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RESEARCH ARTICLE

Herb-Drug Interactions: Effects of *Allium sativum* on the Pharmacokinetics of Common Cardioprotective Agents

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ABSTRACT

The present study assessed the pharmacokinetic interactions of garlic (*Allium sativum*) with cardioprotective medications (amlodipine, losartan, enalapril, and carvedilol) in Sprague-Dawley rats. Rats were administered a moderate dose of garlic homogenate (250 mg/kg) for 30 days before a single administration of each drug. Blood samples were drawn at various time points, and High-Performance Liquid Chromatography (HPLC) was used to analyze pharmacokinetic parameters. Garlic reduced amlodipine (*Cmax,* $T\frac{1}{2}$) and increased elimination. Losartan showed a higher Cmax but lower $T\frac{1}{2}$ and clearance. Enalapril and carvedilol had increased *Cmax, AUC0-24*, and $T\frac{1}{2}$ values, with reduced clearance and distribution. These interactions suggest that garlic alters drug bioavailability, necessitating caution in its clinical use. This study offers new information on the herb-drug interactions of garlic with cardiovascular drugs. These results indicate the ability of garlic to increase drug bioavailability and the need for strict adjustment of the dose to avoid toxicity. These findings underscore the need to consider the dietary and herbal effects on drug metabolism in clinical practice.

Keywords: Amlodipine; Losartan; Enalapril; Carvedilol

INTRODUCTION

In recent years, advancements in medical science have led to significant improvements in diagnostic tools and pharmaceutical therapy. These developments have played a major role in reducing mortality rates in developed countries, enabling the management and treatment of various acute and infectious diseases. However, chronic diseases, such as cardiovascular disorders, remain a growing concern, with treatment strategies primarily focused on symptom management rather than eradication. Although advanced medication can arrest the development of these conditions, its failure to cure them has led to a chronic need for their use, which may result in harmful side effects and a reduction in patients' quality of life. Consequently, most patients resorted to complementary alternative medicine, including herbal medicine, to accompany normal therapy. According to World Health Organization (WHO) estimates, almost 80% of the world's population uses alternative medicines and natural health products for their health care.[1]

In chronic diseases, conventional pharmacological therapies tend to depend on synthetic drugs that act on specific disease mechanisms. Herbs, as part of alternative medicine, can provide distinct therapeutic advantages because they are multi-component in nature. These traditional herbal remedies, although used over a long period across the world, vary from mainstream drugs in the sense that they are composed of multiple bioactive compounds that can interact with each other and with contemporary pharmacological agents. The complexity of such interactions poses potential concerns since these interactions may augment or cancel out the action of mainstream drugs. Thus, it is essential to understand herb-drug interactions to avoid side effects and enhance therapeutic benefits.[2,3]

Herbal remedies, such as garlic, which are commonly used, usually operate by pharmacological principles similar to those of orthodox drugs, such as drug-drug interaction mechanisms.[4] Nutritional aspects, particularly those of fruits, vegetables, and herbs, have also been found to affect human health and play a critical role in the prevention and management of different diseases, such as cardiovascular disease (CVD). Findings from epidemiological research indicate that high consumption of these foods is linked

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to decreased mortality due to chronic diseases, such as CVD and cancer.[5,6] This has generated more interest in the ability of phytochemicals, bioactive plant constituents, to prevent or control these disease states. Garlic (*Allium sativum*) has been recognized for its cardiovascular effects, with an increasing amount of evidence for its use in the prevention and treatment of CVD.[7]

Garlic is a member of the Liliaceae family and has been used as both a food and medicine for centuries. Its medicinally beneficial attributes are largely due to organosulfur compounds, but other bioactive molecules such as peptides, steroids, terpenoids, flavonoids, and phenols also play a role in its medicinal activity.[8] These molecules synergize to exert beneficial effects on cardiovascular health, inflammation, and oxidative stress. Garlic also has essential amino acids, glycosides, minerals such as selenium, and an enzyme such as alliinase, which contribute to its medicinal value.[9,10] Studies have shown that garlic not only plays a role in the overall health of the heart but also interacts with standard heart-protecting medications, possibly contributing to its efficiency. For example, research has indicated that taking garlic along with medications, such as captopril[11] and propranolol[12], enhances heart function and survival rates in animal models of heart disease. In addition, garlic has been demonstrated to synergistically interact with calcium channel blockers and diuretics, such as hydrochlorothiazide[13,14], indicating that its enzymatic activity might significantly contribute to increasing the therapeutic effects of these drugs.

This study aimed to investigate the pharmacokinetic interactions between garlic and some of the most widely used cardioprotective agents, namely, amlodipine, losartan, enalapril maleate, and carvedilol. By understanding the impact of pretreated garlic on the ADME of these drugs in animal models, this study will offer valuable insights into how garlic can influence the efficacy and safety of cardiovascular medication. This study has the potential to inform clinical practice regarding the use of herbal remedies in conjunction with pharmacologic therapy so that patients may gain from the complementary action of both forms of treatment without increasing the risk of adverse drug interactions.

MATERIALS AND METHOD

Experimental Animals

In the current study, in-house bred Sprague-Dawley rats weighing 150–200 g were used. The animals were kept in controlled environments with a temperature of 27 ± 2°C, humidity of 55%, and a 12-hour light/12-hour dark cycle. They were fed normal laboratory chow (Amrut Laboratory Feed, Maharashtra, India) and provided water ad libitum, according to the guidelines of the Committee for the Purpose of Control and Supervision on Experiments on Animals (CPCSEA). The experimental procedure was approved by the Institutional Animal Ethics Committee after careful review and approval.

Procurement of Garlic

Garlic bulbs were bought from S.K.R. Market, Bangalore, India. Garlic cloves were peeled, weighed, chopped, and homogenized with distilled water. The homogenate was centrifuged at 20,124 g for 10 min at 4°C. The supernatant was then separated and used at the indicated concentrations. Three concentrations of the garlic homogenate (GH) were prepared: 0.05, 0.1, and 0.2 gm/ml, equivalent to doses of 125, 250, and 500 mg/kg body weight, respectively. Garlic homogenate was prepared within 30 min.

Reagents and Chemicals

Amlodipine besylate and losartan were obtained from Strides Arcolab, Ltd. (Bangalore). Enalapril maleate and carvedilol were obtained from Medreich Pharma (Bangalore). All the solvents employed in the study were of HPLC grade, while other chemicals and reagents employed were of spectroscopic or analytical grade, received from Sigma-Aldrich Chemical Company (St. Louis, MO, USA).

Liquid Chromatography

The High-Performance Liquid Chromatography (HPLC) instrument employed was a Shimadzu HPLC 10AVP LC solution with a Phenomenex Gemini 5μ C18 110 A 250×4.60 mm column. Detection was achieved using UV absorption at 218 nm. The mobile phase for amlodipine was Buffer (3.5 ml TEM, water, o-phosphoric acid pH 3.0) + Methanol + Acetonitrile (10:7:3). The mobile phase for losartan consisted of Solution A (0.1% phosphoric acid in water) and Solution B (acetonitrile, 3:2). The column temperature was maintained at 30°C. Enalapril was analyzed with a flow rate of 0.6 ml/min, and detection was carried out at 265 nm. For carvedilol, the mobile phase consisted of methanol-50 mM KH2PO4 (pH 2.5) (60:40, v/v) at a flow rate of 1.0 ml/min.

Experimental Methodology

For pharmacokinetic interaction studies, a moderate dose of garlic homogenate (250 mg/kg, p.o.) was selected based on previous findings regarding its safety and efficacy.[11–13] Sprague-Dawley rats of both sexes were divided into four groups, each consisting of six animals (Table 1).

Blood samples (0.5 ml) were collected at the following time points: 0, 0.5, 1, 2, 4, 8, 16, and 24 hours after drug administration via retro-orbital vein puncture under ether anaesthesia. Plasma samples were analyzed immediately, and hypovolemia was prevented by intraperitoneal injection of normal saline (0.5 ml normal saline following each blood

sampling. Plasma samples were stored at -20°C until analysis.

Table 1: Groups and their treatment given to rats

Groups (n=6)		Treatment (p.o) GH=250mg/kg
I	I Control	Amlodipine (2.5 mg/kg) single dose
	Treated	GH 250 mg/kg bw 30 days + Amlodipine single dose
II	II Control	Losartan (30 mg/kg) single dose
	Treated	GH 250 mg/kg bw 30 days + Losartan single dose
III	III Control	Enalapril (10 mg/kg) single dose
	Treated	GH 250 mg/kg bw 30 days + Enalapril single dose
IV	IV Control	Carvedilol (2 mg/kg) single dose
	Treated	GH 250 mg/kg bw 30 days + Carvedilol single dose

Extraction Processes

- **Amlodipine:** 250 μl of plasma was combined with 1 M NaOH (250 μl) and 5 ml $CHCl_3$, then centrifuged at 3500 g. The lower layer was evaporated in a test tube using a Univapo vacuum centrifuge. The dried extract was washed with 0.5 ml $CHCl_3$, then dissolved in 70 μL of a solvent mixture (acetic buffer pH 4.5, methanol, 4:6 v/v). A 50 μl sample was injected into the HPLC system.
- **For losartan,** 150 μL of plasma was combined with 150 μL of HPLC-grade acetonitrile and vortexed for 15 seconds. Following centrifugation at 13,000 g, 50 μL of the supernatant was injected into the HPLC system.
- **Enalapril:** Liquid–liquid extraction was used, and plasma samples were made alkaline to pH 4-5 for better recovery. The levels of enalapril and its metabolite, enalaprilat, were quantified by LC analysis.
- **Carvedilol:** Solid-phase extraction was performed using an octyl-silica column. The sample was processed and 20 μL of the eluent was injected into the HPLC system.

Pharmacokinetic Determination

The pharmacokinetic values for amlodipine, losartan, enalapril, carvedilol, and garlic interactions were examined based on linear elimination kinetics. Plasma concentration-time profiles were produced and the area under the curve (AUC0-24) was calculated using the trapezoidal rule. The peak concentration (Cmax) and peak time (Tmax) were measured directly from the data. The elimination rate constant (Ke) and half-life ($T\frac{1}{2}$) were calculated using a semi-logarithmic plot of the data. The clearance (CL) and apparent volume of distribution (Vd) were calculated using the equation **CL = Vd** $\times$ **Ke**, where Vd is the dose divided by the initial plasma concentration, and Ke is the elimination rate constant. The total area under the curve (AUC) was determined as **AUC0-24 + C24/Ke**, where C24 is the plasma concentration at 24 h.

Statistical Analysis

The statistical significance of the findings was tested using one-way analysis of variance (ANOVA) followed by a post-hoc Student's t-test. Results are presented as the mean $\pm$ SEM, and statistical significance was set at $P < 0.05$.

RESULTS

For Amlodipine, garlic lowered Cmax ($P<0.01$) and plasma half-life ($P<0.05$) but increased the elimination rate constant and volume of distribution ($P<0.001$). The clearance increased but was not significant. In the Losartan group, garlic increased the Cmax and reduced the plasma half-life, elimination rate constant, and clearance ($P<0.05$). The volume of distribution also increased. In the Enalapril + Garlic group, Cmax, AUC_{0-24}, and AUC∞ were considerably higher ($P<0.001$), reflective of increased exposure to the drug. The Tmax in the GH-treated group decreased relative to that of enalapril alone, reflecting quick absorption. The Cmax of a 250 mg/kg dose of GH was notably high and showed increased bioavailability. In the presence of GH, the AUC_{0-24} was notably higher, while elimination half-life ($T\frac{1}{2}$) was also extended to 5.2 hours. Moreover, the volume of distribution and clearance decreased drastically, and the elimination rate constant decreased slightly. Cmax, AUC_{0-24}, and AUC∞ were significantly increased ($P<0.001$) for Carvedilol + Garlic. Tmax was decreased slightly, but $T\frac{1}{2}$ was increased in the case of a 250 mg/kg GH dose. Clearance and Vd also decreased significantly, indicating the retention of drugs in the body for a longer time (Table 2).

The plasma concentration profiles of Drug A alone and in the amlodipine-garlic treated group were compared at various time points. A decrease in AUC was observed when garlic was co-administered, indicating that garlic could induce CYP enzymes, thereby increasing drug metabolism. For Losartan (Drug B), the plasma concentration profile reflected a notable increase in AUC in the losartan-garlic-treated group, indicating inhibition of CYP enzymes, which most probably delayed the metabolism of the drug and extended its systemic residence. In the same manner, the plasma concentration profile of enalapril (Drug C) reflected an increase in AUC with garlic administration, indicating that CYP enzyme inhibition is involved in its metabolism, hence increasing drug exposure. In the case of carvedilol (Drug D), a mild increase in AUC was noted in the carvedilol-garlic treated group, which is probably due to the inhibition of CYP enzymes responsible for its metabolism, leading to decreased clearance and increased drug retention.

Table 2: Pharmacokinetic profile of drug amlodipine (Drug A) and losartan (Drug B), enalapril Maleate (Drug C) and carvedilol (Drug D) of both control and garlic-treated group

Parameter	Drug A	Drug A+GH	Drug B	Drug B+GH	Drug C	Drug C+GH	Drug D	Drug D+GH
C_{max} (μg/ml)	490 ± 20	150 ± 10**	0.18 ± 0.008	0.69 ± 0.1*	68.61 ± 7.58	98.32 ± 12.29***	389 ± 56	512.87 ± 41***
T_{max} (hr)	2 ± 0.8	1.8 ± 0.7*	3.8 ± 1.3	2 ± 0.95	3.9 ± 0.8	2 ± 0.98**	4.0 ± 1.3	3.9 ± 0.95
AUC_{0-24} (μg/h.ml)	1648.35 ± 234	835.247 ± 50	1.448 ± 0.75	2.312 ± 1.2	640.43 ± 131	928.832 ± 78***	343.067 ± 175	4424 ± 238***
AUC_{∞} (μg/h.ml)	1886.03 ± 351	99.54 ± 58	1.5186 ± 0.90	0.354 ± 0.1	801.50 ± 34	1184.47 ± 38***	3514.78 ± 126	4666 ± 342***
K_e (h^{-1})	0.0499 ± 0.002	0.074 ± 0.006	0.981 ± 0.08	2.595 ± 1.81*	0.149 ± 0.43	0.133 ± 0.009	0.198 ± 0.02	0.354 ± 0.1
Cl (ml/g.h)	0.2651 ± 0.09	0.4083 ± 0.1	3.2925 ± 1.39	1.957 ± 1.81*	2495.32 ± 162	2110.64 ± 189***	213.38 ± 1.98	160.1 ± 26***
$T_{1/2}$ (h)	13.88 ± 1.2	9.36 ± 1.0*	13.88 ± 1.2	1.957 ± 0.97	4.651 ± 1.2	5.210 ± 1.0*	3.1 ± 1.2	4.2 ± 0.97*
V_d (ml/g)	5.312 ± 2	5.5312 ± 1.2***	3.356 ± 1.56	7.3305 ± 2.4	16747 ± 356	15869.5 ± 210	1077.676 ± 110	975011 ± 54

GH- Garlic homogenate; mean ± SE (n=6), ★P<0.05, ★★, P<0.01 ,★★★, P<0.001 vs control

DISCUSSION

The research aimed to investigate the pharmacokinetic interactions of garlic (*Allium sativum*) with the cardioprotective medicines amlodipine, losartan, enalapril, and carvedilol with the help of experimental models on rats. Herb-drug interactions have become more prominent in the spotlight because they can increase or decrease the efficacy of medicines and produce beneficial or toxic effects. Although herbal remedies are popular, there have been few reports of major interactions, usually because of underreporting or the generally innocuous nature of most herbs. However, there is new evidence that some herbal remedies, such as garlic, can interact with cardiovascular drugs; therefore, more stringent scientific scrutiny is required.

Amlodipine, a calcium channel blocker (CCB), is commonly used to treat cardiovascular disorders. It inhibits transmembrane influx of calcium ions through calcium channels, mainly in the heart and vascular smooth muscles because of the heterogeneity of calcium channels and the 'use-dependence' nature of CCBs to block preferentially the most active channels. Amlodipine is orally well absorbed with peak blood levels after 6–12 hours and is 60–65% bioavailable. It is subjected to intensive hepatic metabolism through CYP3A4, and the majority of its metabolites are excreted through the urine. The terminal half-life of elimination is 35–50 hours, and steady-state plasma levels are achieved after 7–8 days of uninterrupted administration. The pharmacokinetic profile noted in this study is consistent with earlier reports, validating the slow clearance and long half-life of amlodipine, which justifies its once-daily dosing.[15,16]

Notably, although this work indicates that CYP3A4 is the major metabolizing enzyme, amlodipine has been reported to undergo extensive hepatic metabolism with low first-pass metabolism.[16] This apparent discrepancy calls for future research into the possibility of inter-individual variability in metabolism or the effect of co-administered agents, such as garlic.

Losartan, an angiotensin II receptor blocker, is quickly metabolized to its active metabolite E3174, mainly through CYP2C9. E3174 is 10–40 times more potent at the AT1 receptor than losartan and shows noncompetitive antagonism with slow dissociation from the receptor, resulting in an elimination half-life of 6–9 hours.[17] Although this study did not directly examine the pharmacokinetic interaction of garlic with losartan, other pertinent interactions have been reported. For example, grapefruit juice, an inhibitor of CYP3A4, has been shown to decrease the metabolism of losartan to E3174, which may influence its therapeutic effect.[18] Likewise, phenytoin, another CYP2C9 substrate, is a conversion inhibitor of losartan, indicating that drug-garlic interactions may also occur through such mechanisms.[19]

Garlic (*Allium sativum* L.), commonly prized for its medicinal properties, is rich in bioactive constituents such as

S-allylcysteine (SAC) and S-allylmercaptocysteine (SAMC), which are formed through enzymatic conversion of alliin to allicin. Fresh garlic homogenate (GH) was used in this study to represent the most frequently consumed form with high concentrations of bioactive constituents. GH was administered orally for 30 days to ensure maximum SAC and SAMC levels, which have been reported to have antioxidant and cardioprotective effects.[20,21] These results indicated that GH significantly increased the bioavailability of enalapril and carvedilol. The pharmacokinetic profiles of these drugs varied considerably in GH-pretreated animals, possibly because of the modulation of CYP enzymes by garlic. Higher garlic doses resulted in increased allicin levels, which are typically converted into the antioxidants SAC and SAMC. However, at excessively high concentrations, the incomplete metabolism of allicin may lead to disturbances in biochemical and histological parameters. Enalapril, an angiotensin-converting enzyme (ACE) inhibitor, has been shown to have antihypertensive effects similar to those of garlic-derived allicin. Research has confirmed that garlic lowers blood pressure, triglyceride levels, and insulin levels in a model of hypertension, which supports the potential benefits of enalapril with garlic for better management of cardiovascular effects.[21]

Carvedilol, a non-selective beta-blocker with antioxidant activity, also showed a changed pharmacokinetic profile when co-administered with GH. The elevated bioavailability of carvedilol in GH-treated animals indicated that the bioactive components of garlic regulate CYP enzymes, resulting in increased drug absorption and prolonged action. Similar observations have been made with propranolol, another beta-blocker in which GH substantially increased its bioavailability and half-life.[21] Notably, whereas garlic enzyme inhibition can be proposed to account for the enhanced bioavailability of carvedilol, other processes, including stereoselective metabolism and genetic differences in CYP2D6, might also play a role in the inter-individual variability of carvedilol metabolism.[22] These results indicate that the garlic-carvedilol interaction is more complex than enzyme inhibition.

The findings of this study underscore the significance of incorporating herb–drug interactions in clinical settings. The enhanced bioavailability of enalapril and carvedilol implies the possibility of dose reduction through co-administration with GH, which may reduce adverse effects such as hypotension, cough, syncope, hyperkalaemia, and renal impairment without affecting therapeutic effectiveness. However, careful observation of electrolyte balance is required in such patients, especially those taking diuretics, to avoid conditions such as hypokalaemia, hypochloremic alkalosis, and hyponatremia. Dry mouth, thirst, lethargy, confusion, muscle weakness, oliguria, tachycardia, nausea, and vomiting all require immediate electrolyte determination and corrective management. Although these results suggest some positive interactions with GH co-administration, additional research is needed to establish these interactions in human populations. Future studies should investigate the specific mechanisms underlying the effect of garlic on drug metabolism and its clinical significance in patients undergoing long-term cardiovascular treatment.

CONCLUSION

This study postulates that garlic has the potential to modulate CYP enzymes, modifying the metabolism of amlodipine and losartan but enhancing the bioavailability of enalapril and carvedilol. Such interactions can affect drug efficacy and safety, warranting careful monitoring, particularly in cardiovascular therapy, for extended periods. The decreased clearance and extended half-life of enalapril and carvedilol can enhance the toxicity risks due to drug accumulation. However, moderate consumption of garlic may be useful for blood pressure control, especially in myocardial stress, by minimizing potassium excretion. Further studies are required to verify these observations and determine safe dosing regimens in clinical settings.

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