Review Article

Is Garlic a Safe Remedy: An Overlook Herb-Drug Interaction?

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ABSTRACT

Objective- Traditional systems of medicine are mostly based on the use of herbs for the treatment of various diseases. Studies reveal that herbal products are more popular among the common people due to its fewer side effects, easy availability and low cost. Hence, these herbs are used throughout the world as preventive and curative medicines. However, these important herbs possess active chemical moiety that are responsible for their medicinal property. Thus, in reality, there remains a possibility of herb drug interactions when these are consumed along with other medicines. Unfortunately the concept of herb drug interaction is poorly known among the clinicians as well as common population. Even the scientific world was unable to explore the clinical relevance of herb drug interaction. Studies are being conducted throughout the world to investigate the effects of herb drug interaction, to ensure safety of therapy. In this present article effect of garlic was evaluated when used concurrently with other medicines.

Method- Documentations from original articles and case reports were obtained from various databases and were compiled for this present article.

Result- Total 24 articles documented various interactions of garlic with other synthetic medicines. Anticoagulants, antihypertensives, antiviral, anticancer, antidiabetic, antitubercular drugs were the major classes of drugs that were found to interact with garlic.

Conclusion- Therefore, case reports on adverse reactions due to the intake of garlic posed a threat to the safety of this herb. These findings initiated for exploration of the drugs that may interact with garlic and cause adverse reactions in patients.

Keywords: Adverse Drug Reactions, Garlic, Herb-drug interactions.

INTRODUCTION

Any plant or plant product with medicinal value, used as food or as flavoring agent or medicine are referred to as herbs.[1] Herbs have been known to be used as traditional medicines, in various diseases, from ancient times, in many parts of the world including India. The use of herbal medicine is cost effective with fewer side effects as compared to the modern medicines. According to the estimate given by World Health Organization (WHO), 80% of the world population is dependent on alternate system of medicine and natural health products.[2] One United States (US) based survey depicted more than 50% US adults, on a regular basis, consume herbal medicines and dietary supplements.[3] The anticancer, antimicrobial, antidiabetic, hepatoprotective, nephroprotective effect of various herbs like neem, tulsi, turmeric, ashwagandha, garlic, etc., is well known and has been established through various scientific researches.

Garlic (*Allium sativum*) is used by many populations to impart flavor and aroma in food. Apart from this, garlic also has numerous health benefits and is used in the prevention and treatment of different ailments since ancient times. Garlic was used in the treatment of diarrhea by the early Egyptians and its medicinal importance was portrayed on the walls of ancient temples and papyrus, dating back to 1500 BC. Greek physicians Hippocrates and Galen also used this herb for the treatment of intestinal disorders. Since 2700 BC, Chinese use garlic to treat headache, flu, sore throat and fever. Use of garlic in weakness, cough, skin disease, rheumatism, haemorrhoids etc., was also mentioned in the Vedas, the Indian holy book.[4]

Recent *in vitro* and *in vivo* researches have highlighted the active components in garlic responsible for these medicinal values. Different sulphur compounds present in garlic, γ-glutamyl-S-allyl-L-cysteines and S-allyl-L-cysteine sulfoxides (alliin), allicin, diallyl sulfide, ajoenes owe antibiotic, antimycotic and antibacterial properties. Allicin and other garlic components also possess antihypertensive, hypolipidaemic and hypocholesterolemic properties. Anti-thrombotic effect has been shown by ajoenes. These sulfur compounds in garlic also have anticarcinogenic properties.[5] These active chemical ingredients present in these herbs increase the possibility of interaction of these herbs with the conventional medications, leading to herb drug interactions, thereby causing serious adverse reactions. Drug interaction is defined as "the pharmacologic or clinical response to the administration of a drug combination different from that anticipated from the known effects of the two agents when given alone".[6] Thus garlic drug interaction refers to the effect of the active molecules in garlic on commonly used synthetic drugs. In 1979, it was reported that milk and various dairy products interfere with the absorption of tetracyclines.[7] In 1989, clinicians found grape juice impairs the metabolism of calcium channel blockers, felodipine and nifedipine.[8] Thereafter, case reports from different parts of the world suggested that herb drug interactions may be responsible for altering the efficacy of the synthetic medicines.

Knowledge on herb drug interactions is thus essential to optimize the therapeutic success. The present article evaluated the evidences of garlic drug interactions documented as publications. This review evaluated the reports on garlic drug interactions, the proposed mechanism of these interactions and the consequences of the interactions in brief. Awareness in the society among the common people is very essential in order to reduce the sufferings

from the adverse effects of these herb drug interactions.

METHODS

Evidences were obtained from various original articles and case reports in English language, utilizing different databases and search tools Google/Pubmed from last twelve years. The keywords used for searching were garlic interactions/garlic drug interactions/herb drug interactions. The data obtained from these documentations were classified based on the models of studies, on the different classes of drugs involved in interaction and on the different forms of garlic that were investigated. The proposed mechanisms of these interactions were also covered and the severity of these interactions was highlighted.

RESULTS

Total 24 articles were obtained that reported on interaction of garlic with different drugs, *in vivo*, *in vitro* or in human. Table 1 revealed the list of different drugs, along with their classifications that were reported in human to interact with different forms of garlic. Tables 2 and 3 enlisted the different reports documented *in vivo* and *in vitro* systems respectively. Various forms of garlic were used in different studies and several classes of drugs were found to interact with garlic. The proposed mechanisms of these interactions were also enlisted. The possible mechanisms of interaction were found to be either pharmacodynamic or pharmacokinetic or both. The effects of these interactions were also documented in the tables 1, 2 & 3.

Most of these reported articles (44%) were based on *in vivo* investigations, followed by 32% case reports. Figure 1 highlighted the distribution of different types of reports that were documented as publications.

Figure 2 depicted the distribution of different forms of garlic used in these studies. The most commonly reported form was garlic as supplement, in the form of tablets (44%), while others were garlic homogenate or aqueous extract (16%) and allicin (allyl 2-propenethiosulfinate or diallyl thiosulfinate) (8%). 12% of these studies used aged garlic extracts (AGE), *i.e.,* raw garlic dipped in 15-20% ethanol for about 20 months. Garlic oil, used in few studies, is prepared by steam-distillation method and composed of the different sulfur compounds present in garlic.

Eight different classes of drugs were found to interact with garlic (Figure 3). Among the different classes of drugs that interacted with garlic, most significant were anticoagulants, 32% followed by antihypertensives, 28%.

The proposed mechanism of garlic drug interaction can be classified as pharmacodynamic or pharmacokinetic or both. 72% of the garlic drug interactions were pharmacokinetic in nature whereas pharmacodynamic interaction accounted for 28% (Figure 4).

DISCUSSION

Adverse reactions of synthetic medications are often encountered by the clinicians.[32-33] Though in alternative treatment herbs and dietary supplements are utilized by the common people, but till more information require for their safety issues.[34] Apart from its use as spices, the health-promoting and medicinal values of garlic encouraged its use throughout the world.[35] Anti-tumour, anti-microbial, cardio-protective, immunomodulatory effects of garlic was established and thus it is used as a preventive and curative medicine in various diseases.[36-38] Because of these beneficial effects often garlic is consumed along with other synthetic drugs prescribed by physicians.[39] Adverse effects of garlic when

concomitantly used with other synthetic drugs, thus, pose a threat to the safety of patients. A case report in 1990 suggested significant platelet dysfunction in patient caused due to the excessive use of garlic.[40] Present article focused on the garlic drug interactions that were documented as case studies, clinical trials, *in vivo* or *in vitro* studies and also highlighted different classes of drugs that were more susceptible for interaction with garlic with the possible mechanisms.

The 24 different documented interactions that were enlisted in this review, most of them were from *in vivo* studies and few from cases studies or clinical trials. Anticoagulants, antihypertensives, antiviral, anticancer, antidiabetic, antitubercular drugs were reported to interact with garlic. The adverse effects were nephrotoxicity, gastrointestinal toxicity, increased blood clotting and drug toxicity due to increased drug concentration.

Literature revealed that garlic and its different components, alliin, allicin, allixin, allyl methyl thiosulfonate, 1-propenyl allyl thiosulfonate, γ-L-glutamyl-S-alkyl-L-cysteine, S-allylcysteine, S-allylmercaptocysteine etc. are involved in the regulation of drug-metabolizing enzymes and drug transporters. Cytochrome P450 (CYP450) is a family of isoenzymes, like CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP2E1 and CYP3A4 present in the smooth endoplasmic reticulum of liver and kidney are mainly responsible for metabolism of drug and drug biotransformation.[41] Moreover, ATP-assisted efflux pumps transporter proteins mainly, P-glycoprotein (P-gp) and multidrug resistance associated protein-2 (MRP-2) help in drug molecules mobilisation.[42] Any modification of the isoforms of CYP450 through one or more chemical moieties of garlic may be the reasons of pharmacokinetic interactions. Garlic is found to competitively inhibit the activity of CYP3A4 in drug metabolism. P-gp and MRP-2 are also found to be activated by garlic and its components.[43] Fresh and aged garlic extracts are found to inhibit CYP2C9, CYP2C19 and CYP3A, as well as P-gp activity. Diallyl disulfide, one of the garlic components, inhibits CYP2A6 and CYP2E1 activity. Organosulfur components of garlic, on the other hand, increase the expressions of CYP1A1, CYP2B1 and CYP3A1. Allicin and aged garlic extracts inhibit CYP3A4 activity.[44] Interaction of garlic with antihypertensives, antidiabetics is mostly pharmacodynamic whereas that with anticoagulants, antivirals, antituberculars is pharmacokinetic. Decreased activity of CYP3A4 and induction of P-gp by garlic is responsible for increased clearance and decreased bioavailability of antiviral drug saquinavir. *In vivo* studies also revealed garlic inhibited the metabolism of atorvastatin, a substrate for CYP3A4, which in turn increased the body concentration of the drug and led to adverse reactions.[45] Concomitant use of garlic and isoniazid also decreased the bioavailability of the drug through pharmacokinetic interactions. Chlorzoxazone is metabolized by CYP2E1 enzyme that is inhibited by garlic oil. Hence use of garlic oil along with Chlorzoxazone decreased its metabolism and increased its serum concentration.[18] Warfarin, the most widely used anticoagulant is metabolized by a number of cytochrome P450 enzymes like CYP2C9, CYP1A2, CYP3A4, CYP2C19. Garlic and its various components are known to inhibit most of these CYP450 enzymes and thus affecting the plasma concentration of warfarin. This is the main cause for warfarin interaction with garlic.[46]

Thus garlic being a well-known and widely used herb, its interaction with synthetic drugs that are commonly used by the patients, is of prime importance. Further investigations are essential to standardize

the therapeutic regimens of these interacting drugs. The safe dosage range for garlic also needs to be examined to avoid unwanted affects. Clinicians should document any herb drug interactions they witness, for the benefit of therapy.

CONCLUSION

Use of various herbal medications, known since ancient times, is popular among different populations for treatment of diseases. But often patients are unaware about the combined effect of herbs and synthetic drugs. Effects of garlic on synthetic drug actions were elaborated in this article. Creating awareness among the common people about interactions of drugs and garlic is very essential and justified as this would not only lower the chance of adverse events but also enhance the therapeutic success ensuring safe and effective medication.

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Conflict of Interest

Authors declare they have no conflict of interest

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Table- 1: Garlic drug interactions with their proposed mechanism and effect in human

Sl. No.	Drugs	ATC Classification [Code]	Proposed Mechanism	Study Model (Human)	Garlic-drug interaction	Year of Publication [Reference]
1.	Warfarin	Antithrombotic [B01AA03]	Pharmacokinetic interaction	Human (case reports)	Increased clotting time	2012[9]
2.	Warfarin	Antithrombotic [B01AA03]	Pharmacokinetic interaction	Human (case reports)	Increased clotting time	2013[10]
3.	Warfarin	Antithrombotic [B01AA03]	Pharmacokinetic interaction	Human (case reports)	Increased clotting time	2008[11]
4.	Warfarin	Antithrombotic [B01AA03]	Pharmacokinetic interaction	Human (case reports)	Increased clotting time, Low platelet aggregation	2004[12]
5.	Warfarin	Antithrombotic [B01AA03]	Pharmacokinetic interaction	Human (case reports)	Increased clotting time	2007[13]
6.	Aspirin	Analgesic [N02BA01]	Pharmacokinetic interaction	Human (case reports)	Increased clotting time	2007[13]
7.	Fluindione	Antithrombotic [B01AA03]	Unknown	Human (case reports)	Increased clotting time	2003[14]
8.	Ritonavir	Antiviral [J05AE03]	Pharmacokinetic interaction	Human (case reports)	GI toxicity	2003[15]
9.	Saquinavir	Antiviral [J05AE03]	Pharmacokinetic interaction	Human (Clinical trial)	Decreased plasma concentration	2002[16]
10.	Docetaxel	Antineoplastic [L01CD02]	Pharmacokinetic interaction	Human (Clinical trial)	Reduction in the clearance of docetaxol	2010[17]
11.	Chlorzoxazone	Muscle relaxant [M03BB03]	Pharmacokinetic interaction	Human (Clinical trial)	Increased serum concentration	2005[18]

Table-2: Garlic drug interactions with their proposed mechanism and effect *in vivo*

Sl. No.	Drugs	ATC Classification [Code]	Proposed Mechanism	Study Model (Animal)	Garlic-drug interaction	Year of Publication [Reference]
1.	Dipyridamole	Anticoagulant [B01AC07]	Pharmacokinetic interaction	*In vivo* (Rats)	Decreased plasma concentration	2011[19]
2.	Atenolol	Beta blocker [C07AB03]	Pharmacodynamic interaction	*In vivo* (Rats)	Cardioprotection	2014[20]
3.	Nifedipine	Calcium channel Blocker [C08CA05]	Pharmacokinetic interaction	*In vivo* (Rats)	Increased plasma concentration	2011[21]
4.	Captopril	Angiotensin-converting-enzyme inhibitor [C09AA01]	Pharmacodynamic interaction	*In vivo* (Rats)	At low dose synergistic effect	2010[22]
5.	Propanolol	Beta Blocker [C07AA05]	Pharmacodynamic interaction	*In vivo* (Rats)	At low dose synergistic effect	2010[23]
6.	Hydrochlorothiazide	Diuretics [C03AA03]	Pharmacokinetic, Pharmacodynamic interaction	*In vivo* (Rats)	Increase in bioavailability and half-life, decrease in clearance and elimination rate, Synergistic effect	2009[24]

7.	Propranolol, Hydro-chlorothiazide and Captopril	Beta Blocker [C07AA05], Diuretics [C03AA03] & Angiotensin-converting-enzyme inhibitor [C09AA01]	Pharmacodynamic interaction	*In vivo* (Rats)	Alteration of hypo-lipidemic effect of Garlic	2009[25]
8.	Isoniazid and Rifampicin	Antimyco-bacterials [J04AC01 & J04AB02]	Pharmacokinetic interaction	*In vivo* (Rabbits)	Decreased the bio-availability of isoniazid	2006[26]
9.	Atorvastatin	Lipid modifying agents [C10AA05]	Pharmacokinetic interaction	*In vivo* (Rats)	Nephrotoxicity	2010[27]
10.	Glibenclamide	Antidiabetic [A10BB01]	Pharmacodynamic interaction	*In vivo* (Rats)	Increased hypo-glycemic effect	2013[28]

Table- 3: Garlic drug interactions with their proposed mechanism and effect *in vitro*

Sl. No.	Drugs	ATC Classification [Code]	Proposed Mechanism	Study Model (Animal)	Garlic-drug interaction	Year of Publication [Reference]
1.	Saquinavir and darunavir	Antiviral [J05AE01 & J05AR14]	Pharmacokinetic interaction	*In vitro* (Caco-2 cell)	Decreased absorption	2010[29]
2.	Saquinavir and Darunavir	Antiviral [J05AE01 & J05AR14]	Pharmacokinetic interaction	*In vitro* (Rat hepatocytes)	Inhibition of saquinavir efflux, increase in darunavir efflux	2010[30]
3.	Ritonavir	Antiviral [J05AE03]	Pharmacokinetic interaction	*In vitro* (MDR1-MDCK cells)	Inhibition of ritonavir efflux	2004[31]

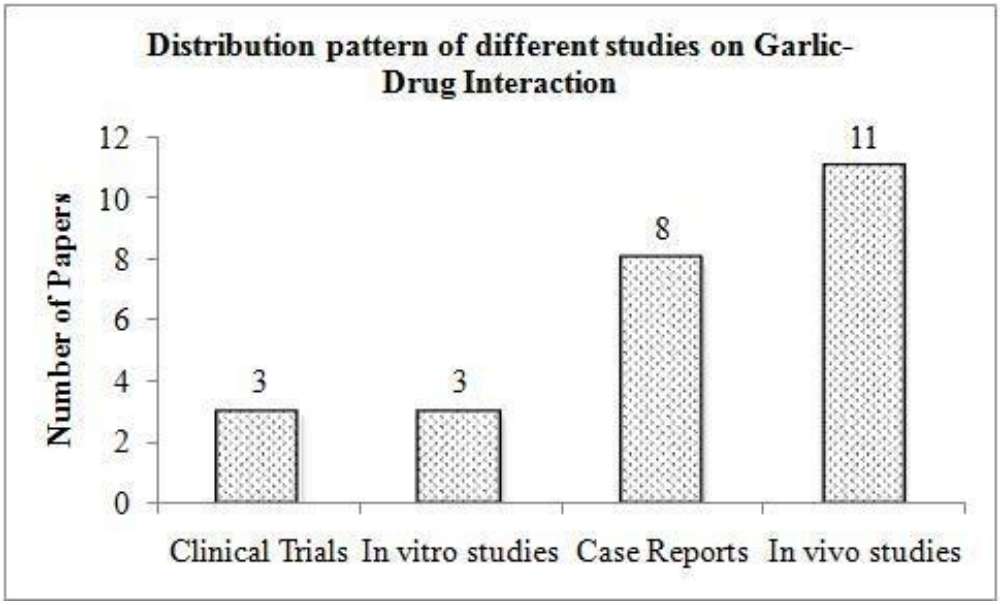

Fig-1: Distribution of different types of published reports on garlic-drug interactions

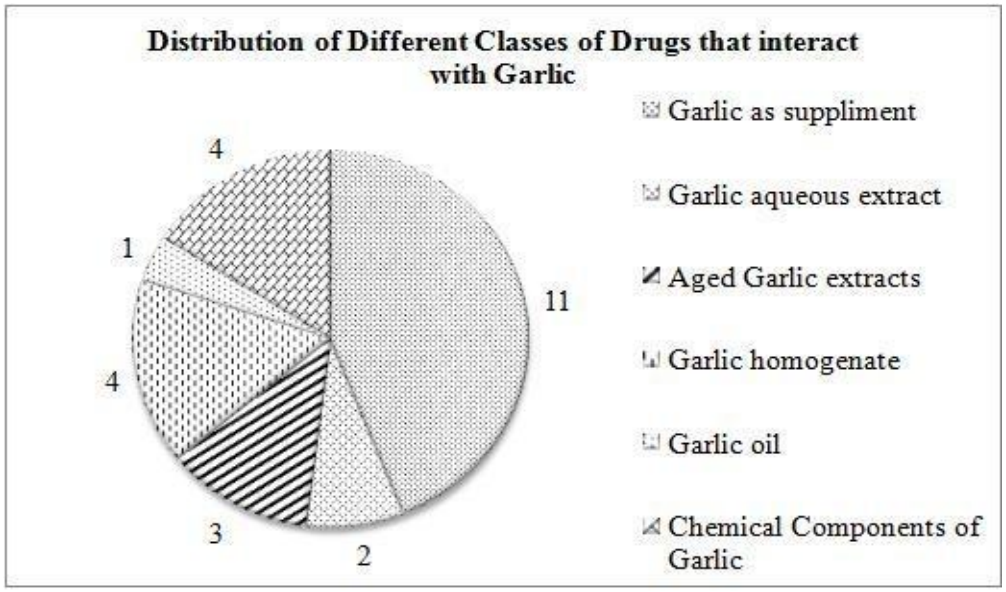

Fig-2: Distribution of different forms of garlic reported in Literature

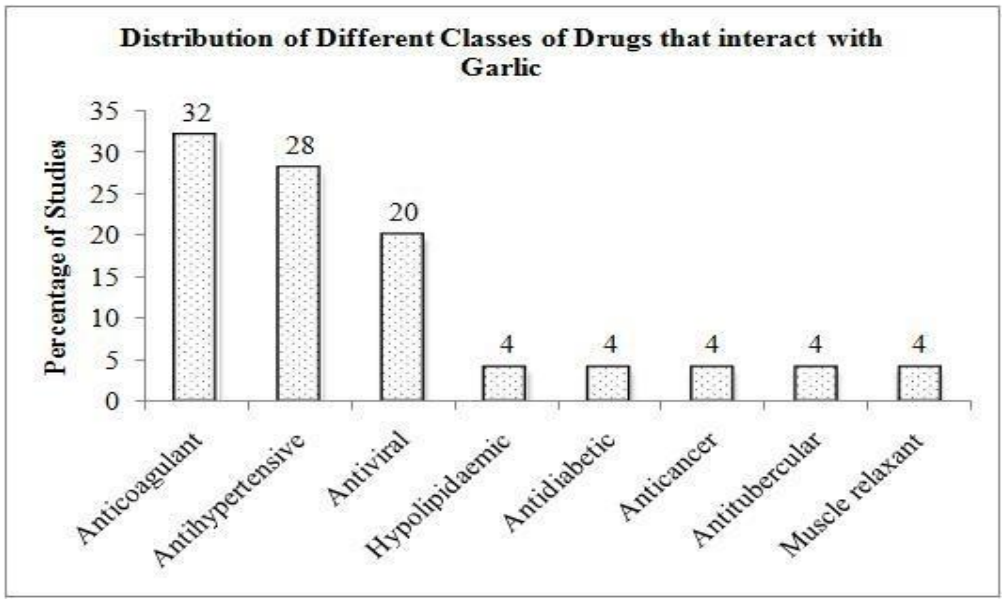

Fig-3: Distribution of different classes of drugs interacting with garlic

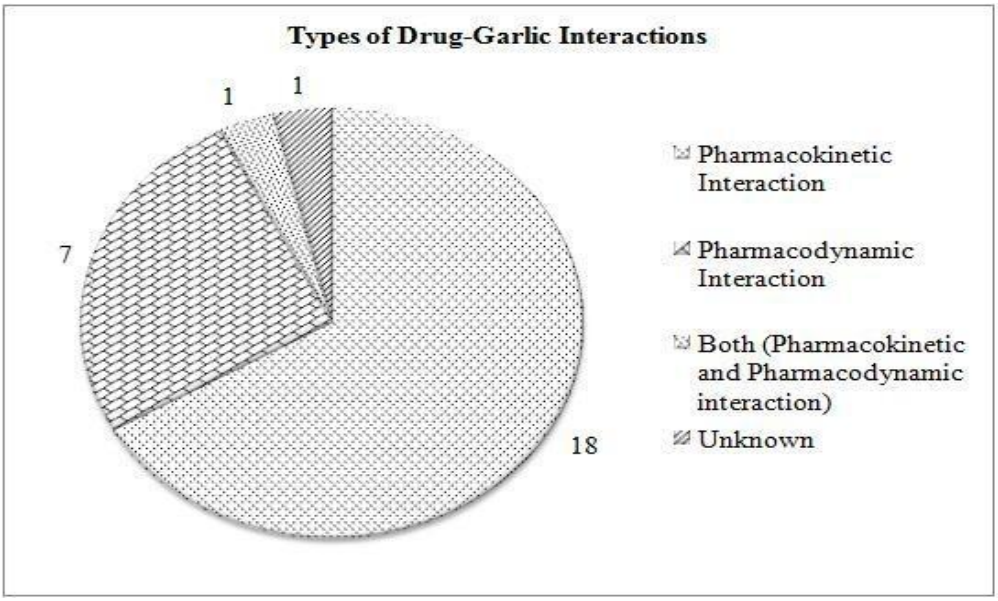

Fig-4: Distribution of proposed mechanisms of garlic-drug interactions