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ANTIHYPERTENSIVE EFFECT OF IRANIAN *CRATAEGUS CURVISEPALA* LIND.: A RANDOMIZED, DOUBLE-BLIND STUDY

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Summary: *The aim of the present study was to investigate the potential antihypertensive effects of extracts of the flavonoid-rich Iranian flower,* Crataegus curvisepala *Lind., a member of the* Rosaceae *family. The hydroalcoholic extract of the leaves and flowers were studied in a double-blind, placebo-controlled clinical trial to determine its effects. A total of 92 men and women with primary mild hypertension, aged 40-60 years, were selected and divided randomly into two groups, receiving either hydroalcoholic extract of* C. curvisepala *Lind. or placebo three times daily for more than 4 months. Blood pressure (BP) was measured each month. Statistical analysis was carried out using Student's* t*-test. The results obtained showed a significant decrease in both systolic and diastolic BP after 3 months* ($p < 0.05$). C. curvisepala *has a time-dependent antihypertensive effect.*

Introduction

Crataegus, an herb belonging to the *Rosaceae* family, is used in the traditional medicinal practice of many ethnic cultures for a variety of diseases. There are more than 200 *Crataegus* species native to Europe, Asia, northern Africa and Brazil. More than 20 species are found widely in the north and central parts of Iran, with *Crataegus curvisepala* Lind. being especially widespread (1, 2). The plant is commonly known as hawthorn (1). Dried flowers, fruits, leaves, and twigs of *C. monogyna* and related *Crataegus* species have been used in folk medicine since the Middle Ages (3).

Crataegus species have been reported to lower blood pressure (BP), increase coronary blood flow, and to be useful for arrhythmias (3-5). Different parts of *C. curvisepala* are traditionally used in the treatment of coronary artery disease (CAD) and hypertension in Iran (2). The phytochemical characteristics of this plant have previously been published (6). Rutin,

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Statistical methods. Data was entered using EPI6 software and statistically analyzed using SPSS 10 software package (SPSS, Inc., Chicago, IL, USA). Student's *t*-test was used for comparison of alterations in systolic and diastolic BP between the drug-treated and placebo groups. A *p*-value of < 0.05 was considered significantly different.

Results

The results showed that both systolic and diastolic BP decreased significantly after 3 months of treatment with 20 drops of plant extract three times a day. Twenty drops of the plant extract were equal to 0.9-1 mg of flavonoids, measured as hyperoside (Table I). The mean BP values in the drug-treated group were 146/93 mmHg and 133/84 mmHg at the beginning and the end of the treatment period, respectively, while in the placebo group the values were 148/95 mmHg and 143/90 mmHg, respectively. Comparison of systolic and diastolic BP values between both groups was carried out using Student's *t*-test at the beginning and the end of the study. At study outset, no statistically significant differences existed between the respective systolic and diastolic BP of each group. However, at study completion, statistically significant differences were observed in the systolic and diastolic BP values of the treated group, but not in those of the placebo group (Table II). The plant extract was observed to produce a statistically significant decrease in both systolic and diastolic BP after 3 months of treatment.

Discussion

Cardiovascular diseases are the most common cause of death in Western societies. Epidemiological studies have shown the risk of cardiovascular disease to increase with increasing BP (14). Hypertension is a major public health problem, affecting a

Table II *Comparison of changes in blood pressure (BP) between plant extract–treated and placebo groups at different time points*

	Treatment		
Variables	Placebo Mean ± SD (n = 46)	Plant extract Mean ± SD (n = 46)	P-value
Systolic BP (mmHg)			
Pre-intervention	148 ± 12.5	146 ± 16.23	0.8
After 1 month	144 ± 7.29	140 ± 4.3	0.14
After 2 months	140 ± 3.53	140 ± 3.49	0.95
After 3 months	142 ± 5.98	135 ± 6.95	0.02*
After 4 months	142 ± 5.73	133 ± 5.97	0.002*
Diastolic BP (mmHg)			
Pre-intervention	95 ± 5.03	92 ± 6.03	0.2
After 1 month	91 ± 2.3	89 ± 2.37	0.07
After 2 months	90 ± 2.51	88 ± 2.49	0.09
After 3 months	91 ± 3.66	87 ± 3.74	0.024*
After 4 months	89 ± 3.29	84 ± 3.51	0.003*

*$p < 0.05$.

hydroxy cinnamic acid, chlorogenic acid and caffeic acid were found in different parts of this plant (6). These compounds are also the most active constituents of the other species of *Crataegus* (7). The antihyperlipidemic effect of this Iranian plant has also been studied (8), and, currently, hawthorn is used primarily for various cardiovascular conditions. It is postulated that flavonoids account for these beneficial effects.

Hawthorn has shown promise in the treatment of New York Heart Association functional class II congestive heart failure in both uncontrolled and controlled clinical trials, and a randomized double-blind pilot study of the hypotensive effect of *C. oxyacantha* on mild, essential hypertension has also been carried out (9).

No previous trials to establish the antihypertensive effect of this Iranian plant on humans have been carried out, and therefore, this study was performed to determine its possible antihypertensive effect.

Materials and methods

Plant collection. The plant was collected in May 1997 from the village of Hamgin, near the city of Dehaghan in the province of Isfahan, at an altitude of 2,300 m. The plant was identified at the Botany Department of Isfahan University and a voucher specimen was deposited in the herbarium of the Pharmacognosy Department, Faculty of Pharmacy and Pharmaceutical Sciences, Isfahan University of Medical Sciences.

Preparation of herbal drops. Air-dried powdered leaves and flowers, at a ratio of 2:1, of *C. curvisepala* were extracted using the percolation method with ethanol 70 for 48 h at a ratio of 1:8, respectively (10).

Preparation of placebo drops. A hydroalcoholic placebo, free from plant material, was used to support the biological activity of the herbal drop.

Standardization of extract. Physicochemical control tests were performed on the extract, including determination of the percentage of the flavonoid, O-glycoside, on the basis of hyperoside, procyanidin, alcoholic degree, residue, color, smell and taste (11, 12).

Selection of patients. The study was a double-blind, placebo-controlled, clinical trial. The Ethics Committee of Isfahan Cardiovascular Research Center (ICRC, a WHO collaborating center) approved the study. Patient informed consent was obtained from all participants. An equal proportion of 92 men and women were selected by simple random sampling. The inclusion criteria included: mild hypertension (systolic BP: 140-160 mmHg, diastolic BP: 90-95 mmHg); age 40-60 years; and not undergoing any medical treatment or dietary therapy. Patients with secondary hypertension, heart disease and renal problems were excluded following complete medical tests which included the determination of potassium levels in blood and urine; creatinine levels; blood cell count; hematocrit; as well as an electrocardiogram. BP was measured in accordance with the World Health Organization standard method using a calibrated zero sphygmomanometer (13).

Patients were adjusted for age, body mass index (BMI) and occupation. They were randomly divided to receive either 20 drops of placebo or plant extract three times daily p.o. for up to 4 months.

Table I *Specifications of the plant extract*

Variables	Properties
Residue	3-4 g/100 ml
Flavonoids (hyperoside)	90-100 mg/100 ml
Procyanidins	130-140 mg/100 ml
Alcoholic degree	60-62°
Color	Dark green
Smell	Aromatic
Taste	Bitter

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large part of the adult population (15, 16), and a relationship exists between BP, stroke and cardiovascular disease. Many studies have indicated that prolonged BP reduction should reduce stroke incidence by approximately 35%-40% (17, 18). The therapeutic efficiency of phytopharmaceutical preparations for treating CAD is still controversial, and pharmacological studies on substances of plant origin with coronary dilating and anti-arrhythmia actions are still ongoing (19).

Numerous studies have been performed to investigate the therapeutic effects of different species of *Crataegus,* mainly on hypertension, ischemic heart disease and cardiac mechanical dysfunction (20). However, inconsistent results were obtained due to the different methods used, and the extracts and compounds investigated. In the present study, no significant alterations in BP were observed during the first and second months of treatment, thus indicating that the effect appeared at least 2 months after start of treatment (Table II). Based on these results obtained from monitoring systolic and diastolic BP over a period of 3 months, it was concluded that a therapeutic decrease in mild hypertension took place after the 3-month period of drug administration.

Despite the bitter taste of the plant extract, no side effects of constipation, hiccups, headaches, vomiting or nausea were reported by patients.

The beneficial health effect of this herbal drug may be improved through different extract processing, increasing dose, or through the preparation of the plant in other phytopharmaceutical forms. We advise the further investigation of the effect of *Crataegus* extract on subjects with moderate and severe hypertension, using a biomarker, such as flavonoids, to obtain exact data on the procedure of the plant extract. By increasing the sample size and matching subjects for confounders such as BMI, age, weight, *etc*., a better understanding of the medicinal effects of *Crataegus* will be obtained.

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