

# Effect of hawthorn extract on blood pressure and lipid profile in patients with stage I hypertension: A placebo-controlled, double-blind randomized trial

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## Abstract

**Aims:** To investigate the possible effects of hawthorn extract on blood pressure & blood lipid profile in patients with stage I hypertension.

**Patients and Methods:** This 12 week randomized, double-blind, placebo controlled study was conducted on newly diagnosed patients with stage I hypertension (n=60). Patients were selected from outpatient clinic in Al-Yarmuk Teaching Hospital, Baghdad and were divided into two groups each comprising of 30 patients, they were given hawthorn extract capsule 450 mg (Willmar Schwabe Pharmaceuticals) twice daily and identical placebo capsule respectively. Systolic and diastolic blood pressure was recorded and fasting lipid profile was done initially and at the end of 4th, 8th and 12th week of treatment. Both of hawthorn and placebo treated group were given diet and exercise plan.

**Results:** After 12 weeks the hawthorn treated group had a significant reduction in both of systolic and diastolic blood pressure ( $p < 0.01$ ), serum total cholesterol ( $p < 0.001$ ) and low density lipoprotein ( $p < 0.001$ ), while the placebo treated group had a non-significant decrease in their blood pressure ( $p > 0.05$ ), serum total cholesterol and low density lipoprotein ( $p > 0.05$ ). High density lipoprotein was significantly increased in patients treated with hawthorn (3.01 mg/dl, 8.13%  $P = < 0.05$ ) compared with placebo group (1.06 mg/dl, 2.8 %  $P = > 0.05$ ) but there was no significant difference in triglyceride detected between two groups.

**Conclusions:** The study suggests that hawthorn does have an effective antihypertensive ability, as well as lipid lowering effects.

**Keywords:** Hawthorn, Hypertension, Hyperlipidemia

## INTRODUCTION

Hypertension is a multifactorial disease widespread all over the world. It is a major risk factor for ischemic heart disease, renal diseases and cerebrovascular accidents. Although genetic and environmental factors contribute to this complex disease, excessive reactive oxygen species have emerged as a central common pathway by which different influences may induce and exacerbate hypertension.<sup>[1-3]</sup> Treatment of hypertension has been a challenging work for the health care professionals because it is a common disease and yet difficult to treat simply because of the complex nature of the underlying

pathophysiologic causes.<sup>[4]</sup> The drug treatment of mild hypertension has been associated with metabolic changes that increase the risk of cardiovascular diseases, resulting in standoff or even a negative overall influence.<sup>[5]</sup> In this concern dietary flavors and various plant products have been assessed.<sup>[5-7]</sup> Hawthorn, the common name for *Crataegus* species, is one of the medicinal plants which have shown some promise.

Hawthorn extract became increasingly used traditionally for the treatment of heart and circulatory problems and considered to be one of the best cardiac tonic found in plant kingdom.<sup>[8]</sup>

Hawthorn extract contains flavonoids particularly oligomeric proanthocyanidins in addition to quercetin, quercetrin, triterpene saponins and vitamin C, which are well-known for their antioxidant properties.<sup>[9]</sup> Several studies have revealed that hawthorn extract is effective in quenching reactive oxygen species, particularly free radicals.<sup>[10, 11]</sup> It has been shown that an extract of hawthorn promoted improvement in tricyclic acid cycle enzyme activity and protected the mitochondria against free radicals induced cardiac injury.<sup>[12]</sup> Several studies shown that patients with myocardial infarction treated with hawthorn extract have displayed improvements in heart rate, decrease in blood pressure, and rise in the left-ventricular ejection fraction.<sup>[13, 14]</sup> In one pilot study, the hawthorn extract has demonstrated promising hypotensive responses in mildly hypertensive patients after 10 weeks of treatment.<sup>[14]</sup> In another study, hawthorn extract has also been shown to favorably affect blood pressure in type 2 diabetics taking prescription medications for hyperglycemia.<sup>[15]</sup> Moreover hawthorn extract demonstrates a lipid lowering effect in animal models of hyperlipidemia.<sup>[16]</sup> However, few long-term clinical studies have so far been carried out with respect to hawthorn effect on blood pressure and lipid profile status. Thus, in the present study, the long-term effect of hawthorn on the above mentioned parameters has been investigated in a double blinded study.

## PATIENTS AND METHODS

This is a 12 weeks randomized, double blind, placebo controlled study conducted in order to comparing the effects of hawthorn extract capsule 450 mg (Willmar Schwabe Pharmaceuticals, Karlsruhe, Germany) twice daily with that of placebo on blood pressure and serum lipids in patients with essential hypertension.

This study was conducted in the Department of Pharmacology in cooperation with Department of Internal Medicine, College of Medicine, Al-Mustansiriya University, from August 2008 to December 2010. The study was agreed by Local Scientific Committee of the institution.

The study was conducted on 60 newly diagnosed patients of essential hypertension who attended medical outpatient clinic of Al-Yarmuk Teaching Hospital, Baghdad-Iraq. All the patients were included when their diastolic blood pressure was >90mmHg but less than 100mmHg and/or systolic blood pressure was >140mmHg but less than 160mmHg (stage 1 hypertension of Joint National Committee (JNC) VII).<sup>[17]</sup> These patients were not taking any anti-hypertensive

medication and unwilling to take allopathic medicine for hypertension. They opted for herbal medicine for management of hypertension. They were enrolled in this study after taking informed and written consent and were divided randomly into 2 groups each comprised of 30 patients and were given hawthorn capsule 450 mg twice daily and identical placebo capsule with same dosing schedule respectively. Furthermore both groups were instructed same diet and exercise plan and were recommended not to change their dietary habits or physical activity during the progress of the study. The patients with stage 2 hypertension of JNC VII, secondary hypertension, diabetes, major target organ damage were not included. In the same way, the patients who were smokers, alcoholics, on contraceptives or lipid lowering drugs were excluded from the study.

In all patients, the blood pressure was measured with a mercury sphygmomanometer with a standard size cuff in accord with recommendations of JNC VII.<sup>[17]</sup> The mean of two or more readings with a gap of at least five minutes was taken at every time of blood pressure recording. The blood pressure was recorded in sitting position, initially and at the end of 4th, 8th and 12th week of treatment.

Blood samples were taken from all the patients after 10-12 hours fasting period, initially and at the end of 4th, 8th and 12th week for the analysis of lipid profile. The total serum cholesterol (TC), triglycerides (TG) and high density lipoprotein cholesterol (HDL) were estimated calorimetrically by enzymatic methods employing test kits provided by Boehringer Mannheim, Germany. Low density lipoprotein cholesterol (LDL) was calculated by Friedwald formula<sup>[18]</sup> as follows:  $LDL = TC - (HDL + TG/5)$ .

## Statistical analysis

All data were analyzed using the statistical package of social sciences (SPSS) version 15 for windows program on the computer. Data were expressed as mean  $\pm$  standard error (SE). Patients' characteristics of two groups were compared by independent samples t-test while patients' characteristics recorded at different time intervals for each group were analyzed using paired samples t-test (within group). A two-tailed probability value (*p* value) less than or equal to 0.05 was considered as significant.

## RESULTS

The demographic characteristics of the study population are shown in table 1. The allocation of patients and their

distribution to the treatment schedule are equally comparable for the listed variables. Out of 60 patients enrolled in study, 57 patients were accompanying throughout the study period. Out of remaining 3 patients, 2 patients were dropped out in placebo group because they not come for follow-up due to unknown reason, 1 patient was dropped in hawthorn group because he has rejected to follow the exercise and diet plan and was excluded from the study.

**Table 1.** Demographic data of hawthorn and placebo treated group. (Values are given as Mean  $\pm$  SE or number).

Variables	Hawthorn (n=30)	Placebo (n=30)	P Value
<b>Patients (Male/Female)</b>	14/16	13/17	---
<b>Age (years)</b>	55 $\pm$ 1.09	53 $\pm$ 0.98	N.S
<b>Body weight (Kg)</b>	77.4 $\pm$ 0.98	75 $\pm$ 0.88	N.S
<b>Height (cm)</b>	166.4 $\pm$ 0.66	165.80 $\pm$ 0.67	N.S
<b>BP systolic(mmHg)</b>	153.95 $\pm$ 3.14	153.08 $\pm$ 2.25	N.S
<b>BP diastolic(mmHg)</b>	93.8 $\pm$ 2.19	92.11 $\pm$ 2.37	N.S

N.S= Not significant using independent samples t-test

Administration of hawthorn extract in a dose of 450mg twice daily significantly decreased systolic ( $p<0.01$ ) and diastolic ( $p<0.01$ ) blood pressure in stage I hypertensive patients at the end of 4th week, however the levels did

not reach up to the normal values of less than 140/90 mm Hg (Table 2). At the end of 8 weeks, further decrease was observed in systolic ( $p<0.001$ ) and diastolic ( $p<0.001$ ) blood pressure and systolic blood pressure lowered to  $139.88 \pm 2.81$  from  $144.79 \pm 2.07$  mm Hg. At the end of 3 months, the systolic ( $136.8 \pm 3.32$  mm Hg) and diastolic ( $84.6 \pm 1.92$  mm Hg) blood pressure reached within the range of normal level ( $>140/90$  mm Hg), as defined by JNC VII criteria. Result of this study revealed that the placebo treated group had a non-significant decrease in both of systolic and diastolic blood pressure ( $p>0.05$ ) (Table 2). Regarding the effects of hawthorn on serum lipid profile, this study showed that use of hawthorn in a dose of 450mg twice daily result in favorable significant effect on serum lipid profile (Table 3). At the end of 12 week it was found that the hawthorn treated group had a significant reduction in mean total cholesterol ( $-24$  mg/dl,  $-10.7\%$ ,  $P=<0.001$ ) and LDL ( $-31$  mg/dl,  $-18.67\%$ ,  $P=<0.001$ ) while the placebo treated group had a non-significant decrease in total cholesterol and LDL. Lipoprotein in term of HDL is significantly elevated in patients treated with hawthorn ( $3.01$  mg/dl,  $8.13\%$ ,  $P=<0.05$ ) compared with placebo group ( $1.06$  mg/dl,  $2.8\%$ ,  $P=>0.05$ ) but this rise in HDL was looked to be time dependent as there was no significant increase observed between week 0 and week 8. Moreover this study showed a small non-significant ( $P=>0.05$ ) decrease in serum triglycerides concentration in both of hawthorn and placebo treated group at the end of 12 week.

**Table 2.** Changes in blood pressure from week 0 to week 4, week 8 & week 12 of treatment with hawthorn and placebo in patients with stage I hypertension. (Values are given as Mean  $\pm$  SE).

Blood pressure	Drugs	Week 0 (mm Hg)	Week 4 (mm Hg)	P Value Week 0 -4	Week 8 (mm Hg)	P Value Week 0 -8	Week12 (mg/dl)	P Value Week 0-12
<b>Systolic</b>	hawthorn	153.95 $\pm$ 3.14 (n=30)	144.79 $\pm$ 2.07 (n=29)	$<0.01$	139.88 $\pm$ 2.81 (n=29)	$<0.001$	136.8 $\pm$ 3.32 (n=29)	$<0.001$
	placebo	153.08 $\pm$ 2.25 (n=30)	150.64 $\pm$ 2.30 (n=28)	N.S	148.64 $\pm$ 2.30 (n=28)	N.S	150.34 $\pm$ 3.05 (n=28)	N.S
<b>Diastolic</b>	hawthorn	93.8 $\pm$ 2.19 (n=30)	89.6 $\pm$ 1.43 (n=29)	$<0.01$	86.4 $\pm$ 2.54 (n=29)	$<0.001$	84.6 $\pm$ 1.92 (n=29)	$<0.001$
	placebo	92.11 $\pm$ 2.37 (n=30)	91.84.2 $\pm$ 3.40 (n=28)	N.S	90.88 $\pm$ 3.21 (n=28)	N.S	91.38 $\pm$ 3.56 (n=28)	N.S

NS= Not significant using paired samples t-test

**Table 3.** Changes in serum lipid profile from week 0 to week 4, week 8 & week 12 of treatment with hawthorn and placebo in patients with stage I hypertension. (Values are given as Mean  $\pm$  SE).

Lipid profile	Drugs	Week 0 (mg/dl)	Week 4 (mg/dl)	P Value Week 0 -4	Week8 (mg/dl)	P Value Week 0 -8	Week12 (mg/dl)	P Value Week 0-12
TC	Hawthorn	226.22 $\pm$ 4.54 (n=30)	215.3 $\pm$ 4.08 (n=29)	<0.05	206.3 $\pm$ 4.93 (n=29)	<0.01	201.97 $\pm$ 5.10 (n=29)	<0.001
	Placebo	224.45 $\pm$ 2.25 (n=30)	221.64 $\pm$ 2.10 (n=28)	N.S	220.64 $\pm$ 2.95 (n=28)	N.S	220.98 $\pm$ 3.05 (n=28)	N.S
TG	Hawthorn	203.03 $\pm$ 8.59 (n=30)	202.61 $\pm$ 8.93 (n=29)	N.S	201.66 $\pm$ 8.93 (n=29)	N.S	202.59 $\pm$ 8.81 (n=29)	N.S
	Placebo	201.43 $\pm$ 4.98 (n=30)	200.03 $\pm$ 4.76 (n=28)	N.S	199.42 $\pm$ 4.65 (n=28)	N.S	199.89 $\pm$ 4.48 (n=28)	N.S
HDL	Hawthorn	37 $\pm$ 1.67 (n=30)	38.85 $\pm$ 1.73 (n=29)	N.S	39.9 $\pm$ 1.48 (n=29)	N.S	40.01 $\pm$ 1.53 (n=29)	<0.05
	Placebo	37.51 $\pm$ 2.54 (n=30)	38.03 $\pm$ 2.64 (n=28)	N.S	37.93 $\pm$ 2.21 (n=28)	N.S	38.58 $\pm$ 2.87 (n=28)	N.S
LDL	Hawthorn	166.57 $\pm$ 4.66 (n=30)	151.42 $\pm$ 4.60 (n=29)	<0.05	144.42 $\pm$ 4.63 (n=29)	<0.01	135.42 $\pm$ 4.59 (n=29)	<0.001
	Placebo	163 $\pm$ 3.37 (n=30)	162.2 $\pm$ 3.45 (n=28)	N.S	159.2 $\pm$ 3.45 (n=28)	N.S	159.3 $\pm$ 3.56 (n=28)	N.S

TC = Total Cholesterol, TG = Triglyceride, HDL = High Density lipoprotein, LDL = Low Density Lipoprotein, n= Number of patients, NS= Not significant using paired samples t-test.

## DISCUSSION

This study was carried out to determine the effects of hawthorn on both of systolic and diastolic blood pressure in addition to lipid profile in stage 1 hypertensive patients. The results of the present study demonstrate that treatment with hawthorn in a dose of 450mg twice daily for 12 week result in significant decrease in both of systolic and diastolic blood pressure 9.5%, 11% respectively. Moreover it causes significant decrease in total cholesterol 10.7 % and LDL 18.67 %, whereas it causes significant increase in HDL 8.13%.

Previous studies about the effect of hawthorn extract on blood pressure shown that hawthorn have a promising reduction in diastolic blood pressure compared with placebo ( $P = 0.081$ ).<sup>[14, 19]</sup> Moreover Walker et al displayed a significant reduction in diastolic blood pressure in patients with type 2 diabetes taking prescribed medication plus hawthorn extract compared with type 2 diabetes patients taking prescribed medication alone.<sup>[15]</sup> In our study, hawthorn showed significant reduction effects not only in diastolic blood pressure but also in systolic blood pressure compared with placebo ( $P = 0.001$ ). The reason for this difference between our study and the previous studies may be related to different in sample size, patients inclusion criteria and dose and duration of treatment with hawthorn extract. The possible mechanism behind the reduction in blood pressure may relate to the effects of hawthorn on the vaso-relaxant nitric oxide (NO). Many studies

revealed that hawthorn extract has vasodilation effect due to an enhanced release of the NO from the vascular endothelium.<sup>[20-23]</sup> In one study, hawthorn extract induced concentration dependent relaxation in rat artery and this relaxation could be completely abolished by N-nitro-L-arginine (L-NNA), a nitric oxide synthase (NOS) inhibitor, and the soluble guanylyl cyclase inhibitor.<sup>[21]</sup> This suggests that hawthorn extract stimulation of NO release is mediated by endothelial NOS. Moreover the endothelium-dependent vasorelaxant effect of hawthorn has further been demonstrated in the human mammary artery.<sup>[22]</sup> Furthermore, it has been found that antioxidative effects of hawthorn may also inhibit the metabolism of NO, thus increasing its potency.<sup>[23]</sup> On an average at the end of this study, there was a drop of 17 mm Hg in systolic and 9 mm Hg in diastolic blood pressure and this statistically significant decline in blood pressure is vital in terms of its long term morbidity and mortality from cardiovascular diseases. Randomized controlled studies have shown that in patients with mild 10 mm Hg in, lowering of diastolic blood pressure 5-6 mm Hg and systolic blood pressure 10 mm Hg reduces stroke risk by about one third and risk of coronary events by about one sixth.<sup>[24, 25]</sup>

It is well known that presence of dyslipidemia is more frequent in hypertensive than in normotensive subjects.<sup>[26]</sup> The ideal antihypertensive drug should lower blood pressure without aggravating the serum lipid profile or preferably produce a favorable shift in serum lipid levels. In our study treatment with hawthorn



significantly effected plasma lipid levels while in the placebo group small but non-significant alterations in all lipid parameters were observed which might be explained by the exercise and dietary advice stated to patients at the time of beginning of study. This is the first clinical study to show a significant reduce in total cholesterol and LDL and significant increase in HDL by using hawthorn extract in patients with stage I hypertension. The onset of lipid lowering effects was evident as early as 4 weeks and become more advanced and greater with time. Several previous preclinical studies reported that the hawthorn extract reduce concentrations of total cholesterol as well as LDL, and TG in mouse as well as rat, hamster and rabbit models of hyperlipidemia.<sup>[27-30]</sup> Moreover hawthorn extract also cause significant decrease in lipid deposits in rabbit liver and aorta.<sup>[30]</sup> It has been found that reductions in total cholesterol in hamsters fed high fat diet following treatment with hawthorn were accompanied by an increased expression of the liver enzyme cholesterol hydroxylase (rate-limiting enzyme in the synthesis of bile acid from cholesterol) and lower levels of intestinal acyl-CoA: cholesterol acyltransferase (an enzyme involved in cholesterol uptake and absorption by the intestine), resulting in decreased blood lipid concentrations.<sup>[31]</sup> Furthermore, treatment of human hepatocyte cells line with hawthorn extract induced a 5.6-fold upregulation of LDL-receptor transcription in addition to downregulated ApoB (ApoB is a structural component of serum LDL particles) synthesis in a concentration dependent manner.<sup>[32]</sup> These in turn modulate both lipogenesis and lipolysis, resulting in reduced blood lipid concentrations.

The changes in lipid parameters observed in our study are in accordance with the previous preclinical studies that demonstrate hypolipidemic effect of hawthorn extract in animal models of hyperlipidemia.<sup>[16, 27-30]</sup> The statistically significant reduction in serum lipid profile in this study is important in terms of its protective effects against morbidity and mortality from cardiovascular diseases because hypercholesterolemia is an independent risk factor for developing cardiovascular disease.<sup>[33]</sup>

In conclusion, the present study suggests that long term administration of hawthorn has significant blood pressure lowering effect along with hypolipidemic effects in patients with stage 1 hypertension. Thus, it may show beneficial as a natural remedy to such patients. Though, further long term placebo controlled study with a large number of patients is necessary to further establish its various therapeutic potential.

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