A REVIEW OF STUDIES OF GARLIC (ALLIUM SATIVUM) ON SERUM LIPIDS AND BLOOD PRESSURE BEFORE AND AFTER 1994: DOES THE AMOUNT OF ALLICIN RELEASED FROM GARLIC POWDER TABLETS PLAY A ROLE?

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ABSTRACT

Objective: To identify studies measuring garlic powder tablets effects on systolic and diastolic blood pressure and to investigate if studies published prior to January 1994 would perform better than those published later.

Methods: Using MEDLINE (January 1966 through December 2004) studies involving human subjects that examined the effect of garlic (Allium sativum) on serum lipids and blood pressure were obtained. Studies that were conducted using garlic in the form of garlic powder tablets were included in the data extraction. Correlation coefficients were calculated for total serum cholesterol, systolic and diastolic blood pressure with respect to date of publication. Trials published prior to January 1994 were placed into an "earlier" group and compared to the "latter" group of studies published from January 1994 onward.

Results: Eighteen trials were identified whereupon the inverse associations between total serum cholesterol, systolic and diastolic blood pressures with respect to time of publication were correlated (−0.614, −0.627, and −0.587 respectively, $p < 0.05$). No significant associations were observed between systolic and diastolic blood pressure with respect to total serum cholesterol (0.388 and 0.431 respectively). The following differences between the earlier and later groups were observed for total serum cholesterol (31.4 ± 19.0 vs. 3.5 ± 5.8 mg/dl, $p = .004$); systolic blood pressure (11.0 ± 9.2 vs. 2.0 ± 4.4 mmHg, $p = .133$) and diastolic blood pressure (5.8 ± 3.4 vs. 0.9 ± 2.4 mmHg, $p = .018$).

Conclusions: Publications published prior to January 1994 performed better than those published after January 1994, suggesting that allicin may be responsible for the antihypertensive effects of garlic powder tablets. However, a lack of correlation between changes in total serum cholesterol and blood pressure suggests that other organosulfur compounds may also play a role in the antihypertensive mechanisms of garlic. (J Chiropr Med 2005;4:182–190)

Key Indexing Terms: Garlic; Allicin; Alliin; Alliinase; Blood Pressure; Hypertension

INTRODUCTION

According to the World Health Organization 17 million people around the globe die of cardiovascular disease each year.[1] In the United States coronary heart disease is the leading cause of premature death and the American Heart Association estimates that coronary artery disease affected approximately 12.9 million people in the United States during 2000.[2] Increased total serum cholesterol levels, and in particular elevated levels of low-density lipoprotein (LDL) cholesterol, are directly associated with an increased incidence of coronary artery disease.[3] Statistics published by the American Heart Association in 2002 suggest that 42 million American adults have total serum cholesterol levels greater than 240mg/dL.[2] High blood pressure (as defined as systolic and/or diastolic pressure greater than 140 and 90 mmHg respectively or prescribed antihypertensives) is also directly associated with an increased incidence of coronary artery disease,[3] and the

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American Heart Association estimates that 50 million American adults are considered hypertensive.[2] Therefore, interventions designed to address hypercholesterolemia and hypertension are imperative to reduce the loss of life attributed to cardiovascular disease.

The protective actions of garlic (*Allium sativum*) against cardiovascular disease have been investigated extensively and evidence from numerous studies suggest that garlic can bring about the normalization of plasma lipids, enhancement of fibrinolytic activity, inhibition of platelet aggregation and reduction of blood pressure.[4] Since 1975 there have been more than 50 human studies on lipid-lowering effects of garlic and garlic preparations,[5] and the hypotensive effects of garlic were published as far back as 1921.[6] Two meta-analyses published in 1994 found that garlic was effective in reducing total serum cholesterol and high blood pressure.[7–8] The authors found that garlic was able to provide a 12% reduction in total serum cholesterol beyond the final levels achieved with placebo. They also found that garlic was able to provide a 7.7 and 5.0 mmHg reduction of systolic and diastolic blood pressure, respectively, beyond the final levels achieved with placebo alone.

However, in 2000 a meta-analysis[9] was published which found that garlic's effects on reducing total serum cholesterol was modest at best, and the authors concluded that garlic was not an efficient method for reducing total serum cholesterol. Upon closer inspection of this latter meta-analysis, Lawson et al[10] observed that 5 of the 6 latest clinical trials found no significant reduction in total serum cholesterol in contrast to many earlier studies. Lawson et al therefore performed another meta-analysis which compared the earlier positive trials versus later negative trials. They observed a significant difference in garlic's effect on total serum cholesterol between trials published before and after January 1994 with reductions of 12.8% versus 1.8%, respectively. The authors of this analysis also presented data showing that the subjects in garlic trials published after January 1994 received less allicin than those in studies published before January 1994. They observed that the allicin release potential by garlic powder tablets used in publications prior to January 1994 was 44% versus 15% for tablets used in trials published after January 1994. They also found that the garlic powder tablets used in the later studies disintegrated in acid in about half the time (2.46 versus 1.26 hours). Lawson et al[10] concluded that a problem in tablet design after 1993 led to less effective alliinase protection and subsequent inactivation of alliinase by gastric acid in the stomach; thereby reducing the effectiveness of allicin formation from alliin.

Garlic consists of several organosulfur constituents such as γ-glutamylcysteine, S-allyl cysteine, alliin, allicin and ajoene.[11] Although a number of these organosulfur constituents have been identified as inhibitors of cholesterol metabolism,[12] it is believed that allicin is the primary active compound responsible for inhibiting cholesterol biosynthesis.[12,13] However, it is currently not well understood which organosulfur compound is responsible for the antihypertensive effects observed with garlic supplementation.[14–16]

If the vasodilatory effects of garlic are more dependent upon the water soluble organosulfur compounds such as γ-glutamylcysteine or S-allyl cysteine, then deficiencies in garlic tablet formation should not be a factor since protection of the enzyme alliinase is not required for their presence and absorption into the gastrointestinal tract. Therefore, with respect to the antihypertensive effects of garlic, no difference should be observed across dates of publication. However, if allicin is predominately responsible for the antihypertensive effects of garlic, then it would be expected that garlic powder tablet trials published prior to January 1994 would perform better than those published after January 1994 in reducing systolic and diastolic blood pressure. This study investigated if there was a difference in the associations between total serum cholesterol, systolic and diastolic blood pressures with respect to time of study publication.

METHODS

Data Sources

Using MEDLINE (January 1966 through December 2004) all published studies involving human subjects which examined the effect of garlic (*Allium sativum*) on serum lipids and blood pressure were obtained using the search terms in combinations of "garlic" OR "Allium Sativum" AND "cholesterol" OR "lipid" AND "blood pressure" OR "hypertension". Additional publications were identified from the bibliographies of previously retrieved papers. There

were no language restrictions, but published abstracts were not included in the analysis.

Data Extraction

Studies conducted using garlic in the form of a garlic powder tablets were included in the data extraction. Data was extracted from the published reports and the following items were documented: number of subjects; mean age or age range; garlic powder tablet dose/day and dose regimen used; duration of treatment; study design (baseline comparisons versus control group designs which may include randomization and blinding); withdrawals from study; number and type of adverse effects noted; number of subjects noting garlic body odor; baseline and post treatment measures of total serum cholesterol, systolic blood pressure and diastolic blood pressure.

Data Analysis

The data was tabulated and entered into a Microsoft Excel (Microsoft Corp, Redmond, WA) spreadsheet. Correlation coefficients were calculated for total serum cholesterol, systolic and diastolic blood pressure with respect to date of publication. Correlation coefficients were also calculated for total serum cholesterol with respect to systolic and diastolic blood pressure. The studies were divided into two groups based on their date of publication. Studies published prior to January 1994 were placed into the "earlier" group while the remaining studies published from January 1994 onward were placed into the "later" group. January 1994 was designated the cut off date between the earlier and later groups based on the publication by Lawson et al,[10] which found that there were substantial differences between tablets manufactured and used in studies published before and after January 1994. The mean change from baseline was calculated for total serum cholesterol (mg/dl), and systolic blood and diastolic blood pressures (mmHg) for both the earlier and later groups.

Statistical Analysis

All data were expressed descriptively as means and standard deviations. Differences between the earlier and later groups with respect to baseline and percent change from baseline were compared using the Mann-Whitney test (U-test) for non-parametric data. Comparison of all categorical data was performed using chi-square analysis. Analysis of the data was performed using SPSS version 12.0 (SPSS Inc., Chicago, IL) and all tests were conducted at the 5% probability level.

RESULTS

A total of 18 trials were identified which included an examination of the effects of garlic powder tablets on blood pressure and total serum cholesterol.[17–34] A summary of the trials with respect to design, duration and dosage of garlic powder per day, as well as the pre and post systolic and diastolic blood pressures are presented in Table 1. All but one of the eighteen trials utilized Kwai garlic powder tablets (Lichtwer Pharma, Berlin, Germany), whereas the only exception utilized Futura Hvidlog Forte garlic powder tablets (Dansk Droge, Ishoj, Denmark).[17] The associations between total serum cholesterol, systolic blood pressure and diastolic blood pressure with respect to time of publication were all significantly correlated ($p < 0.05$). Figures 1–3 present the correlation coefficients between these three associations. Although the mean change in diastolic blood pressure was more strongly associated with changes in total serum cholesterol, no significant associations were observed between systolic and diastolic blood pressure with respect to total serum cholesterol as observed in Figures 4 and 5.

Eleven[24–34] of the 18 trials that were published prior to January 1994 were placed into the "earlier group", but only 4 of the remaining 7[18,20,21,23] studies published from January 1994 onward were placed into the "later group". One trial was excluded because it consisted of a pediatric population with an average age of 13.9 years.[19] A second study was excluded because the trial was conducted on a normo-lipidaemic population.[17] A third trial was excluded as it was statistically determined to present as an outlier.[22] The characteristics of the earlier and later groups are presented in Table 2. There were no statistically significant differences in subject characteristics between the two groups, although the earlier group (1988 to 1993) tended to consist of an older population with higher total serum cholesterol concentrations and higher systolic and diastolic blood pressures. The differences between earlier and later groups with respect to mean changes between baseline and post treatment total serum cholesterol and blood pressure measures are presented in Table 3.

Adverse effects and garlic odor noted by subjects were observed in both the earlier and later groups,

TABLE 1
SUMMARY OF TRIALS INVESTIGATING THE EFFECT OF GARLIC (*ALLIUM SATIVUM*) POWDER TABLETS ON SYSTOLIC AND DIASTOLIC BLOOD PRESSURE

Author and Year [Ref]	Study Design*	Sample Size	Mean Age	Duration (weeks)	Dose Garlic Powder/day (mg)	Blood Pressure Systolic		Blood Pressure Diastolic	
						Before	After	Before	After
Turner et al. 2004 [17]	R, DB, PC	29	49.6	12	900	111	114	73.5	72.5
Ziaei et al. 2001 [18]	R, SB, PC	50	24.6	8	800	122.6	122.3	79.7	79.4
McCrindle et al. 1998 [19]	R, DB, PC	15	13.9	8	900	122	124.8	83	82.7
Isaacsohn et al. 1998 [20]	R, DB, PC	24	58	12	900	119.3	117.1	73.2	72.1
Simons et al. 1995 [21]	R, DB, PCO	28	53.6	12	900	127	119	80	76
Santos and Johns 1995 [22]	R, DB	36	57.6	16	600	151	124	96	79
Saradeth et al. 1994 [23]	R, DB, PC	31	37.7	15	900	125	127.4	80.8	82.7
Kiesewetter et al. 1993 [24]	R, DB, PC	32	59.9	12	800	125	125	84.7	81.7
Jain et al. 1993 [25]	R, DB, PC	20	48	12	900	129	130	82	81
Santos and Grunwald 1993 [26]	R, DB, PC	25	53	12	900	145	120	90	80
Holzgartner et al. 1992 [27]	R, DB	47	56.5	12	900	143.4	135.4	82.8	78.6
Grunwald et al. 1992 [28]	BC	45	58.4	18	600	158.4	147.2	96.3	92.3
Kiesewetter et al. 1991 [29]	R, DB, PC	30	23.8	4	800	116	116	74	67
Auer et al. 1990 [30]	R, DB, PC	24	58	12	600	171	152	102	89
Vorberg and Schneider 1990 [31]	R, DB, PC	20	50	16	900	145	138	90	86
Harenberg et al. 1988 [32]	BC	20	53.3	4	600	136.5	125.5	86	81
Kandziora 1988 [33]	R, DB	20	56	12	600	130	110.5	85	79.9
Kandziora 1988 [34]	R, DB, PC	20	43–65	12	600	130	109.2	85	77.4

* R (randomized); DB (Double Blind); SB (Single Blind); PC (Placebo Control); PCO (Placebo Cross Over); BC (Baseline Comparison).

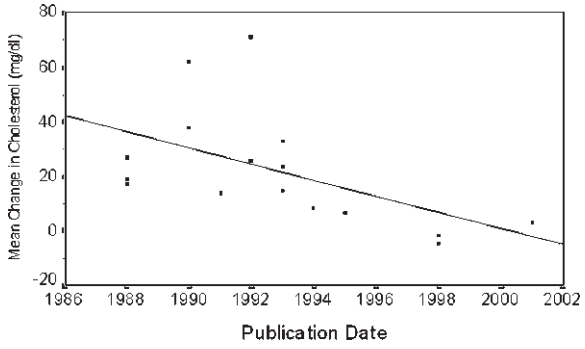

Figure 1. Association between mean change from baseline of total serum cholesterol and date of publication (r = −0.614, p = 0.009).

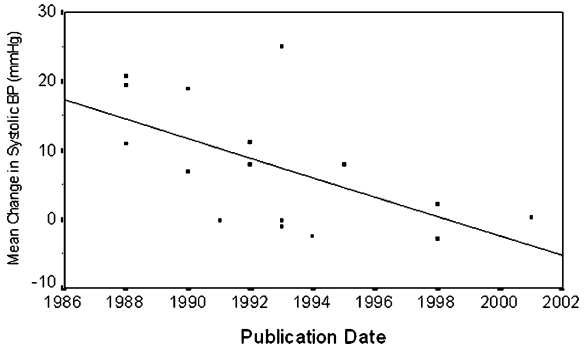

Figure 2. Association between mean change from baseline of systolic blood pressure and date of publication (r = −0.627, p = 0.007).

however not all studies presented data which clearly identified whether these effects were observed. One of the 4 later publications made no mention with regard to observations of perceived garlic odor. Five of the 11 earlier publications made no mention to whether adverse effects were observed, while 6 of the 11 made no mention to whether garlic odor was perceived by subjects. Forty-two of 168 (25.0%)

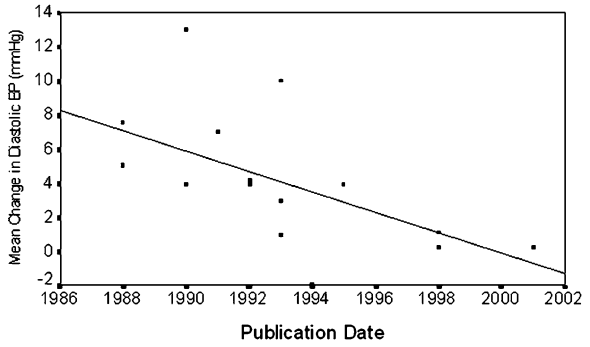

Figure 3. Association between mean change from baseline of diastolic blood pressure and date of publication (r = −0.587, p = 0.013).

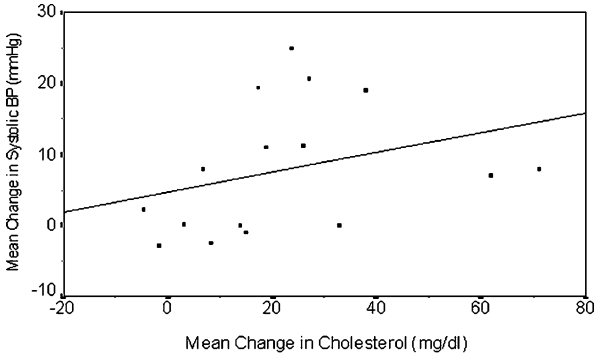

Figure 4. Association between mean change from baseline of systolic blood pressure and total serum cholesterol (r = 0.388, p = 0.124).

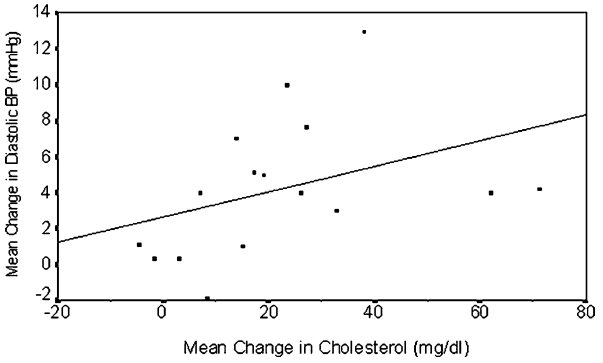

Figure 5. Association between mean change from baseline of diastolic blood pressure and total serum cholesterol (r = 0.431, p = 0.084).

subjects in the earlier group perceived garlic odor, while 32 of 102 (31.4%) subjects in the later group perceived garlic odor. There was no significant difference in the percentage of subjects perceiving garlic odor between the earlier and latter groups. Ten of 193 (5.2%) subjects in the earlier group experienced adverse side effects, while 14 of 133 (10.5%) subjects in the later group experienced adverse side effects. There was no significant difference between the earlier and latter groups. The majority of adverse side effects reported were related to gastrointestinal complaints such as nausea, increased belching and flatulence, none of which were considered serious in nature.

TABLE 2
COMPARISON OF BASELINE AND STUDY CHARACTERISTICS

	1988 TO 1993	1994 TO 2001
NO. PUBLICATIONS	11	4
MEAN AGE	51.7 ± 10.5	43.5 ± 15.3
MEAN BASELINE TOTAL SERUM CHOLESTEROL (MG/DL)	274.4 ± 24.9	253.5 ± 21.7
MEAN BASELINE SYSTOLIC BLOOD PRESSURE (MMHG)	139.0 ± 15.8	123.5 ± 3.3
MEAN BASELINE DIASTOLIC BLOOD PRESSURE (MMHG)	87.1 ± 7.4	78.4 ± 3.5
MEDIAN DURATION OF TRIAL (WEEKS)	12	12
MEDIAN DOSE OF GARLIC POWDER/DAY (MG)	800	900

DISCUSSION

Allicin, an organosulfur constituent of garlic, is responsible for the inhibition of HMG-CoA reductase, and thereby results in a decrease in total serum cholesterol concentration.[12,13] However, the metabolites responsible for the antihypertensive effects of garlic have not yet been elucidated, although a few authors have noted that allicin or its metabolites may be responsible for the inhibition of angiotensin-converting enzyme (ACE) activity,[16] or the activation of endothelial nitric oxide synthase (eNOS) which produces the endogenous vasodilator nitric oxide.[14,15]

In this review it was observed that the effects of garlic powder tablets on lowering both systolic and diastolic blood pressure inversely correlated with the date of publication. It was also observed in this review that mean changes in systolic and diastolic blood pressure were greater in the studies published prior to January 1994 compared to the studies published after January 1994 (although the difference in systolic blood pressure was statistically non-significant). The difference in total serum cholesterol observed in this review between the garlic powder tablet trials published before and after January 1994 parallel the findings by Lawson et al.[10] In

TABLE 3
MEAN CHANGE FROM BASELINE

	1988 TO 1993 (N = 11)	1994 TO 2001 (N = 4)	P-VALUE
TOTAL SERUM CHOLESTEROL (MG/DL)	31.4 ± 19.0	3.5 ± 5.8	.004
SYSTOLIC BLOOD PRESSURE (MMHG)	11.0 ± 9.2	2.0 ± 4.4	.133
DIASTOLIC BLOOD PRESSURE (MMHG)	5.8 ± 3.4	0.9 ± 2.4	.018

Lawson et al's study they presented data which showed that subjects in garlic trials published after January 1994 received less allicin than those in studies published before January 1994. This finding along with the data presented in this review may suggest that allicin does play a significant role in the mechanism for reducing systolic and diastolic blood pressure.

A pilot study published in 1993[35] using only 9 subjects found that garlic powder tablets reduced both systolic and diastolic blood pressure (although it should be noted that this study investigated acute changes in blood pressure with high doses of garlic powder-2400mg). Alternately, two studies published in 2001 and 2002[36,37] found no significant differences in systolic or diastolic blood pressure when subjects were supplemented with garlic powder tablets. These latest trials directed Lawson et al[10] to analyze the garlic powder tablets used in one of these studies.[36] They found that the brand utilized in this particular trial expressed a very low allicin release potential.

To understand why a garlic powder tablet would present with a low allicin release potential, it is important to recognize that allicin must be enzymatically formed by the action of the vacuolar enzyme alliinase. This enzyme will act upon garlic's most abundant sulfur compound alliin. Allicin formation is not a problem for raw garlic since its formation is complete within 6 seconds after cloves are crushed or chewed.[38] However, it is a problem for supplements since allicin formation is rapidly and irreversibly inhibited below pH 3.5, the usual range for gastric juice.[38] Hence any garlic powder supplement that intends to represent fresh garlic must be able to protect alliinase until it can convert alliin to allicin in the non-acidic environment of the small intestine.

Based on the therapeutic importance of protecting the alliinase enzyme, Lawson et al[39] tested 24 known brands of enteric-coated garlic powder tablets they found that 83% of the brands released less than 15% of their allicin release potential. They hence concluded that the low allicin release was due to impaired alliinase activity via its deactivation by gastric juices. Therefore, if alliinase is to be protected so to provide the allicin concentration required to have a mechanistic effect on reducing total serum cholesterol, then in a similar fashion, systolic and diastolic blood pressure reduction should also be dependent upon the protection of alliinase. The protection of alliinase through the acidic environment of the stomach will therefore enhance the allicin release potential from garlic powder tablet supplementation, thereby providing more allicin for intestinal absorption, and hence drive the mechanistic action of reducing systolic and diastolic blood pressures as observed in garlic powder trials prior to 1994.

It was also observed that the correlation coefficients between total serum cholesterol and both parameters of blood pressure were not significantly associated with each other. This may suggest that additional independent interactions, possibly related to the various constituents of garlic other than allicin, may be involved via different mechanisms in relation to blood pressure and cholesterol reduction. Therefore the mechanisms of action unique to the reduction of either cholesterol or blood pressure may be independently hinged upon the absorption of a variety of different organic constituents of garlic.

For instance, the water soluble organosulfur compound S-allyl cysteine (SAC) has been shown to be active in reducing cholesterol synthesis,[39,40] but may have no effect on reducing blood pressure[41] (although it should be noted that this study utilized normotensive subjects). If SAC is not dependent upon alliinase for its presence, then differences in the magnitude of effects between blood pressure and cholesterol reduction may be observed, especially if large quantities of SAC are absorbed by the gastrointestinal tract. However, in experiments us-

ing aged garlic extract, whereupon SAC is the prime organosulfur constituent, it has been shown that SAC up-regulates the production of nitric oxide which therefore can contribute to blood pressure reduction.[42] Two separate studies using aged garlic extracts support the effects of systolic and diastolic blood pressure reduction.[43–44] It is important to point out that both of these studies were published after 1994 (1996 and 2004), and supports the notion that with aged garlic extract, the protection of alliinase is not required since allicin is not the primary active constituent of this form of garlic preparation. More importantly this may suggest that not all forms of garlic are therapeutically equal, especially in light of the fact that garlic powder tablets may not be providing the necessary physiological amount of allicin. Therefore concerning reducing blood pressure, aged garlic extract may possibly be found to be a more effective therapeutic form of garlic in comparison to garlic powder tablets.

Another possible explanation for why the correlation coefficients between total serum cholesterol and both parameters of blood pressure were not significantly correlated with each other is that allicin decomposes to produce many other organosulfides such as diallyl-disulfide,[45] which is an effective inhibitor of cholesterol synthesis,[12] but has been shown to be ineffective in reducing blood pressure.[46] Although the production of allicin may be limited due to the inactivation of the enzyme alliinase, the small concentration of allicin that is formed and absorbed may still exert a differential effect between cholesterol and blood pressure reduction via its conversion to other various organosulfur compounds.

The non-significant correlation observed between cholesterol and blood pressure may also be due to the fact that all garlic trials analyzed used hypercholesterolemic subjects, while only half of the clinical trials used normotensive subjects. Therefore, this lack of correlation may be due to ceiling effects created by using normotensive subjects since the magnitude of blood pressure reduction would permit less room for change compared to the magnitude of cholesterol reduction change in subjects who had clinically elevated total serum cholesterol levels. This proposed effect was observed in the aged garlic extract study conducted by Durak et al[45] in which no significant changes were observed in systolic or diastolic blood pressures for normotensive subjects, while significant changes were observed for subjects who were hypertensive (blood pressure changes between normotensive and hypertensive subjects respectively: systolic 2.2 vs 22.1 mmHg; diastolic 2.6 vs 13.4 mmHg).

A few methodological flaws must be addressed regarding this review. It first must be noted that due to the heterogeneity between studies reviewed, some caution must be taken when interpreting these results. The first caution is based on the varied designs employed by these studies as only 11 of the 18 publications utilized randomized, double blind, placebo controlled trials. The second caution is based on the varied study sample sizes (range = 15 to 50 subjects) and population characteristics because even though all but one of the trials utilized hypercholesterolemic subjects, 2 of the trials consisted of only female patients with preeclampsia[18] and another consisted of a group of hypercholesterolemic children.[19] Although the pediatric and normolipidemic trials were excluded from the earlier versus later group comparative analysis, the later group on average was older and possessed higher baseline total serum cholesterol levels, as well as higher baseline systolic and diastolic blood pressures when compared to the earlier group. However, differences in these baseline measures between groups were non-significant. The observed higher baseline total serum cholesterol and blood pressure measures for the later group may well likely be a factor of their greater average age, since total serum cholesterol and blood pressure will progressively increase with advancing age.[47] However a simpler explanation is that a few of the trials in the later group consisted of patient populations that possessed greater degrees of hypertension and hypercholesterolemia.

Heterogeneity was also observed between groups with respect to the dosage of garlic powder provided. However, it was the later group who was provided with a higher median dosage of garlic powder (900 mg/day), yet this group presented with the least change in total serum cholesterol and systolic and diastolic blood pressures when compared to the earlier group, which was provided with a lower median dosage (800 mg/day). The percentage of subjects in the later group who reported adverse effects (10.5%) was double that of those who reported adverse effects in the earlier group (5.2%). It could be hypothesized that this observation has to do with changes in the manufacture of garlic tablets prior to January 1994, but it is most likely due to

better methodology and subject reporting as carried out in the later studies. It was observed that approximately 25 to 30% of the subjects in both groups reported a garlic odor which is confirmation of subject compliance and that the manufacture of the garlic powder tablets utilized in these trials was sufficient enough to provide subjects in both the earlier and later groups with an ample concentration of garlic constituents.

One must be cautious in making conclusions about the antihypertensive effects of garlic based on studies with garlic powder tablets since a problem may be in the formulation design of the particular garlic powder tablets used in these trials. It is possible that other forms of garlic supplementation, such as aged garlic extract, may possess a better therapeutic outcome in regard to hypertension, however further studies need to be conducted before knowing this for certain.

CONCLUSIONS

Of the eighteen publications used in this review, which investigated garlic powder tablet effects on lowering both systolic and diastolic blood pressure, there appeared to be a relationship between efficacy and date of publication. A similar relationship has previously been observed between garlic powder tablet efficacy in reducing total serum cholesterol and date of publication. Studies utilizing garlic powder tablets published prior to January 1994 performed better that those published after January 1994. Since the garlic powder tablets used in studies published after January 1994 have been shown to provide inadequate protection to the enzyme alliinase, it may suggest that the organosulfur compound allicin is one of the factors responsible for the antihypertensive effects of garlic. These findings should be considered during the development of future studies of the effects of garlic powder tablets on systolic and diastolic blood pressure.

REFERENCES

1. The World Health Organization. CVD prevention and control: missed opportunities [website]. Geneva, Switzerland: The Association; 2003 [cited 2003 Sept 25]. Available from: http://www.who.int/cardiovascular_diseases/prevention_control/en/
2. American Heart Association. Heart disease and stroke statistics - 2003 update. Dallas, TX: American Heart Association; 2002.
3. Castelli W, Garrison R, Wilson P, Abbott R, Kalousdian S, Kannel W. Incidence of coronary heart disease and lipoprotein cholesterol levels: The Framingham Study. JAMA 1986;256:2835–8.
4. Rahman K. Historical perspectives on garlic and cardiovascular disease. J Nutr 2001;131:977S–9S.
5. Banerjee S, Maulik S. Effect of garlic on cardiovascular disorders: a review. Nutr J 2002;1:4.
6. Leoper M, DeBray M. Hypotensive effect of tincture of garlic. Prog Med 1921;36:391–2.
7. Silagy C, Neil A. Garlic as a lipid lowering agent: a meta-analysis. J R Coll Phys Lond 1994;28:39–45.
8. Silagy C, Neil A. A meta-analysis of the effect of garlic on blood pressure. J Hypertens 1994;12:463–8.
9. Stevinson C, Pittler M, Ernst E. Garlic for treating hypercholesterolemia: a meta-analysis of randomized clinical trials. Ann Intern Med 2000;133:420–9.
10. Lawson L, Wang J, Papadimitriou D. Allicin release under simulated gastrointestinal conditions from garlic powder tablets employed in clinical trials on serum cholesterol. Planta Med 2001;67:13–8.
11. Agarwal K Therapeutic actions of garlic constituents. Med Res Rev 1996;16:111–24.
12. Gebhardt R, Beck H. Differential inhibitory effects of garlic-derived organosulfur compounds on cholesterol biosynthesis in primary rat hepatocyte cultures. Lipids 1996;31:1269–76.
13. Gebhardt R, Beck H, Wagner K. Inhibition of cholesterol biosynthesis by allicin and ajoene in rat hepatocytes and HepG2 cells. Biochim Biophys Acta 1994;1213:57–62.
14. Das I, Khan N, Sooranna S. Potent activation of nitric oxide synthase by garlic: a basis for its therapeutic applications. Curr Med Res Opin 1995;13:257–63.
15. Pedraza-Chaverri J, Tapia E, Medina-Campos O, Granados M, Franco M. Garlic prevents hypertension induced by chronic inhibition of nitric oxide synthesis. Life Sci 1998;62:71–7.
16. Sharifi A, Darabi R, Akbarloo N. Investigation of antihypertensive mechanism of garlic in 2K1C hypertensive rat. J Ethnopharm 2003; 86:219–24.
17. Turner B, Molgaard C, Marckmann P. Effect of garlic (Allium sativum) powder tablets on serum lipids, blood pressure and arterial stiffness in normo-lipidaemic volunteers: a randomized, double-blind, placebo-controlled trial. Br J Nut 2004;92:701–6.
18. Ziaei S, Hantoshzadeh S, Rezasoltani P, Lamyian M. The effect of garlic tablet on plasma lipids and platelet aggregation in nulliparous pregnants at high risk of preeclampsia. Eur J Obst Gynecol Rep Bio 2001; 99:201–6.
19. McCrindle B, Helden E, Conne W. Garlic extract therapy in children with hypercholesterolemia. Arch Pediatr Adolesc Med 1998;152: 1089–94.
20. Isaacsohn J, Moser M, Stein E, et al. Garlic powder and plasma lipids and lipoproteins: a multicenter, randomized, placebo-controlled trial. Arch Inter Med 1998;158:1189–94.
21. Simons L, Balasubramaniam S, Konigsmark M, Parfitt A, Simons J, Peters W. On the effect of garlic on plasma lipids and lipoproteins in mild hypercholesterolemia. Atherosclerosis 1995;113:219–25.
22. Santos O, Johns R. Effects of garlic powder and garlic oil preparations on blood lipids, blood pressure and well being. Br J Clin Res 1995; 6:91–100.
23. Saradeth T, Seidl S, Resch K, Ernst E. Does garlic alter the lipid pattern in normal volunteers? Phytomed 1994;1:183–5.
24. Kiesewetter H, Jung F, Jung E, et al. Effects of garlic coated tablets in peripheral arterial occlusive disease. Clin Invest 1993;71:383–6.
25. Jain A, Vargas R, Gotzkosky S, McMahon G. Can garlic reduce levels of serum lipids? A controlled clinical study. Am J Med 1993;94:632–5.
26. Santos O, Grunwald J. Effect of garlic powder tablets on blood lipids and blood pressure-a six month placebo controlled double blind study. Br J Clin Res 1993;4:37–44.
27. Holzgartner H, Schmidt U, Kuhn U. Comparison of the efficacy and tolerance of a garlic preparation vs. bezafibrate. Arzneim-Frosch 1992;42:1473–7.
28. Grunwald J, Heede J, Albrecht R, et al. Effects of garlic powder tablets on blood lipids and blood pressure-the Danish multicentre Kwai study. Eur J Clin Res 1992;3:179–86.
29. Kiesewetter H, Jung F, Pinder G, Jung E, Mrowietz C, Wenzel E. Effect of garlic on thrombocyte aggregation, microcirculation and other risk factors. Int J Clin Pharm Ther Tox 1991;29:151–5.
30. Auer W, Eiber A, Hertkorn E, et al. Hypertension and hyperlipidemia: garlic helps in mild cases. Br J Clin Pract (Suppl) 1990;69:3–6.

31. Vorberg G, Schneider B. Therapy with garlic: results of a placebo-controlled, double blind study. Br J Clin Pract 1990;44:7–11.
32. Harenberg J, Giese C, Zimmermann R. Effect of dried garlic on blood coagulation, fibrinolysis, platelet aggregation and serum cholesterol levels in patients with hyperlipoproteinemia. Atherosclerosis 1988; 74:247–9.
33. Kandziora J. The blood pressure lowering and lipid lowering effect of a garlic preparation in combination with a diuretic. Arzt Forschung 1988;35(3):3–8.
34. Kandziora J. Antihypertensive effectiveness and tolerance of a garlic medication. Arzt Forschung 1988;35(1):1–8.
35. McMahon G, Vargas R. Can garlic lower blood pressure? A pilot study. Pharmacotherapy 1993;13:406–7.
36. Gardner C, Chatterjee L, Carlson J. The effect of a garlic preparation on plasma lipid levels in moderately hypercholesterolemic adults. Atherosclerosis 2001;154:213–20.
37. Andrianova I, Fomchenkov I, Orekhov A. Hypotensive effect of long-acting garlic tablets Allicor (a double blind placebo-controlled trial). Ter Arkh 2002;74:76–8.
38. Lawson L, Hughes B. Characterization of the formation of allicin and other thiosulfinates from garlic. Planta Medica 1992;58:345–50.
39. Lawson L, Wang J. Low allicin release from garlic supplements: a major problem due to the sensitivities of alliinase activity. J Agric Food Chem 2001;49:2592–9.
40. Yeh Y, Liu L. Cholesterol-lowering effect of garlic extracts and organosulfur compounds: human and animal studies. J Nutr 2001;131: 989S–93S.
41. Liu L, Yeh Y. S-Alk(en)yl cysteines of garlic inhibit cholesterol synthesis by deactivating HMG-CoA reductase in cultured rat hepatocytes. J Nutr 2002;132:1129–34.
42. Yeh Y, Lin R, Yeh S, Evans S. Garlic reduces plasma cholesterol in hypercholesterolemic men maintaining habitual diets. In: Ohigashi H, Osawa T, et al, editors. Food factors for Cancer Prevention. Tokyo, Japan: Springer-Verlag; 1997. p. 226–30.
43. Morihara N, Sumioka I, Moriguchi T, Uda N, Kyo E. Aged garlic extract enhances production of nitric oxide. Life Sci 2002;71:509–17.
44. Steiner M, Khan H, Holbert D, Lin R. A double-blind crossover study in moderately hypercholesterolemic men that compared the effect of aged garlic extract and placebo administration on blood lipids. Am J Clin Nutr 1996;64:866–70.
45. Durak I, Kavutcu M, Aytac B, et al. Effects of garlic extract consumption on blood lipid and oxidant/antioxidant parameters in humans with high blood cholesterol. J Nutr Biochem 2004;15:373–7.
46. Amagase H, Petesch B, Matsuura H, Kasuga S, Itakura Y. Intake of garlic and its bioactive components. J Nutr 2001;131:955S–62S.
47. Kaye A, DeWitt B, Anwar M, et al. Analysis of responses of garlic derivatives in the pulmonary vascular bed of the rat. J Appl Physiol 2000;89:353–8.
48. Neaton J, Wentworth D. Serum cholesterol, blood pressure, cigarette smoking, and death from coronary heart disease. Overall findings and differences by age for 316,099 white men. Multiple Risk Factor Intervention Trial Research Group. Arch Intern Med 1992;152: 56–64.