

Clinical Trial of Combined *Thymus daenensis* Celak and *Ziziphus Jujube* Mill Syrup in Primary Hypertension

Davoud Hasani¹, Hassan Ahanghar^{2*}, Mohsen Bahrami¹, Sadrollah Ramezani^{3,4}, Mohammad Kamalinejad⁵, Elham Faghihzadeh⁶

¹ Department of Persian Medicine, Zanjan University of Medical Sciences, Zanjan, Iran

² Department of Cardiology, Zanjan University of Medical Sciences, Zanjan, Iran

³ Zanjan Pharmaceutical Biotechnology Research Center, Zanjan University of Medical Sciences, Zanjan, Iran

⁴ University of Sistan and Baluchestan, Zahedan, Iran

⁵ School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran

⁶ Department of Biostatistics and Epidemiology, Zanjan University of Medical Sciences, Zanjan, Iran

* **Corresponding Author:** Hassan Ahanghar, Department of Cardiology, Zanjan University of Medical Sciences, Zanjan, Iran.
E-mail: Ahanghar@zums.ac.ir

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Abstract

Introduction: Hypertension is the most important disease that can cause heart failure, renal dysfunction, stroke and sudden death in a large population throughout the world. The excessive side effects of the chemical drugs that are used in the treatment of hypertension have attracted attention to herbal medicine.

Methods: This study was designed as a randomized clinical trial on both males and females with first and second stage of hypertension. The patients who met inclusion criteria and none of the exclusion criteria were enrolled in the study. The patients were allocated with random blocked dividing between the case and control group with the same group size. The patients in the control group used placebo and patients in case group used mixed therapeutic syrup of *Ziziphus Jujube* and *Thymus daenensis* Celak. The syrup was used twice a day with a dose of 5 ml for each time. In order to study the effects of *Ziziphus* and *Thymus* on blood biomarkers, it was checked in two stages.

Results: Findings reveal that the mixture of herbal syrup could significantly reduce Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) in hypertensive patients ($p = 0.002$). The reduction in SBP and DBP at the end of the study was 11.84 and 8.03 mmHg, respectively. Also, the mean arterial pressure compared to the baseline decreased to 8.35%. Regards to other parameters, the results of the experiments at the beginning and end of the study showed that Complete Blood Count (CBC), Fasting Blood Sugar (FBS), cholesterol, low-Density Lipoproteins (LDL), High-Density Lipoprotein (HDL), Aspartate Aminotransferase (AST), Alanine Transaminase (ALT), Alkaline Phosphatase (ALP), Blood Urea Nitrogen (BUN), and creatinine were in the normal laboratory range.

Conclusion: According to results it can be stated that jujube and thyme can be considered as a miraculous combination in controlling blood pressure, to minimize secondary complications caused by hypertension.

Keywords: Cardiovascular Disease, Persian Traditional Medicine, Blood Pressure, *Thymus Daenensis*, *Ziziphus Jujube*

Introduction

High blood pressure has been highly regarded as affecting other disorders and increasing mortality during human life.¹ High blood pressure increases with age, by which more than half of the individuals with 60 to 69 year's old are affected.² Blood pressure is one of the most important risk factors for coronary heart disease especially in advanced industrialized societies.³ About 90 to 95% of hypertension are the primary type and are influenced by genetic, physiological and pathogenic risk factors (obesity, increased salt consumption, alcohol, low exercise life style, stress, and diet), and uncorrectable risk factors (heredity, age, gender, and

race) and only the 5 to 10% remaining, are secondary hypertension due to kidney, vascular, endocrine, neurological, gestational disorders and drug responses.⁴ High blood pressure causes inflammation and destruction of the walls of the arteries, and the destruction of the arterial walls prepares the field for fat accumulation in the arterial walls and formation of atherosclerosis plaque, heart attacks, retinopathy, stroke, environmental diseases and kidney failure.⁵

In industrial societies, it is estimated that 90% of middle-aged or elderly women and men have blood pressure during their life. The risk of hypertension rises

with age and it increases to 65.4% among the adults over the age of 60 years. The latest US prevalence rate for hypertension in adults over the age of 18 years is 30.9%, or close to one out of every three people.⁶ The prevalence of hypertension in urban and rural communities of Iran has been proven to be 30.5% and 29.2%.⁷ Also, the prevalence of hypertension in 15-64 year-old Iranians in 2007 was 26.6%.⁸ In addition to the high and increasing incidence of this disease, it doubles the incidence of the risk of cardiovascular disease including coronary artery disease, congestive heart failure, ischemic or hemorrhagic ischemic attack, kidney failure and peripheral vascular disease.² Framingham Heart Study (FHS) demonstrated that the risk of all complications of coronary heart disease increases with high blood pressure.⁹ This disease has been less controlled worldwide. For instance, in Cameroon, India and China less than 10% of people with hypertension have been controlled.¹⁰ If high blood pressure is not controlled, 50% of patients will be affected by complications such as CHF and CAD and also, 33% due to CVA and finally about 10 to 15% due to renal failure will die.¹¹

The selection of anti-hypertensive drugs is the most important part of the treatment of hypertension and plays an important role in improving and controlling the complications of the disease.¹² By using appropriate anti-hypertensive drugs, 30-40% of stroke, 20-25% of MI and 50% of heart failure have decreased.¹³ A modern therapeutic attitude should not target only blood pressure but also normalize vascular structure and function. Thus, much improved population-wide and individual methods to the inhibition and control of hypertension are necessary. This is due to the fact that more than a quarter of the world adult population is already hypertensive and this number is projected to growth to 29% of population (1.56 billion by 2025).¹⁴ Even today, in the century of combinatorial chemistry, secondary metabolites of plants are still a main source for the development of new drugs.¹⁵ About 50% of the drugs presented to the market during the last two decades have been derived from naturally occurring components. The potential use of natural products has also been successfully illustrated in the field of hypertension in various research articles in which hypotension induced by plant extracts were assessed on different mechanism of actions including: K^+ and Ca^{2+} channel function, the Nitric Oxide (NO) system, the

eicosanoid system, the adrenergic blockade, angiotensin receptors blocker, inhibition of Angiotensin Converting Enzyme (ACE) and diuretic action.¹⁴

Plants have always been an exemplary source of drugs and many of the currently available medicines have been directly or indirectly derived from them. For this reason, the research, development and use of natural products as therapeutic factor especially those derived from medicinal and aromatic plants have been increased in recent years. Arterial hypertension is a common and progressive disorder that possesses a main risk for cardiovascular and renal diseases. Therefore, the medicinal plants are safe and easy to use.^{14,16} Numerous researchers have also reported the useful health benefits of thyme on cardiovascular diseases. Generally, the medicinal plants and trees belong to different plant families, organs and growth types had useful effects on cardiovascular disease namely hypertension such as *Thymus vulgaris*,^{17,18} *Berberis vulgaris*,¹⁹ *Origanum vulgare*,²⁰ *Artemisia*,²¹ *Salvia cinnabarina*,²² *Acanthopanax sessiliflorus*,²³ *Senecio serratuloides* DC,²⁴ *Ficus carica*,²⁵ *Syzygium cumini*,²⁶ *Hyptis fruticosa*,²⁷ *Hymenocardia acida* Tul,²⁸ *Crateva adansonii* DC.ssp. *adansonii*,²⁹ *Azadirachta Excelsa*,³⁰ and *Eucommia ulmoides* Oliv.³¹ Plant metabolites namely volatile extracts and compounds have emerged as promising therapeutic agents. Indeed, these compounds in addition to having beneficial bioactivities, are generally more amenable and present less side effects, allowing better patient tolerance.³² Hypotensive effects of medicinal plants due to its phytochemicals namely essential oil and extracts (terpenes, alkaloids, flavonoids, polyphenols, phenolic acids, coumarins, stilbenes, phenylethanoid, phenylpropanoid glycosides, cinnamic acids and peptides such as carvacrol,^{33,34} thymol,^{35,36} citronellol,³⁷ α -Terpineol,³⁸ diterpenoid,²² Flavones,¹⁸ jujuboside B, and Betulinic acid,³⁹ luteolin, chrysoeriol, p-coumaric acid,²¹ galegine,⁴⁰ and oleuropein⁴¹ have been reported in experimental trials on normotensive model rats under *in vitro* conditions.¹⁴ Summarily, a few researches investigated cardiovascular effect of *Z. jujube* and showed that hydroalcoholic extract of *Z. jujuba* diminishes the severe L-NAME hypertension in rats.³⁹

Different species of *Thymus* (Lamiaceae) are commonly used their foliage parts for treat various disease in Iranian traditional medicine as herbal tea, decoction, infusion and etc. Also in Iranian cuisines, it is common

to use thyme for different purposes because of its flavor and aroma.⁴² Furthermore, Jujube is usually called red date which is the fruit of *Ziziphus jujuba* Mill. that belongs to the Rhamnaceae family and has been commonly consumed as a food supplement.⁴³

In literature, there are some reports on the thyme medicinal plant affecting high blood pressure and there are no any reports on native species of *Thymus* to Iran namely *T. daenensis* yet and also their mixture with jujube. Therefore, the aim of the present study was to evaluate the hypotensive activities of handmade syrup of jujube and thyme mixture on high blood pressure in clinical trial experiments.

Materials and Methods

Trial Design

This research was designed as a Randomized Clinical

Trial (RCT) study on male and female's with first and second stage of hypertension. The patients who met the inclusion criteria and none of the exclusion criteria were enrolled in the study. The patients were allocated with random blocked dividing between the case and control group with the same group size. The study was confirmed by the ethics committee of Zanjan University of Medical Sciences with the trial number of IRCT2015031821512N1.

Participants

The study's inclusion and exclusion criteria are provided in Table 1. An informed consent was obtained from patients after elaborating the study to them. This study was conducted in the Cardiology Clinic of Zanjan University of Medical Sciences for ten months.

Table 1. The Study's Inclusion and Exclusion Criteria

Inclusion Criteria
• Age 30 – 75 years
• SBP greater than or equal to 140 and DBP greater than or equal to 90 mmHg which are uncontrolled despite medical management for the past year.
• The patients have been diagnosed at least within one year past.
Exclusion Criteria
• Severe or malignant hypertension that is greater than or equal to 200/140 mmHg or that requires emergency injection or multiple drug therapy to control blood pressure.
• History of secondary hypertension
• Symptoms of end organ damage
• Sudden increase in blood pressure more than 15 mmHg at any time of this study.
• Different types of cardiac arrhythmias
• Symptomatic heart valve disease
• Impairment of liver function
• Pregnancy or breast-feeding
• Treated or untreated malignancies during the past 5 years
• Serum potassium more than 5.2 or less than 3.5 equivalent per litre at the first visit
• Any medical or surgical disorder that researcher could interpret it as a confounding factor for the study.

Intervention

The ripen and dried fruits of *Ziziphus Jujube* Mill. (Rhamnaceae) and aerial parts of *Thymus daenensis* Celak (Lamiaceae) from Zanjan were used to make the herbal syrup for treatments. The patients in the control and case groups received placebo and hand-made therapeutic syrup, respectively.⁴⁴ The syrup was used twice a day with a dose of 5 ml each time (after breakfast and at night after dinner). The placebo was produced by 50 g of sucrose and standard food dye.

For the follow up, the atrial blood pressure of arms was measured exactly according to 10th edition of Braunwald's heart disease book. In each visit, the patients were asked in case of any side effects of the

syrup. The blood biomarkers namely Complete Blood Count (CBC), Fasting Blood Sugar (FBS), cholesterol, Low-Density Lipoproteins (LDL), High-Density Lipoprotein (HDL), Aspartate Aminotransferase (AST), Alanine Transaminase (ALT), Alkaline Phosphatase (ALP), White Blood Cell (WBC), Red Blood Cell (RBC), Hemoglobin (HB), Hematocrit (HCT), Mean Corpuscular Volume (MCV), Platelet (PLT), Blood Urea Nitrogen (BUN), Na⁺, K⁺, and creatinine were checked twice, at the beginning and end of the study.⁴⁸

Outcomes

The primary outcome showed that SBP and DBP biomarkers were reduced (based on the patient's

problem) and the secondary outcome demonstrated that the blood pressure of participants were kept under control and within normal range. Both data were measured according to the Braunwald's heart disease 10th edition book's protocol.⁴⁸

Sample Size

The sample size of the study was calculated by considering the decrease of blood pressure by 15 mmHg through five times of measurement (first based on blood pressure and other four were repeated measures) and with deviation of 20 mmHg. The sensitivity of the study was considered as 80% and specified as 95%. According to the following formula, 18 patients were assigned to the control group and 18 patients to the case group.

$$n = \frac{\left(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta} \right)^2 (S_1^2 + S_2^2)}{(\mu_1 - \mu_2)^2}$$

S1: Standard deviation of studied variables in case group.

S2: Standard deviation of studied variables in control group.

μ_1 : Mean of studied variables in case group.

μ_2 : Mean of studied variables in control group.

Randomization

The patients were randomized into case and control groups by blocked randomization method.

Blinding

All of the patients and their care givers were blinded.

Statistical Analysis

Changes in the primary outcome (blood pressure)

analyzed by independent samples t-test, repeated measures and regression analysis. In this study, the significant level was considered to be $p < 0.05$.

Results

To conduct this study, 49 patients participated. Accordingly, 13 patients who did not meet the inclusion criteria were deprived from the study. The other 36 patients were divided into two groups of 18; one group was the drug group and the other group was given a placebo. All patients of the control group completed the study period of two months, but six patients in the control group did not cooperate with us for the study. Thirteen males and 17 females contributed to the study and the mean of BMI was 29.12 kg/m² (Table 2).

Table 2: Demographic and BMI Results

Parameter	Hypertensive	
	Untreated	Treated
Female	7	10
Male	5	8
BMI	29.62	30.41

The results indicated that 5 ml of herbal therapeutic syrup (a combination of thyme and jujube) twice daily for eight weeks in the patients with stage I and II hypertension which were treated with multiple anti-hypertensive drugs, could significantly reduce SBP ($p = 0.002$). This reduction was tangible since the second week, but at the end of the eighth week it became significant (Table 3).

The results also showed that this combination is capable to reduce DBP significantly in hypertensive patients ($p = 0.002$). Reduction in DBP became significant at the end of the eighth week ($p = 0.002$). The amount of SBP and DBP at the end of the study was 11.84 mmHg and 8.03 mmHg, respectively (Table 3).

Table 3. Initial to Final (8 weeks) Mid Blood Pressure and p -value

Week	Mid Systolic BP		Mid Diastolic BP	
	Treated Group	Untreated Group	Treated Group	Untreated Group
	1	144.44 ± 2.857	137.75 ± 3.119	90.556 ± 2.876
2	134.17 ± 2.770	132.83 ± 3.641	83.168 ± 1.801	78.083 ± 1.917
4	129.61 ± 2.896	127.50 ± 2.395	80.056 ± 1.933	78.833 ± 1.537
6	127.78 ± 2.542	134.75 ± 4.021	79.389 ± 1.129	81.750 ± 1.591
8	124.72 ± 2.318	137.75 ± 3.220	76.333 ± 1.526	83.417 ± 1.196
p -value *	0.002	0.500	0.002	0.985

*Based on the repeated measure test

As noted, in the case group the decrease in SBP and DBP at the end of the eighth week of treatment was

significant ($p = 0.002$) (Figure 1). The Mean Arterial Pressure (MAP) in the treated group compared to the

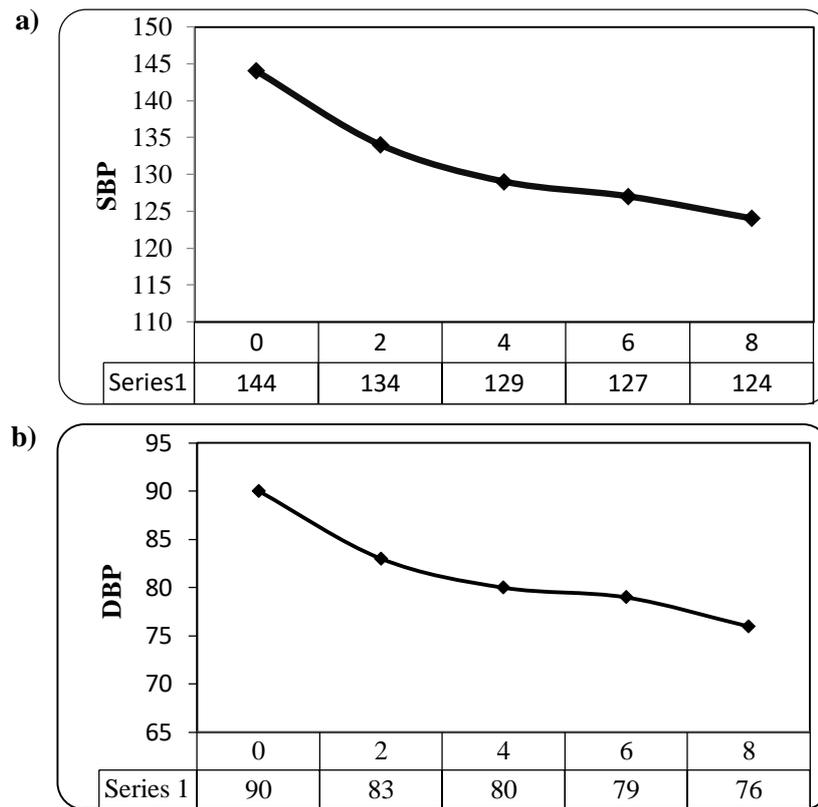


Figure 1. Mean Decrease in Systolic (SBP) and Diastolic Blood Pressure (DBP) in Case Group from Beginning to the End of the Study.

baseline decreased to 8.35%. Base MAP was 144.44 mmHg and at the end of the intervention was 124.72 mmHg. The decrease in average of DBP at the end of eight weeks was significant ($p = 0.002$).

Similarly, the effects of herbal mixture syrup of jujube and thyme on blood biomarkers namely CBC, FBS, LDL, HDL, AST, ALT, ALP, Na, K, BUN, cholesterol, and creatinine were checked at two times (at the beginning and end of the study). Generally, the amount of some parameters such as FBS, AST, and creatinine after eight weeks' consumption increased

significantly from 90.17, 20.23, and 0.99 to 92.3, 22.47, and 1.03, respectively. The results of the experiments at the end and beginning of the study indicated that CBC, FBS, cholesterol, LDL, HDL, AST, ALT, ALP, BUN, and creatinine were in the normal laboratory range. The herbal syrup did not show any significant changes in biochemical tests including cholesterol, CBC, TG, LDL, ALT, ALP, and BUN. The side effects of the syrup were diminishing the contractility of the heart, hearing noises in the ears and vertigo (Table 4).

Table 4. FBS, AST, and Creatinine and Their p -value Variations from Beginning to the End of the Study

	First Week	Eight Weeks	p -value
FBS	90.17 ± 14.403	92.30 ± 17.462	0.044
AST	20.23 ± 7.342	22.47 ± 6.86	0.038
Creatinine	0.99 ± 0.111	1.03 ± 0.104	0.033
WBC	6.8107 ± 1.803	6.204 ± 1.340	0.152
RBC	4.74 ± 1.615	4.69 ± 0.685	0.522
HB	14.003 ± 1.261	14.24 ± 0.426	0.796
HCT	40.88 ± 3.386	4.46 ± 3.456	0.804
MCV	85.07 ± 1.483	85.41 ± 5.683	0.288
PLT	255.15 ± 8.705	233.33 ± 7.673	0.146
HDL	38.73 ± 19.50	40.47 ± 18.57	0.355
LDL	96.53 ± 29.88	97.5 ± 27.44	0.685
Cholesterol	169.3 ± 41.51	173.47 ± 47.482	0.090
BUN	33.17 ± 8.942	35.53 ± 8.454	0.054
ALT	25.23 ± 12.805	25.57 ± 11.605	0.429
ALP	184.33 ± 49.496	189.10 ± 51.767	0.316

Discussion

The results of this clinical trial which were performed on 36 people, demonstrated the high value of the selected product of Iranian traditional medicine (jujube and thyme mixture syrup) in decreasing high blood pressure in the hypertensive patients. As indicated, this herbal drug has been able to make significant changes over the course of 8 weeks, both in SBP and DBP.

The benefits of anti-hypertensive drugs are associated with a decrease in blood pressure. Reducing SBP by 10-12 mmHg and also DBP by 5.5 mmHg, decreased the risk of stroke by 35-40% and the risk of heart disease decreased by 16-12% within five years. Reducing blood pressure also decreased the risk of heart failure by more than 50%. Standard doses of anti-hypertensive drugs will be able to reduce the DBP by an average of 10-8 mmHg of SBP and 7-4 mmHg of DBP.¹

In a double-blind and randomized clinical trial study of hypertensive patients (n = 50), whose blood pressure was not controlled but according to the physician's opinion, there was no need to change the drug and they were not prescribed chemically. The effects of old garlic on decreasing blood pressure was examined. In this study, four capsules containing 960 mg of old garlic extract were administered to the intervention group for 12 weeks. At the end of the study, the SBP in the intervention group was on average less than the control group ($p = 0.03$). In this study, the changes in DBP was not significant ($p = 0.242$).⁴⁵

A randomized and double-blind clinical trial was conducted on the effect of olive leaf extract on patients with stage I hypertension compared to captopril (Indonesia, 2010).⁴⁶ About 500 mg of olive leaf extract was given to participants twice a day for eight weeks. In addition, captopril at a therapeutic dose (n = 232) was given to the participants. In this study, the participating patients discontinued their blood pressure medication and entered the study after four weeks (the course of preparation with a diet). At the end of the study in both groups (8 weeks), the mean SBP and DBP showed a significant decrease compared to the baseline ($p < 0.001$), but there was no significant difference between the two groups ($p > 0.05$). In the olive leaf extract group, the mean reduction of SBP and DBP compared to the baseline was 4.5 ± 8.5 mmHg and 11.5 ± 8.5 mmHg, respectively. In the treated group with captopril, this decrease in SBP and DBP was 13.7

± 6.6 and 6.4 ± 2.5 mmHg, respectively.¹²

In Boston university, the effects of sour tea on blood pressure decrease in hypertensive patients and mild blood pressure on 66 people who did not receive any medication were studied in a randomized, double-blind and placebo-controlled clinical trial for 6 weeks.⁴⁷ At the end of the study, SBP decreased significantly in the group receiving the drug in comparison to the placebo group (2.7 mmHg) ($p = 0.0030$). The DBP was not significantly different from that in the beginning of the study (3.1 mmHg) ($p = 160.0$). In this research, the response of patients with higher blood pressure to the drug was more appropriate than those with lower blood pressure.⁴⁸

Seied-Ebrahimi et al., examined the effect of daily intake of canola or sunflower oil (30 g) on hypertension and other factors in hyperlipidemia menopausal women in a double-blind clinical trial of 44 Iranian patients for eight weeks. A significant decrease was observed in SBP (approximately 6.2 mmHg) in canola compared to sunflower users ($p = 0.077$). At the end of the study, the SBP (approximately 6 mmHg) in the canola group was decreased significantly ($p = 0.02$). There was no significant difference in SBP in the sunflower group, and no significant difference was observed in both groups in regards to DBP.⁴⁹ Also, a clinical trial study was carried out in order to investigate the effects of pomegranate on blood pressure and inflammation. Accordingly, improvement in the vascular function in 13 patients with high blood pressure indicated that short-term use of pomegranate juice significantly reduced the SBP from -11.3 ± 8123.38 to -11.16 ± 7.94 and DBP from 5.25 ± 82.69 to 0.385 ± 78.08 ($p < 0.05$).⁵⁰

It is concluded from the current research that the anti-hypertensive effect of a mixture syrup of thyme and jujube may be due to the presence of different phytochemicals such as terpenoids, flavonoids, flavones and phenols through different mechanisms. Carvacrol is the major compound of essential oil of many plants such as *Thymus* species and it can be concluded that the hypotensive effects of our mixture syrup may to be attributed to *Thymus*. Aydin et al., revealed that carvacrol decreased heart rate, mean arterial pressure and SBP and DBP of the anesthetized rats. Also, carvacrol exhibited hypotension and to inhibit N((omega))-nitro-L-arginine methyl ester (L-NAME)-induced hypertension. They reported the

involvement of cardiac L-type calcium channel blocking actions are suggested for the hypotensive actions of carvacrol was assumed. However, supplementary studies are necessary to isolate these component(s) of plants and clarify their exact mechanism of action.³⁴

Jujube fruit is rich in potassium and studies have shown that potassium in the diet is associated with lower blood pressure.¹³ In laboratory studies, jujube has the potential to inhibit glomerular accumulation, thus prolonging BT and protecting blood vessels and organs against thromboembolic attacks.⁵¹ Also, the anti-inflammatory and antioxidant activity of jujube fruit powder and thyme has been proven.^{13,52,53}

The results of sex-related tests at the beginning and end of the current study showed that despite the positive and high protective changes in blood counts (FBS, AST, and creatinine), they became significant after eight weeks. It seems that if the treatment can be continued for a longer period of time (3 to 4 months), we could see significant positive effects of this drug on the lipid profile too.

The results of the current study and previous studies indicate that the effect of jujube and thyme on SBP (19.72 mmHg) is approximately effective than other herbs and drug compounds. The results of the present study demonstrated the high clinical value of the selected combination of jujube and thyme, which with an average reduction of 19.72 mmHg of SBP and a mean reduction of 14.23 mmHg of DBP can be considered as a miraculous combination in controlling blood pressure and in minimizing secondary complications caused by hypertension. The advantage of herbal and natural products over ordinary medicines in hypertension is that these herbal products can improve the overall health of patients and can eventually help them to have healthier lives via reducing different parameters related to blood pressure.

Conclusion

It is possible that *Thymus daenensis* Celak. and *Ziziphus Jujube* Mill. plants possess some active compound(s) namely carvacrol, thymol, jujuboside B and Betulinic acid and some minerals such as potassium that are possibly responsible for the detected hypotensive activity. Moreover, these results further validate the traditional use of these medicinal herbs in Iranian folklore medicine. Consumption of the mixture syrup could be considered in the context of both

dietary and pharmacological interventions for high blood pressure (hypertension). It is worth mentioning that no complications were observed after eight weeks consumption of this herbal syrup product.

Conflict of Interest

The authors declare no conflicts of interest.

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