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Efficacy of a traditional herbal formula based on *Colchicum autumnale* L. (Rhazes tablet) in low back pain: A randomized controlled clinical trial

Research Article

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Abstract

Background: Low back pain (LBP) is one of the most common and costly chronic diseases in the world today. The use of herbal medicines based on *Colchicum autumnal* is one of the solutions recommended by Persian medicine for treatment of LBP. One of these products is Rhazes tablet. This study aimed to determine effect of the Rhazes tablet on LBP pain relief and symptoms. Methods: Fifty patients with chronic LBP, aged 19-59 years old, who had LBP for more than 12 weeks, were enrolled in the study. Patients were randomly divided in to intervention group (n=26) and control group (n=24). The patients in the intervention and control groups were treated with Rhazes tablet + Ibuprofen pearl (400mg) PRN and placebo tablet + Ibuprofen pearl (400mg) PRN, respectively. All patients received one tablet in the first week, 2 tablets in week 2-4 and 3 tablets in week 5-8. Pain severity was measured and recorded using VAS and Roland-Morris Disability Questionnaire for all patients at weeks 0, 4 and 8. Results: The results indicated that Rhazes tablet as a traditional Persian medicine caused a significant reduction in LBP in the intervention group compared to control group ($P<0.039$). Using the Rhazes tablet for 8 weeks reduced pain severity in the group suffering from severe pain from 50% in the first visit to 15.4% in the third visit; while the pain severity was increased from 20% to 25% in the control group. In the intervention group, a woman in the fifth week of study got severe diarrhea, and the severity was decreased by reducing the number of Rhazes tablet. In the intervention group, a man experienced increased libido in the fourth week of study. Conclusion: Rhazes tablet can be used as a pharmacological intervention to reduce pain in patients with LBP. Results showed promising effects of Rhazes tablet on pain relief and LBP symptoms.

Keywords: Low back pain, traditional Iranian medicine, Rhazes tablet, Colchicum autumnal, disability, medicinal plant.

Introduction

Low back pain (LBP) is one of the most common social and economic problems in today's world. It is also the second most common reason for referral to doctors and the absenteeism from work after common cold and the fifth common cause of hospitalization and the third most common cause of surgery (1, 2). The annual rate of LBP is 30-40%, and 75-85% of people experience LBP in their lifetime in some ways. The prevalence of LBP in the United States is between 15% and 20%, 25 to 45% in Europe, 28.5% in Canada and in Iran (3, 4). There are various methods to reduce the LBP complications, such as early startup, restoration of natural physical activity (without heavy work), pharmacological interventions including non-steroidal anti-inflammatory drugs (NSAID), physiotherapy, medical belts and surgery that induce temporary relief in many cases (5). Considering the high prevalence of LBP and its complications, finding new treatment strategies in this field is valuable in order to achieve low cost and effective treatment with the least adverse effects. Traditional medicines are sources of thousand years' human medical experiences and a good resources of medical hypothesis for clinical trials (6, 7). Rhazes (Al-Razi or Rasis) (854–925 AC), was a Persian polymath, physician, alchemist, philosopher, and important figure in the history of medicine, invented a tablet (an herbal product based on Colchicum autumnal for treatment of LBP. This herbal Formula has been introduced in Persian medicine literatures as a affective treatment for

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LBP. The aim of this study is to determine the effect of Rhazes tablet on patients with chronic LBP in a randomized double-blinded controlled trial.

Materials and methods

Study setting and sample recruitment

After receiving approval from the ethics committee of Tehran University of Medical Sciences (No. 1395.462) and registration in the Iranian registry of clinical trials (IRCT20180227038884N1), this randomized controlled trial was conducted on 50 patients with chronic LBP. The patients were visited by the same physician at days 0, 28, 56 from the beginning of the intervention. All patients had been filled Informed consent form after explaining the aims, advantages and disadvantages of the study.

Preparation of the drug and placebo

Rhazes tablets

The product is composed of powder of *Colchicum autumnale* (Root), *Terminalia Chebula* (Fruit), *Aloe vera* (Powder of dried latex of leaves), *Astragalus gossypinus* (Gum), *Cuminum cyminum* (Fruit), *Zingiber officinale* (Rhizome), *Piper nigrum* (Fruit), *Commiphora wightii* (Gum), and *Pistacia lentiscus* (Gum) in the same weight.

Dried samples of above herbs were purchased from the traditional herbal market, Tehran, Iran. Authentication and deposition of the herbs and preparation of the Rhazes tablets were conducted at Niak lab.

Determination of total phenolic content

Total phenolic content of each tablet was determined using folin-ciocalteu reagent (8) . For this purpose, tablet was powdered. Distilled water was added to powdered tablet (150 mg) up to 10 mL. The mixture was sonicated for 5 min and then filtered. Filtrate (1 mL) was mixed with folin-ciocalteu reagent (1.5 mL) which previously diluted 10-fold with distilled water, and allowed to stand at room temperature for 5 min. 1.5 mL of bicarbonate solution (60 g/L) was added to the mixture. After incubation for 90 min at room temperature, the absorbance was measured at 725 nm using a UV-visible spectrophotometer (GBC, Cintra 40). Total phenolics were quantified by calibration curve obtained from measuring the absorbance of the known concentrations of gallic acid standard solutions. All tests were carried out in triplicate and the results were expressed as gallic acid equivalents (mg GAE/g dry weight).

Determination of total flavonoid content

Total flavonoid content of each tablet was determined by the aluminum chloride colorimetric method(8) . For this purpose, tablet was powdered. Distilled water was added to powdered tablet (400 mg) up to 10 mL. The mixture was sonicated for 5 min and then filtered. Concisely, 1 mL of filtrate was added to 10 mL volumetric flask containing 4 mL of double distilled water. 0.3 mL NaNO2 (5%) was added to the flask and 5 min later 0.3 mL AlCl3 (10%) was added. After 6 min, 2 mL NaOH (1 M) was added and the total volume was made up to 10 mL and the flask contents were thoroughly mixed. The absorbance level was measured versus blank at 510 nm (GBC, Cintra 40). Total flavonoid contents were represented as mg catechin equivalents (CE) per one gram dry extract according to the catechin standard solutions.

Placebo tablets

The placebo was made from starch, which looked exactly like a drug in terms of color, appearance, weight, and size.

Patient selection

This double-blind, randomized clinical trial was conducted in School of Persian medicine, Tehran University of Medical Sciences in Tehran. Fifty patients with chronic LBP, aged 19-59 years old, who had LBP for more than 12 weeks, were enrolled in the study. Patients were randomly divided in the intervention group (n=26) and control group (n=24). The study was designed double blind for the physician and the patients and simple method was used for randomization.

The inclusion criteria included patients aged 19 to 59 years with chronic LBP complaints, no surgical indication and no history of trauma, suspected malignancy and steroid use, and chronic infection, non-pregnant and non-lactating women. The subjects were divided into two groups. The intervention group were treated with Rhazes tablet + Ibuprofen pearl (400mg) PRN and placebo group which were treated with placebo tablet + Ibuprofen pearl (400mg). All patients received one tablet in the first week, 2 tablets in 2-4 weeks and 3 tablets in 5-8 weeks 1 hour after each meal (breakfast, lunch, and dinner). In all samples, the VAS and Roland-Morris Disability Questionnaire (RMDQ) at weeks 0,4, and 8 was completed and recorded in the patients' profile along with Ibuprofen registration sheet and drug complications report paper at the beginning of the treatment (week zero) and the end of weeks 4 and 8. While extracting the results, only the questionnaire of patients who participated in the study at least until the end of the fourth week. At the end of the eighth week, the scores of the VAS and RMDQ of subjects in week 0, 4, and 8 were compared with each of her and also compared with those of the other group (9, 10) .

Statistical Analyses

SPSS software (IBM SPSS for Windows, Version 20.0, IBM Corp., Armonk, NY, USA) was used for Statistical analyses. Repeated measure ‹Friedman's non-parametric test and paired t-test were used to compare the results. P-values of less than 0.05 were considered statistically significant.

Results

Determination of total phenolic and total flavonoid content

The total phenolic content of each tablet was 945.4 ± 6.74 mg GAE/g respectively. The total flavonoid content of each tablet was 382.15 ± 4. 33 mg of CE/g of dry extract respectively by reference to the related standard curves.

Clinical trial

A total of 50 patients from both groups were present until the end of the study and were followed up. Of these, 54% were female and 46% were male, with an average age of 43 years (Standard deviation of 8.9). The mean BMI was 46.26 with a standard deviation of 3.88.

Comparison of pain intensity in three times with Friedman test showed that the pain intensity of the samples in the control group was statistically significant (p-value≤0.001).

Table 1: Comparison of pain intensity in the intervention and control groups in first, second and third visits.

Group	Time	N	Mean	Std. Deviation	p-value
Exposure	Before	26	2.35	0.797	p-value ≤0.001
	After 4 weeks	26	1.69	0.788	
	After 8 weeks	26	1.04	0.528	
Control	Before	24	2.08	0.584	0.607
	After 4 weeks	24	2.12	0.448	
	After 8 weeks	24	2.21	0.588	

To compare the Roland-Morris test scales in three times, a repeated measurement was used in both intervention and control groups.

Table 2 shows that the test score before intervention in the two groups does not have a significant difference (p-value=0.822) and the two groups are identical. The difference between the scores of the Roland-Morris test after 4 weeks (p-value=0.049) of treatment and 8 weeks (p-value=0.000) of treatment in the intervention and control groups was significant.

Table 2: Test score before intervention in the two groups

Time	Group	Mean	Std. Deviation	N	p-value
Before	exposure	11.62	4.691	26	0.822
	control	11.33	4.050	24	
After 4 weeks	exposure	8.31	4.889	26	0.049
	control	10.71	3.263	24	
After 8 weeks	exposure	4.35	3.273	26	0.000
	control	10.46	3.489	24	

The Repeated measures test also showed that in the intervention group, the Roland-Morris scores were significantly different in each of the three incremental measurements, ie, the status of the samples in the second turn was better than the first one, and in the third turn, recovery was still greater than before. Also, the difference between the third-order Roland-Morris score and the second turn is significant (p-value ≤0.001).

Table 3: The Repeated measures test between two groups

Exposer	Time	Mean	Std. Error	p-value	95% Confidence Interval	
					Lower Bound	Upper Bound
Exposure	Before	11.615	0.862	0.000	9.882	13.349
	After 4 weeks	8.308	0.822		6.656	9.960
	After 8 weeks	4.346	0.663		3.014	5.678
Control	Before	11.333	0.897	0.131	9.529	13.137
	After 4 weeks	10.708	0.855		8.989	12.428
	After 8 weeks	10.458	0.690		9.072	11.845

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The Roland-Morris Disability Questionnaires showed that the disability level in the intervention group in the fourth and eighth weeks was significantly lower than the control group (P<0.002) (Figure 1).

The results indicated the significant reduction in the pain severity in the intervention group. Therefore, it can be concluded that the Rhazes tablet reduced the pain in the intervention group compared with the placebo in the control group (P<0.039).

Figure 1: Roland-Morris Disability Questionnaires in the intervention and control groups First, second and third visits

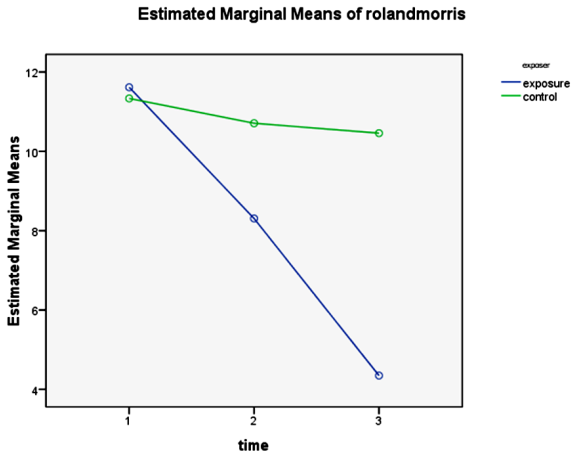
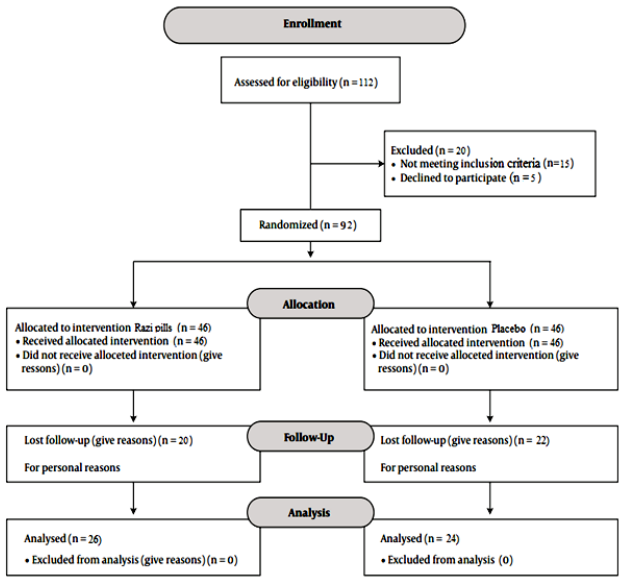


Figure 2: Study flowchart



Discussion

LBP is a common disorder and a considerable economic burden in industrialized countries. A large number of patients with LBP use complementary and alternative medicine for relief of their pain. Finding effective and suitable therapy is vital for these patients, clinicians and policy makers. numerous herbal medications have been applied in treatment of LBP.

Comparing the results of the pain severity variable before and after the study showed that Rhazes tablet significantly decreased the pain severity based on the VAS scale in the patients with LBP. The Roland-Morris Disability Questionnaires also demonstrated that the disability level in the intervention group. In the fourth and eighth weeks was significantly lower than the control group. Also, comparing the results of pain intensity based on VAS values in patients with LBP at the end of the fourth and eighth weeks of the study showed that the severity of pain decreased significantly at the end of the fourth week compared to the eighth week.

According to our search in available databases (PUBMED, EMBASE) there is no definite research on Rhazes Tablet formula. However, there are many studies about positive effects of herbal drugs on LBP. For example, Frerick et al. investigated the effect of red pepper on chronic LBP in the clinical trial, and the results showed that the severity of pain in red pepper-treated patients was significantly less than that of the control group (11). Chrubasik et al also investigated the effect of willow bark on the LBP and the result showed a significant reduction in the severity of pain in the group consuming the product than that of the control group (12). The results of this of revealed that the highest reduction in the pain severity was observed in week 4 as well as willow bark in Chrubasik et al study. The pain reduction rate was reduced by 53.87% at the end of the study compared to than at the beginning of study.

Primary mechanisms of pain reduction in Rhazes Tablet are related to the herbal ingredients. So, a brief look to the agents lead to better understanding of the effects:

Colchicum autumnal is a member of the Colchicaceae plant family and over 100 species of this plant exist around the world. The main active ingredient of this herb is colchicine, a kind of alkaloid, was found to be effective in control of the pain and inflammation (13, 14). Colchicine is a natural product originally extracted from plants of the genus Colchicum autumnal (autumn crocus) and has been used to treat gouty arthritis for centuries (15). Studies have demonstrated that low-dose colchicine is effective for the management of acute gout flares as well as for long-term prophylactic maintenance (16). Oral intake of colchicine has inhibited the expansion of edema in rats and has displayed anti-inflammatory characteristics(17). The precise mechanism of action of colchicine in pain relief remains uncertain (18, 19). It has been recognized that colchicine binds to both α- and β-tubulin, and make a complex which inhibits microtubules formation. Thus, routes of inflammatory mediators creation that need microtubules, such as recruitment of cytosolic component (mitochondria) or proteins (kinases), are disposed to colchicine treatment (20). Also, Colchicine

reduces the process of inflammation and, as a consequence, the remission and treatment of gout attacks. Colchicine also works in the treatment of other chronic inflammatory diseases (21, 22).

Aloe vera as a medicinal herb is containing a number of pharmacologically-active elements useful for the treatment of different diseases such as radiation burns, ulcers, arthritis, and diabetes. It contains vitamins (vitamin A, C, E, and B12, that act as antioxidants), 8 enzymes (aliases, alkaline phosphatase, amylase, bradykinase, carboxypeptidase, catalase, cellulase, lipase, and peroxidase (23, 24). Bradykinase reduces excessive inflammation, and others cause sugars and fats breakdown), minerals (calcium, chromium, copper, selenium, magnesium, manganese, potassium, sodium and zinc), 12 anthraquinones (which are laxatives), and hormones (Auxins and gibberellins that act in wound healing and have anti-inflammatory effects) (25, 26).

Aloe vera is potent anti-inflammatory agent (12, 27). It decreases prostaglandin E2 production by cyclooxygenase pathway inhibition. Previous investigation has indicated that the C-glucosyl chromone as a novel anti-inflammatory compound exists in Aloe vera (28, 29). Aloe vera gel has been used dermally to decrease joint pains by tradition. Phytochemical analysis of Aloe vera revealed the existence of flavonoids, alkaloids, resins, tannins, steroids and other chemical substances (30, 31).

Studies have shown that carboxypeptidase (one of the Aloe vera ingredients) could deactivate bradykinin, which is a powerful factor causing pain during the acute inflammation. Furthermore Salicylic acid, which is found in Aloe vera, works as a painkiller, analgesic, and anti-inflammatory factor by inhibiting the production of prostaglandins (32, 33).

Terminalia chebula has strong antioxidant effects and protects cellular organelles from the radiation-induced damage (34). Terminalia chebula is effective for healing wounds and treats wounds quickly, as indicated by the increased rates of contraction and decreased periods of epithelialization. Biochemical studies show a significant increase in total protein, DNA, and collagen content in the granulation tissues of treated wounds. In addition, this plant has antimicrobial and antioxidant properties. These results confirm the beneficial effects of Terminalia chebula on the acceleration of healing (35, 36).

Commiphora wightii resin produced from Commiphora wightii is reported for many therapeutic effects in Ayurvedic medicine. The essential oils derived from peptides are effective in the treatment of rheumatism, arthritis, hyperlipidemia, and obesity. It also has anti-inflammatory and antimicrobial and anti-fungal effects. Commiphora wightii essential oil includes polymyrecene, Z-gugglusterone and myrecene, dimyrecene, E-gugglusterone, gugglusterone-I, gugglusterone-II, and gugglusterone-III. These isolates have been useful in curing rheumatism, arthritis, hyperlipidemia, obesity, inflammation, atherosclerosis, wrinkles, acne and other diseases (37, 38).

Astragalus gossypinus is a large genus of herb and shurb, belonging to family Fabaceae. The analgesic effects of Astragalus gossypinus gum, on stomach pains and headache have been reported in Persian medicine (39, 40).

Cuminum cyminum has been used in traditional medicine to treat some disorders like hyper-lipidemia, cancer, and diabetes. The presence of monoterpene compounds, Linalool, γ-terpinene α-pinene and β-pinene contribute largely to anti-inflammatory activity of the Cuminum cyminum (41) . There are also several reports on the anti-oxidant properties of this plant.

Zingiber officinale contains numerous known ingredients such as gingerols, beta-carotene, capsaicin, caffeic acid, and curcumin. Furthermore, salicylate is one of the other components which have been found in ginger (42). Ginger inhibits both cyclooxygenase (COX) and lipooxygenase together, to prevent leukotriene production (43). One study in 2010 has been demonstrated that daily intake of ginger led to the moderate-to-large decrease in muscle pain following exercise-induced muscle injury. Their results have shown ginger's efficacy as a pain reliever (11, 44).

Pipper nigrum is known for its pungent constituent piperine (effective ingredient in black pepper). Based on the modern cell, animal, and human studies, piperine has been found to have immune-modulatory, anti-oxidant, morphine like and anti-inflammatory properties (45, 46).

Conclusion

In the present study, the effectiveness of Rhazes formula in pain reduction (by using VAS score) and improving quality of life (by Roland-Morris questionnaire) were surveyed in patients with chronic LBP in a double-blind trial. The results of this trial indicated that Rhazes tablet reduces the pain and improve quality of life of patients with LBP.

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