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## Review

# Effect of *Allium sativum* on cytochrome P450 and possible drug interactions

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## SUMMARYY

*Allium sativum* (Family Amaryllidaceae or Liliaceae) is used worldwide for various clinical uses like hypertension, cholesterol lowering effect, antiplatelets and fibrinolytic activity etc. Due to these common house hold uses of *Allium sativum*, as a herbal supplements, and failure of patients to inform their physician of the over-the-counter supplements they consume leads to drug-nutrient interactions with components in herbal supplements. Today these types of interactions between a herbal supplement and clinically prescribed drugs are an increasing concern. *In vitro* studies indicated that garlic constituents modulated various CYP (cytochrome P450) enzymes. CYP 3A4 is abundantly present in human liver and small intestine and contributes to the metabolism of more than 50% of commonly used drugs including nifedipine, cyclosporine, erythromycin, midazolam, alprazolam, and triazolam. Extracts from fresh and aged garlic inhibited CYP 3A4 in human liver microsomes. The in vivo effects of garlic constituents are found to be species depended and the dosing regimen of garlic constituents appeared to influence the modulation of various CYP isoforms. Studies have indicated that the inhibition of various CYPs by organosulfur compounds from garlic was related to their structure also. Studies using *in vitro, in vivo,* animal and human models have indicated that various garlic constituents can be the substrates, inhibitors and or inducers of various CYP enzymes. The modulation of CYP enzyme activity and expression are dependent on the type and chemical structure of garlic constituents, dose regime, animal species and tissue, and source of garlic thus this review throws light on the possible herb drug interaction with the use of garlic.

**Key words:** *Allium sativum*; Cytochrome P450

## INTRODUCTION

Plant products contain bioactive phytochemicals that are finding increasing importance in foods as nutraceuticals and in herbal products as medicinal principles. Herbal products are a very diverse category of plant products and extracts; for example, they are known as by different names in various countries like dietary supplements (United States), natural health products (Canada), phytomedicines (Europe), and traditional medicines (developing countries). In developing countries, the World Health Organization reports that approximately 80% of the world populations rely on traditional medicine, mainly of herbal sources, in their primary healthcare (Chan, 2003). Indications for traditional medicine

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in developing countries include more serious conditions (malaria, AIDS, parasitic diseases, etc.) than herbal products in the developed countries, which are usually indicated as self- care products. The popularity of over-the-counter herbal products, nutraceuticals, and medicinal products from plants or other natural sources has increased dramatically in developed countries and is one of the reasons for adverse reaction. *Allium sativum* (Family Amaryllidaceae or Liliaceae), is a perennial plant that is cultivated worldwide and is used as a spice or medicinal herb it contains 0.1 - 0.36% of a volatile oil composed of sulfur-containing compounds: allicin, diallyl disulfide, diallyl trisulfide, and others. These volatile com-pounds are generally considered to be responsible for most of the pharmacological properties of garlic. Garlic has been used clinically for its cholesterol-lowering activity. Supplementation with commercial preparations providing a daily dose of at least 10 mg allicin or a total allicin potential of 4,000 mcg can lower total serum cholesterol levels by about 10% to 12%; LDL (Low Density Lipids) cholesterol will decrease by about 15%; HDL(High Density Lipids) cholesterol levels will usually increase by about 10%; and triglyceride levels will typically drop 15% (Lau *et al.*, 1983; Norwell *et al.*, 1983; Ernst, 1987; Kendler, 1987). In a 1979 population study, researchers studied three populations of vegetarians in the Jain community in India who consumed differing amounts of garlic and onions (Sainani *et al.*, 1979a,b) Numerous favorable effects on blood lipids, were observed in the group that consumed the largest amount. Garlic is also used in Hypertension (Petkov, 1979; Foushee *et al.*, 1982; Silagy *et al.*, 1994). The meta-analysis from various studies concluded that garlic preparations designed to yield allicin can lower systolic and diastolic blood pressure by 11 mmHg and 5.0 mmHg over a one to three month period. Moreover patients with increased platelet aggregation were given dried garlic preparation containing 1.3% allicin for 4 weeks (Kiesewetter *et al.*, 1991) and it resulted in disappearance of spontaneous platelet aggregation, improved microcirculation of the skin decreased plasma viscosity and blood pressure and blood glucose level. Moreover Garlic preparations standardized for allicin content significantly increased serum fibrinolytic activity in humans (Chutani *et al.*, 1981; Legnani *et al.*, 1993). This increase occurs within the first 6 h after ingestion and continues for up to 12 h.

Compounds such as drugs or nutrients like garlic compete with each other for metabolism by P450s or inactivate P450 enzymes may thereby affect the bioavailability of certain drugs, potentially leading to severe clinical manifestations. Herbal supplements are largely unregulated, and many patients do not inform their physician of the over the counter supplements they consume. Therefore, drug-nutrient interactions with components in herbal supplements and clinically prescribed drugs present an increasing concern. Moreover, It is now established that naturally occurring chemicals, at dietary levels of intake, can modulate the hepatic and extrahepatic expression of cytochrome P450 levels resulting in marked changes in the metabolism of drugs that lead to adverse drug interactions. Changes in cytochrome P450 activity will be particularly relevant in the clinic when they concern drugs with a low therapeutic index, where plasma levels have to be maintained within a narrow concentration range to ensure maximum benefit with the minimum of adverse effects. Elevated cytochrome P450 activity, translated into a more rapid metabolic rate, may result in a decrease in drug plasma concentrations to subtherapeutic levels and total loss of the pharmacological effect. Conversely, suppression of cytochrome P450 activity may trigger a rise in plasma drug levels leading to an undesirable exaggerated pharmacological effect and the appearance of toxic symptoms commensurate with overdose.

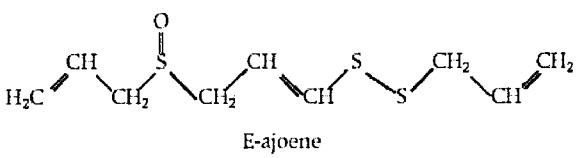
Despite the popular believe that nutraceuticals are safe, these products are pharmacologically active and have inherent risk. Although the risk may be low in many cases where the product is

used alone, of particular interest here are the many interactions that have been reported with enzymes affecting drug disposition. These include CYP 3A4 (Ameer *et al.*,1997; Barnes *et al.*, 2001; Ioannides, 2002; Harris *et al.*, 2003; Zhou, 2003; Huang *et al.*, 2004; Izzo, 2004), 1A1 (Guerra *et al.*, 2000; Sun *et al.*, 2000; Ueng *et al.*, 2002; Gorski *et al.*, 2004; Guo *et al.*, 2004), 1A2 (Guerra *et al.*, 2000; Maliakal *et al.*, 2001; Mathews *et al.*, 2002; Ueng *et al.*, 2002; Harris *et al.*, 2003; Zhou, 2003), 1B1 (Chun *et al.*, 2003), 2A1, 2B (Guerra *et al.*, 2000; Ueng *et al.*, 2002), 2C, 2D6 (Guerra *et al.*, 2000; Foster *et al.*, 2001c, 2002, 2003; Chatterjee *et al.*, 2003; Zhou, 2003), 2E1 (Brady *et al.*, 1991; Kwak *et al.*, 1995; Zuber *et al.*, 2002; Wang *et al.*, 2004), 3A1 (Guerra *et al.*, 2000), 3A5/7 (Foster *et al.*, 2001b, 2002, 2003) 30 ± 32, 4A/F (Brigelius-Flohe *et al.*, 2003), C19 (Hodek *et al.*, 2002), P-glycoprotein (MDR1, ABCB1) (Choi *et al.*,1998; Lin *et al.*, 1999; Budzinski *et al.*, 2001; Deferme *et al.*, 2002; Dresser *et al.*, 2003; Wortelboer *et al.*, 2003), MRP1 (Wortelboer *et al.*, 2003), MRP2 (Wortelboer *et al.*, 2003), cyclooxygenase I and II (Wu *et al.*, 2002), flavin-containing monooxygenease (Foster *et al.*, 2001a), glutathione S-transferase P1-1 (van Zanden *et al.*, 2003), N-acetyltransferase (Ferreira *et al.*, 2003), monoamine oxidase B (Lin *et al.*, 2003), steroid X receptor (Wentworth *et al.*, 2000), and uridine diphosphoglucuronosyl transferase (Venkataramanan *et al.*, 2000).

Phytochemicals in herbal products are not subject to the same level of rigorous testing in animals and humans which is routinely undertaken with synthetic chemicals, so that their ability to perturb xenobiotic-metabolizing enzyme systems is not known and, as a result, possible interactions with medicinal drugs cannot be predicted. This problem is further compounded by the fact that the purity and composition of herbal products is not always assured and may vary considerably among various preparations and between batches, in marked contrast to synthetic drugs. Furthermore, herbal products are particularly popular among older people who are more likely to be receiving conventional medication and are also more sensitive to chemicals.

## CHEMICAL CONSTITUENTS OF GARLIC

When garlic is cut and the parenchyma is destroyed, alliin is the major cysteine sulfoxide liberated (Block *et al.*, 1986). Alliin is acted upon by the enzyme allinase (alliin lyase) to produce allicin by the following reaction. Allicin [S-(2-propenyl)2-propene-1 sulfinothioate or diallylthiosulfinate ] is an odoriferous compound and the main component of freshly crushed garlic homogenates. Garlic also contains S-propylcysteinesulfoxide (PCSO) and S-methylcysteine-sulfoxide (MCSO) (Zieger *et al.*, 1989; Lawson, 1992; Edwards *et al.*, 1994; Calvey *et al.*, 2000). PCSO can generate over 50 compounds depending on temperature as well as water content (Kubec *et al.*, 1999). The action of allinase on the mixture of alliin, S-propylcysteine sulfoxide and S-methylcysteine sulfoxide can produce a number of other molecules including: allyl methane thiosulfinate, methyl methanethiosulfinate and other mixed or symmetrical O thiosulfinates ($R^2 6^2 6^2 R'$), where R and R' are methyl, propyl and allyl groups (Fig. 1). GC/MS analysis of garlic extract has shown the presence of 3-vinyl-6H-1,2-dithiin and 3-vinyl-4H-1,2-dithiin. Other volatile components of garlic are diallyldisulfide (DADS), dimethyltrisulfide (DATS) and sulfur dioxide (Kubec *et al.*, 1999). Methanolic extracts of garlic contain a number of nonpolar compounds, among them optically active compounds E- and Z- 4,5,9- trithiododeca-1,6,11-triene-9- oxide (Block *et al.*, 1986). The E isomer, the major component, is commonly called E-ajoene and has the structure




E-ajoene

**Fig 1.** Chemical structure of E-ajoene.

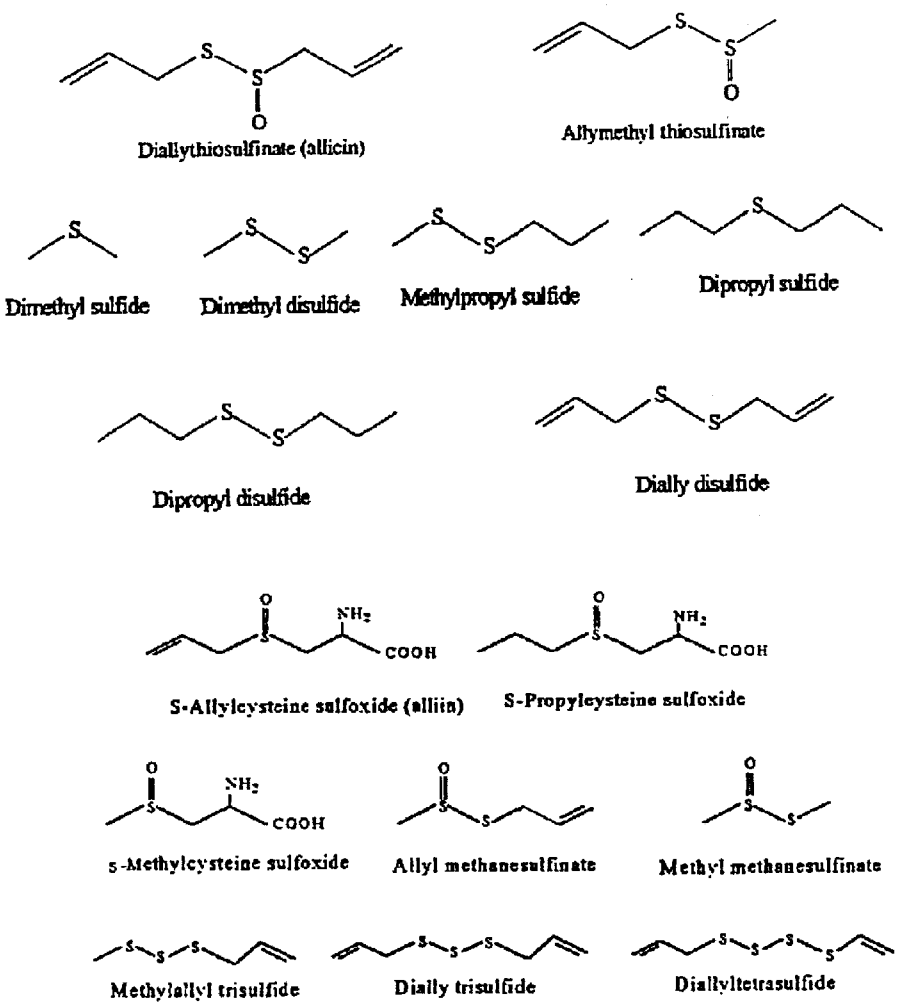



Fig. 2. Other chemical constituents of garlic.

as shown in Fig. 1. Other garlic preparations contain a number of compounds of interest. For example, the major organosulfur compounds in aged garlic extracts are S-allylcysteine (SAC) and S- allylmercaptocysteine (SAMC) (Imai *et al.*, 1994). Garlic oil is enriched in the volative components of garlic such as diallyldisulfide and dimethyl trisulfide (Fig. 2).

## PHARMACOLOGY

### Pharmacokinetics

Pushpendran *et al.* (1980) studied the uptake and metabolic fate in mice of labelled DADS given at a sublethal dosage. They reported that DADS was rapidly absorbed but owing to its low plasma concentrations, it was not possible to determine accurately the related pharmacokinetic parameters. However, the uptake of DADS in the liver was observed only during the first 2 h after dosing, and DADS was transiently detected in plasma and was totally undetectable in the urine, with a maximal concentration in the liver 90 min after i.p. administration. A total of 8% of the radioactivity present in the liver was identified as DADS. In addition, several *ex vivo* and *in vitro* systems have

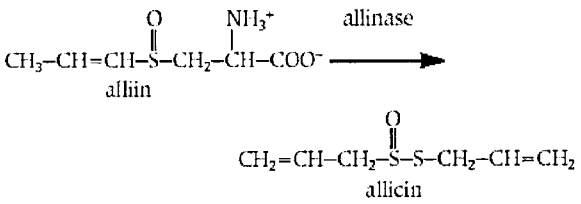



**Fig. 3.** Break down of allin by allinase.

been used to analyse and identify the metabolites of DADS. In a study using an isolated perfused rat liver, DADS appeared to be converted to allylmercaptan (AM) (Fig. 3) (Egen-Schwind *et al.*, 1992a). In primary rat hepatocytes, the metabolites of DADS have been analysed (Sheen *et al.*,1999) and within 120 min the majority of DADS disappeared from the extracellular fluid and was converted to AM and allyl methyl sulphide (AMS) (Fig. 3). The amount of AM was greater than the amount of AMS. Lawson and Wang (1993) reported that DADS was converted to AM in presence of blood before reaching the liver or other organs. All these results suggest that the metabolism of DADS occurred by way of reduction and methylation. Furthermore, under other experimental conditions, the oxidation of DADS has been reported (Teyssier *et al.*, 1999). Previous experiments in our laboratory have demonstrated the oxidation of DADS in allicin in the presence of human liver microsomes (Teyssier *et al.*, 1999). Other naturally occurring organosulphur compounds such as diallyl sulphide (Brady *et al.*, 1991) and dipropyl disulphide (Teyssier and Siess, 2000) have also been shown to be oxidized. Similarly, Mitchell (1988) pointed out the importance of the *S*- oxidation of sulphides by monooxygenases as a pathway in the biotransformation of several sulphur-containing compounds.

The pharmacokinetic behavior of allicin (3-hydroxy-5-methoxy-6-methyl-2-penthyl-4H-pyran-4-one) was investigated. In an experimental animal mice, allicin was quickly absorbed, based on the observation of a maximum level (C max) at 5 min (T max) on peroral administration. The bioavailability of allicin in mice after peroral administration was estimated two times higher than that of alliin (16.5%) (Guo *et al.*, 1990). Allicin is likely metabolized to oxidative substances by an oxidation enzyme such as P-450 after administration. Especially, an alkyl group on the side chain would be easily oxidized. It is suggested that allicin might be metabolized to another kind of compound or transformed to phase II metabolites, such as glucuroide or sulfuric acid conjugates, in a living body.

**Role of cytochrome P450**

Garlic (*Allium sativum* L.) and garlic products generally have been regarded as safe, but conflicting reports in the literature make it difficult to unequivocally establish the clinical efficacy and safety of these products either alone or in the presence of therapeutic products.

*In vitro* studies indicated that garlic constituents modulated various CYP enzymes. CYP3A4 is abundantly present in human liver and small intestine (Shimada, 1994; Rendic *et al.*, 1997) and contributes to the metabolism of more than 50% of commonly used drugs including nifedipine, cyclosporine, erythromycin, midazolam, alprazolam, and triazolam (Soons *et al.*, 1992; Watkins, 1994; Wacher *et al.*, 1995; Rendic *et al.*, 1997; Thummel *et al.*, 1998; Guengerich *et al.*, 1999). In animal studies, organosulfur compounds present in garlic in substantial amounts, such as the lipophilic thioethers allyl sulfides, products of allicin (*S*-allylcysteine sulfoxide) oxidation, have displayed anticarcinogenic activity (Mori *et al.*, 1998), and this prompted research into their mechanism of action, including their effects on the cytochrome P450 system, because of its role in the bioactivation of chemical carcinogens. Treatment of rat with diallyl sulfide, diallyl disulfide, allyl methyl sulfide and allyl mercaptan selectively led to suppression of hepatic CYP2E1 (Brady *et al.*, 1991a; Haber *et al.*, 1994; Kwak *et al.*, 1994; Reicks *et al.*, 1996; Guyonnet *et al.*, 2000; Yang *et al.*, 2001). In contrast, the hepatic expression of CYP2B, CYP3A and, to a lesser extent,

CYP1A was elevated following treatment with diallyl disulfide, diallyl sulfide, dipropyl sulfide and dipropyl disulfide (Dragnev *et al.*,1995; Guyonnet *et al.*, 2000). The decline in CYP2E1 activity was accompanied by a drop in apoprotein levels without change in mRNA levels, suggesting that these compounds were functioning as mechanism-based inhibitors (Kwak *et al.*, 1994; Reicks and Crankshaw, 1996). Indeed, it appears that these organosulfates are metabolized by CYP2E1 to generate metabolites that interact irreversibly with, and impair the activity of, this cytochrome P450 enzyme (Brady *et al.*, 1991b; Jin and Baillie, 1997; Yang *et al.*, 2001). Diallyl sulfide is converted to diallyl sulfoxide, which is further metabolized to the sulfone (Jin and Baillie, 1997). The metabolite responsible for the inactivation of CYP2E1 appears to be an epoxide of diallyl sulfone (Premdas *et al.*, 2000). This cytochrome P450 isoform catalyses the metabolism of volatile halogenated anaesthetics such as enflurane and halothane, and it is feasible that intake of garlic supplements may prolong their anaesthetic effect. It is relevant to point out that, at least in rat, exposure to organosulfates such as diallyl disulfide also stimulates the activities of conjugating enzymes such as glutathione *S*-transferases, UDP-glucuronosyl transferases and quinone reductase (Wargovich *et al.*, 1992; Haber *et al.*, 1994; Guyonnet *et al.*,1999; Munday and Mundsay, 1999).

Extracts from fresh and aged garlic inhibited CYP 3A4 in human liver microsomes (Shimada *et al.*, 1994). A number of garlic preparations (aged, odorless, oil, freezed-dried) and three varieties of fresh garlic bulbs (Common, Elephant, and Chinese) have been examined for their potential to alter cDNA expressed human CYP2C9*1, 2C*2, 2C19, 2D6, 3A4, 3A5 and 3A7 activities by Foster *et al.* using an invitro fluorometric microtitre plate assay (Foster *et al.*, 2001). Small changes in the lipophilic (or polar) nature of the extraction solvents used in assays can greatly alter the results of the assays. A garlic product was extracted with a sequential series of solvents ranging in lipophilicity from hexane (yellowgreen extract) followed by chloroform (brown-green), ethyl acetate (bright red), methanol (orange-red), 55% ethanol (light peach color), and finally water (very faint peach color) (Foster *et al.*, 2001). Results suggesting the presence of fluorescent substances were observed when testing the aliquots of ethyl acetate (169.9%) and hexane (157.0%) extracts against 3A4. The chloroform and methanol extracts also had high inhibition with values of 97.6% and 87.5%, respectively, but the weaker solvents in this sequential extraction protocol, 55% ethanol and water, were less inhibitory (20.6% and 6.3%, respectively). A series of nonsequential extracts also gave high activity in all extracts. As differences in the inhibitory effect of aqueous and methanolic extracts of fresh and aged garlic cloves on 3A4-mediated metabolism were noted previously, the three varieties were extracted under four different conditions. Results varied with variety, but in general, distilled water and phosphate buffer extracts gave the strongest overall suppression effect in isoform-mediated metabolism of marker substrates. It was seen that extracts of fresh garlic, and samples of garlic oil, freeze dried garlic, and aged garlic showed an inhibitory effect on CYP2C9*1, 2C19, 3A4, 3A5 and 3A7 mediated metabolism of a marker substrate, whereas the CYP2D6 was not affected by garlic. Extracts of fresh garlic stimulated CYP2C9*2 metabolism of the marker substrate. Various organosulphur compounds were considered responsible for the modulating effects on CYP. For example, diallyl sulfide (DAS, a major flavor compound from garlic) is sequentially converted to diallyl sulfoxide (DASO) and diallylsulfone (DASO2) mainly by CYP2E (Teyssier *et al.*, 1999). DAS, DASO, and DASO2 are all competitive inhibitors of CYP2E. In addition, DASO2 is a suicide inhibitor of CYP2E, forming a complex leading to autocatalytic destruction (Jin and Ballie, 1997). The organ sulfur compounds 4-4'-dipyridyl disulfide, di-n-propyl disulfide and DAD were also potent competitive inhibitors of Coumarin 7-hydroxylase(CYP1A2) with a Ki value of 0.06,

1.7 and 2.1 μM respectively Thus could result in the food drug interaction with Coumarin derivatives (Fujita and Kamataki, 2001).

The *in vivo* effects of garlic constituents was found to be species depended. *In vivo* studies in the mouse indicated that garlic administration increased CYP2E and 1A2 levels, although it did not change the total content of hepatic CYP (Kishimoto *et al.*, 1999) however, several studies in the rat indicated that the administration of garlic constituents (e.g. DAD decreased the CYP2E activity and /or protein level, but increased or did not alter the CYP1A2 levels, although it did not alter the CYP1A2, CYP2B1 and CYP3A activities and or protein levels (Dalvi, 1992; Haber *et al.*, 1994, 1995) for example, treatment of rat with DAD increased the activities of CYP2B1/2, but decreased that of the nitrosodimethylamine demethylase (CYP2E) and protein level of CYP2E in the liver as determined by western blotting analysis (Haber *et al.*, 1995) similarly treatment of rats with DAS, DADS, or ally methyl sulfide caused a significant decrease in the activity of p-nitro phenol hydroxylase (CYP2E1 And CYP2E 1 protein levels but no change in benzphetamine N- demethylase(CYP2B) and ethoxyresorufin O-deethylase(CYP1A2) activities (Reicks and Crankshaw, 1996) similar to the rat, acute oral administration of the garlic oil extract and DAS in human volunteers caused insignificant decrease in CYP2E activity using chloroxazone as probe substrate (Loizou and Cocker, 2001). The dosing regimen of garlic constituents appeared to influence the modulation of CYP isoforms. A single dose of garlic oil in rat resulted in a significant inhibition of hepatic CYP catalyzed reactions including aminopyrine N-demethylase (CYP2C) and aniline hydroxylase (CYP2E) activity, but administration of garlic for five days led to a significant increase in the hepatic CYP activities (Fitzsimmons and Collins, 1997). Short or long term administration of rats with garlic constituents (e.g. DAS, DAD, dipropyl sulfide, and Diallyl trisulfide) resulted in a decreased activity and expression of CYP1A2 and CYP2B1 (Dalvi, 1992; Haber 1994, 1995). However, long term administration (e.g. 6 to 7 weeks) led to an enhanced activity and expression of CYP1A2 and CYP2B1 at mRNA and protein levels (Sheen *et al.*, 1999a,b) except that dipropyl disulfide significantly increased the activity of CYP2E (Guyonnet *et al.*, 2000). The Expression of CYPA at protein and mRNA levels was enhanced by DAS, DAD and diallyl trisulfide, although its activity was not altered (WU *et al.*, 2002). In addition, treatment of rats with garlic constituents also modulated hepatic antioxidant enzyme activities. For example, garlic oil and DAD inhibited glutathione peroxidase activity; whereas DAD and DAS enhanced the glutathione reductase activity (Sheen *et al.*, 1999a,b).

Studies have indicated that the inhibition of various CYPs by organosulfur compounds from garlic was related to their structure. An increase in the number of sulfur atoms in the molecule resulted in an enhanced effect on the inhibition on CYP2E and induction of CYP1A2 and CYP2B1 (Wu *et al.*, 2002) compounds containing methyl groups had little or no effect on CYPs (Siess *et al.*, 1997) compounds with two propyl groups or two allyl groups provoked a pleiotropic response on drug metabolizing enzymes which may be inhibitory or inductive. Dipropyl sulfide, and DAD induced CYP1A1 and CYP2B1 activity, but decreased that of CYP2E1 and CYP3A4. These modifications of enzyme activities were accompanied by an increase of protein levels of CYP2B1 and 2B2, and a decrease in CYP2E1 (Siess *et al.*, 1997).

Recent studies indicated that oral administration garlic preparation for three weeks in humans decreased the plasma AUC and Cmax of the protease inhibitor saquinavir, a known substrate for CYP3A (Fitzsimmons and Collins, 1997; Piscitelli *et al.*, 2001) This may be caused by induction of CYP3A4 in the gut mucosa, resulting in diminished systemic concentrations. However, as saquinavir is also a known substrate of PgP, increased efflux by induction of PgP cannot be excluded (Kim *et al.*,

1998). However, administration of garlic for four days did not significantly alter the pharmacokinetics of ritonavir, another HIV-1 protease inhibitor that is a substrate of CYP3A4 (Choudhri *et al.*, 2000). These negative results may be explained by the short-term garlic administration. Ritonavir, but not sequinavir, is also both inhibitor and inducers of CYPs, so that single doses do not reflect concentrations at steady state, which may also affected the results. Markowitz *et al.* (2003) reported contradictory findings with no effect on 2D6-mediated metabolism of dextromethorphan and 3A4-mediated metabolism of alprazolam with no significant differences in pharmacokinetic parameters at baseline and after garlic extract treatment. Foster *et al.* (2001a) demonstrated that garlic had an antagonistic or synergistic effect on antibiotics, indicating that herbal effects on host drug disposition mechanisms may also affect response to antibiotics. Ward *et al.* (2002), using *Staphylococcus aureus* ATCC 29,213 or *Escherichia coli* ATCC 25,922 as the indicator organisms, showed that all garlic products increased the MIC of norfloxacin-sensitive organism to greater than fourfold above sbaseline. With *Escherichia coli* ATCC 25,922, the greatest product-antibiotic interaction was with the ampicillin-sensitive organism. Garlic, Echinacea, and zinc products all caused large increases in the MIC to ampicillin over baseline values.

Botanicals such as herbal products and nutraceuticals are often regarded as low risk because of the long history of human use, their natural origin, or simply because the concentration of active principles is lower than conventional drugs. All products have risk when combined with other products, even those that when used traditionally may be considered safe. Now a days literature report of adverse drug events and clinical studies with herbal products are increasing. All products have risk, with risk generally increasing in patients who have confounding health, genetic, and environmental factors, including polypharmacy. Health care professionals should inform their patients on risk that may be associated with combined use of drug and herbal products containing active constituents of garlic.

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