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Comparison of the effect of topical *Hedera helix* L. extract gel to diclofenac gel in the treatment of knee osteoarthritis

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Highlights

- Herbal remedies can significantly reduce the pain and inflammation caused by osteoarthritis
- *H. helix* gel has a relatively similar effect to diclofenac gel.
- Pain reduction in *H. helix* gel group was significantly higher than that of the placebo group
- *H. helix* gel is recommended as a natural therapeutic agent.

Abstract

Objective: The aim of this study was to comparatively investigate the effect of the topical 1% *Hedera. helix* extract gel to 1% diclofenac gel on knee osteoarthritis.
Methods: A total of 150 patients with primary osteoarthritis were randomly divided into three groups: 1% *H. helix* gel-treated, 1% diclofenac gel-treated, and placebo-treated. The topical gels were applied for 3-5 minutes three times a day for 6 weeks. Celecoxib capsules were also administered daily. The effects of the gels were evaluated compared to placebo gel using the visual analogue scale (VAS) and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC).
Results: Pain reduction was significantly more pronounced in 1% *H. helix* gel group than in the placebo group (P=0.021), but was not significantly different from the pain reduction in diclofenac gel group (P=0.416). Both 1% *H. helix* gel and diclofenac gel significantly reduced morning stiffness, daytime stiffness, and physical function compared to placebo group (P<0.05). Reduction in pain, morning stiffness, and daytime stiffness were higher in 1% *H. helix* gel group than in diclofenac gel group, but the difference was not statistically significant (P>0.05).
Conclusion: 1% *H. helix* gel has a relatively similar effect to diclofenac gel on pain severity, morning stiffness, daytime stiffness, and physical function in patients with knee osteoarthritis, and therefore is recommended as a natural therapeutic agent with optimal efficiency to supplement chemical drugs used for knee osteoarthritis.
Keywords: Osteoarthritis; Diclofenac; *Hedera helix* L.; Phytotherapy; Complementary Medicine.

Iranian clinical trial registration center code: IRCT20110514006480N14

1. Introduction

Knee osteoarthritis is a common, debilitating chronic disease that leads to cartilage destruction, bone changes, and decline in quality of life (Nikniaz et al, 2014; Silverwood et al. 2015). Studies have shown that about one-third of the people aged over 45 years suffer from osteoarthritis. (Dahai et al. 2017). Osteoarthritis will be the fourth leading cause of disability worldwide by 2020 due to increased life expectancy, sedentary lifestyle, and obesity rate (Yu et al. 2015). The prevalence of this disease worldwide is rising, especially in the people aged 40-50 years (Harle and Fleck, 2008). In Iran, its incidence rate is 17.3% and is comparatively higher in women (Haq and Davatchi, 2011). The symptoms of the disease include joint swelling, motor constraints in walking, and increased pain **(**Yennan et al. 2010). There is no definite treatment for osteoarthritis and therefore return to normal daily activities remains unachievable; thus, the main purpose in treating the disease is to reduce pain, maintain joint movement, and minimize disability in the patients (van der Ploeg et al. 2010). Drug therapy does not prevent or reverse osteoarthritis, and is used as an adjuvant therapy to non-pharmacologic treatments (van der Ploeg et al. 2010; Beck et al. 2005).

Today, nonsteroidal anti-inflammatory drugs (NSAIDs), including diclofenac, are topically applied to relieve pain in these patients. Diclofenac is an anti-inflammatory and analgesic drug and also the most effective prostaglandin inhibitor, which reduces joint swelling and stiffness and is used to treat rheumatic disorder (Beck et al. 2005; Altman et al. 2015). Diclofenac and other NSAIDs that reduce inflammation inside the joint also cause certain side effects and may also interact with other drugs taken by the patient (da Costa et al. 2016; Herrero et al. 2017). Topical diclofenac can lead to certain symptoms such as allergies, skin rashes, swelling, redness, itching and bronchospasm. In addition, diclofenac lead**s** to systemic hepatic, renal, and less frequently, digestive and neurological side effects, thereby limiting its use in clinical settings (Bruggemann et al 1990). Other treatments include corticosteroid shot into the joint (Herrero et al. 2017), acupuncture (Brinkhaus et al. 2007)**,** strong painkillers, and major surgical interventions including knee arthroscopy, correction of knee axis misalignment, cartilage transplantation, and ultimately knee replacement (Wallace et al. 2017, Skou et al. 2017).

Given the increased prevalence of osteoarthritis and the side effects of NSAIDs, it is assumed that medicinal plants can be used for osteoarthritis due to the positive attitude of people towards traditional medicine and pharmaceutical properties of some plants **(**Jabbari et al. 2016; Dehghan et al. 2018).

Herbal remedies including soybean and avocado extracts can significantly reduce the pain and inflammation caused by osteoarthritis. *Sambucus ebulus* L. has also been shown to be effective in reducing the symptoms of osteoarthritis due to flavonoids, phenols, and anthocyanins (Jabbari et al. 2016). *Hedera helix* (commonly called ivy) is an evergreen climbing plant with deep green, glossy, coriaceous leaves. It is a species of the Araliaceae family, with cytotoxic, antiproliferative antimicrobial, antifungal, antiprotozoal, and anti-inflammatory activities (Rashed, 2013; Uddin et al. 2011). *H. helix* is also used in cosmetics (Gumushan-Aktas and Altun, 2016).

The recent studies have demonstrated the chemical constituents, pharmacological effects and therapeutic importance of *H. helix*, leading the authors to considering the plant as a promising medicinal agent with a wide range of pharmacological activities so that it can be utilized for several medical applications because of its efficacy and safety; *H. helix* also possesses bronchiolytic,effects in the treatment of chronic bronchial asthma, anti-inflammatory, analgesic, immunological, anticancer, antimutagenic, antimicrobial, anti-parasitic, gastrointestinal, and antithrombin, and anti-allergic activities (Wolf et al. 2011; Hofmann et al. 2003; Lurquin et al. 2012; Rauf et al. 2014; Uddin et al. 2011; Al-Snafi, 2018; Jones, 2009).

English ivy spontaneously grows in Western, Central, and Southern Europe and has also been introduced to North America and Asia (Lutsenko et al. 2017). In 2004, α-hederin, a type of triterpenoid saponin isolated from the pure extract of *H. helix* leaf, was demonstrated to be the main compound responsible for the therapeutic effect of this plant (Hegener et al, 2004). *H. helix* also contains other compounds such as flavonoids and alkaloids (Mendel et al, 2011). The results of one study also confirmed the effectiveness of *H. helix* leaves on the lung and bronchus infections (Lutsenko et al. 2017). Considering the need for supplementation with natural agents to reduce the dose and side effects of chemical drugs, in this study, for the first time, the effect of the *H. Helix* extract, in the form of a 1% gel, in the treatment of primary knee osteoarthritis, was compared with that of diclofenac gel. For this purpose, the effects of the two gels on the severity of knee pain, morning stiffness, daytime stiffness, and physical function were investigated and compared.

2. Methods

2.1 H. helix extract preparation and formulation

The leaves of *H. helix* were authenticated in Medical Plants Research Center, SKUMS, Iran and a plant specimen was deposited (Herbarium No. 473). The maceration method was employed to prepare the extract. The next step was solvent selection for extraction, for which 70% ethanol solvent was selected based on previous studies (Rai, 2013; Süleyman et al. 2003). In fact, hydro alcoholic solution could isolate more glycoside compounds like saponin compounds. For this purpose, 1000 ml ethanol 70% was added to 200 g *H. helix* powder and the solution was left at laboratory temperature for 48 h. Then, the extract was filtered through filter paper and the pulp was squeezed to discharge. The solvent was evaporated by a rotary evaporator. Then, the concentrated extract was frozen and stored at -20ºC until use. To prepare *H. helix* 1% gel, the gel maker hydroxypropyl methylcellulose (HPMC) (2-3%), ethanol (20%), glycerin (4-5%), dried extract (1%), and water were used.

2.2. Study protocol

The protocol of this randomized, double blind placebo, controlled clinical trial conducted in 2016 was approved by the Ethics Committee of Shahrekord University of Medical Sciences (approval code: IR.SKUMS.REC.1395.40) and then registered in the Iranian Registry of Clinical Trials **(**code**:** IRCT20110514006480N14**)**. The study population consisted of 150 patients referring to Imam Ali Clinic affiliated with Shahrekord University of Medical Sciences and private offices across Shahrekord diagnosed with knee osteoarthritis**.** Samples were selected by convenience sampling (Figure 1). Sample size was based on a study that reported the analgesic efficacy of diclofenac before and after the intervention 9.9±3.51 and 7.8±3.9, respectively (Emad et al. 2008)

and with alpha=0.05, delta=2.1 and power=0.8 in each group based on Stata software and Sample Size Calculation Formula. Sample size was calculated 50 patients in each arm of the study.

Inclusion criteria were primary osteoarthritis in at least one knee with orthopedic diagnosis based on radiological criteria in knee image, having experienced pain for at least 2 weeks before treatment, and having age above 45 years. The people who had secondary osteoarthritis, active liver or kidney disease, peptic ulcer, diabetes, thyroid and parathyroid diseases, and coagulation disorders, consumed anticoagulant drugs, had history of ischemic or hemorrhagic stroke or deep vein thrombosis, allergy to any anti-inflammatory drug, alcohol abuse, drug abuse, acute trauma, skin diseases or infection or wounds at the site where the gel was applied, used corticosteroids of any type and other topical drugs at the site where the gel was applied, orally used other analgesics and other effective compounds for the treatment of osteoarthritis up to 10 days before beginning of the study, and had pregnancy, history of local fractures, and deformities leading to osteoarthritis and articular diseases were not enrolled in the study.

All patients provided written informed consent to participate in the study after the research purpose was explained to them. After participants were matched by age, they were divided into three groups of 50 each by block random allocation with Random Allocation Software (Saghaei et al. 2004), and each group used only one of the tubes of 60 g of diclofenac 1% gel, *H. helix* extract 1% gel, and placebo (The placebo contains a gel base without herbal extract.). The participants and researcher were blind to the contents of the tubes.
Demographic data were collected and **t**he Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and a standard instrument to measure pain, namely, visual analogue scale (VAS) were administered to participants. The WOMAC has been studied in several studies and its validity and reliability have been confirmed (Stucki et al. 1998). The VAS is the most widely used instrument across the world to measure pain. The WOMAC measures the effects of pain on the patient's function and joint stiffness. The validity of this instrument in Iranian patients with knee osteoarthritis was studied in 2014 and was calculated at 0.917 by using Cronbach's alpha coefficient (Ebrahimzadeh et al. 2014).
In order to control the pain of patients during the study period, Celecoxib 200 mg capsules were administered daily in addition to topical gel in all three groups. The patients applied the gel three times a day for six weeks and each time they applied the gel **on** the painful area for 3-5 minutes. Patients were followed up before and one, two, three, and six weeks after treatment. Both knees were treated in the patients complaining of pain in both knees, but the pain in the knee with more severe pain was assessed. Patients were asked not to use other medications during the course of the treatment without informing the researcher. They were also asked to discontinue using the gel if they experienced redness or itching and burning at the site where they applied the gel or suffered gastrointestinal side effects.

2.3. Data analysis

Data analysis was conducted using descriptive statistics such as measures of central tendency and, depending on data distribution, analytical statistics such as ANOVA, Kruskal-Wallis test, repeated measures ANOVA, and chi-squared test in the STATA software. $P < 0.05$ was considered significance level.

3. Results

The aim of this study was to comparatively investigate the effects of 1% *H. helix* gel and 1% diclofenac gel in the treatment of primary knee osteoarthritis. Of the 150 studied patients, 5 ones were excluded from the follow-up due to personal reasons. The final number of participants in the 1% *H. helix* gel-treated group, diclofenac gel-treated group, and placebo group was 48, 49, and 48, respectively. Of the patients, 100 (69%) were female and 45 (31%) were male. The groups were matched by gender. Demographic characteristics of the patients are presented in Table 1.

Regarding the comparison of pre- and post-treatment data in the three groups, the mean values of pain severity, morning stiffness, daytime stiffness, and physical function before and after treatment were significantly different ($P < 0.05$). There was no significant difference among the three treatment groups before treatment, but the overall comparison of the mean difference values of the four variables before and after treatment showed significant differences (Table 2). Comparison of mean difference in pain severity after the treatment showed a significant difference between the three groups ($P = 0.026$). In this study, patients have not reported any allergic reactions. Also, according to the study of Lutsenko et al. (2010), health risks or side effects or proper administration of the designated therapeutic dosages of H. helix are not recorded (Lutsenko et al. 2010).

In the extract-treated group, pain severity decreased by 1.39 ± 1.02 and in the diclofenac and placebo groups, it decreased by 1.1 ± 1.06 and 0.85 ± 0.79, respectively. Therefore, treatment with *H. helix* gel improved the pain more effectively.

The paired comparison of mean difference values followed by post hoc test**,** showed a significant difference in pain severity between *H. helix* gel group and placebo group ($P = 0.021$), but not between *H. helix* gel group and diclofenac gel group ($P = 0.416$). In addition, pain severity in diclofenac group and placebo group were not significantly different (Table 2).

Comparison of data on morning stiffness, daytime stiffness, and physical function in the three groups is presented in Table 2. According to these results, treatment with *H. helix* gel or diclofenac gel, compared to placebo, decreased morning stiffness and daytime stiffness more markedly. Treatment with *H. helix* gel caused a decrease in patients' physical function score (indicating improvement) compared to placebo**.** However, the effect of diclofenac on the reduction in physical function was comparably more pronounced.

Paired comparison followed by post hoc test showed significant differences in morning stiffness, daytime stiffness, and physical function between the *H. helix* gel group and the placebo group, but the difference was not statistically significant. In addition, morning stiffness, daytime stiffness, and physical function in diclofenac group and placebo group were significantly different.

Therefore, the *H. helix* gel and diclofenac gel significantly changed morning stiffness, daytime stiffness, and physical function compared to placebo **(**Table 2).

Figure 2 illustrates how the studied variables changed before treatment and one, two, three, and six weeks after treatment. The results of repeated measures ANOVA showed a significant

difference in pain, morning stiffness, daytime stiffness, and physical function between the three groups at different intervals (P = 0.00) (Figure 2).

4. Discussion

This study was conducted with the aim of comparing the effects of 1% *H. helix* extract gel and 1% diclofenac gel on primary knee osteoarthritis. In this study, pain, morning stiffness, daytime stiffness, and physical function before treatment up to 6 weeks after treatment were investigated. There was no significant difference in pain relief between the diclofenac and placebo groups, but the effect of 1% *H. helix* extract gel was significantly higher than that of the placebo gel, indicating the greater effect of this gel in reducing the pain severity**,** but both **1% *H. helix* and diclofenac** gels, compared to placebo gel, caused significant differences in the improvement of joint stiffness, daytime stiffness, and physical function. In fact, the plant gel (1%) exhibited almost similar effect to that of diclofenac gel in improving pain, morning stiffness, daytime stiffness, and physical function**.** The mean difference in the reduction in pain severity, morning stiffness, and daytime stiffness in the *H. helix* 1% gel-treated group was higher than that in the diclofenac gel-treated group, but the difference was not statistically significant, with the main effects of the two treatments being similar. The results of repeated measures ANOVA also showed that there was a significant difference in pain severity, morning stiffness, daytime stiffness, and physical function between the groups at studied intervals, and that the effects of treatment gels increased over time.

Diclofenac is used as a strong inhibitor of cyclooxygenase and reduces pain and joint swelling and stiffness in arthritis and other rheumatic disorders**.** Diclofenac produces analgesic and anti-inflammatory effects by reducing the production of prostaglandins and thromboxane (Tonussi and Ferreira, 1994). The use of this medicine leads to numerous side effects, including nausea, diarrhea, bleeding, and stomach ulcer. In topical application, allergic reactions and rash are also likely (Bruggemann et al, 1990).

In addition, this drug interacts with antihypertensive drugs in the elderly such as angiotensin converting enzyme inhibitors. It also increases the risk of heart attacks and stroke in patients (Grosser et al, 2017). Because similar effects were observed in improving the patient's pain, morning stiffness, daytime stiffness, and physical activity for *H. helix* extract 1% gel, and that the mean recovery after treatment with this gel was slightly better compared to that after diclofenac use, then the *H. helix* 1% gel can be a good supplement or alternative to diclofenac**.** Bruhlmann et al. reported that the use of diclofenac gel effectively reduced pain compared to placebo group (Bruhlmann and Michel, 2003).

In the study of Amorndoljai and Taneepanichskul, ginger extract did not cause any significant difference before or after treatment compared to diclofenac, but reduction in pain and morning stiffness was more pronounced in patients treated with ginger than in those treated with diclofenac (Amorndoljai et al. 2017). The findings on the effect of medicinal plants in improving the symptoms of osteoarthritis are consistent with the present study. The effect of *H. helix* extract on knee osteoarthritis has not yet been studied. However, the study of Cwientzek et al. (2011) on the effect of the *H. helix* extract in improving the symptoms of acute bronchitis, showed that the α-hederin present in the plant leaf increased the activity of β-2 adrenergic receptor in the bronchi, relaxed the smooth muscles of the bronchi, and increased the secretion of the surfactant.

In this study, it was also observed that the *H. helix* extract was well tolerated by the patients and caused very few, including gastrointestinal, side effects **(**Cwientzek et al. 2011).

In a clinical trial, *H. helix* was found to be a safe and effective alternative drug for the treatment of acute cough (Schaefer et al, 2016). Zeil et al. (2014) also observed that children with mild uncontrolled asthma, despite the regular inhaled corticosteroid, benefitted from supplemental treatment with *H. helix* leaf extract syrup. These findings can be attributed to the anti-inflammatory effects of *H. helix* extract and confirm the observations in the study. The evidence suggests that the plant extract contains triterpenoid saponins and anti-inflammatory and analgesic effects of triterpenoid saponins inhibit the synthesis of the induced nitric oxide and clooxygenase 2 (Hegener et al. 2004; Suh et al. 1998), which can be one of the potential mechanisms of the analgesic effects of *H. helix* extract. Based on the review results of this plant; *H. helix* has 4.8-12.1% saponins including triterpene saponins (2.5–6%): the bidesmosidic glycosides of hederagenin: hederacoside C (1.7–4.8%), hederacoside D (0.4–0.8%), hederacoside B (0.1–0.2%), and monodesmoside α-hederin (0.1–0.3%)(Lutsenko et al. 2010; Demirci et al. 2004). So the approximate amount of saponin in 200 g of this plant is equal to 9.6-24.2 g. The analgesic effect of the plant can also be partly attributed to flavonoids and their direct effect**s** on the synthesis of prostaglandins (Alcaraz and Hoult,1985). Because prostaglandins are a major contributor to inflammation and also stimulate direct pain receptors and increase their susceptibility to other agents, such as bradykinin (Hochain et al. 2000; Toker et al. 2004), *H. helix* extract may decrease the synthesis and secretion of prostaglandins due to phenolic compounds and flavonoids.

In the study of Rai (2013), the anti-inflammatory effect of *H. helix* extract (75 mg) was very similar to that of diclofenac and significantly different from that of placebo. Intraperitoneal injection of the extract caused an 88.89% inhibition of the formalin-induced paw edema as compared to diclofenac (94.44%). Because the formalin-induced paw edema in mice is very similar to human arthritis, significant reduction in the symptoms of arthritis after *H. helix* treatment can explain its potential against inflammation and arthritis (Rai, 2013).

Other studies have demonstrated the anti-inflammatory effects of *H. helix* on acute and chronic inflammation in male rats, so that in a study, both saponin purified extract (SPE) and crude saponin extract (CSE) of the plant exhibited anti-inflammatory effects. The most potent screened extract was the CSE but was less active than indomethacin. The extracts were more effective in the first phase of acute inflammation than in the second phase; it seems that they may block histamine and/or serotonin release in a better way than prostaglandin and/or bradykinin. According to the chronic inflammation model, the extracts may exert their activities by inhibiting the functions of macrophages and fibrosis (Suleyman et al. 2003).

In the next experiment, the anti-inflammatory potential of α-hederin and hederacoside C given orally was investigated in carrageenan-induced acute paw edema in rats.(Gepdiremen et al. 2005). In the first and second phases of acute inflammation, α-hederin and hederacoside C were ineffective. Hederacoside C showed an anti-inflammatory effect in the second phase which may be due to the blockage of bradykinin or other mediators of inflammation. One study was conducted to investigate the impact of *H. helix* constituents on hyaluronidase and elastase enzymes activity which increases in chronic inflammatory conditions, e.g. venous insufficiency symptoms. The results confirmed that sapogenins non-competitively inhibited hyaluronidase activity in a dose-dependent manner (Rai, 2013).

In response to stress and inflammatory insults, chondrocytes in osteoarthritis produce a variety of matrix-degrading enzymes, including metalloproteinases and aggrecanases. The expression of these degradative enzymes is dysregulated in chondrocytes osteoarthritis, and their increased and aberrant expression and activities greatly contribute to cartilage degradation during osteoarthritis development and progression. As the signaling pathways involved in inflammatory and biomechanical stress are similar and may also induce and amplify the expression of cytokine and chemokine genes, it therefore remains controversial whether inflammatory mediators are primary or secondary regulators of cartilage damage and defective repair mechanisms in osteoarthritis (Smith, 1999; Lee et al. 2013). Although cytokines and their receptors, proteinase activities, and signaling kinases have been considered as targets in the treatment of osteoarthritis, recent evidence about early stress-induced and inflammation-induced events involved in the presymptomatic onset of the disease could provide valid biomarkers for diagnosis and new therapeutic strategies (Otero and Goldring, 2011). Overall, the role of inflammation in the pathogenesis of osteoarthritis has been recently demonstrated.

This study, in line with previous studies that demonstrated the analgesic and anti-inflammatory effects of *H. helix*, showed that the effect of the herbal gel (1%) in improving the symptoms in people with knee osteoarthritis was optimal. Clearly, further studies are needed to confirm this proposition. The limitations of this study include the withdrawal of five patients and the need for follow-up of patients for proper use of the drug and lack of studying potential side effects.

5. Conclusion

In this study, the 1% *H. helix* gel exhibited similar effects to those of diclofenac gel in improving the symptoms of knee osteoarthritis. Therefore, given the anti-inflammatory effects of *H. helix* extract and the results of this study, this plant is recommended as a natural therapeutic agent and an optimal supplementation to chemical drugs to reduce pain, morning stiffness, and daytime stiffness, as well as to improve the physical function in patients with knee osteoarthritis. Because the effect of *H. helix* gel on the treatment of osteoarthritis has not yet been adequately studied, more comprehensive studies with larger sample size and more detailed investigation of the side effects of the plant are recommended.

Declarations of interest: **Nil**.

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Tables

Table 1: Demographic characteristics of patients in study groups

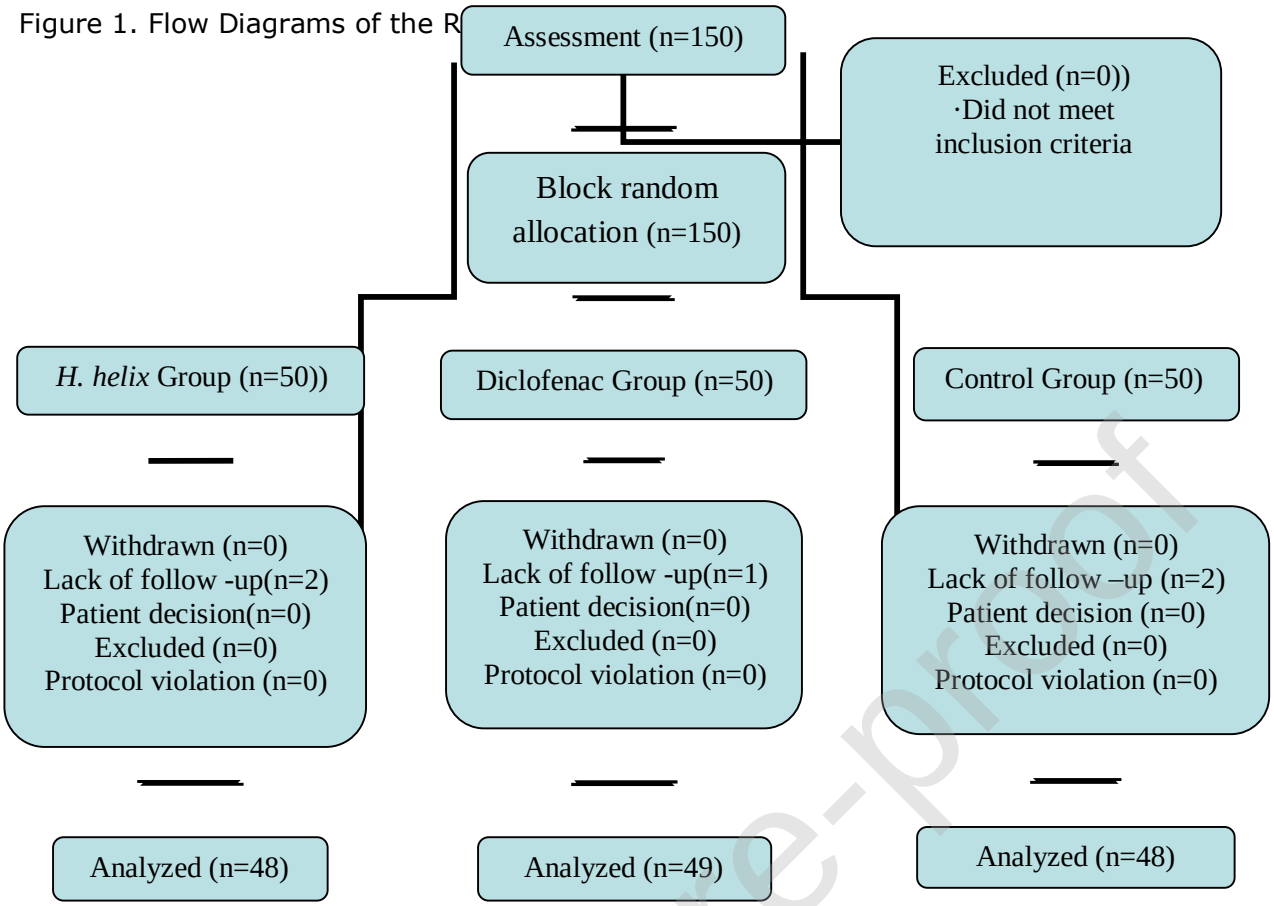
groups Variables		*H. helix* N=48(100%)	Diclofenac N=49(100%)	placebo N=48(100%)	total N=145(100%)
Gender	Male	12(25%)	17(34.7%)	16(33.3%)	100(69%)
	Female	36(75%)	32(65.3%)	32(66.7%)	45(31%)
Marital status	Non-married	0(0%)	2(4.1%)	0(0%)	2(1.4%)
	Married	48(100%)	47(95.9)	48(100%)	143(98.6%)
Age (yr)	45-54	18(37.5%)	18(36.7%)	12(25%)	48(33.1%)
	55-64	13(27.1%)	17(34.7%)	19(39.6%)	49(33.8%)
	65-75	17(35.4%)	14(28.6%)	17(35.4%)	48(33.1%)
Education level	Under high school diploma	27(56.3%)	21(42.9%)	31(64.6%)	79(54.5%)
	High school diploma	10(20.8%)	9(18.4%)	8(16.7%)	27(18.6%)
	Higher than high school diploma	11(22.9%)	19(38.8%)	9(18.8%)	39(26.9%)
Occupation	CLERK	9(18.8%)	2(4.1%)	1(2.1%)	12(8.3%)
	LABORER	0(0%)	1(2%)	2(4.2%)	3(2.1%)
	Self-Employed / Housewife	39(81.3%)	46(93.9%)	45(93.8%)	130(89.7%)

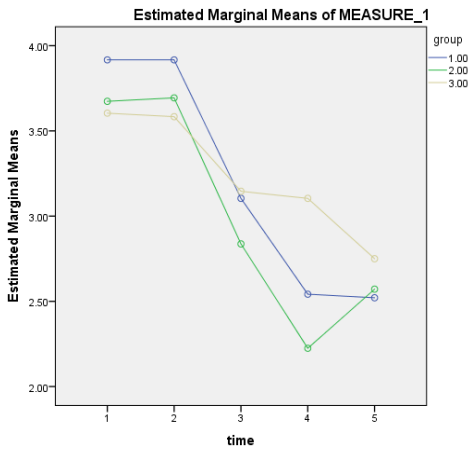
Table 2: Comparison of severity of knee pain, morning stiffness, daytime stiffness, and physical activity among studied groups

groups / variables		study groups (Mean±SD)			p-value *			
		H. helix (A)	Diclofenac (B)	placebo (C)	Comparison of three groups	Paired comparison		
						A;B	A;C	B;C
Severity of knee pain	Before treatment	3.91±0.76	3.67±0.68	3.6±0.73	092.0	-	-	-
	After treatment	2.52±1.09	2.57±1.08	2.7±0.91	521.0	-	-	-
	Mean difference	1.39±1.02	1.1±1.06	0.85±0.79	026.0	0.416	0.021	0.633
	p-value	<0.05	<0.05	<0.05				
Morning stiffness	Before treatment	2.06±0.63	1.95±0.64	1.81±0.64	0.16			
	After treatment	1.08±0.7	1±0.61	1.41±0.64	0.005	1	0.042	0.007
	Mean difference	0.97±0.63	0.95±0.61	0.39±0.6	0.001	1	0.002	009/0
	P-value	<0.05	<0.05	<0.05				
Daytime stiffness	Before treatment	1.52±0.68	1.2±0.54	1.29±0.64	0.123			
	After treatment	0.6±0.73	0.38±0.57	0.81±0.67	0.008	331.0	378.0	006.0
	Mean difference	0.91±0.64	0.89±0.54	0.47±0.58	0.000	1	001.0	002.0
	P-value	<0.05	<0.05	<0.05				
Physical function	Before treatment	60.56±16.10	58.47±14.55	54.4±15.56	0.141			
	After treatment	31.17±17.33	26.43±21.94	43.27±19.01	000.0	0.7	0.009	0.000
	Mean difference	29.40±17.67	32.04±18.38	11.13±14.80	000.0	1	0.000	0.000
	P-value	<0.05	<0.05	<0.05				

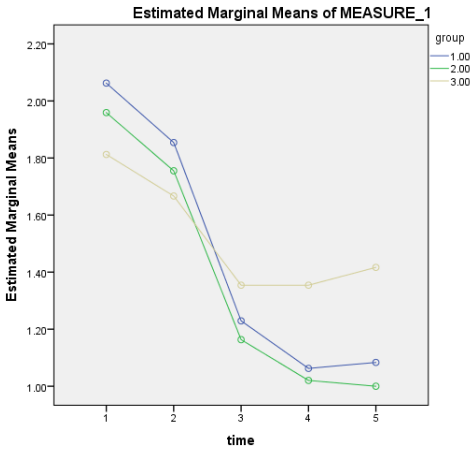
*The difference is significant at $P < 0.05$

Figure 1. Flow Diagrams of the R

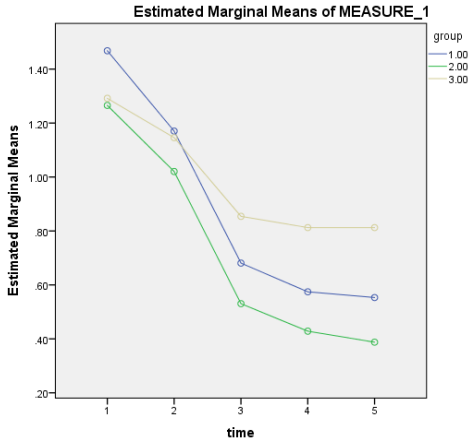




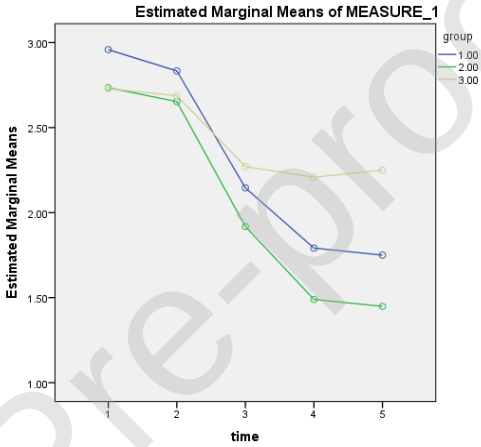
A) severity of knee pain



B) morning stiffness



C) daytime stiffness



D) physical function

Figure 2: Comparison of studied variables at different measurement intervals (before treatment and one, two, three, and six weeks after treatment) in studied groups