 (37.0%)
	Rest	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Moment	11 (100%)	8 (100%)	8 (100%)	27 (100%)
	Walking	1 (9.09%)	5 (62.5%)	4 (50%)	10 (37.0%)

27	Exertion	1 (9.09%)	1 (12.5%)	0 (0%)	2 (7.41%)
	Walking & Exertion	9 (81.82%)	2 (25%)	4 (50%)	15 (55.5%)

Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) was also used in questionnaire form for pain, stiffness, physical function before and after inclusion of treatment changes were analysed in a visual analogue scale (VAS) with scoring 1-10 after every 4weeks till 12 weeks to compare the effectiveness of given treatment in all the three groups. Maximum possible score 10 shows sever problem and minimum possible score1 denotes mildness. It was measured as if the treatment is effective the individual score will reduce after taking the treatment.

Assessment of all the Participants was done before and after giving the study medication for pain, tenderness, swelling, stiffness, fatigue, restricted movements, and deformity at every 4 week interval of time. It was measured in the scale of 0-3, where 0 = no symptoms, 1 = mild symptoms, 2= Symptoms sufficient to cause distress/difficulty in performing routine work and 3=symptoms very sever/patient unable to perform his routine work.

Statistical Analysis

All participants diagnosed with osteoarthritis were divided into three groups. Group I-Standard care, Group II-Standard + Tablet Turmocin, Group III Standard+ Tablet Turmocin plus. We compared effect of the treatment by Analyze WOMAC Osteoarthritis Index score Paired T test were used to see the effectiveness every individual participant in all the three groups. Analysis of Variance (ANOVA) were used to compare post treatment mean score across the groups and t test were used for post hoc comparison to find out significant difference between groups. Wilcoxon test were used to see change in the Symptoms in each group.

Distribution of participants at enrollment Table 1.2

Gender	STD (N=12)	STD+Turmocin (N=12)	STD+Turmocin Plus (N=12)	TOTAL (N=36)
Male (%)	1 (8.33%)	4 (33.33%)	1 (8.33%)	6 (16.67%)
Female (%)	11 (91.67%)	8 (66.67%)	11 (91.67%)	30 (83.33%)

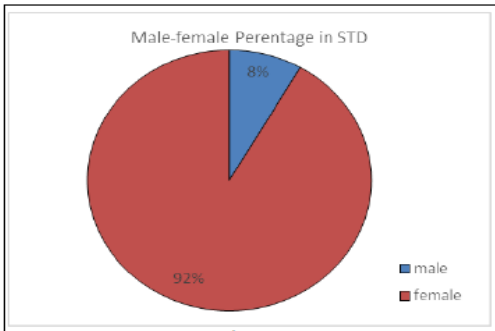


Figure 1

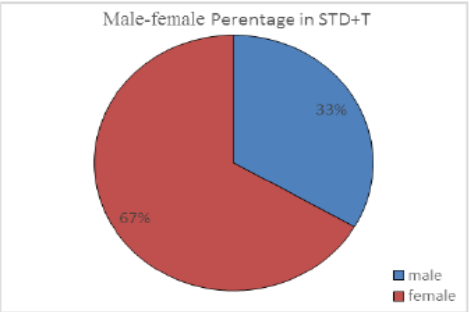


Figure 2

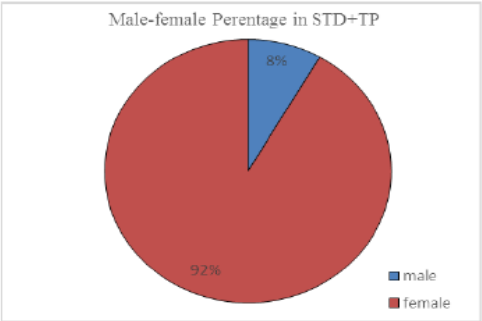


Figure 3

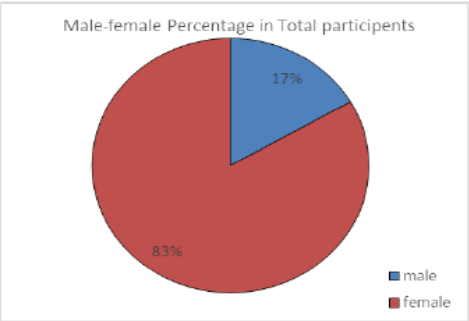


Figure 4

Male Female participants percentage at end of study table 1.3

Gender	STD (N=11)	STD+Turmocin (N=8)	STD+Turmocin Plus (N=8)	TOTAL (N=27)
Male (%)	1(9.09%)	2(25%)	1(12.5%)	4(14.81%)
Female (%)	10(90.91%)	6(75%)	7(87.5%)	23(85.19%)

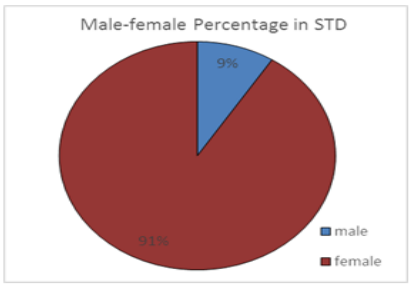


Figure 5

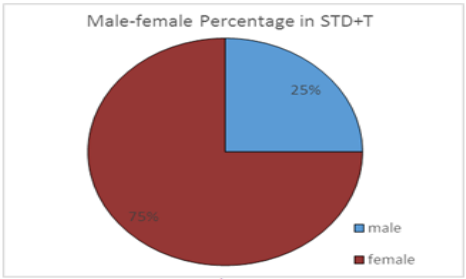


Figure 6

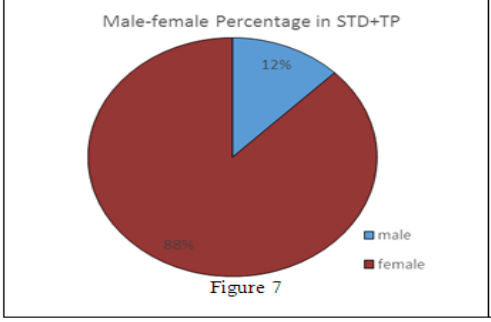


Figure 7

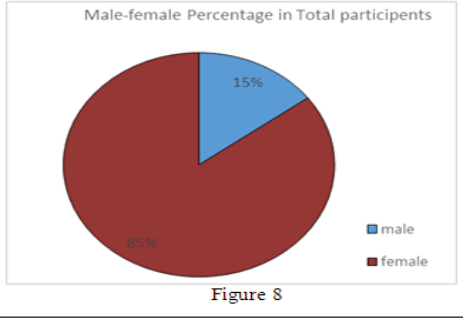


Figure 8

Measure of Treatment Effectiveness

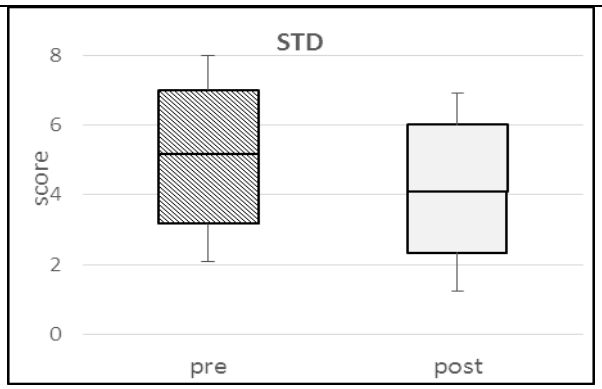


Figure. 9: comparing Pre and Post Score in group I.

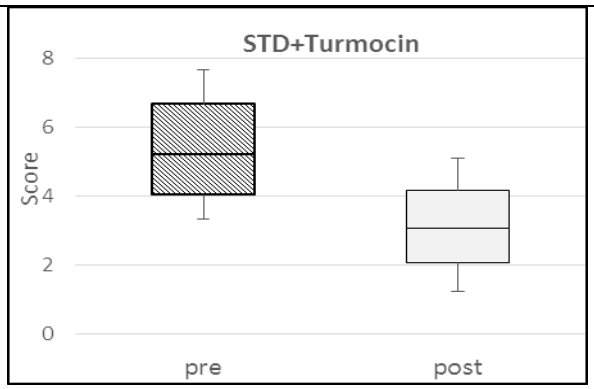


Figure. 10: comparing Pre and Post Score in group II.

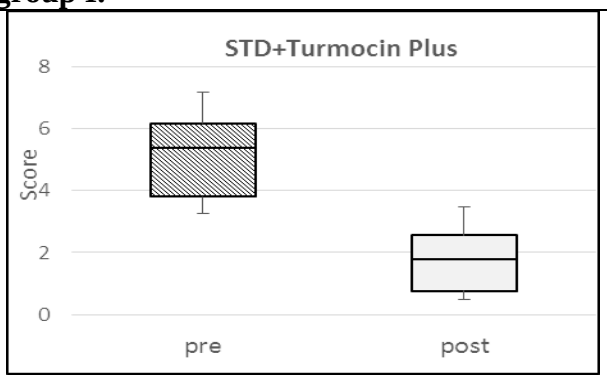


Figure. 11: Comparing Pre and Post Score in group III.

Box plots compared the treatment effectiveness pre and post mean of total score in all the groups. It is showing that after treatment total mean score is decreased as compare to before treatment. All the treatment is found to be effective in osteoarthritis.

Table 1.4: comparing effectiveness using paired t test.

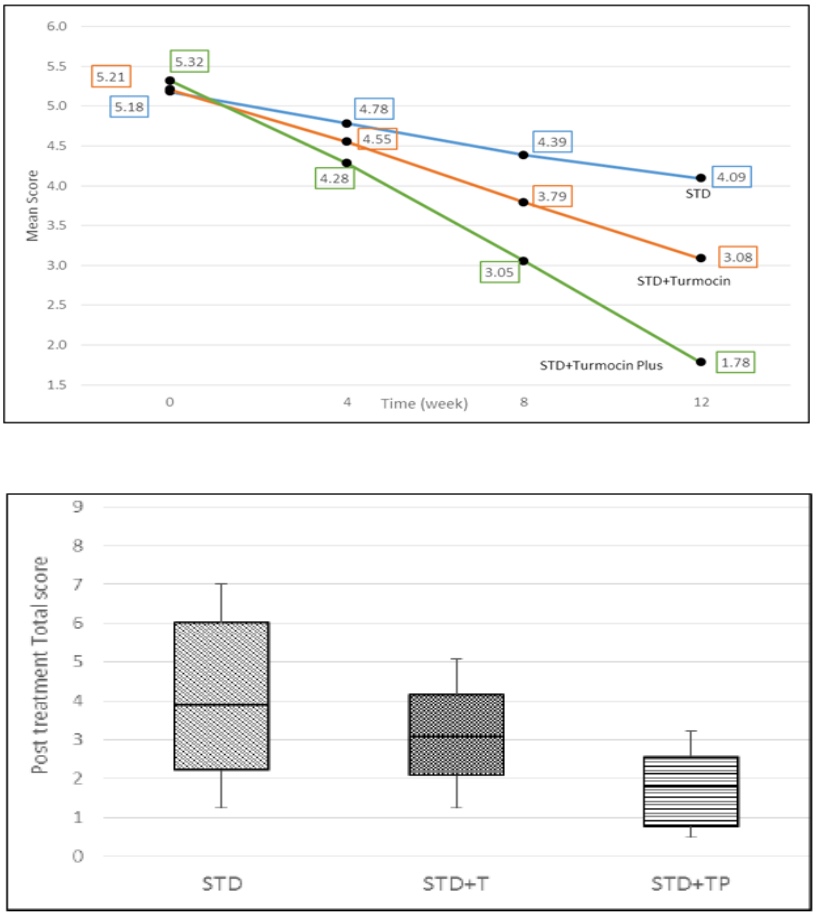
		Pre	Post	P value
Treatment	**Parameter**	**Mean (SD)**	**Mean (SD)**	
STD	**Pain**	5.44 (2.03)	4.33 (2.01)	0.003
	Stiffness	3 (1.77)	1.82 (1.52)	0.008
	PF	5.8 (2.21)	4.76 (2.09)	0.004
	Total	5.18 (2.02)	4.09 (1.92)	0.003
STD + Turmocin	**Pain**	5.3 (1.61)	3.25 (1.45)	0.003
	Stiffness	3.75 (1.81)	1.5 (0.65)	0.004
	PF	5.7 (1.37)	3.55 (1.58)	<0.001
	Total	5.21 (1.44)	3.08 (1.30)	0.001
STD +Turmocin Plus	**Pain**	5.5 (1.68)	1.75 (0.99)	<0.001
	Stiffness	4.44 (1.72)	1.25 (0.76)	<0.001
	PF	5.65 (1.55)	2.03 (1.01)	<0.001
	Total	5.39 (1.56)	1.78 (0.93)	<0.001

RESULT

1. Table 1.4 shows P values which were calculated by using paired t test at level of significance (α) 0.05 for Standard treatment, standard + Turmocin tablet and standard +

Turmocin plus tablet. All P values <0.05 shows that there is significant difference between pre and post treatment mean score. Post-treatment mean score is significantly lower as compare to pre-treatment mean score in all subscales like Pain, stiffness, physical Function in all the groups. These observations giving strong evidence of effectiveness in osteoarthritis.

Total mean score was compared for all the groups. It was measured before treatment and at 4 week, at 8 week and at 12 week. Observations show that after every 4 week there was a decrease in mean of total score (Figure 12). In all the three groups participant's from Group III shows minimum mean Score of 1.78 after 12 week as compare to group II as 3.08, and group I as 4.09.



Graph. 13: comparing post mean score in all three groups.

Table 1.5: comparing Post treatment mean score of all three groups using ANOVA.

Parameter	STD	STD+T	STD+TP	P VALUE
Pain	4.08 (1.93)	3.25 (1.45	1.75 (0.99)	0.008
Stiffness	1.85 (1.6)	1.5 (0.65)	1.25 (0.76)	0.552
PF	4.54 (2.06)	3.55 (1.58)	2.03 (1.01)	0.007
Total	4.09 (1.91)	3.08 (1.3)	1.78 (0.93)	0.011

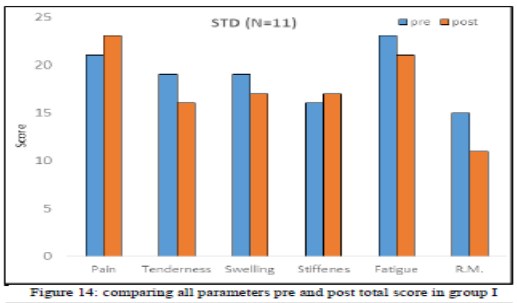


Figure 14: comparing all parameters pre and post total score in group I

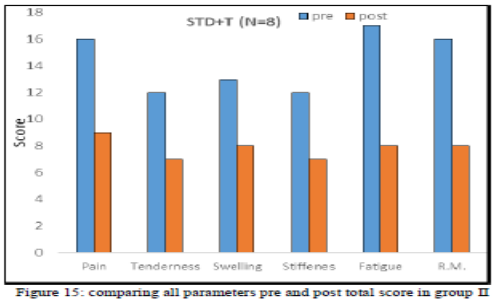


Figure 15: comparing all parameters pre and post total score in group II

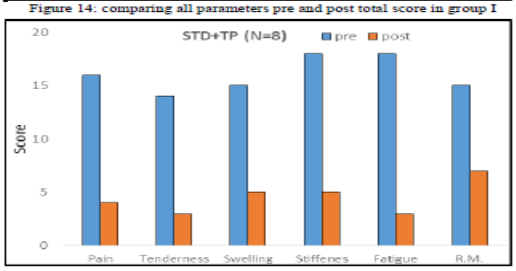


Figure 16: comparing all parameters pre and post total score in group III

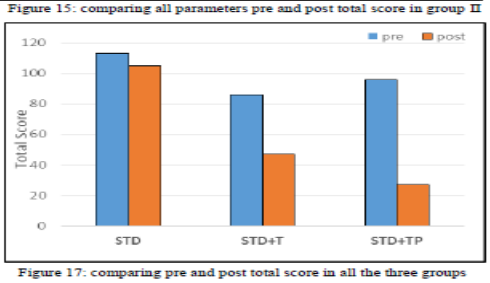


Figure 17: comparing pre and post total score in all the three groups

Using ANOVA at level of significance (α) 0.05 comparisons of post treatment mean score for pain, stiffness and physical function was evaluated. It was found that there is significant difference in mean score of pain, physical function and overall total score with p value <0.05 table1.5. In case of stiffness p value > 0.05 shows there is no significant difference between mean score in all the groups. Post hoc comparison using t test revealed that group III [mean=1.78 SD=0.93] total mean score was lower as compare to group II [mean=3.08, SD=1.3, p value =0.036] as well as with group I [mean=4.09, SD=1.91 p value=0.006] Found that all parameter's mean score in group III is significantly lower as compared to other two groups table 1.5.

Analysis of symptoms

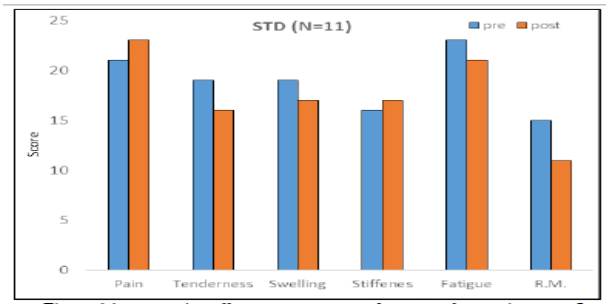


Figure 14: comparing all parameters pre and post total score in group I

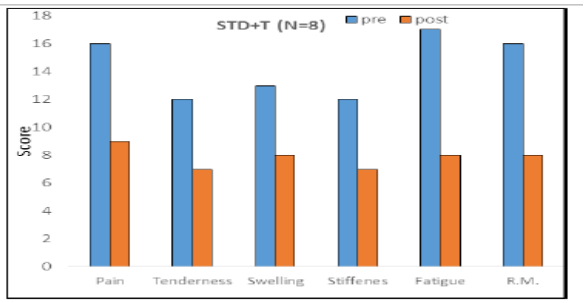


Figure 15: comparing all parameters pre and post total score in group II

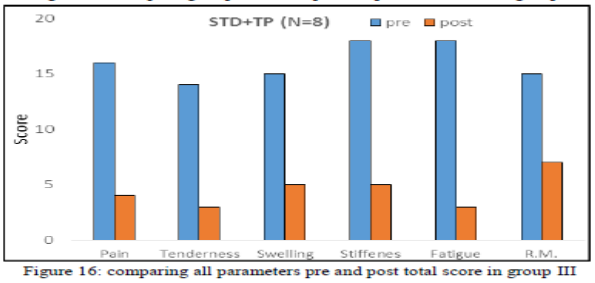


Figure 16: comparing all parameters pre and post total score in group III

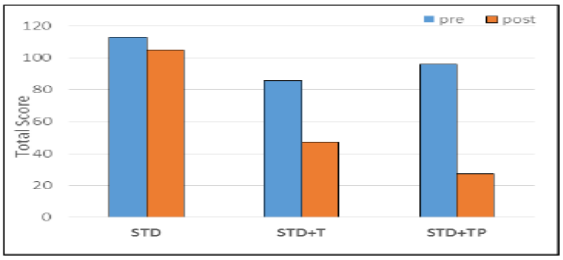


Figure 17: comparing pre and post total score in all the three groups

Table 1.5: comparing all parameter pre and post mean score in all groups using Wilcoxon test.

	STD			STD + Turmocin			STD +Turmocin Plus		
Parameter	**pre**	**Post**	**p value**	**pre**	**post**	**p value**	**pre**	**post**	**P value**
Pain	1.91(0.83)	2.1(0.88)		1.86(0.90)	1.14 (0.90)		1.86(0.69)	0.4 (0.55)	
Tenderness	1.73(0.65)	1.6(0.52)		1.43(0.53)	0.86 (0.90)		1.71(0.49)	0.2 (0.45)	
Swelling	1.73(0.79)	1.7(0.95)		1.43(0.79)	0.86 (0.90)		1.71(1.11)	0.2 (0.45)	
Stiffens	1.45(1.04)	1.6(1.07)		1.43(0.98)	0.86 (0.69)		2.14(0.90)	0.6 (0.55)	
Fatigue	2.09(0.94)	2(0.82)		2.00(0.82)	0.86 (0.69)		2.29(0.49)	0.4 (0.55)	
R.M.	1.36(1.21)	1(0.94)		1.86(0.90)	0.86 (0.38)		1.86(0.69)	0.8 (0.45)	
Total	10.18(4.38)	9.55(4.39)	0.079	10.75(3.77)	5.88 (3.23)	0.014	12 (3.38)	3.3 (2.20)	0.007

3. Changes in symptoms after taking the treatments for all the group has been analysed as parameters using Wilcoxon test as mentioned. P values<0.05 in group II (STD + turmocin) and group III (STD + turmocin plus) shows that there is significant change in symptoms mentioned in table 1.5.

DISCUSSION

Osteoarthritis is an inflammatory condition[33] and use of turmuric is well documented in vedic period (6000 – 4000 BC.)[34], Charaka Samhita (1000-1500 B.C)[35], Sushruta Samhita(100 -1500 B.C)[36], Ashtanga Hridya[37], sharita Samhita[38], Cakradata[39], Sarangdhar[40], gadanigraha[41], Bhaisajya Ratnavali[42], Yogaratnakar[43], Bhavaprakash[44], Vangasen Samhita[45] and with modern view its importance in therapeutic use came reported first in year 1748.[46] Comparative effectiveness of available standard care with turmeric whole rhizome and pure turmeric extract was a unique approach attempted in present study. Pain in OA usually treated with NSAIDS however majority of individuals experience unwanted serious effects[10] like gastric ulceration, haemorrhage, and perforation[9] hence such individuals investigate the safe treatments. In this study treatment effectiveness were compared and individuals taking turmocin plus tablet showed the most effective in comparison to the selected parameters. Osteoarthritis treatment mainly aims at relieving pain, swelling, improving joint mobility, stiffness, increasing the strength of the joints, minimizing the disabling effects of the disease[47] and similar parameters were observed in this study. In this comparison effectiveness of the three groups evaluated. Using Analysis of variance (ANOVA), it was found that there is a significant difference in WOMAC Score across the group with p value=0.011. In the post hoc analysis T test shows that group III [mean=1.78

SD=0.93] total mean score was lower as compare to group II [mean=3.08, SD=1.3 p value =0.036] as well as with group I [mean=4.09, SD=1.91 p value=0.006].

Comparative effectiveness for all the total parameters were calculated and pre and post treatment mean (SD) for the symptoms were calculated as 10.18 (4.38) & 9.55 (4.39) for standard treatment with p value 0.079, 10.75 (3.77) & 5.88 (3.23) for Standard in addition with turmocin tablet with p value evaluated as 0.014 plus, and best results were observed as 12 (3.38) & 3.3 (2.20) with p value 0.007 in all the three. In this study effectiveness of pure extract of curcumin in combination of pepper reduced the symptoms very effectively as compared to the combination whole rhizome and pepper. There is a need of study with bigger sample size to find the adverse events with the study formulations of turmocin and turmocin plus as in present study with small samples size no adverse events were reported. Pilot study in OA with similar parameters is been suggested by the investigator as a treatment comparison to standard care to turmocin plus tablet only to see the alone effects. Such trial will give a new way for the management of OA in a better and safe way in near future.

CONCLUSION

In this study all the given treatments found to be effective but group III participants has more relief at end of the study as compare to other groups. It shows the standard + turmocin plus treatment is more effective. Since ancient times turmeric is been advised for various illness by using currently available advanced research techniques, controlled trials, new indications can be explored. Research on Ayurveda formulations may give new effective treatments as with current study drug has a roots back to 6000 years still found to be effective and no resistance reported till date.

REFERENCES

1. WHO Department of Chronic Diseases and Health Promotion. Available at: http://www.who.int/chp/topics/rheumatic/en/.
2. Kim IJ, Kim HA, Seo YI, et al. Prevalence of knee pain and its influence on quality of life and physical function in the Korean elderly population: a community based cross-sectional study. J Korean Med Sci., 2011; 26(9): 1140–1146.
3. Du H, Chen SL, Bao CD, et al. Prevalence and risk factors of knee osteoarthritis in Huang-Pu District, Shanghai, China. Rheumatol Int., 2005; 25(8): 585–590.

4. Yoshida S, Aoyagi K, Felson DT, Aliabadi P, Shindo H, Takemoto T. Comparison of the prevalence of radiographic osteoarthritis of the knee and hand between Japan and the United States. J Rheumatol, 2002; 29(7): 1454–1458.
5. Cho HJ, Chang CB, Kim KW, et al. Gender and prevalence of knee osteoarthritis types in elderly Koreans. J Arthroplasty, 2011; 26(7): 994–999.
6. Pal CP, Singh P, Chaturvedi S, Pruthi KK, Vij A. Epidemiology of knee osteoarthritis in India and related factors. Indian journal of orthopaedics, 2016 Sep; 50(5): 518.
7. Khorsandi L, Orazizadeh M, Bayati V, Ahmadi K. Combination Of Curcumin and Piperine Improves Osteoarthritis In An Animal Model. Asian Journal of Phytomedicine and Clinical Research, 2014; 2(4): 221-230.
8. Hungerford DS. Treating osteoarthritis with chondroprotective agents. Orthopedic Special Edition, 1998; 4: 39-42.
9. Lanas A. Nonsteroidal antiinflammatory drugs and cyclooxygenase inhibition in the gastrointestinal tract: a trip from peptic ulcer to colon cancer. The American journal of the medical sciences, 2009 Aug 1; 338(2): 96-106.
10. Brien S, Prescott P, Bashir N, et al. Systematic review of the nutritional supplements dimethyl sulfoxide (DMSO) and methylsulfonylmethane (MSM) in the treatment of osteoarthritis. Osteoarthritis Cartilage, 2008 Apr 14.
11. Najm WI, Reinsch S, Hoehler F, et al. S-Adenosyl methionine (SAMe) versus celecoxib for the treatment of osteoarthritis symptoms: A double-blind cross-over trial. BMC Musculoskelet Disord, 2004; 5: 6.
12. Khan MU, Jamshed SQ, Ahmad A, Bidin MA, Siddiqui MJ, Al-Shami AK. Use of complementary and alternative medicine among osteoarthritic patients: a review. Journal of clinical and diagnostic research: JCDR, 2016 Feb; 10(2): JE01.
13. Aggarwal BB. Curcumin: the Indian solid gold.
14. Gupta SC. Multitargeting by turmeric, the golden spice: From kitchen to clinic.
15. Prasad S, Gupta SC, Tyagi AK, Aggarwal BB. Curcumin, a component of golden spice: from bedside to bench and back. Biotechnology advances, 2014 Nov 1; 32(6): 1053-64.
16. Henrotin Y, Priem F, Mobasheri A. Curcumin: a new paradigm and therapeutic opportunity for the treatment of osteoarthritis: curcumin for osteoarthritis management. Springerplus, 2013; 2: 1-9.
17. Anand P, Kunnumakkara AB, Newman RA, Aggarwal BB. Bioavailability of curcumin: problems and promises. Molecular pharmaceutics, 2007 Nov 14; 4(6): 807-18.

18. Paramasivam M, Poi R, Banerjee H, Bandyopadhyay A. High-performance thin layer chromatographic method for quantitative determination of curcuminoids in Curcuma longa germplasm. Food Chemistry, 2009 Mar 15; 113(2): 640-4.
19. Gupta SC, Patchva S, Aggarwal BB. Therapeutic roles of curcumin: lessons learned from clinical trials. The AAPS journal, 2013 Jan 1; 15(1): 195-218.
20. Basnet P, Skalko-Basnet N. Curcumin: an anti-inflammatory molecule from a curry spice on the path to cancer treatment. Molecules, 2011 Jun 3; 16(6): 4567-98.
21. Lao CD, Ruffin MT, Normolle D, Heath DD, Murray SI, Bailey JM, Boggs ME, Crowell J, Rock CL, Brenner DE. Dose escalation of a curcuminoid formulation. BMC complementary and alternative medicine, 2006 Dec; 6(1): 10.
22. Kalpravidh RW, Siritanaratkul N, Insain P, Charoensakdi R, Panichkul N, Hatairaktham S, Srichairatanakool S, Phisalaphong C, Rachmilewitz E, Fucharoen S. Improvement in oxidative stress and antioxidant parameters in β-thalassemia/Hb E patients treated with curcuminoids. Clinical biochemistry, 2010 Mar 1; 43(4-5): 424-9.
23. Changtam C, de Koning HP, Ibrahim H, Sajid MS, Gould MK, Suksamrarn A. Curcuminoid analogs with potent activity against Trypanosoma and Leishmania species. European journal of medicinal chemistry, 2010 Mar 1; 45(3): 941-56.
24. Lim HS, Park SH, Ghafoor K, Hwang SY, Park J. Quality and antioxidant properties of bread containing turmeric (Curcuma longa L.) cultivated in South Korea. Food Chemistry. 2011 Feb 15; 124(4): 1577-82.
25. Péret-Almeida L, Cherubino AP, Alves RJ, Dufossé L, Gloria MB. Separation and determination of the physico-chemical characteristics of curcumin, demethoxycurcumin and bisdemethoxycurcumin. Food Research International, 2005 Oct 1; 38(8-9): 1039-44.
26. Aditya NP, Chimote G, Gunalan K, Banerjee R, Patankar S, Madhusudhan B. Curcuminoids-loaded liposomes in combination with arteether protects against Plasmodium berghei infection in mice. Experimental parasitology, 2012 Jul 1; 131(3): 292-9.
27. Amalraj A, Gopi S. Journal of Traditional and Complementary Medicine.
28. Yue GG, Chan BC, Hon PM, Kennelly EJ, Yeung SK, Cassileth BR, Fung KP, Leung PC, Lau CB. Immunostimulatory activities of polysaccharide extract isolated from Curcuma longa. International journal of biological macromolecules, 2010 Oct 1; 47(3): 342-7.

29. Tapal A, Tiku PK. Complexation of curcumin with soy protein isolate and its implications on solubility and stability of curcumin. Food Chemistry, 2012 Feb 15; 130(4): 960-5.
30. Panahi Y, Saadat A, Beiraghdar F, Nouzari SM, Jalalian HR, Sahebkar A. Antioxidant effects of bioavailability-enhanced curcuminoids in patients with solid tumors: A randomized double-blind placebo-controlled trial. Journal of Functional Foods, 2014 Jan 1; 6: 615-22.
31. Zhan PY, Zeng XH, Zhang HM, Li HH. High-efficient column chromatographic extraction of curcumin from Curcuma longa. Food Chemistry, 2011 Nov 15; 129(2): 700-3.
32. Shoba, G.; Joy, D.; Joseph, T.; Majeed, M.; Rajendran, R.; Srinivas, P.S. Influence of piperine on the pharmacokinetics of curcumin in animals and human volunteers. Planta Med., 1998; 64: 353–356.
33. Berenbaum F. Osteoarthritis as an inflammatory disease (osteoarthritis is not osteoarthrosis!). Osteoarthritis and Cartilage, 2013 Jan 1; 21(1): 16-21.
34. Ravindran PN, Babu KN, Sivaraman K. Turmeric: the genus Curcuma. CRC press, 2007; Mar 1.p.410.
35. By Dr. B.K. Twivedi and Dr. Pradipkumar Goswami, Charaka Samhita, Chikitsa part-3, pub-Chaukhambha krishnadas Academy, Varanasi, 221001.
36. By Kaviraj Dr. Ambikadutta Shastri, Sushrut Samhita, part-1, Edition 2012 and part-2, Uttara Tantra, Edition 2013, pub-Chaukhambha Sanskrit sanshan, Vranasi, 221001.
37. Dr. Brahmananda Tripathi, Astanga Hrdayam, pub-Chaukhamba Sanskrit pratishthan, Reprint-2015, Delhi, 110007.
38. ByHarihara Prasad Tripathi, HaritaSamhita, pub-Chaukhambha Krishnadas Academy, Edition, 2009.
39. Cakradatta, Edited and Translated by Priya Vrat Sharma, pub-Chaukhambha, Vranasi, Edition 2007.
40. By Prof. K.R. SrikanthaMuthy, Sarangdhar Samhita, pub Chaukhambha Orientalia Varanasi, Edition 2012.
41. ByIndradeva Tripathi, Gadanigraha, part-2, Edited by Sri Ganga sahaya Pandey, pub-Chaukhambha Sanskrit Sansthan, Varanasi, Third Edition, 1994.
42. Bhaisajya Ratnavali of Govindadas, pub-Chaukhambhaprakashan, Varanasi 221001.
43. By P. V. Tiwari and Asha Kumari, Gogaratnakar, part-2, Edition 2010, Pub-Chaukhambha Viswabharati, Varanasi 221001.

44. ByProf. K.R. Srikantha Murthy, Bhavaprakasa, Madhyam and Uttar khana.Vol-2, Pub-Chaukhambha Krishnadas Academy, Edition-Third, 2005.
45. BY Nirmal Saxena, Bangasen Samhita, Vol-2, Edition 2004, pub- Chaukhambha Sanskrit Series.
46. Loeber CC. De curcuma officinarum. diss Inaug Halae. 1748.
47. Moyer RF, Ratneswaran A, Beier F, Birmingham TB: Osteoarthritis year in review Mechanics—Basic and clinical studies in osteoarthritis. Osteoarthritis Cartilagem, 2014; 22: 1989–2002.