RESEARCH

24(102), March - April, 2020

ISSN 2321–7359 EISSN 2321–7367

Medical Science

The effectiveness of Zingiber Zerumbet ointment compared to Diclofenac Gel on clinical symptoms of patients with Knee Osteoarthritis: A double-blind Randomized Controlled Trial (RCT)

Hassan Kiani Ahmadabadi[1], **Mohammad Reza Vaez-Mahdavi**[2]✉, **Seyed Shamsa Shariatpanahi**[3], **Mohammad Kamalinejad**[4], **Tooba Ghazanfari**[5], **Farhad Jafari**[6]

[1]Department of Iranian Traditional Medicine, Faculty of Medicine, Shahed University, Tehran, Iran
[2]Immunoregulation Research Center, Shahed University, Tehran, Iran
[3]Department of Internal Medicine, Mostafa Khomeini hospital, Shahed University of Medical Sciences, Tehran, Iran
[4]Department of Pharmacology, School of Medicine, Shaheed Beheshti University of Medical Sciences, Tehran, Iran
[5]Department of Immunology, Medical Faculty, Shahed University, Tehran, Iran
[6]Department of Health and Social Medicine, Shahed University, Tehran, Iran

✉**Corresponding author**
Immunoregulation Research Center, School of Medicine, Shahed University, Tehran, Iran
Email: mohammadrezavaezmahdavi@gmail.com

Article History
Received: 13 November 2019
Reviewed: 15/November/2019 *to* 27/December/2019
Accepted: 28 December 2019
Prepared: 29 December 2019
Published: March - April 2020

Citation
Hassan Kiani Ahmadabadi, Mohammad Reza Vaez-Mahdavi, Seyed Shamsa Shariatpanahi, Mohammad Kamalinejad, Tooba Ghazanfari, Farhad Jafari. The effectiveness of Zingiber Zerumbet ointment compared to Diclofenac Gel on clinical symptoms of patients with Knee Osteoarthritis: A double-blind Randomized Controlled Trial (RCT). *Medical Science*, 2020, 24(102), 734-743

RESEARCH ARTICLE

General Note

Article is recommended to print as color digital version in recycled paper.

ABSTRACT

Background and Purpose: Osteoarthritis is a joint disease in which cartilage and bone tissues are gradually destroyed. The disease is a global problem and its prevalence is higher in Asia than Europe and the United States. According to WHO recommendations on the use of medicinal plants in the regional nature of any country, the present study aimed to evaluate the effectiveness of Zingiber zerumbet ointment compared with Diclofenac gel on clinical manifestations of patients with knee osteoarthritis. *Material and Method:* The present double-blind clinical randomized controlled trial (RCT) was conducted on patients with knee osteoarthritis in Tehran (Iran) from February 2017 to September 2018. In the present study, the first group (intervention) consumed Zingiber zerumbet ointment and the second group (positive control) consumed diclofenac gel at a dose of 1 g every 8 hours for 4 consecutive weeks. In the study, the severity of symptoms (pain, stiffness and physical functioning) were considered as the initial outcomes by the WOMAC (Western Ontario and McMaster Universities Arthritis Index), and the experimental tests, namely the CBC, Cr, BUN, ALP, ALT, AST, CRP, IL1, and IL6 were considered as secondary outcomes of study. *Results:* The present study was conducted on 92 patients with Osteoarthritis (drug group: 48 individuals; positive control group: 44 individuals). In the present study, two groups were similar in terms of demographic characteristics. The research results indicated differences in scores of physical functioning (drug group = -11.94, MD of Control+ group = -6.43, P <0.001), Pain (MD of drug group = -3.94, MD of Control+ group = -2.43, P-value = 0.039), Stiffness (MD of drug group= -1.31, MD of Control+ group= -0.91, P-value= 0.135). Furthermore, further results indicated that except for CRP and Bun variables, other Laboratory variables had no significant changes in two groups, Zingiber zerumbet ointment and Diclofenac gel. Furthermore, both groups were similar in terms of number of taken acetaminophen pills. *Conclusion:* Given that Zingiber zerumbet ointment has an herbal base and its use in reducing symptoms of osteoarthritis is very simple and effective, is use can be recommend in improving symptoms for osteoarthritis.

Keywords: Knee osteoarthritis, Zingiber zerumbet ointment, Iranian medicine.

1. INTRODUCTION

Osteoarthritis (OA) is a joint disease in which cartilage and bone tissues are gradually destroyed. The disease is a global problem and its prevalence is higher in Asia than Europe and the United States. The knee joint is the most common joint with osteoarthritis in Asian societies (Fransen et al., 2011 and Tehrani-Banihashemi et al., 2014 and Kwok et al., 2010). Thirty-seven percent of people over the age of 60 have radiographic evidence of knee disease. Furthermore, 7 percent of adults have symptomatic hand diseases and 17 percent of those older than 45 years of age have symptomatic knee involvement (Yohannes and Caton, 2010). Studies have reported the higher prevalence of osteoarthritis in Iran than some Asian and European countries. In general, 20% of people have osteoarthritis in different joints; and the prevalence of knee osteoarthritis has been reported 20.5% in men and women at all ages (Tehrani-Banihashemi et al., 2014). Osteoarthritis is the main cause of long-term disability, especially in older people. Furthermore, the lower limb osteoarthritis is the most common cause of difficulty in walking or climbing stairs (Harrison and Longo, 2015). OA reduces the quality of life and causes depression, and has major economic effect in society due to its direct and indirect costs (Yohannes and Caton, 2010 and Harrison and Longo, 2015). Osteoarthritis is a chronic disease that has no definite treatment; and its therapies are often supportive and palliative. The treatment of osteoarthritis can be classified into three categories: 1- Drug therapy, 2- Non-drug therapy (complementary and alternative) and 3- Surgery. Surgery is an invasive, costly and non-applicable for some patients; and the drug therapy, including acetaminophen and NSAIDS is not recommended by therapists due to gastrointestinal, kidney, edema and hypertension complications. Therefore, despite the lower effect of non-drug therapy, such as the use of topical NSAIDs like topical diclofenac than oral drugs, it has less gastrointestinal and systemic complications, and this it is approved by the FDA (Food and Drug Administration) (Sinusas, 2012 and Kasper and Fauci, 2015). Many attempts have been made to obtain new drugs to control symptoms of these patients, including pain such as the use of monoclonal tansomb antibody and intra-articular injection of platelet-rich plasma than can diminish the use of these methods with a variety of efficiency, complications, durability and expensiveness (Spierings et al., 2013 and Kon et al., 2010). Therefore, the use of inexpensive, safe and affordable therapies such as the use of traditional medicine methods are ideal and desirable to control symptoms and treat Osteoarthritis (Harris et al., 2012 and

Hughes et al., 2013 and Naseri, 2004 and Naseri et al., 2007). The use of Zingiber zerumbet product is a proper treatment for treating joint pain from the traditional Iranian perspective (Kapoor M et al., 2010 and Kasper et al., 2015 and Baraf et al., 2012). Bitter ginger with a scientific name of Zingiber zerumbet (ZZ) is from the ginger family. The plant is grown in tropical areas such as Malaysia and is highly utilized for medical purposes. Various effects have been reported for this plant, including anti-inflammatory, anti-fever, analgesic, anti-ulcer, anti-oxidant, antimicrobial, anti-platelet aggregation effects, anticancer and immune response modulation (Prakash et al., 2011 and Zakaria et al., 2011). The roots of this plant have been traditionally used to relieve cough, stomach pain, dyspepsia, colic and anti-parasite (20 and can verify anti-inflammatory effects of this plant. Given that the World Health Organization has recommended the use of long-lasting medicinal herbs by accepting specific guidelines (World Health Organization, 2005). The present study aimed to evaluate the effectiveness of Zingiber zerumbet ointment compared to diclofenac gel on clinical symptoms of patients with knee osteoarthritis.

2. MATERIAL AND METHODS

The present study was a double-blind randomized controlled trial and aimed to evaluate the effect of Zingiber zerumbet ointment on the treatment of knee osteoarthritis in Tehran (Iran) from February 2017 to September 2018. The research population consisted of patients with knee osteoarthritis and inclusion criteria referred to the rheumatology clinic of Shahid Mostafa Khomeini Hospital. Participants were visited in person if they had the following inclusion criteria: 1- Willing to participate in the study, 2- Outpatient patients with knee osteoarthritis based on ACR clinical criteria including pain and having at least three out of five conditions (aged over 50, knee stiffness for less than 30 minutes in the morning, Crepitus in moving knee, bone sensitivity, non-feeling of heat in the examination, and bone prominence), 3- Non- pregnancy and lactation, 4- No history of knee surgery, 5- Absence of manifest mental illness, 6- Absence of active physical illness, 7- No secondary osteoarthritis such as rheumatoid arthritis and gout, infectious arthritis, metabolic arthritis, and traumatic arthritis. After necessary explanations by the presenter, informed consent forms were signed by patients. The diagnosis of knee Osteoarthritis was done by the physician based on the ACR criteria. In the present study, patients were randomly classified into intervention and positive control groups using the random block assignment method (as AB, BA) in the first visit after confirmation of the disease.

The exclusion criteria of study were as follows: 1- Patient's unwillingness to continue to participate in the project, 2- Incidence of any drug intolerance, and 3- The use of parallel therapy in the treatment of knee osteoarthritis. After selecting patients, they randomly entered into two groups respectively. Intervention group: topical application of 1g of Zingiber zerumbet ointment every 8 hours for 4 consecutive weeks. Positive control group: Topical use of 1g of diclofenac gel every 8 hours for 4 consecutive weeks. In the present study, essential drugs were made by the researcher pharmacist and encoded without mentioning the drug name and put in containers and packaged in the same shape; and the participants were asked to consume the drug for 4 weeks according to the same instructions.

In the present study, enough 325-mg acetaminophen was given to patients in the same boxes and they were allowed to use acetaminophen tablets for up to 6 tablets per day if they had pain. Finally, acetaminophen boxes were given to researchers to count number of consumed actinophene tablets at the end of study. In the study, the severity of symptoms (pain, stiffness and limitation of physical activity of knee) was measured as a preliminary outcome by the WOMAC (Western Ontario and McMaster universities Index of osteoarthritis) questionnaire at the beginning and end of second and fourth weeks and experimental tests, namely the CBC, Cr, BUN, ALP, ALT, AST, CRP, IL1, and IL6 were used at the beginning and end of the fourth week, and the number of consumed acetaminophen was considered as the secondary outcome of study at the end of the fourth week. Measurement of Interleukin 1 and Interleukin 6 levels was done using ELISA method by the R&D kit of company. In the study, the patients were also asked to note and report to researchers if they observed any side effects of drugs. The WOMAC was a 24-item questionnaire (5 questions for pain assessment, 2 questions for assessing knee dryness and 17 questions for evaluating physical function) on a 5-point Likert scale (4= very high, 3= high, 2= medium, 1= Low, 0= no) in which the respondents were asked to respond to the incidence of symptoms. Validity and reliability of questionnaire were confirmed by internal and external studies (Escobar et al., 2002). The study was approved by the Medical Ethics Committee of Shahed University on 5/4/2017 and registered with a code of IR.Shahed.REC.1395.233. It was also registered and approved at the Iranian Registry of Clinical Trials (IRCT) on 21/1/2018 with a code of IRCT20170428033670N1.

Drug and placebo preparation methods

First, the root of plant Zingiber zerumbet was prepared from the pharmacy market of Tehran and detected in each herbarium of Faculty of Pharmacy of Shahid Beheshti University of Medical Sciences (herbarium code: SEMU-8095), and the plant root was

washed with water and dried, then powdered and the hydroalcoholic extract was prepared by adding water and alcohol. Finally, the filtered extract was distilled by distillation device in a vacuum; and the resulting dry extract was obtained. The product zingiber zerumbet was prepared from 5% Zingiber zerumbet extract and Eucerin grade 400, and the Zingiber zerumbet Powder form was prepared. The obtained product and the diclofenac gel 1% were encoded in the same containers (by taking into account the smell and color).

Statistical analysis and sample size

Descriptive statistics (mean, standard deviation, correlation, frequency and percentage) and inferential statistics (Chi-square test, independent t-test, Mann-Whitney test, repeated-measure ANOVA and Friedman test) were performed proportional to normal ad or lack of response variable using K-S test. In the study, SPSS 21 was used and the significance level was 5%. In the study, the same size was 43 according to d= 0.8, $\alpha = 0.05$, $\beta = 0.1$ based on $n = 2\left(Z_{\frac{\alpha}{2}} + Z_{\beta}\right)^2 / d^2$ formula. 14 samples were added to this number by consideration of 30% sample loss. Finally, 57 samples were considered in each group of the present study.

3. RESULTS

In the study, 200 participants were studied; and 114 ones had the inclusion criteria, and eventually 92 participants remained at the end of study (Figure 1). Table 1 presents demographic characteristics of participants in two groups. Based on the information off this table, we can ensure the distribution of demographic and basic variables of participants in the study. In Table 2, the mean and standard deviation of physical functioning, pain, stiffness and total WOMAC variables were measured before, two weeks and a month after the intervention. Based on reported results of this table, it can be seen that all four mentioned variables were significantly decreased during the study. The results also indicated that except for the Stiffness variable, the Physical Functioning and Pain significantly decreased in the intervention group compared to the control group. According to the Table 3, except for the CRP and Bun variables, other variables, namely the ESR, HB, Hct, PLT, Rbc, Smooth, Sgpt, Wbc, Alkp and Cr had no significant changes in intervention and control groups. In Table 4, two groups were compared in terms of number of acetaminophen tablets and also the mean and SD of Interleukin 1 and Interleukin 6 concentration according to the two groups in end of study have shown in table 5. Results indicated similar functions of both drug and positive control groups in terms of mentioned variables. Figure 2 & 3 shows the total score of the WOMAC during the course of the treatment, the vertical axis of the WOMAC score and the horizontal axis of the time (P-Value=0.001).

Table 1 The base line variables according to the two groups

		Treatment				
Categorical variables		**Drug (n=48)**		**Diclofenac (n=44)**		**P-value**
		N	**%**	**N**	**%**	
Gender	Male	15	31.3%	8	18.2%	0.228
	Female	33	68.8%	36	81.8%	
Marriage	Single	1	2.1%	1	2.3%	0.950
	Married	47	97.9%	43	97.7%	
Academic Education	No	42	87.5%	40	90.9%	0.742
	Yes	6	12.5%	4	9.1%	
Continuous variables		**Drug**			**Control +**	
		Mean	**SD**	**Mean**	**SD**	**P-value**
Age	year	53.5	11.7	57.6	10.6	0.082
BMI	Kg/m2	30.3	4.04	28.9	4.29	0.111
Pain	(0-20)	10.43	3.54	10.90	3.12	0.506
Physical Function	(0-68)	30.04	9.61	29.75	9.97	0.887
Stiffness	(0-8)	3.10	1.51	2.59	1.33	0.090
Total (WOMAC)	(0-96)	44.04	12.79	42.7	13.37	0.625
Interleukin 1	Pg/ ml	1.208	1.961	2.695	6.192	0.355
Interleukin 6	Pg/ ml	2.104	2.076	4.64	8.22	0.505

The p-value calculated using chi square test for categorical variables and t-test or Mann-Whitney Test for continuous variable.
BMI: Body Mass Index, WOMAC: Western Ontario and McMaster universities Index of osteoarthritis, SD: Standard Deviation.

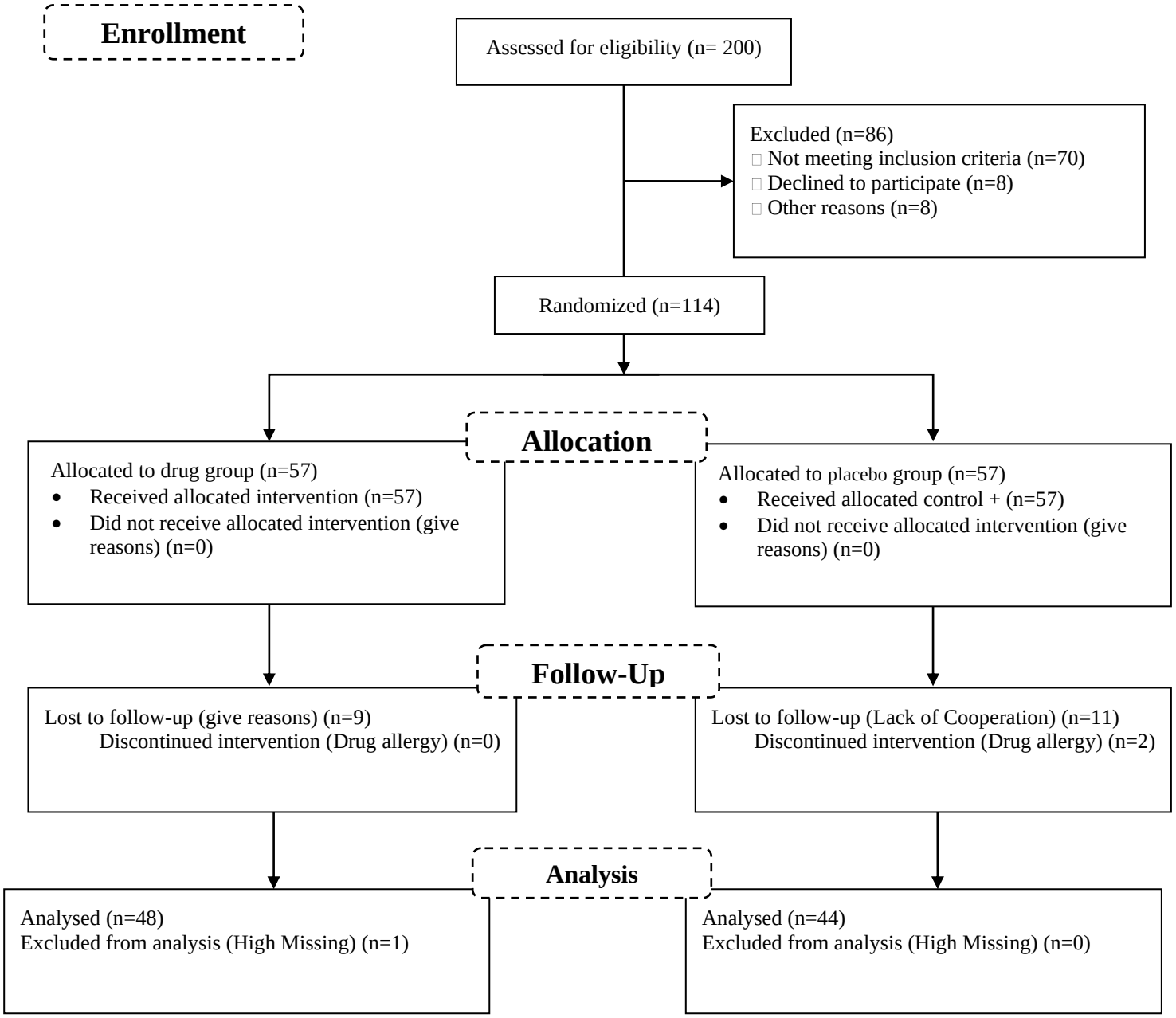

Figure 1 Follow diagram of study

Table 2 Physical Functioning, Pain, Stiffness and Total WOMAC score during study according to the two groups

		Time							
		Base Line		2th week after study		1 month after study		P-value	P-value
		Mean	SD	Mean	SD	Mean	SD		
Physical Functioning	Drug	30.04	9.61	19.67	10.25	18.10	10.97	<0.001	<0.001
	Control+	29.75	9.98	24.91	9.35	23.32	9.55	<0.001	
Pain	Drug	10.90	3.12	7.27	3.55	6.96	4.35	<0.001	0.039
	Control+	10.43	3.55	8.52	3.32	8.00	3.45	<0.001	
Stiffness	Drug	3.10	1.52	1.85	1.41	1.79	1.61	<0.001	0.135
	Control+	2.59	1.34	1.84	1.20	1.68	1.29	<0.001	
Total WOMAC	Drug	44.04	12.79	28.79	14.49	26.63	15.93	<0.001	0.001
	Control+	42.70	13.37	35.27	12.73	33.07	13.15	<0.001	

SD: Standard Deviation, The P-value 1 is based on Repeated Measurement analysis or *Friedman* Test.

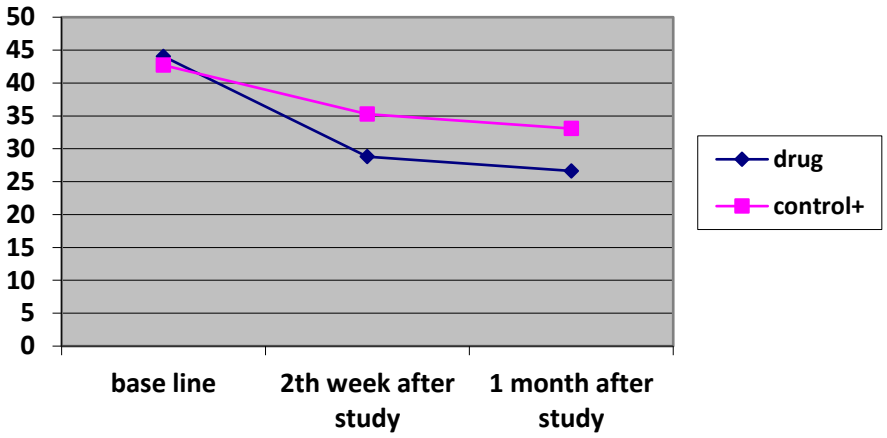

Figure 2 The total score of the WOMAC during the course of the treatment

Table 3 The mean secondary outcomes before and after treatment according to the two groups

Variables	Group	Mean	SD	Mean	SD	Diff	P-value
ESR	Drug	16.89	13.93	12.57	8.3	-4.32	0.143
	Control+	13.39	10.36	11.89	6.33	-1.5	0.473
		P-value	0.902	P-value	0.786		
CRP	Drug	2.84	2.89	2.02	4.03	-0.82	0.011
	Control+	1.3	1.16	0.74	0.91	-0.56	0.005
		P-value	0.014	P-value	0.085		
HB	Drug	13.54	1.39	13.53	1.55	-0.01	0.082
	Control+	13.78	0.92	13.65	1.23	-0.13	0.187
		P-value	0.545	P-value	0.916		
Hct	Drug	41.57	9.73	40.68	4.36	-0.89	0.118
	Control+	41.68	2.59	41.47	3.28	-0.21	0.449
		P-value	0.472	P-value	0.391		
Plt	Drug	248.37	69.39	250.43	63.89	2.06	0.812
	Control+	231.95	58.21	237.31	56.65	5.36	0.427
		P-value	0.217	P-value	0.597		
Rbc	Drug	4.77	0.5	4.74	0.51	-0.03	0.175
	Control+	4.74	0.3	4.73	0.4	-0.01	0.495
		P-value	1.000	P-value	0.991		
Sgot	Drug	20.89	8.67	19.86	5	-1.03	0.148
	Control+	20.83	5.67	21.88	5.41	1.05	0.162
		P-value	0.198	P-value	0.270		
Sgpt	Drug	24.24	13.41	20.43	6.39	-3.81	0.681
	Control+	21.8	9.44	21.89	8.99	0.09	0.293
		P-value	0.359	P-value	0.625		
Wbc	Drug	6.47	1.17	6.52	1.42	0.05	0.299
	Control+	6.32	2.02	6.53	3.07	0.21	0.405

		P-value	0.132	P-value	0.226		
	Drug	183.24	57.41	175.97	55.82	-7.27	0.813
Alkp	Control+	176	43.55	178.2	37.08	2.2	0.651
		P-value	0.741	P-value	0.309		
	Drug	16.16	5.82	14.96	6.14	-1.2	0.042
Bun	Control+	14.46	3.82	16.09	4.85	1.63	0.047
		P-value	0.310	P-value	0.194		
	Drug	0.82	0.25	0.8	0.19	-0.02	0.784
Cr	Control+	0.8	0.2	0.82	0.18	0.02	0.139
		P-value	0.857	P-value	0.769		

SD: Standard Deviation, the P-value1 is based on paired sample t-test or Wilcoxon Signed Ranks Test, P-value 2 is based on independent sample t-test or Mann-Whitney Test

Table 4 The mean and SD of number of acetaminophen pills according to the two groups in end of study

Continuous variables		Drug		Control +		
		Mean	SD	Mean	SD	P-value
Acetaminophen Pills	Number	3.92	5.92	4.64	5.68	0.554

Table 5 The mean and SD of Interleukin 1 and Interleukin 6 concentration according to the two groups in end of study

		Drug		Control +		
		Mean	SD	Mean	SD	P-value
Interleukin 1	Pg/ml	1.581	3.176	2.723	5.473	0.085
Interleukin 6	Pg/ml	2.664	2.908	5.644	8.46	0.177

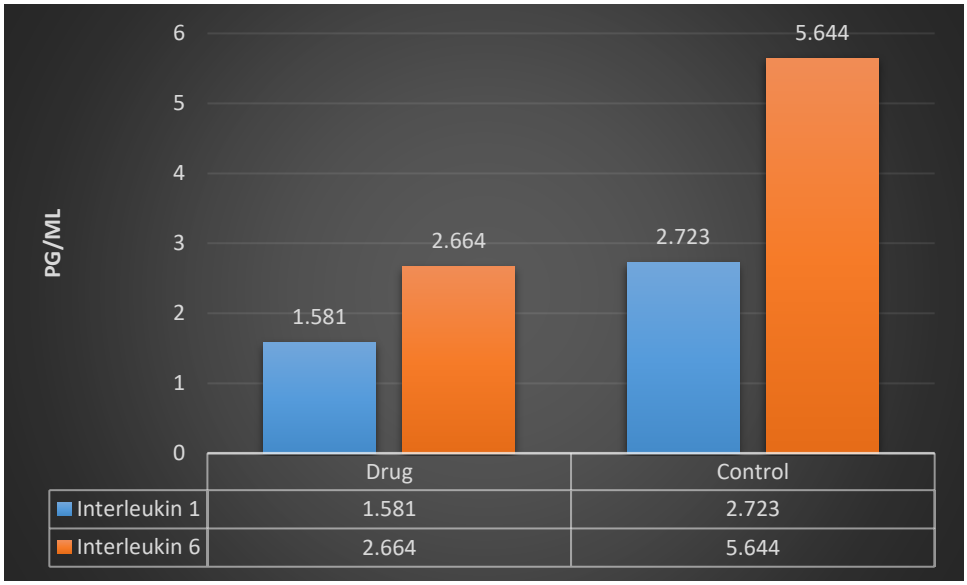

Figure 3 Mean of Interleukin 1 and Interleukin 6 concentration in drug and control groups

4. DISCUSSION

Results of the present study aimed to evaluate the effectiveness of Zingiber zerumbet ointment compared to the diclofenac gel on clinical symptoms of patients with knee osteoarthritis indicating that Zingiber zerumbet ointment reduced the mean of Physical

Functioning, Pain and Stiffness variables in terms of diclofenac gel. Results of the present study about the Zingiber zerumbet ointment were consistent with results of previous studies (Baraf et al., 2012 and Baraf et al., 2010 and Barthel et al., 2009 and Niethard et al., 2005). Zakaria et al. studied the impact of analgesic and anti-inflammatory effects of Zingiber zerumbet ointment and indicated that the extract Zingiber zerumbet had analgesic and anti-inflammatory effects due to anti-inflammatory and analgesic Opioid, Bradykinin and histamine pathways (Zakaria et al., 2010).

The results also indicated that the mean score of Physical Functioning decreased by -11.94 units in group Zingiber zerumbet ointment after a month of consumption, while this change it was almost a half of that amount and equal to -6.43 in the diclofenac gel group. In this regard, results of study were consistent with a research by Khodadoust et al. who investigated the effect of topical consumption of dill oil in comparison with diclofenac gel and found that Zingiber zerumbet ointment had higher effect than Diclofenac gel and dill oil. Furthermore, results of the present study had better results than a research by Barzi et al., who investigated the impact of joint ointment which was a natural combination of the traditional Iranian medicine, on the reduction of pain and improving the function of patients with joint arthritis (Mehdi Barzi et al., 2008). Compared to a study by Shoara et al., who studied the effect of topical use of chamomile oil on the treatment of knee osteoarthritis, the present study indicated that the Zingiber zerumbet ointment had better therapeutic function than the chamomile oil (Shoara et al., 2015).

In comparison to a study by Soleimani et al., who studied the effect of topical use of Nerium Oleander oil on the treatment of knee osteoarthritis, results of the present research indicated that Zingiber zerumbet ointment had a better function than chamomile oil in pain reduction and knee stiffness (Soleimani et al., 2014). Further results also indicated that the mean of Pain variable after a month in the Zingiber zerumbet ointment group decreased by about -3.94 units, but the reduction was -2.43 in the diclofenac gel group. This change in the group Zingiber zerumbet ointment was significant compared to diclofenac gel. The pain relief effects of Zingiber zerumbet ointment were also proven in previous studies (Khalili Shomia et al., 2012). Previous studies indicated that analgesic effects of Zingiber zerumbet ointment in oral and intravenous administration of extract Zingiber zerumbet reduced pain and edema in animal samples (Somchit, 2012). The impact of Zingiber zerumbet ointment was probably due to the fact that Zingiber zerumbet ointment plays role in inhibiting the glutaminergic pathway, the TRPV1 receptor and activating the pathway of l-arginine, nitric oxide, cGMP, Protein kinase C and channel-dependent effects of K (Somchit, 2012). Another reason for effect of Zingiber zerumbet can be seen in the presence of its active ingredient, Zerumbone. In an animal model, Somchit et al. indicated an anti-inflammatory effect of 20mg/kg of Zerumbone resembled Piroxicam 20mg/ kg. Studies also indicated that Zerumbone could reduce the inflammatory process in the induced osteoarthritis model in mice by inhibiting immune cells of MHC II (Ganabadi and Kadir, 2009 and Chien et al., 2008 and Somchit et al., 2005).

In terms of stiffness variable and despite the fact that the difference in mean of Stiffness variable at the end of study was higher in the group Zingiber zerumbet ointment at the beginning of study (mean difference= -1.31) than the diclofenac gel (mean difference= -0.91), the difference was statistically equal in both groups. According to results, except for CRP and Bun variables, other variables, including ESR, HB, Hct, PLT, Rbc, Smooth, Sgpt, Wbc, Alkp and CR had no significant change in two groups of Zingiber zerumbet ointment and diclofenac gel. The result indicated the lack of complications in the use of both drugs. Two groups were also similar in terms of number of acetaminophen pills.

Despite the fact that previous studies reported the mediating roles of inflammatory factors and the cytokine environment for osteoarthritis (Kapoor et al., 2010 and Fernandes et al., 2002). Results for variables, Interleukin 1 and 6 indicated no significant difference between two groups before and after the intervention. However, it should be noted that the inflammation was not the only factor involved in the pathogenesis of osteoarthritis and other factors such as age, race, obesity, and inappropriate use of joint were also involved in its emergence (Attur et al., 1998 and Gabay, 2006). Finally, the strengths of study included the double-blind nature, random allocation, appropriate sample size, and control of confounders.

5. CONCLUSION

Given that the use of Zingiber zerumbet ointment is riskless and it easily and effectively decreases symptoms of osteoarthritis, Zingiber zerumbet ointment can recommend for improving symptoms of osteoarthritis.

Funding:
This research received no external funding.

Conflicts of Interest:
The authors declare no conflict of interest.

REFERENCE

1. Attur MG, Patel IR, Patel RN, Abramson SB, Amin AR. Autocrine production of IL-1 beta by human osteoarthritis-affected cartilage and differential regulation of endogenous nitric oxide, IL-6, prostaglandin E2, and IL-8. Proc Assoc Am Physicians 1998; 110:65-72.
2. Baraf HS, Gold MS, Clark MB, Altman RD. Safety and efficacy of topical diclofenac sodium 1% gel in knee osteoarthritis: a randomized controlled trial. Phys Sportsmed 2010; 38:19-28.
3. Baraf HS, Gold MS, Petruschke RA, Wieman MS. Tolerability of topical diclofenac sodium 1% gel for osteoarthritis in seniors and patients with comorbidities. The American journal of geriatric pharmacotherapy 2012; 10:47-60.
4. Barthel HR, Haselwood D, Longley S, Gold MS, Altman RD. Randomized Controlled Trial of Diclofenac Sodium Gel in Knee Osteoarthritis. Semin Arthritis Rheum 2009; 39:203-12.
5. Chien TY, Chen LG, Lee CJ, Lee FY, Wang CC. Anti-inflammatory constituents of Zingiber zerumbet. Food Chem 2008; 110:584-9.
6. Escobar A, Quintana JM, Bilbao A, Azkárate J, Güenaga JI. Validation of the Spanish version of the WOMAC questionnaire for patients with hip or knee osteoarthritis. Western Ontario and McMaster Universities Osteoarthritis Index. Clin Rheumatol [Internet] 2002; 21:466-71.
7. Fernandes JC, Martel-Pelletier J, Pelletier J-P. The role of cytokines in osteoarthritis pathophysiology. Biorheology 2002; 39:237-46.
8. Fransen M, Bridgett L, March L, Hoy D, Penserga E, Brooks P. The epidemiology of osteoarthritis in Asia. Vol. 14, International Journal of Rheumatic Diseases 2011; 14:113-21.
9. Gabay C. Interleukin-6 and chronic inflammation. Arthritis Res Ther. 2006; 8 Suppl 2:S3.
10. Ganabadi S, Kadir SF. ZiTumboiHi's Effect on Major Histocompatibility Complex Type II Cells in Synovial Membrane of Osteo Arthritic Joint. Research Journal of Veterinary Sciences 2009; 2:14-20.
11. Harris PE, Cooper KL, Relton C, Thomas KJ. Prevalence of complementary and alternative medicine (CAM) use by the general population: A systematic review and update. International Journal of Clinical Practice 2012; 66:924-39.
12. Harrison TR, Longo DL. Harrison's manual of medicine. McGraw-Hill Medical 2015.
13. Hughes GD, Aboyade OM, Clark BL, Puoane TR. The prevalence of traditional herbal medicine use among hypertensives living in South African communities. BMC Complement Altern Med. 2013; 13:38.
14. Kapoor M, Martel-Pelletier J, Lajeunesse D, Pelletier J-P, Fahmi H. Role of Proinflammatory Cytokines in the Pathophysiology of Osteoarthritis. Nat Publ Gr 2010; 7:33–42.
15. Kasper D, Fauci A, Hauser S, Longo D, Jameson J, Loscalzo J. Harrison's Principles of Internal Medicine. Star 2015; 2958.
16. Khalili Shomia S, Safavi M, Yahyavi SH, Farahani H. The Effect of Diclofenac Gel on the Pain Intensity Related to Vein Puncture using Angiocatheter: a Randomized Clinical Trial. IJN 2012; 25:45-53.
17. Kon E, Buda R, Filardo G, Di Martino A, Timoncini A, Cenacchi A, et al. Platelet-rich plasma: Intra-articular knee injections produced favorable results on degenerative cartilage lesions. Knee Surgery, Sport Traumatol Arthrosc 2010; 18:472-9.
18. Kwok WY, Vliet Vlieland TPM, Rosendaal FR, Huizinga TWJ, Kloppenburg M. Limitations in daily activities are the major determinant of reduced health-related quality of life in patients with hand osteoarthritis. Ann Rheum Dis 2010; 70:334-6.
19. Mehdi Barzi D, Naseri M, Faghih Zadeh S, Kamalinezhad M, Bahrami M. Efficacy of Herbal Joint Ointment "A" in the Treatment of Primary Knee Osteoarthritis: A Randomized Double Blind Clinical Trial. Daneshvar Medicine 2008; 16:49-56.
20. Naseri M, Ghafari F, Shirzad M. Ibn Sina's view on the use of drugs in traditional Iranian medicine. Summary of Seminars on Traditional Medicine and Medicinal Herbs 2007; 9:54-64.
21. Naseri M. Traditional Iranian medicine and its development using the World Health Organization's guidelines. Daneshvar Med 2004; 11:53-66.
22. Niethard FU, Gold MS, Solomon GS, Liu JM, Unkauf M, Albrecht HH, et al. Efficacy of topical diclofenac diethylamine gel in osteoarthritis of the knee. J Rheumatol 2005; 32:2384-92.
23. Prakash RO, Rabinarayan A, Kumar MS. Zingiber zerumbet (L.) Sm, a reservoir plant for therapeutic uses: a review. International Journal of Research in Ayurveda and Pharmacy 2011; 2:1-22.
24. Shoara R, Hashempur MH, Ashraf A, Salehi A, Dehshahri S, Habibagahi Z. Efficacy and safety of topical Matricaria chamomilla L.(chamomile) oil for knee osteoarthritis: a randomized controlled clinical trial. Complementary therapies in clinical practice 2015; 21:181-7.
25. Sinusas K. Osteoarthritis: Diagnosis and Treatment. Am Fam Physician 2012; 1:49-56.
26. Soleimani H, Kamalinejad M, Kor NM, Najafizadeh SR, Askarfarashah M, HoseiniYekta N, et al. A preliminary study on the efficacy of Nerium oleander L. extract on clinical symptoms in patients with knee osteoarthritis. European Journal of Experimental Biology 2014; 4:295-8.
27. Somchit MN, Shukriyah MH, Bustamam AA, Zuraini A. Anti-pyretic and analgesic activity of Zingiber zerumbet. International Journal of Pharmacology 2005; 1:277-80.

28. Somchit MN. Zerumbone isolated from Zingiber zerumbet inhibits inflammation and pain in rats. J Med Plants Res [Internet] 2012; 6:753-7.
29. Spierings ELH, Fidelholtz J, Wolfram G, Smith MD, Brown MT, West CR. A phase III placebo- and oxycodone-controlled study of tanezumab in adults with osteoarthritis pain of the hip or knee. Pain 2013; 154:1603-12.
30. Tehrani-Banihashemi A, Davatchi F, Jamshidi AR, Faezi T, Paragomi P, Barghamdi M. Prevalence of osteoarthritis in rural areas of Iran: A WHO-ILAR COPCORD study. Int J Rheum Dis 2014; 17:384–8.
31. World Health Organization: National policy on traditional medicine and regulation of herbal medicines- report of a WHO global survey. Who 2005:156.
32. Yohannes AM, Caton S. Management of depression in older people with osteoarthritis: A systematic review. Aging Ment Health [Internet] 2010; 14:637–51.
33. Zakaria ZA, Mohamad AS, Chear CT, Wong YY, Israf DA, Sulaiman MR. Antiinflammatory and antinociceptive activities of zingiber zerumbet methanol extract in experimental model systems. Med Princ Pract 2010; 19:287–94.
34. Zakaria ZA, Yob NJ, Jofrry SM, Affandi MMRMM, Teh LK, Salleh MZ. Zingiber zerumbet (L.) Smith: A review of its ethnomedicinal, chemical, and pharmacological uses. Evidence-based Complementary and Alternative Medicine 2011; 2011:543216.