Garlic–drug interactions

Garlic has been valued for centuries for its culinary and medicinal properties. The Herbal Medicines Research and Education Centre **assesses the quality of the interaction literature to guide informed clinical use.**

Garlic (*Allium sativum*) is one of the most popularly used herbal supplements with putative antibacterial, antiparasitic, anti-atherogenic, antilipidaemic, antihypertensive and immunostimulant activities.[1] Admonition against the concomitant use of garlic with antithrombotic drugs is replete in the professional literature. These reports appear theoretically derived, based on experimental pharmacological activity. Few case reports describing garlic–drug interactions exist and are inadequately described. Clinical investigations have emerged to illuminate interactions with anti-retroviral drugs. Our series continues by appraising the evidence for garlic–drug interactions with particular emphasis on their clinical significance.

Antithrombotics

Increased INR and clotting times were attributed to the use of commercial garlic products by two patients previously stabilised on warfarin.[2] A review reported several practitioners' observations of increased INR and prothrombin times from garlic and warfarin co-administration in patients previously stabilised on the drug.[3] These reports lack adequate details for evaluation. Interestingly, any change in INR is unexpected, in that garlic constituents are not expected to affect the clotting cascade, only platelets.[4] More plausible is that garlic may augment warfarin activity.[5] One case of spinal epidural haematoma[6] and two cases describing post-operative bleeding complications[7,8] have been associated with garlic ingestion. Inadequately recorded details limit the utility of these adverse event reports.

The antithrombotic potential of garlic, garlic extracts and oils has been well documented in experimental studies.[1,9] Several mechanisms for the anti-aggregatory activity have been elucidated *in vitro*, including inhibition of collagen-, ADP-, arachidonic acid-, epinephrine-, and thrombin-induced platelet aggregation.[9] Although allicin is considered the primary contributor to antiplatelet activity, ajoene (a secondary degradation product of alliin), has demonstrated dose-dependent and reversible inhibition of platelet aggregation *in vitro* and *in vivo*. However, ajoene may not be present in many garlic preparations.[1] Adenosine, alliin, vinydithiins, dialkyoligosulphides, and methyl allyl trisulphide (a minor garlic constituent) have also demonstrated antiplatelet effects.[9] The antiplatelet and fibrinolytic activity of fresh garlic, garlic oil and garlic powder have been clinically investigated in healthy volunteers and in artherosclerotic, hyperlipidaemic and hypercholesterolaemic patients.[1,9]

Antiretrovirals

In an open-label, crossover experiment, acute garlic supplementation (Natural Source Odourless Garlic Life Brand; 2 x 5 mg soft gelatin capsules equivalent to 1 g fresh garlic daily for 4 days; allicin undetected) to 10 healthy volunteers resulted in a slight (but not significant) reduction in the ritonavir concentrations after a single dose. The complexities of both ritonavir and garlic metabolism could not be separated in this study, particularly following the acute garlic dosing regimen.[10]

Chronic garlic supplementation (two GarliPure caplets, Natrol, daily for 21 days; dose equivalent 2 x 4 g cloves garlic daily; 4.64 mg/caplet allicin and 11.2 mg/caplet allicin) in 10 healthy volunteers was associated with a significant reduction in saquinavir plasma concentrations. Moreover, pharmacokinetic values returned only to 60–70 per cent of baseline following a 10-day washout period. An interesting bimodal distribution of the effect of garlic was observed. Garlic was proposed to have an effect on the bioavailability, as opposed to the systemic clearance, of saquinavir that was probably mediated by changes in CYP450 and/or P–glycoprotein (P–gp) in the gut mucosa.[11]

Hypoglycaemics

Reduced glucose levels in a female taking chlorpropamide and a curry containing garlic and karela (*Momordica charintia*) has been reported[12,13]; however, based on the available information, cannot be causally attributed to garlic. Hypoglycaemic activity has been documented for an alcoholic garlic extract

Garlic–drug interaction reports		
Level of evidence	**Drug/mechanism**	**Clinical significance**
Controlled clinical trial in patients	• n/a	• n/a
Controlled clinical trial in healthy subjects	• n/a	• n/a
Open-label human study	• Ritonavir/saquinavir • Cytochrome P450 • No effect	• Paracetamol • Decreased drug levels • Inhibition of 2E1, no effect on 3A4 and 2D6 isozymes
Case reports or series	• Warfarin • Unclear	• Chlorpropamide • Loss of glycaemic control
Animal studies	• Paracetamol • Hepatoprotective effects	• Cytochrome P450 • Inhibition/induction CYP450; 3A, 2B induction; 2E1 ihibition
In-vitro studies in animal or human tissue	• Cytochrome P450 • Inhibition of various CYP isozymes	• P–gp • Little to moderate effect

following oral administration to rabbits (dose equivalent to 50 g dry garlic powder). The hypoglycaemic effect was 59 per cent of the activity of 500 mg tolbutamide.[1,14]

A reduction in blood sugar concentrations and an increase in insulin have been observed following administration of allylpropyl disulfide (a garlic constituent) to healthy volunteers. However, garlic has reportedly exhibited hypoglycaemic actions in diabetic patients but not in healthy subjects.[1] The hypoglycaemic activity of garlic requires greater exposition.

Paracetamol

Investigating potential chemoprotective effects, aged garlic extract (equivalent to 6–7 garlic cloves) administered daily for three months to 16 healthy volunteers did not significantly affect the metabolism of paracetamol (1 g single oral dose at monthly intervals) or measured metabolites, other than slightly increased sulphate conjugation.[15]

Oral administration of organosulfide compound homogenates from fresh garlic to mice[16] and diallyl sulphide to rats[17] conferred time- and dose-dependent protective effects against paracetamol-induced hepatotoxicity. The hepatoprotective effect of garlic requires further inquiry.

Cytochrome (CY)P450 and P–gp substrates

Various whole garlic preparations were observed to inhibit CYP3A4, 3A5, 2C9*1 and 2C19 activities with little-to-moderate effect on P–gp activity *in vitro*.[18] Allicin has demonstrated potent inhibition of CYP2C9, and 2C19 but not 1A2, 2D6, or 3A4.[19] A single dose of garlic oil administered to rats was shown to inhibit CYP450 activity; however, daily administration for five days increased CYP450 activity.[20] Supplementation of various volatile oil constituents to rats for 15 days induced CYP3A and CYP2B (and to a lesser extent, CYP1A) enzyme activity.[21] No effect on CYP3A4 or CYP2D6 activity was observed in 14 healthy volunteers following oral administration of garlic extract (Kwai, 3 x 600 mg twice daily) for 14 days.[22] Administration of garlic oil (500 mg tid) to 12 healthy volunteers for 28 days had no effect on CYP3A4, however, was associated with a 39 per cent reduction in CYP2E1 activity.[23] CYP2E1 inhibition by diallyl sulphide *in vitro* and by volatile oil constituents of garlic in rats has been documented.[21] This activity might provide explanation for garlic's suggested chemopreventive effects (as many mutagens require activation by CYP2E1).[24] CYP2E1 also catalyses the metabolism of volatile halogenated anaesthetics, such as enflurane and halothane, and garlic may theoretically prolong their anaesthetic effect.[21,24] There is no further evidence to support this possible interaction. More investigation is required to establish the effect of garlic on *in-vivo* CYP450 and P–gp mediated drug metabolism.

Pharmacists – garlic considerations

Garlic and garlic-product constituent variation has a large impact on drug interaction potential. Garlic may be administered as cloves, minced bulb, oil-filled capsules and tablets.[25] Alliin is present in intact garlic bulbs and is enzymatically converted to allicin — thought to be primarily responsible garlic's physiological effects[1] — by allinase when garlic is crushed.[1,9]

Dried garlic preparations lack allicin but contain allinin and allinase, thereby retaining allicin-releasing potential.[1] However, as allinase is inactivated in the stomach, enteric coating of preparations is essential to allow conversion of alliin to allicin in the small intestine[25] and may also protect the ajoenes and vinyldithiins.[26]

Garlic preparations produced by heat or solvent extraction processes are rich in secondary alliin metabolites, such as

ajoene, but thought to be devoid of allinase and subsequently of allicin-releasing potential.[1] It is also unclear to what extent these secondary compounds are formed in the body and contribute to similar pharmacological activities of fresh garlic.[1] Fermented garlic preparations may be devoid of active sulphur-containing compounds altogether.[1]

It should be established if 'odourless' garlic preparations are due to the product formulation or if they are devoid of the odoriferous active principles.[1] Commercial preparations may be standardised to fixed alliin and allicin content[27], garlic oil[28], or allicin yield.[1] The concentration of active principles present in garlic preparations used in studies is difficult to establish. Moreover, the percentage of active constituents in fresh garlic reportedly varies by a factor of 10.[1] The mechanism of action of organosulphur components may involve several enzymes and the possibility of cumulative interactions exists.[26] The recommended garlic dose is equivalent to 4 g fresh garlic daily.[1] Although it is possible that excess intake of garlic products may promote associated adverse effects or drug interactions, the vast majority of individuals should not experience these difficulties. ◗

For references, please see http://www.pharm.usyd.edu.au/hmrec

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