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ORIGINAL ARTICLE

# Time-released garlic powder tablets lower systolic and diastolic blood pressure in men with mild and moderate arterial hypertension

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**Numerous clinical investigations that have focused on the hypotensive effects of garlic-based preparations have led to controversial results that may be partially because of differences in the composition of the preparations and in the biological responses they induce. It is possible that garlic powder tablets with a prolonged mode of action could induce more potent biological effects. In this double-blind, placebo-controlled trial with an active control arm, the hypotensive action of time-released garlic powder tablets (Allicor) was compared with that of regular garlic pills (Kwai) in 84 men with mild or moderate arterial hypertension. After an 8-week placebo treatment run-in phase, patients were randomized either to 600 mg Allicor ($n$=30) or to placebo ($n$=20) daily for 8 weeks. In addition, in the open-label branch, patients received either 2400 mg Allicor daily ($n$=18) or 900 mg Kwai daily ($n$=16). Allicor treatment (600 mg daily) resulted in a reduction of both systolic and diastolic blood pressures by 7.0 mm Hg (95% confidence interval (95% CI): 5.3–8.7) and 3.8 mm Hg (95% CI: 2.7–4.8), respectively. Increasing the Allicor dosage to 2400 mg daily did not provide any additional benefit. Treatment with Kwai resulted in the same decrease in systolic blood pressure (5.4 mm Hg, 95% CI: 1.9–8.8) as that seen with Allicor, but no decrease in diastolic blood pressure was observed with Kwai. Different effects of Allicor and Kwai on diastolic blood pressure may be because of the prolonged action of Allicor, which allows better bioavailability of the vasoactive constituents of garlic powder. The results of this study show that time-released garlic powder tablets are more effective for the treatment of mild and moderate arterial hypertension than are regular garlic supplements.**
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**Keywords:** arterial hypertension; garlic; placebo-controlled trial

## INTRODUCTION

The medicinal use of garlic (*Allium sativum*) dates back thousands of years, but there was little scientific support of its therapeutic and pharmacological properties until recently, with the extensive evaluation of the anti-atherosclerotic and cardiovascular-protective effects of raw garlic and garlic-based dietary supplements. The results of numerous clinical investigations have shown that garlic may produce beneficial effects on different cardiovascular risk factors: garlic is known to reduce serum cholesterol levels in humans, inhibit cholesterol biosynthesis, lower arterial blood pressure, suppress low-density lipoprotein oxidation, lower plasma fibrinogen and increase fibrinolytic activity, thus possessing anti-atherosclerotic properties.[1–6] Among all risk factors for atherosclerosis, arterial hypertension, along with dyslipidemia, is thought to be the most potent factor that greatly increases the risk of cardiovascular diseases.[7,8] Clinical investigations that focused on the effect of garlic in arterial hypertension have revealed its moderate hypotensive action in most studies;[9–13] however, controversial data exist.[14] These discrepancies may be because of several factors, including a lack of consistency among studies in relation to dosage, standardization of garlic preparations and period of treatment. Not all garlic preparations may be assumed equivalent in their composition and, more importantly, in the biological response they precipitate. The recently developed garlic powder-based dietary supplement, Allicor, is characterized by a prolonged mode of action that differentiates it from other products on the market. We have hypothesized that time-released garlic powder tablets may provide more potent pharmacological effects. To test this hypothesis, we carried out a double-blind, placebo- and active-controlled study of hypotensive action of Allicor

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in comparison with regular garlic powder tablets (Kwai) in men with mild and moderate arterial hypertension.

## METHODS

### Subjects and study design

This study was a randomized, placebo-controlled, double-masked outpatient clinical trial with an active control arm carried out in 84 men (35–70 years old) with newly diagnosed mild and moderate arterial hypertension. The study was carried out in accordance with the Declaration of Helsinki Principles of 1975 and the revisions from 1983. This study was approved by the institutional review board at the Institute for Atherosclerosis Research for the protection of human subjects in research. All participants gave their informed consent before their inclusion in the study. The included participants had no diseases demanding continuous administration of cardiotropic, sugar-lowering drugs or diuretics. The patients who were admitted had a systolic blood pressure (SBP) between 150 and 160 mm Hg and a diastolic blood pressure (DBP) between 90 and 115 mm Hg after an 8-week placebo-treated acclimatization phase. The study participants were either randomly switched to 600 mg Allicor daily (INAT-Farma, Moscow, Russia) (one tablet containing 300 mg garlic powder twice a day, $n=30$) or continued to receive a placebo of identical appearance ($n=20$). Some patients were randomly switched to the open-label branch of the study and received either 2400 mg Allicor daily (two tablets four times a day, $n=18$) or 900 mg Kwai (Lichtwer Pharma GmbH, West Berlin, Germany) daily (one tablet containing 300 mg garlic powder three times a day, $n=16$). Randomization was carried out with the use of a random number generator. The treatment period in all groups lasted for 8 weeks. The baseline data on clinical and demographic characteristics of study participants are presented in Table 1. All participants received similar dietary and behavioral recommendations and consumed a low-salt diet.

### Blood pressure measurements

Arterial blood pressure was measured at the time of inclusion and every 4 weeks thereafter for 16 weeks of the study. Blood pressure measurement was always performed in the morning on the right and left arms, in supine, sitting and standing positions. The results of the second and the third measurements were recorded, and the mean value of a total of 12 measurements was used as an integral estimate of arterial blood pressure.

### Statistical analysis

Data were processed using the SPSS 10.1.7 statistical program package (SPSS, Chicago, IL, USA). After examination of the variable distribution, the Mann–Whitney statistics were used for between-group comparisons, the Wilcoxon statistics were used for within-group effect assessments, and one-way ANOVA (analysis of variance) was used for comparisons of the treatment effects between groups. Results are expressed in terms of means, s.e.m. and 95% CI (95% confidence interval), if applicable. Significance was defined at the 0.05 level of confidence.

## RESULTS

### Subject enrollment and compliance

A total of 90 participants were included in the study. During the treatment period, six patients discontinued study medications, one in the Allicor (2400 mg daily) group and one in the Kwai group, because of gastrointestinal complaints, and four at their own request (one in the Allicor (2400 mg daily) group and three in the Kwai group). None of the patients discontinued study medications in the Allicor (600 mg daily) group nor in the placebo group. There were no side effects from Allicor, including gastrointestinal complaints. Thus, 84 participants were evaluated at the end of the 8-week treatment period (30 in the 600 mg Allicor group; 18 in the 2400 mg Allicor group; 20 in the placebo group; and 16 in the Kwai group).

### Baseline characteristics

Table 1 summarizes the baseline characteristics of study participants according to their treatment assignments. The groups did not differ significantly in demographic and clinical characteristics either at the time of inclusion or after the 8-week placebo-treated run-in phase. Thus, subsequent analyses of changes in SBP and DBP were conducted without using additional parameters as covariates.

### SBP

During the 8-week placebo-treated run-in phase of the study, SBP in the total group was lowered by $3.2 \pm 0.7$ mm Hg (95% CI: 1.7–4.6, $P<0.001$). Further dynamics of SBP are shown in Figure 1.

In the patients who received 600 mg Allicor daily, SBP was lowered by $5.5 \pm 0.8$ mm Hg (95% CI: 3.8–7.2, $P<0.001$) after 4 weeks and by $7.0 \pm 0.8$ mm Hg (95% CI: 5.3–8.7, $P<0.001$) after 8 weeks of treatment (Figure 1). The difference in SBP changes between Allicor-treated and placebo groups was statistically significant after 4 and 8 weeks of treatment ($P<0.001$).

Treatment with 2400 mg Allicor daily also resulted in a statistically significant reduction in SBP. After 4 weeks of treatment, SBP was lowered by $5.4 \pm 0.5$ mm Hg (95% CI: 4.4–6.5, $P<0.001$), and after 8 weeks it was lowered by $9.3 \pm 0.7$ mm Hg (95% CI: 7.8–10.9, $P<0.001$) (Figure 1). The difference in SBP changes between Allicor-treated and placebo groups was statistically significant after 4 and 8 weeks of treatment ($P<0.001$). The hypotensive effect of 2400 mg Allicor daily did not differ significantly from that of the 600 mg daily group ($P=0.092$).

**Table 1 Baseline demographic and clinical characteristics of study participants**

| *Variable* | *Allicor (600 mg daily)* | *Allicor (2400 mg daily)* | *Kwai (900 mg daily)* | *Placebo* |
|---|---|---|---|---|
| Number of patients, *n* | 30 | 18 | 16 | 20 |
| Age, years | 51.5 ± 2.1 (47.2–55.9) | 50.9 ± 2.4 (45.8–55.9) | 52.2 ± 2.5 (46.9–57.5) | 52.7 ± 2.5 (47.4–58.0) |
| Alcohol consumption, *n* (%) | 12 (40.0) | 7 (38.9) | 7 (43.8) | 8 (40.0) |
| Smoking history, *n* (%) | 12 (40.0) | 7 (38.9) | 7 (43.8) | 8 (40.0) |
| Family history of hypertension, *n* (%) | 3 (10.0) | 2 (11.1) | 2 (12.5) | 2 (10.0) |
| Cardiovascular history, *n* (%) | 6 (20.0) | 4 (22.2) | 4 (25.0) | 4 (20.0) |
| Body mass index, kg m$^{-2}$ | 25.3 ± 0.6 (24.0–26.5) | 25.5 ± 0.8 (23.9–27.1) | 25.3 ± 0.8 (23.7–26.9) | 26.0 ± 1.0 (23.8–28.1) |
| SBP, mm Hg at the inclusion to the study | 158.0 ± 2.8 (152.4–163.6) | 154.0 ± 3.4 (146.9–161.1) | 156.9 ± 2.8 (151.0–162.8) | 154.8 ± 3.2 (148.1–161.5) |
| After run-in phase | 155.6 ± 2.5 (150.5–160.7) | 153.1 ± 2.7 (147.3–158.9) | 152.1 ± 2.7 (146.3 ± 157.9) | 149.8 ± 2.8 (143.9–155.7) |
| DBP, mm Hg at the inclusion to the study | 97.0 ± 1.0 (94.9–99.1) | 95.0 ± 0.6 (93.6–96.4) | 97.5 ± 1.0 (95.4–99.6) | 96.1 ± 1.3 (93.4–98.9) |
| After run-in phase | 96.0 ± 0.9 (94.2–97.9) | 94.6 ± 0.5 (93.5–95.8) | 96.4 ± 0.8 (94.7–98.2) | 94.4 ± 1.4 (91.5–97.2) |

Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure.
Data for age, body mass index and blood pressure are presented as means ± s.e.m. and 95% CI given in parentheses.

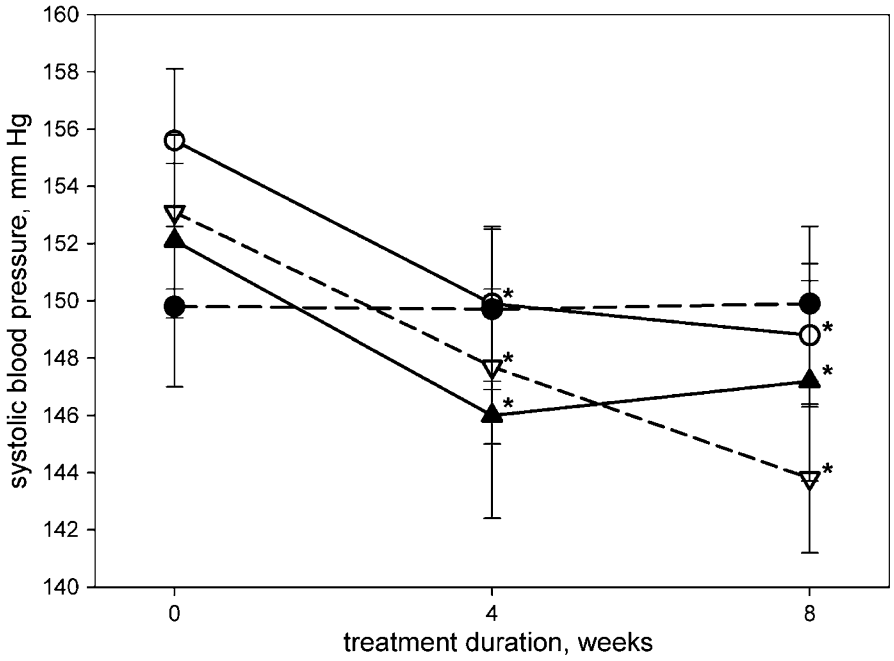


**Figure 1** The dynamics of systolic blood pressure. Open circles/solid line, 600 mg Allicor daily; solid circles/long dash, placebo; open triangles/short dash, 2400 mg Allicor daily; solid triangles/solid line, 900 mg Kwai daily. Asterisk indicates a significant difference from the beginning of the treatment phase; $P<0.05$, Wilcoxon signed-rank test.

In patients who received 900 mg Kwai daily, SBP was lowered by 5.3 ± 1.5 mm Hg (95% CI: 2.1–8.6) after 4 weeks of treatment ($P$=0.006), and the same effect was observed at the end of the study (SBP decreased by 5.4 ± 1.6 mm Hg, 95% CI: 1.9–8.8, $P$=0.010) (Figure 1). The difference in SBP changes between Kwai-treated and placebo groups was statistically significant after 4 and 8 weeks of treatment ($P$=0.009 and $P$=0.011, respectively). The effect of 900 mg Kwai daily on SBP did not differ significantly from that of 600 or 2400 mg Allicor daily.

### DBP

During the 8-week placebo-treated run-in phase of the study, DBP in the total group was lowered by 1.0 ± 0.4 mm Hg (95% CI: 0.3–1.7, $P<0.001$). Further dynamics of DBP are shown in Figure 2.

In those patients who received 600 mg Allicor daily, DBP was lowered by 2.5 ± 0.6 mm Hg (95% CI: 1.1–3.8, $P<0.001$) after 4 weeks. By the end of the study, DBP decreased by 3.8 ± 0.5 mm Hg (95% CI: 2.7–4.8, $P<0.001$) (Figure 2). The difference between DBP changes in Allicor and placebo groups was statistically significant ($P<0.001$).

The treatment with 2400 mg Allicor daily also resulted in a statistically significant reduction in DBP. After 4 weeks of treatment, DBP was lowered by 2.0 ± 0.4 mm Hg (95% CI: 1.2, 2.8, $P<0.001$), and after 8 weeks it was lowered by 3.2 ± 0.5 mm Hg (95% CI: 2.2–4.2, $P<0.001$) (Figure 2). The difference in DBP changes between Allicor-treated and placebo groups was statistically significant after 4 and 8 weeks of treatment ($P<0.001$). There was no statistically significant difference between the effects of 600 and 2400 mg Allicor daily on DBP.

Treatment with 900 mg Kwai daily did not result in a statistically significant decrease in DBP compared with placebo. After 4 weeks of treatment, DBP changed by −0.9 ± 1.1 mm Hg (95% CI from −3.2 to 1.4, $P$=0.156), and after 8 weeks it changed by −1.0 ± 1.2 mm Hg (95% CI from −3.6 to 1.5, $P$=0.088) (Figure 2). The difference in DBP changes between Kwai-treated patients and placebo recipients was observed after 4 weeks ($P$=0.046), but not after 8 weeks of treatment ($P$=0.179).

## DISCUSSION

The results of this study have shown that the garlic-based dietary supplement, Allicor, produces a statistically significant hypotensive effect on both SBP and DBP in men with mild and moderate arterial hypertension. These data are similar to the results from earlier studies that showed the hypotensive effects of garlic products.[9–14] However, most earlier studies were non-randomized and non-placebo-controlled. Thus, the results of this randomized, placebo-controlled, double-masked clinical trial provide substantial evidence for the hypotensive effectiveness of garlic.

Valid comparisons of the hypotensive effects of two different garlic-based preparations, namely Allicor and Kwai, are made possible from this study. Both Allicor and Kwai induced moderate, but statistically significant, decreases in SBP that developed within the first 4 weeks of treatment, and garlic administration for an additional 4 weeks did not result in any additional hypotensive action. The effects of Kwai and Allicor on SBP did not differ significantly, although the dosages recommended by the manufacturers differed (900 and 600 mg per day, respectively). Thus, the maximum possible hypotensive effect of garlic was achieved at the 600 mg per day dose, and further increases in dosage did not provide additional benefits. In support of this idea, the four-fold increase in Allicor dosage to 2400 mg per day did not produce more prominent hypotensive effects on either SBP or DBP. Taken together, these findings show that the mechanisms of hypotensive action of garlic-based preparations may be quite different from those of conventional pharmacological agents used in the treatment of arterial hypertension and may be referred to complex biological regulation of blood pressure.

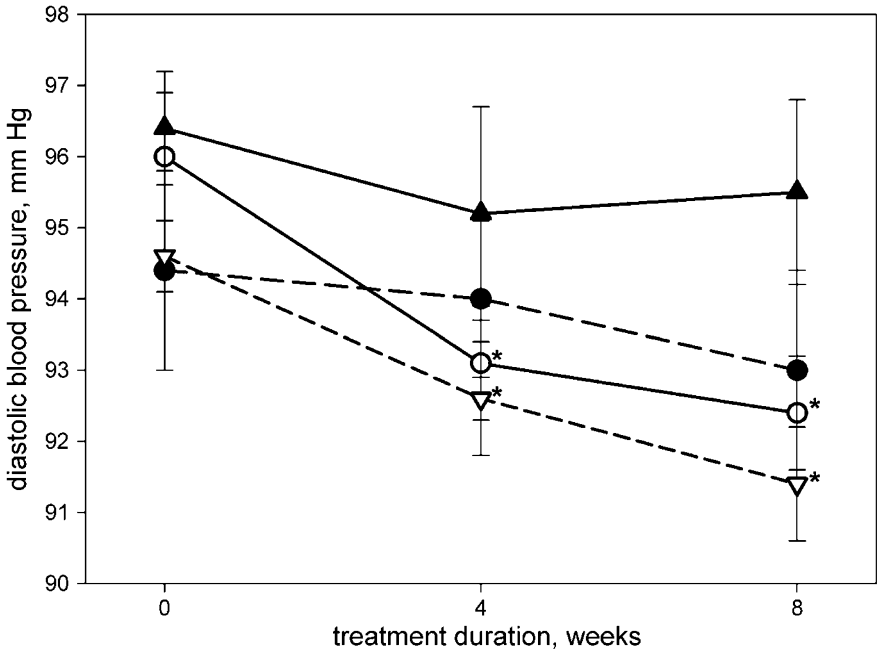


**Figure 2** The dynamics of diastolic blood pressure. Open circles/solid line, 600 mg Allicor daily; solid circles/long dash, placebo; open triangles/short dash, 2400 mg Allicor daily; solid triangles/solid line, 900 mg Kwai daily. Asterisk indicates a significant difference from the beginning of the treatment phase; $P<0.05$, Wilcoxon signed-rank test.

The mechanisms of hypotensive action of garlic-based preparations and garlic components remain rather obscure. Results from several animal studies show that garlic constituents are able to decrease blood pressure in hypertensive animals by producing vasodilating effects at the level of the arterial wall.[15–27] Although allicin, an active ingredient released from garlic that is thought to be a systemic vasodilator, does not alter the activity of vascular prostacyclin synthase, it dilates the mesenteric circulation in cats independent of prostaglandin release or a β-adrenergic mechanism.[16] In terms of relative vasodilator activity, allicin was 100-fold less potent than sodium nitroprusside and many orders of magnitude less potent than isoproterenol; however, it significantly diminished the pulmonary pressor response to ventilatory hypoxia in isolated perfused rat lung. In addition, pulmonary vasodilator responses to allicin were independent of the synthesis of endothelial-derived relaxing factor or the activation of soluble guanylate cyclase.[18] Garlic can prevent chronic inhibition of nitric oxide synthesis by L-NAME (*N*-omega-nitro-L-arginine methyl ester) in rats, thus preventing L-NAME-induced arterial hypertension.[24] In rats, garlic completely inhibited acute hypoxic pulmonary vaso constriction and induced significant dose-dependent vasorelaxation in both endothelium-intact and mechanically endothelium-disrupted pulmonary arterial rings, thus showing a combination of endothelium-dependent and endothelium-independent mechanisms for the development of the hypotensive effect.[23] It was also shown that garlic juice possesses a direct relaxing effect on the smooth muscles of the aorta, trachea, intestines and isolated rabbit hearts *in vitro*.[28] Garlic may provide a depressing effect on automaticity and tension development in the isolated rat heart, suggesting a β-adrenoreceptor-blocking action.[17] The hypotensive effects of garlic constituents may also be explained in part by a significant biphasic diuretic and natriuretic response and by an inhibitory dose-dependent effect on the kidney Na, K-ATPase.[29–31] Finally, aqueous garlic extract, as well as allicin and ajoene, can open potassium ion channels, causing membrane hyperpolarization that closes about 20% of the L-type $Ca^{2+}$ channels, the consequence of which is vasodilatation.[32,33]

It is necessary to note that in our study, Allicor, but not Kwai, induced a statistically significant decrease in DBP. The inconsistencies in results obtained in different studies are often explained by differences in components used during supplement preparation, the quantity of the preparation provided, the duration of the study and the influence of the manufacturing process on the composition of the garlic product; moreover, biological responses to different preparations may vary greatly. Garlic contains various organosulfur compounds, amino acids, vitamins and minerals.[34] Sulfur-containing compounds such as allicin, ajoene and cicletanine and various sulfoxides may be responsible for the hypotensive activity of garlic. Many garlic-based products are present on the market now. They can be classified into four groups, that is, garlic essential oil, garlic oil macerate, garlic powder and garlic extract. Compared with other garlic preparations, dehydrated garlic powder is thought to retain the same ingredients as raw garlic, both water-soluble and organic-soluble, although the proportions and amounts of various constituents may differ significantly.[35,36] Both Allicor and Kwai contain just garlic powder, but Allicor is a time-released preparation; its biological effect lasts for 12–16 h after administration of a single dose.[37] DBP lowering in Allicor-treated participants may be explained by the presence of remnants of bioactive compounds in the circulation. The difference between Kwai and Allicor in their biological effects may be due to slower disintegration of Allicor tablets during digestion. This process results in the absorption of bioactive compounds in a dispensed manner, providing low and steady concentrations of active metabolites to the circulation. The different effects of Allicor and Kwai on DBP may be due to prolonged action of Allicor, which may allow better bioavailability of the vasoactive constituents of garlic powder.

Hypertension is an acknowledged major risk factor for cardiovascular disease and death in both men and women. Despite a historical

focus by clinicians on the importance of DBP risks, epidemiological data from numerous large-scale studies have clearly shown that both SBP and DBP are important determinants of cardiovascular risk, even in mild and moderate arterial hypertension.[8,38,39] In addition, even high-normal blood pressure is associated with an increased risk of cardiovascular disease.[40] It is generally thought that rigid normalization of blood pressure may prolong life and reduce the cardiovascular sequelae of hypertension, possibly including coronary heart disease.[41] Thus, the moderate and statistically significant hypotensive effect of the time-released garlic-based dietary supplement, Allicor, may provide considerable benefits for the dietary prevention of cardiovascular diseases.

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