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Review

Garlic (*Allium sativum* L.): Adverse effects and drug interactions in humans

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Garlic (*Alllium sativum* L., Fam *Liliaceae*) is used medicinally mainly for the treatment of hypercholesterolemia and prevention of arteriosclerosis. Clinical trials have consistently shown that "garlic breath" and body odor are the most common (and well-documented) complaints associated to garlic intake. Case reports have highlighted the possibility that garlic use may cause allergic reactions (allergic contact dermatitis, generalized urticaria, angiedema, pemphigus, anaphylaxis and photoallergy), alteration of platelet function and coagulation (with a possible risk of bleeding), and burns (when fresh garlic is applied on the skin, particularly under occlusive dressings). Consumption of garlic by nursing mothers modifies their infant's behavior during breast-feeding. Finally, garlic may enhance the pharmacological effect of anticoagulants (*e.g.* warfarin, fluindione) and reduce the efficacy of anti-AIDS drugs (*i.e.* saquinavir).

Keywords: Alternative and complementary medicine / Herb-drug interaction / Herbal medicine / Garlic / Safety

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1 Introduction

Herbal medicinal products are highly popular. Surveys show, for instance, that 9.3% of the adult population uses natural health products and 57% of users also reported taking a conventional medicine in the same period [1]. Most users perceive that herbs are efficacious, and in some instances, more efficacious than conventional medicines. This perception may be a major contributing factor influencing the sustained and increasing popularity of herbs [2]. Although herbs are often promoted as natural and therefore harmless, they are not free from adverse effects. An observational study indicated that herbal supplements are associated with adverse events that include all levels of severity, organ systems, and age groups [3]. Moreover, another survey has recently shown that 21% of older adults are currently taking at least one herbal product or dietary supplement, and potential for adverse drug reactions is apparent in 19% of respondents [4]. Therefore, the current popularity of herbal products renders necessary the evaluation of their safety.

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Abbreviations: AGE, aged garlic extract; **CYP**, cytochrome P450

Garlic (*Allium sativum* L. Fam *Liliaceae*) is one of the best-researched/best-selling herbal remedies and is also commonly used as a food and a spice [5 – 10].

Garlic is the top-selling herbal supplement in the USA, where sales in the food, drug, and mass market channel were estimated at $ 26,244,200. [11]. Pharmacological actions of garlic include antibacterial, antiviral, antifungal, antihypertensive, blood glucose lowering, antithrombotic, antimutagenic and antiplatelet actions [5, 6]. These activities are related to the volatile sulfur compounds (alliin, allicin, diallyl disulfide, ajoene and many others), which are also responsible for the pungent of these vegetables [12]. Traditionally, garlic has been used both orally and topically for many purposes, most consistently perhaps to prevent and treat infections and as a way of maintaining general health [6]. In modern phytotherapy, garlic is mainly used to treat hypercholesterolemia and for the prevention of arteriosclerosis [5, 10].

Recent reviews on garlic have focused on the dermatological adverse events [13], on the chemiopreventive and anticancer effects [14 – 18], on the antidiabetic [19], antithrombotic, antiplatelet, antihypertensive [14, 20], neuroprotective [21], antioxidant [22] actions and on the protective effects on dementia and heart-disease risk [23]. The aim of the present review is to summarize the adverse events (including herb-drug interactions) associated with garlic use in humans. The description and the discussion of animal studies as well as experimental studies aiming at under-

standing the possible molecular mechanisms behind the adverse effects were not the primary object of the present review.

2 Garlic odor

Garlic can cause malodorous breath or body odor. The German Commission E reports that "the odor of garlic may pervade the breath and skin" [24]. Usually developing after several days of garlic powder ingestion, this odor is perceived on the breath and skin [9]. Tamaki and Sonoki analyzed volatile sulfur compounds arising from grated raw or heat-treated garlic; it was found that the higher the volatile sulfur compound level, the stronger the garlic flavor or malodor was. Raw garlic showed a strongest smell than heat-treated garlic [25].

Controlled clinical trials as well as observational studies have consistently shown that "garlic breath" and body odor are the most common complaints associated to garlic intake. A meta-analysis of 13 randomized, double-blind, placebo-controlled trials of garlic monopreparations, ten of which assessed the effects of a standardized garlic powder preparation at doses of 600 – 900 mg daily for 8 – 12 weeks, for the treatment of hypercholesterolemia, reported that the most common adverse event was "garlic breath" and body odor [26]. Furthermore, 1997 participants at an observational study were interviewed at the start of the study and after 8 and 16 weeks of treatment with garlic powder (3×300 mg/day, coated tablets). Garlic odor was the most frequent complaint (27%) [27]. Finally, a double-blind study using a fivefold crossover design was conducted in 123 subjects to determine the incidence of garlic odor as function of the ingested dose (garlic powder in tablet form, LI 111). The incidence of slight and moderate garlic odor was 10% in the placebo group, 24% at a dose of 300 mg/day, 36% at 600 mg/day, 40% at 900 mg/day, and 45% at 1200 mg/day [28]. In conclusion, garlic odor is the most common unpleasant effect associated with garlic intake.

3 Allergic reactions

The allergenic potential of garlic is well recognized, and allergens have been identified as diallyl disulfide (which is considered to be the primary allergen), allylpropyl sulfide and allicin (the latter may be an irritant) [7, 29]. Garlic also contains a not-yet identified high molecular-weight protein that presumably leads to systemic allergic reactions [13]. German Commission E reports that garlic in rare instances may cause allergic reactions [24] and this has been confirmed by an observational study, which showed that allergic reactions occurred in 1.1% of users of garlic at therapeutic doses (3×300 mg/day garlic powder, taken in the form of coated tablets) [27]. Case reports of allergic reactions associated to garlic use (as a food or as a medicine) include allergic contact dermatitis, generalized urticaria, angiedema pemphigus and anaphylaxis.

Allergic contact dermatitis is a delayed type IV allergic reaction of the skin with varying degrees of erythema, edema, and vesiculation resulting from cutaneous contact with a specific allergen [30]. Cases of allergic contact dermatitis due to topical or oral treatment medical treatment with garlic have been reported. A 78 year old Major, with a history of volar hand eczema, presented with a generalized eczema. Four months earlier, the patient had started scratching the itchy dry skin of his lower legs, causing excoriations and small erosions especially on his left leg. His wife treated his legs with hydrocortisone cream and emollients, but from time to time she also crushed cloves of garlic diluted in water as wet dressing. Gradually, the dermatitis got worse and spread to his trunk and arms. Allergic contact dermatitis was confirmed when testing with non-irritating concentrations of garlic powder and diallyl disulfide [31]. Burden and colleagues reported the case of a 58 year old who presented vesicular hand dermatitis (cheiropompholix). Nine months previously, he started taking garlic extract for treating hyperlipideamia. His hands flared up severely and persisted for eight months until he ran out of garlic tablets, when it resolved. Prior to this, he had prepared food using garlic without any problems. Allergy to garlic was confirmed at patch testing (positive reaction to extracts of garlic) and with a double-blind oral provocation test to the garlic tablets [32].

Urticaria is a relatively common form of allergic reaction that causes raised red skin welt. Urticaria is generally caused by direct contact with an allergenic substance, or an immune response to food or some other allergen. Pires *et al*., 2002 [33] reported a case of IgE-mediated urticaria after contact and ingestion of raw garlic in a 16 month old boy. Skin prick and prick-prick tests were positive with commercial garlic extract. Contact challenge was positive with raw garlic and negative with cooked garlic. Oral challenge with raw garlic was positive with generalized urticaria, within 10 min after ingestion. Oral challenge with cooked garlic was negative. No cross-reactivity between onion and garlic was found [33].

Angiedema is related, but not similar, condition to urticaria, where similar types of swelling occur in a lower layer of the skin, mouth or throat. Angiedema and urticaria, may, however, occur together [30]. A 35 year old woman was admitted at an allergy centre because of many episodes of systemic urticaria and angiedema during the last two years, all of which were associated with the ingestion of foods containing both raw or cooked garlic. Moreover, she had noted that garlic manipulation caused contact urticaria. A positive skin reaction to garlic extract was observed [34]. Garlic, onion and asparagus belong to the *Liliaceae* family. Sanchez-Hernandez and colleagues evaluated the possible allergic cross-reactivity in this botanical family. Two

patients with an established diagnosis of IgE-mediated contact urticaria caused by cooked white asparagus (as demonstrated by rub test, prick test, and specific IgE test) showed a positive result in the prick-prick test with native onion and garlic [35].

Anaphylaxis is a sudden, severe, potentially fatal, systemic allergic reaction that can involve various areas of the body. Causes of anaphylaxis include foods, drugs and insect stings. Anaphylaxis occurs when subjects are exposed to a trigger substance, *i.e.* the allergen, to which they have already become sensitized [30]. A 23 year old woman with previous history of allergy to pollen and dried fruit, and food-dependent, exercise-induced anaphylaxis for which no specific food could be identified as responsible, experienced an anaphylactic reaction after eating young garlic (unripe garlic plant whose bulb is not completely developed). A few minutes after eating young garlic with eggs and shrimp, without previous exercise, she presented generalized urticaria and facial angiedema, followed by a feeling of sickness, hypotension, and loss of consciousness. She was taken to the emergency clinic and treated with intravenous fluids, epinephrine, diphenhydramine, and hydrocortisone, Her symptoms resolved over 24 h. Prick-prick tests with young garlic and garlic were positive [36].

Pemphigus is a skin disease characterized by large thin-walled blisters (bullae) arising from normal skin or mucous membrane. Diet may play a role in the induction and/or exacerbation of pemphigus [37, 38]. A 49 year old Italian builder presented a few, sparse erosive lesions he had been noticing for ten months on his scalp, nose, upper chest and glans penis. Some erosion had shown a tendency to a slow but complete re-epithelialization resulting in long-lasting brown macular lesions; others had turned into chronic scaling and crusting, while the ones located on the glans penis remained persistent. Asked about any drug intake and his food habits, the patient denied taking any medicine but informed the medical staff he very much liked spicy dishes, particularly garlic. On a onion- and garlic-free diet, the patient did not show any new lesions for several months. A check of the pemphigus antibodies in his serum revealed a minimal decrease to a titer of 1:80 [38]. Consistently, an experimental investigation has evidenced that three compounds of garlic (*i.e.* allylmercaptan, allylmethylsulfide, allyl sulfide) are able to provoke acantholysis (a breakdown of a cell layer in the epidermis, as it happens in pemphigus) of normal human skin cultured *in vitro* [39].

In summary, topical application or oral use (as a food or as a medicine) of garlic may cause allergic reactions ranging from contact dermatitis to anaphylaxis (Table 1). Non-severe allergic reactions may occur in approximately 1% of users of garlic at therapeutic doses.

Table 1. Summary of garlic adverse effects

Adverse effect	Type of exposure	Source of evidence
Breath or body odour	Oral medical use (standardized garlic powder in coated tablet form)	Randomized controlled trials, observational studies
Allergic reactions (allergic contact dermatitis, urticaria/angiedema, pemphigus anaphylaxis)	Topical application or oral use (as a food or as a medicine)	Multiple case reports for allergic contact dermatitis and urticaria. Single case reports for anaphylaxis and pemphigus
Photoallergy	Topical application of diallyl disulfide	A case report and a case series
Cutaneous manifestations (garlic burns)	Topical application (under occlusive dressings) of fresh garlic for medical purposes or for self-mutilation	Multiple case reports
Coagulation alterations (spinal epidural hematoma, increased clotting time, post-operative bleeding, retrobulbar hemorrhage)	Excessive dietary garlic intake or garlic tablets	Single case reports
Gastrointestinal adverse effects (mild: nausea, bloating, flatulence severe: small intestinal obstruction, epigastric and esophageal pain, hematemesis, hematochezia)	Garlic coated tablets	Mild adverse events: randomized clinical trials, observational studies Severe adverse events: single case reports
Others (Hypotensive effects, myocardial infarction, Meniere's disease)	Oral use as a food or medicine	Observational study for hypotensive effects; single case reports for myocardial infarction and Meniere's disease
Herb drug interactions (warfarin, fluindione, saquinavir)	Oral use as a food or medicine	Two cases for warfarin, one case for fluindione, a clinical study for saquinavir

4 Occupational allergy

Garlic has long been recognized as an occupational hazard amongst chefs, housewives and those who practise herbal remedies as highlighted by a number of observational studies in occupational allergic patients. For example, Hiorth and Roed-Petersen found that garlic and onion were among the major type IV allergens incriminated in 33 occupational dermatoses in food handlers [40]. Sinha and colleagues showed that 44 out of 53 subjects (mainly housewives) having contact dermatitis on the fingerprints had positive patch tests to garlic [41]; Cronin and colleagues demonstrated that hand eczema in 47 out of 50 allergic caterers was due to garlic contact [42]. Lembo and colleagues found that garlic was causative of allergy in eight out of 155 patients affected with various eczemas [43]. Kanerva and colleagues found that garlic was causative of hand (or finger) dermatitis in five out of 1000 patients with occupational skin disease [44]. Anibarro and colleagues demonstrated allergic asthma induced by garlic dust in seven out of 12 patients with symptoms of bronchial asthma [45]. Fernandez-Vozmediano and colleagues found that 60% of patients (n=75, mainly housewives) who were clinically suspected of having a potential contact allergy were positive for diallyl disulfide [46]. Finally, a small study showed that garlic is an important sensitizer in curry chefs: positive patch test to diallyl disulfide was seen in four out of 13 chefs with hand dermatitis [47].

The potential allergenic properties of garlic in causing occupational allergies has been also revealed by the publication of several case reports/case series. In such cases, garlic allergy was confirmed using a wide variety of tests including scratch testing, IgE to garlic using radioallegosorbent test, polystyrene tube solid phase radioimmunoassay technique, bronchial challenge test and skin prick test. Occupational allergic manifestations associated to garlic use include contact dermatitis and respiratory adverse events.

Contact dermatitis, particularly affecting the fingertips, is a recognized presentation of garlic allergy. Cases of occupational allergic contact dermatitis include eczematous eruption on the finger-tips of the left hand in a 24 year old cook [48]; hand dermatitis in a 49 year old Italian fitter and turner with a regular contact with garlic during food preparation [49]; sub-erythrodermic eczematous reaction in a 54 year old Asian man who had been in periodic contact with pure garlic powder in the preceding seven months [50]; eczematous rash over both forearms in a 51 year old woman two months after coming into contact with garlic [51]; eczema of the hands in three cooks [52]; eczema in three cooks who showed positive reactions to piece of garlic and onion [53]; burning sensation, rush and swelling of the left hand in a 42 year old female cook [54]; itchy eruption affecting the fingertips of a 48 year old right-hander maintenance carpenter, who did the household cooking approximately 4 – 5 nights per week [55]; itching, fissuring and redness of the fingertips in a 41 year old Chinese janitor [56].

Many cases of respiratory adverse events (*i. e.* asthma, dyspnoea, cough, rhinitis, rhinoconjunctivitis) associated with occupational exposure to garlic (contact or inhalation) have been also reported. The first report of garlic-induced asthma dates back to 1940, when Henson described a foreman working in the sausage department of a wholesale meat packing plant. The patient's asthmatic symptoms disappeared after the garlic powder was substituted for "kernels" [57]. It was not until 1981, however, that Falleroni *et al.* [58] published the first case of garlic asthma with a demonstrated positive bronchial challenge. Other cases of occupational allergy with adverse respiratory symptoms associated to garlic occupational exposure include severe asthma in an atopic patient who subsequently developed marked adverse response after ingestion of garlic [59]; asthma, rhinitis and conjunctivitis in two children helping their parents with the harvesting of garlic in France [60]; bronchial asthma and allergic rhinitis in two sausage makers and allergic rhinitis in one teacher at the hotel and catering school in Finland [61]; bronchial asthma in a 32 year old butcher which was also allergic to other aromatic herbs including thyme and rosemary [62]; rhinitis and asthma in a 16 year old boy, who helped his father load a van with strings of garlic, a task which raised a large amount of dust from the stored garlic [63]; cough, dyspnoea, and chest tightness in a 30 year old electrician working in a spice processing plant [64].

In summary, occupational allergic reactions are well-documented adverse effects associated to garlic use. Contact dermatitis is the most common occupational allergic reaction. Other occupational allergic reactions include asthma, dyspnoea, cough and rhinitis. These may occur following contact or inhalation of garlic.

5 Photoallergy

Photoallergy is a delayed immunologic type of photosensitivity involving a chemical substance to which the individual has previously become sensitized, combined with radiant energy. The reaction may occur 1 – 2 days after sun exposure. Photoallergic reactions to plants occur very rarely; documented examples include reaction to *Partheneum hysterophorus*, psoralens and *Frullania* [65]. Diallyl disulfide, a common ingredient in lip products, has been shown to induce photoallergic reactions [65, 66]. A case of contact dermatitis limited to the lips has been reported in a 56 year old woman. Her reaction typically occurred 24 h after sunlight exposure [66]. Furthermore, Alvarez and colleagues reported three cases of photocontact allergy to diallyl disulfide. Photoallergic contact dermatitis was manifested as recurrent pruritic eruption that was most prominent on the face, "V" area of the chest, back, and forearms

in one case; eruption involving the face and the neck in another case; and a pruritic eruption that involved the upper chest, neck, arms, and cheeks. In all cases, dermatitis was aggravated by exposure to sunlight. All three patients had positive photo patch-test results to diallyl disulfide [65].

6 Cutaneous manifestations

There is evidence that the medical use of garlic may induce allergic (described in Section 5, see paragraph 4, Allergic reactions) and non-allergic (irritant) contact dermatitis [67]. Garlic, in its fresh, crushed-clove form, is a potent irritant and, under occlusive dressings, this potency is enhanced [68 – 81]. Garlic irritants include sulfur compounds such as isothiocyanates [13]. The possibility that garlic may cause irritant contact dermatitis (known as "garlic burns") has been highlighted by a number of case reports/case series, both in infants and in adults (Table 2). Compared to infants, a longer exposure time seems to be generally needed for causing burns in adults. The cases involved the feet, wrists, hand, trunk, breast, and forehead. The garlic was applied to treat asthma, skin lesions, pain, and fever, and in some instances, for self-mutilation. Garlic burns have been also induced for self-mutilation in order to avoid military duty [69, 79, 81] or without a precise rational motive [74]. In all cases, the burns were successfully managed with conservative treatment alone [68 – 81].

7 Coagulation alterations

Garlic has complex cardiovascular effects including antiplatelet, antithrombotic and fibrinolytic activity [5, 6]. Clinical studies have reported significant reductions in platelet aggregation and mixed effects on fibrinolytic activity [82]. There is also evidence that some of the antiplatelet activity might be irreversible and thus it has been suggested that patients cease ingestion at least seven days prior to surgery [83]. Few case reports have highlighted the possibility that garlic may increase the risk of bleeding, particularly in patients undergoing surgery.

Rose and colleagues reported a case of spontaneous spinal epidural hematoma causing paraplegia secondary to a qualitative platelet disorder from excessive garlic ingestion [84]. An increase of the clotting time was observed in a healthy 32 year old woman six day before a cosmetic surgery. The subject admitted to heavy garlic dietary intake preoperatively and was taken completely off garlic. One week later, during which she had a garlic-free diet, her clotting time was normalized [85]. German and colleagues [86] reported the case of a 72 year old man who was admitted in acute urinary retention and was catheterized. He was not on any medication apart from garlic tablets which he had taken for many years for medical purposes. Four days later he underwent transurethral resection for prostatic benign hyperplasia. The resection was "bloody" and hemostasis was only moderate. Because of continuing hemorrhage, he underwent a repeat cystoscopy 4 h later. At operation, no specific sites of bleeding were identified but there was a general ooze from the whole of the prostatic cavity. He required four units of blood and made a full recovery. Studies of platelet function were performed three months after resuming his normal dose of garlic tablets. These tests showed a failure of platelet aggregation in the presence of collagen, confirming a platelet coagulation defect [86]. Finally, a case of bilateral retrobulbar hemorrhage with elevated intraocular pressure during strabismus surgery has been reported in a 54 year old woman. The patients stated that he had been taking odorless garlic tablet ingestion (prescribed by a naturopath) prior to surgery. On the day prior to surgery, she had consumed five tablets (approximately 5 g of an equivalent fresh bulb) [87].

In conclusion, excessive dietary garlic intake or garlic as a medicine has been associated with coagulation alterations, as revealed by few case reports. Causality, however, has not been fully demonstrated.

8 Gastrointestinal adverse effects

The 1998 German Commission E monograph on garlic reports that "in rare instances there may be gastrointestinal symptoms, changes to the flora of intestine" [24]. Gastrointestinal irritation may occur particularly if the clove is eaten raw by individuals not accustomed to ingesting garlic or even after the intake of garlic tablets [7]. Intragastric infusions of uncooked garlic, in quantities of 0.75 g or more caused a significant increase in exfoliation of gastric surface epithelial cells in human subjects [88]. Moreover, Hoshino and colleagues [89] reported that oral administration of dehydrated raw garlic powder caused severe damage to the gastric mucosa, dehydrated boiled garlic powder caused reddening of the mucosa, whereas aged garlic extract (AGE, which is considered to be virtually devoid of the active sulfur-containing compounds) did not cause any undesirable effects and also protects intestinal mucosa in experimental studies [90]; on the other hand, oral administration of enteric-coated tablets caused loss of epithelial cells at the top of crypts in the ileum [89].

Clinical studies have shown that garlic may cause mild gastrointestinal complaints following administration of therapeutic doses of garlic [35, 27, 82]. During the course of the observational study, the side effects occurring in a total of 1997 patients on treatment with 900 mg daily garlic powder per coated tablets (three tablets/day) included gastrointestinal complaints (incidence of adverse effects: 6% nausea, less than 0.8% bloating) [27]. Furthermore, in randomized, double-blind trials, mild gastrointestinal symptoms were the most common problems reported

Table 2. Case reports and case series of garlic "burns" caused by local application of garlic

Subject	Reason for using garlic	Details on garlic application	Description of garlic burn	Treatment/Healing	First Author Year [Ref]
17 month old child	Fever and diarrhoea	The mother was instructed to make a paste of 50% crushed garlic cloves and 50% petroleum jelly	Partial thickness burns to both feet	Burns healed in approximately two weeks with topical silver, sulfadiazine, and sterile dressings applied twice daily	Parish 1987 [67]
Three men	Self-inflicted in order to avoid military duty	The soldiers applied fresh ground garlic to the lower legs and antecubital fossa	Erythematous, vesicular rash where garlic was applied	Patients were successfully treated	Kaplan 1990 [68]
Eight patients	Fungal and other infections	Patients rubbed the cut end of a fresh garlic bulb onto the skin at the groin, neck, lower limb, hand or face	Contact dermatitis in the region of the skin where garlic was applied	The patients were treated successfully with topical fluorinated steroid	Lee 1991 [69]
6 month old boy	NR	The child's father followed the grandmother's instructions, which were to fix crushed garlic cloves by adhesive band onto both wrists of the baby, exactly over the pulse area for 6 hours, and then to remove them	Second-degree chemical burns on both wrists	The lesions healed within 3 weeks leaving cicatrices	Garty 1993 [70]
6 year old girl	Minor erosion caused by a shoe	The child's grandmother applied crushed garlic cloves under a bandage over the affected area for 2 days prior to admission.	Necrotic ulcer on the foot	The lesion healed within 32 days, without leaving a scar	Canduela 1995 [71]
38 year old woman	Self-diagnosed *Candida*	On a suggestion of a friend, the patient crushed fresh garlic and applied it to the left breast in the form of a poultice, sparing the areolar and nipple regions. She noted an almost-immediate burning sensation upon application but nonetheless left the poultice in place for 2 full days	Burn of the left breast with areas of skin loss and ulcerations, crusting, hyperpigmentation, and granulation tissue formation	The skin was cleansed and the patient was discharged on 1% silver sulfadiazinine cream.	Roberge 1997 [72]
19 year old female	Self-inflicted without a rationale motive	She self-induced the rash by local application of garlic	Multiform eruption of 3 weeks duration	The patient was referred for psychiatric evaluation and treatment	Hallel-Halevy 1997 [73]
3 month old girl	cold	Following the advice of a relative, the parents applied some crushed garlic bulbs to the ankles and dorsa of the feet. The feet were then wrapped with bandages	Severe vesicobullous eruptions on both ankles and feet approximately 8 h after garlic application	The blisters were punctured and debridement of the wound was carried out. Flamazine was applied to the affected areas. The patient had an uneventful recovery with complete wound healing in 3-weeks time	Rafaat 2000 [74]
42 year old woman	Chronic intra-articular pain	The patient applied 15 freshly sliced cloves of garlic fixed to the left knee with film for three hours	Erythematous rash to the knee mimicking second degree burns	Lesion did not healed in 14 days. Necroctomy and split skin transplantion were performed after 24 days	Hviid 2000 [75]
29 year old woman	NR	The patient applied a compress of crushed garlic wrapped in cotton wool for 18 h	Painful rash on the right side of her chest and upper abdomen	The lesions healed with scarring	Farrell 2001 [76]

Table 2. Continued

Subject	Reason for using garlic	Details on garlic application	Description of garlic burn	Treatment/Healing	First Author Year [Ref]
50 year old men	asthma	The patient followed the healer's instruction which were to fix crushed garlic cloves by adhesive bandages onto the forehead for 8 h and then to remove them	Second-degree burn on his forehead	The patient was treated conservatively, allowing the burned area to close by s econdary intention	Baruchin 2001 [77]
Two 18 year old men	Self-inflicted with the intent of exemption from work	Patients applied crushed garlic to the dorsum of their knees, ankles, and feet	Second-degree burns where garlic was applied	Patients were successfully treated	Lachter 2003 [78]
60 year old man	Chronic diabetic neuropathy	At the recommendation of a family member, the patient applied crushed raw garlic to his feet and covered them with occlusive bandages for approximately 12 h	Burns to both feet followed by low-grade fever and increasing wound erythema	The lesions resolved without incident over the next 4 weeks	Dietz 2004 [79]
3 men	Self-inflicted in order to avoid military duty	The soldiers applied fresh garlic to the legs and feet.	Second-degree burns	Treatment included removal on any residual garlic, and soaks and cool compresses with topical steroids	Friedman 2006 [80]

NR, not reported

besides garlic breath and body odor [26]. Unproven gastrointestinal tract adverse effects, which have been highlighted by single case reports or case series include small intestinal obstruction, epigastric and esophageal pain, hematemesis and hematochezia [82].

There are no data on garlic hepatotoxicity in humans. Animal studies suggest that garlic with high dose has the potential ability to induce liver damage, but low doses (up to 0.25 g/kg administered for four weeks) are safe [91].

9 Other adverse effects

During the course of an observational study (n=1997 patients) on commercial garlic powder (300 mg garlic powder per coated tablets, 1 tablet taken three times daily), there were relatively frequent reports of orthostatic circulatory problems (1.3% incidence of hypertension) [27].

A case of acute myocardial infarction probably related to excessive consumption of garlic has been reported in a 23 year old non smoker, non-alcoholic, vegetarian male. There was no family history of coronary artery disease and no history of acute physical or emotional stress. The patient categorically attributed this incidence to increased consumption of garlic on the previous night. He also referred that he had similar pain twice in the past, when also he had consumed an excess of garlic [92]. A case of food allergy with symptoms of Meniere's disease have been described in a Czech report [93]. Finally, Park and colleagues have recently reported a case of a subject with hypersensitivity to garlic extract, but totally insensitive to capsaicin (the active ingredient of chilli) [94].

10 Pregnancy and lactation

The active ingredients of plant extracts are chemicals that are similar to those in purified medications, and they have the same potential to cause serious adverse effects during pregnancy. There are no rigorous scientific studies of the safety of dietary supplements (including garlic) during pregnancy, and the Teratology Society has stated that it should not be assumed that they are safe for the embryo or fetus [95].

A recent systematic review [96] retrieved one randomized, single-blind trial [97] which compared garlic (n=50) with placebo (n=50) for the prevention of preeclampsia and its complication during the third trimester of pregnancy. No significant differences in reported side effects were observed, except for garlic odor, which was reported more likely in the garlic group (34%) than in the placebo group (4%). Eight subjects claimed a slight feeling of nausea in the garlic group and two subjects in the placebo group. The percentage of caesarean section was 62% in the garlic group and 46% in the placebo group. No perinatal morbidity and mortality in the two groups was observed [96, 97]. Garlic ingestion by pregnant women significantly alters the odor of their amniotic fluid. Mennella and colleagues [98] analyzed amniotic fluid samples from ten pregnant women undergoing routine amniocentesis procedure. Approxi-

mately 45 min prior to the procedure, five of the women ingested placebo capsules, whereas the remaining five ingested capsules containing the essential oil of garlic. The odor of the amniotic fluid obtained from four of the five women who had ingested the garlic capsules was judged to be stronger or more like garlic than the paired samples collected from the women consuming placebo capsules.

There is also evidence that consumption of garlic by nursing mothers modifies their infant's behavior during breast-feeding [99 – 101]. By evaluating the milk samples by a sensory panel, Mennella and Beauchamp [99] revealed that garlic ingestion significantly and consistently increased the perceived intensity of the milk odor; this increase in odor intensity was not apparent 1 h after ingestion, peaked in strength 2 h after ingestion, and decreased thereafter. Infants were attached to the breast for longer periods of time and sucked more when the milk smelled like garlic [99]. Further evidence comes from a blinded, placebo-controlled study involving 30 nursing women. The results indicated that infants who had no prior exposure to garlic odor in their mother's milk spent more time breast feeding after their mothers ingested garlic capsules than did infants whose mothers had repeatedly consumed garlic [100].

In summary, in view of the paucity of clinical data, doses of garlic greatly exceeding amounts used in foods should not be taken during pregnancy and lactation.

11 Herb-drug interactions

One important safety concern with the widespread herbal use is the potential interaction of herbal medicines with conventional drugs. This issue is especially important with respect to drugs with narrow therapeutic indexes such as the anticoagulant drug warfarin [102, 103]. Herbal medicine follow modern pharmacological principles. Hence, herb-drug interactions are based on the same mechanisms as drug-drug interactions. Herb-drug interactions can thus have both a pharmacokinetic (changes to plasma drug concentration) and pharmacodynamic (drugs interact at receptors on target organs) basis [104]. Pharmacokinetic interactions have been more extensively studied and *in vitro* and *in vivo* studies indicated that the altered drug concentrations by co-administered herbs may be attributable to the induction (or inhibition) of hepatic and intestinal drug-metabolizing enzymes (particularly cytochrome P450 (CYP)), and/or drug transporters such as P-glycoprotein [102].

CYP is the most important phase I drug-metabolizing enzyme system, responsible for the metabolism of a variety of drugs. The benzodiazepines alprazolam and midazolam, as well as the anticancer drug docetaxel are extensively used as probe for CYP 3A4 activity because they are entirely metabolized by intestinal and hepatic CYP 3A4. One study showed that a 28 day treatment with garlic oil did not have a significant effect on the pharmacokinetics of midazolam in the elderly (12 healthy volunteers between the ages of 60 and 76 years) [105]. Another study showed that treatment with garlic extract for 14 days did not affect the pharmacokinetics of alprazolam in 14 healthy volunteers [106]. Finally, a 12 day treatment with garlic did not alter the disposition of docetaxil in ten women with metastatic breast cancer [107]. Collectively, these trials indicate that garlic has no effect on CYP enzymes in humans *in vivo*. Consistently, a number of water-soluble garlic components of AGE have been shown to not affect human CYP *in vitro* [108].

P-glycoprotein is a ubiquitous efflux drug transporter that affects a number of drugs. P-glycoprotein appears to limit the cellular transport from intestinal lumen into epithelial cells and also enhances the excretion of drugs out of hepatocytes and renal tubules into the adjacent luminal space [109]. Like CYP, P-glycoprotein is vulnerable to inhibition, activation, or induction by herbs (*e.g.* St John's wort) and plant constituents (*e.g.* curcumin, piperine, quercetin) [110]. In an *in vitro* study using recombinant human P-glycoprotein membranes, raw garlic and garlic products were found to exert low-to-moderate inhibitory effects on the activity of P-glycoprotein [111]. However, *in vivo* evidence is lacking.

Clinical evidence suggests that taking garlic can result in pharmacokinetic or pharmacodynamic interactions that might represent a potential risk to patients taking conventional medicines [102, 103], particularly in subjects under anticoagulant [102, 112] or antiretroviral therapy [113].

Garlic has complex cardiovascular effects including antiplatelet activity and hence could theoretically interact with anticoagulant/antiplatelet drugs [102, 112, 114]. Two cases of increased international normalized ratio in patients previously stabilized on warfarin have been reported. These increases were attributed to the ingestion of garlic products, since there had been no other changes to medication or habits in either case. One patient had started taking garlic pearls, the other garlic tablets but in both cases clotting times were roughly doubled [115]. An increase of international normalized ratio has also been described in a subject taking the anticoagulant drug fluindione [116]. These reports, however, contained inadequate information to assess the likelihood of an interaction. Recently, Macan and colleague [117] have suggested that AGE is relatively safe and poses no serious hemorrhagic risk for closely monitored patients on warfarin therapy.

Many people infected with HIV look to natural health products to supplement their conventional medical care, and clinicians, understandably, are concerned about drug interactions [118]. Most anti-HIV drugs are mainly cleared by the intestinal and hepatic CYP 3A4 and are also substrates for P-glycoprotein [113]. A significant decline in the plasma concentrations of the protease inhibitor saquinavir was observed in healthy volunteers after administration of garlic for three weeks [119]. Because there were similar

reductions in the magnitude of all concentration parameters (area under the curve and C_{max}, 51 – 54% reduction), the authors suggested that garlic affected the bioavailability of saquinavir rather than its systemic clearance. These parameters remained below baseline after a 10 day washout period, suggesting that there may be a long-lived systemic metabolite of garlic or a production of saquinavir metabolites that autoinduce metabolism [113]. Although it has been hypothesized that changes in saquinavir bioavailability could be secondary to induction of intestinal CYP and/or P-glycoprotein (saquinavir is a known substrate of CYP 3A4 and P-glycoprotein) [112], experimental evidence on humans raised against these mechanisms (see above). While garlic administration reduces plasma concentration of saquinavir, another trial showed that acute dosing of garlic over four days, did not significantly alter the single-dose pharmacokinetics of the protease inhibitor ritonavir [120]. The reason for the discrepancy in the interaction of garlic and saquinavir or ritonavir is presently unclear. Ritonavir is a substrate of CYP 3A4 and P-glycoprotein. The lack of interaction could be explained by the short duration of garlic administration, and a longer duration of garlic therapy may be required to observe a significant decrease in ritonavir plasma concentrations [110].

A preliminary report described the case of two HIV-infected patients who developed severe gastrointestinal toxicity from ritonavir after ingesting garlic supplements [121]. Symptoms recurred after re-challenge with low-dose ritonavir, suggesting that elevated ritonavir concentrations were not the cause. It has been hypothesized that ritonavir could inhibit the metabolism of garlic active ingredients (pharmacokinetic interaction) or it could potentiate the toxic effect of garlic on the intestinal tract (pharmacodynamic interaction) [112].

Other conventional drugs which might interact with garlic include the antidiabetic chlorpropamide and the analgesic drug paracetamol (acetaminophen). A fall in glucose levels has been reported in a 40 year old diabetic woman taking chlorpropamide and a carry containing garlic and karela [122]. This event is likely due to an additive effect on glucose levels, since both garlic and karela possess hypoglycemic effects. The report, however, contained inadequate information to assess the likelihood of an interaction. A clinical trial suggested that garlic changes some pharmacokinetic variables of paracetamol (acetaminophen) after 1 to 3 months treatment [123]. Specifically, it was found that commercial AGE (approximately equivalent to six to seven cloves of garlic) had no effect on oxidative metabolism, but caused a slight increase in sulfate conjugation of the drug. However, it is very unlikely that these pharmacokinetic changes are of major clinical significance.

Finally, a clinical trial showed chewed raw garlic significantly reduced cholesterol and triglyceride levels, but did not decreased significantly cyclosporine serum level in renal transplant recipients [124]

12 Conclusions

Garlic appears to be generally safe. However, clinical trials, case reports and case series have highlighted the possibility that this herb may cause adverse effects, including herb-drug interactions (Table 1). Complaints that have been documented in clinical trials include "smelly" breath/body odor and mild gastrointestinal symptoms (nausea, flatulence, bloating). Garlic odor is the most well-documented adverse effect associated to garlic use. Multiple case reports also suggest that oral intake of garlic (as a food or as a medicine) may cause allergic reactions, although the published case reports do not allow us to definitely conclude that a causal relationship exists. Application of garlic on the skin may cause contact dermatitis through both primary irritation (garlic burns) and allergic mechanisms (allergic contact dermatitis). Other reported, but not proven, adverse effects include esophageal and abdominal pain, small intestinal obstruction, Meniere's disease, bleeding, and myocardial infarction (the last two mentioned represent potentially the most serious adverse effects). The frequency of adverse effects and whether they varied by different preparations have been rarely studied. Few studies have been published on the use of garlic during pregnancy or lactation. In view of this, doses of garlic greatly exceeding amounts used in foods should not be taken during pregnancy and lactation.

13 References

[1] Singh, S. R., Levine, M. A., Natural health product use in Canada: analysis of the National Population Health Survey, *Can. J. Clin. Pharmacol*. 2006, *13*, 240 – 250.

[2] Clement, Y. N., Morton-Gittens, J., Basdeo, L., Blades, A., *et al*., Perceived efficacy of herbal remedies by users accessing primary healthcare in Trinidad, *BMC Complement. Altern. Med*. 2007, *7*, 4.

[3] Palmer, M. E., Haller, C., McKinney, P. E., Klein-Schwartz, W. *et al.*, Adverse events associated with dietary supplements: an observational study. *Lancet* 2003, *361*, 101 – 106.

[4] Marinac, J. S., Buchinger, C. L., Godfrey, L. A., Wooten, J. M. *et al.,* Herbal products and dietary supplements: a survey of use, attitudes, and knowledge among older adults, *J. Am. Osteopath. Assoc*. 2007, *107*, 13 – 20.

[5] Capasso, F., Gaginella, T. S., Grandolini, G. Izzo, A. A., *Phytotherapy. A quick reference to herbal medicine,* Springer-Verlag, Berlin Heidelberg 2003.

[6] Ernst, E., Pittler, M. H., Wider, B., *The Desktop guide to complementary and alternative medicine,* Mosby Elsevier, Philadelphia 2006.

[7] Barnes, J., Anderson, L. A., Phillipson, J. D., *Herbal medicine,* Parmaceutical Press, London Chicago 2002.

[8] Johns Cupp, M., *Toxicology and clinical pharmacology of herbal products,* Humana Press, Totowa New Jersey 2000.

[9] Schulz, V., Hansel, R., Blumenthal, M., Tyler, V. E., *Rational phytotherapy*, Springer-Verlag, Berlin Heidelberg 2004.

[10] Rotblatt, M., Ziment, I., *Evidence-based herbal medicine,* Hanley & Belfus INC, Philadelphia 2002.

[11] Blumenthal, M., Ferrier, G. K. L., Cavaliere, C., Total Sales of Herbal Supplements in United States Show Steady growth, *HerbalGram,* 2006, *71*, 64 – 66.

[12] Lanzotti, V., The analysis of onion and garlic, *J. Chromatogr A*. 2006, *1112*, 3 – 22.

[13] McGovern, T. W., LaWarre, S., Botanical briefs: garlic – *Allium sativum. Cutis* 2001, *67*, 193 – 194.

[14] Ariga, T., Seki, T., Antithrombotic and anticancer effects of garlic-derived sulfur compounds: a review, *Biofactors* 2006, *26*, 93 – 103.

[15] Shukla, Y., Kalra, N., Cancer chemoprevention with garlic and its constituents, *Cancer Lett*. 2007, *247,* 167 – 181.

[16] Ross, S. A., Finley, J. W., Milner, J. A., Allyl sulfur compounds from garlic modulate aberrant crypt formation, *J. Nutr.* 2006, *136*, 852S – 854S.

[17] Wargovich, M. J., Diallylsulfide and allylmethylsulfide are uniquely effective among organosulfur compounds in inhibiting CYP2E1 protein in animal models, *J. Nutr.* 2006, *136*, 832S – 834S.

[18] Milner, J. A., Preclinical perspectives on garlic and cancer, *J. Nutr.* 2006, *136*, 827S – 831S.

[19] Ahmad, M. S., Ahmed, N., Antiglycation properties of aged garlic extract: possible role in prevention of diabetic complications, *J. Nutr.* 2006, *136*, 796S – 799S.

[20] Rahman, K., Lowe, G. M., Garlic and cardiovascular disease: a critical review, *J. Nutr.* 2006, *136*, 736S – 740S.

[21] Chauhan, N. B., Multiplicity of garlic health effects and Alzheimer's disease, *J. Nutr. Health Aging* 2005, *9*, 421 – 432.

[22] Atmaca, G., Antioxidant effects of sulfur-containing amino acids, *Yonsei Med. J.* 2004, *45*, 776 – 788.

[23] Borek, C., Garlic reduces dementia and heart-disease risk, *J. Nutr.* 2006, *136*, 810S – 812S.

[24] Blumenthal, M., Busse, W. R., Goldberg, A., Gruenwald, J. *et al.*, (Eds.), *The Complete German Commission E Monographs-Therapeutic Guide to Herbal Medicine,* American Botanical Council, Austin TX 1998.

[25] Tamaki, T., Sonoki, S., Volatile sulfur compounds in human expiration after eating raw or heat-treated garlic, *J. Nutr. Sci. Vitaminol.* 1999, *45*, 213 – 222.

[26] Stevinson, C., Pittler, M. H., Ernst, E., Garlic for treating hypercholesterolemia. A meta-analysis of randomized clinical trials, *Ann. Intern. Med.* 2000, *133*, 420 – 429.

[27] Beck, E., Grunwald, J. *Allium sativum* in der Stufentherapie der Hyperlipidaemie, *Med. Welt* 1993, *44*, 516 – 520.

[28] Schmidt, U., Schenk, N., Geruchsbildung bei repetiert Einnahme von standardisierten Knoblauchpulver-Dragees Kwai (LI 111) in Abbhangigkeit von der Tagesdosis, *Wissenschaftlicher Bericht,* 1992.

[29] Papageorgiou, C., Corbet, J. P., Menezes-Brandao, F., Pecegueiro, M. *et al.,* Allergic contact dermatitis to garlic (*Allium sativum* L.). Identification of the allergens: the role of mono-, di-, and trisulfides present in garlic. A comparative study in man and animal (guinea-pig), *Arch. Dermatol. Res.* 1983, *275*, 229 – 234.

[30] Braunwald, E., Fauci, A. S., Kasper, D. L., Hauser, S. L., *et al*., *Harrison's Principles of internal medicine*, The McGraw-Hill Companies, New York 2001.

[31] Bojs, G., Svensson, A., Contact allergy to garlic used for wound healing, *Contact Dermatitis* 1988, *18*, 179 – 181.

[32] Burden, A. D., Wilkinson, S. M., Beck, M. H., Chalmers, R. J., Garlic-induced systemic contact dermatitis, *Contact Dermatitis* 1994, *30*, 299 – 300.

[33] Pires, G., Pargana, E., Loureiro, V., Almeida, M. M., *et al*., Allergy to garlic, *Allergy* 2002, *57*, 957 – 958.

[34] Asero, R., Mistrello, G., Roncarolo, D., Antoniotti, P.L., *et al*., A case of garlic allergy, *J. Allergy Clin. Immunol.* 1998, *101*, 427 – 428.

[35] Sanchez-Hernandez, M. C., Hernandez, M., Delgado, J., Guardia, P., *et al.*, Allergenic cross-reactivity in the Liliaceae family, *Allergy* 2000, *55*, 297 – 299.

[36] Perez-Pimiento, A. J., Moneo, I., Santaolalla, M., de Paz, S. *et al.,* Anaphylactic reaction to young garlic, *Allergy* 1999, *54*, 626 – 629.

[37] Brenner, S., Pemphigus and diet. Have we solved the mystery of fogo selvagem? *Adv. Exp. Med. Biol*. 1999, *455*, 267 – 269.

[38] Ruocco, V., Brenner, S., Lombardi, M. L., A case of diet-related pemphigus, *Dermatology* 1996, *192*, 373 – 374.

[39] Brenner, S., Ruocco, V., Wolf, R., de Angelis, E., *et al.*, Pemphigus and dietary factors. *In vitro* acantholysis by allyl compounds of the genus Allium, *Dermatology* 1995, *190*, 197 – 202.

[40] Hjorth, N., Roed-Petersen, J., Occupational protein contact dermatitis in food handlers, *Contact Dermatitis* 1976, *2*, 28 – 42.

[41] Sinha, S. M., Pasricha, J. S., Sharma, R., Kandhari, K. C., Vegetables responsible for contact dermatitis of the hands, *Arch. Dermatol.* 1977, *113*, 776 – 779.

[42] Cronin, E., Dermatitis of the hands in caterers, *Contact Dermatitis* 1987, *17*, 265 – 269.

[43] Lembo, G., Balato, N., Patruno, C., Auricchio, L., *et al.,* Allergic contact dermatitis due to garlic (*Allium sativum*), *Contact Dermatitis* 1991, *25*, 330 – 331.

[44] Kanerva, L., Estlander, T., Jolanki, R., Occupational allergic contact dermatitis from spices, *Contact Dermatitis* 1996, *35*, 157 – 162.

[45] Anibarro, B., Fontela, J. L., De La Hoz, F., Occupational asthma induced by garlic dust, *J. Allergy Clin. Immunol.* 1997, *100*, 734 – 738.

[46] Fernandez-Vozmediano, J. M., Armario-Hita, J. C., Manrique-Plaza, A., Allergic contact dermatitis from diallyl disulfide, *Contact Dermatitis* 2000, *42*, 108 – 109.

[47] Hubbard, V. G., Goldsmith, P., Garlic-fingered chefs. *Contact Dermatitis* 2005, *52,* 165 – 166.

[48] Jappe, U., Bonnekoh, B., Hausen, B. M., Gollnick, H., Garlic-related dermatoses: case report and review of the literature, *Am. J. Contact Dermat.* 1999, *10*, 37 – 39.

[49] Delaney, T. A., Donnelly, A. M., Garlic dermatitis. *Australas J. Dermatol.* 1996, *37*, 109 – 110.

[50] Bassioukas, K., Orton, D., Cerio, R., Occupational airborne allergic contact dermatitis from garlic with concurrent Type I allergy, *Contact Dermatitis* 2004, *50*, 39 – 41.

[51] Hughes, T. M., Varma, S., Stone, N. M., Occupational contact dermatitis from a garlic and herb mixture, *Contact Dermatitis*. 2002, *47*, 48.

[52] Rudzki, E., Wladzinski, A., Contact eczema in nurses, *Przegl. Dermatol.* 1978, *65*, 549 – 552.

[53] van Ketel, W. G., de Haan, P., Occupational eczema from garlic and onion, *Contact Dermatitis* 1978, *4*, 53 – 54.

[54] Eming, S. A., Piontek, J. O., Hunzelmann, N., Rasokat, H., Severe toxic contact dermatitis caused by garlic, *Br. J. Dermatol.* 1999, *141*, 391 – 392.

[55] Moyle, M., Frowen, K., Nixon, R., Use of gloves in protection from diallyl disulfide allergy, *Australas J. Dermatol.* 2004, *45*, 223 – 225.

[56] Mitchell, J. C., Contact sensitivity to garlic (Allium), *Contact Dermatitis* 1980, *6*, 356 – 357.

[57] Henson, G. E., Garlic: an occupational factor in the etiology of bronchial asthma, *J. Fla. Med. Assoc.* 1940, *27*, 86.

[58] Falleroni, A. E., Zeiss, C. R., Levitz, D., Occupational asthma secondary to inhalation of garlic dust, *J. Allergy Clin. Immunol.* 1981, *68,* 156 – 160.

[59] Lybarger, J. A., Gallagher, J. S., Pulver, D. W., Litwin, A., *et al*., Occupational asthma induced by inhalation and ingestion of garlic. *J. Allergy Clin. Immunol.* 1982, *69*, 448 – 454.

[60] Couturier, P., Bousquet, J., Occupational allergy secondary inhalation of garlic dust, *J. Allergy Clin. Immunol.* 1982, *70*, 145.

[61] Seuri, M., Taivanen, A., Ruoppi, P., Tukiainen, H., Three cases of occupational asthma and rhinitis caused by garlic, *Clin. Exp. Allergy* 1993, *23*, 1011 – 1014.

[62] Lemiere, C., Cartier, A., Lehrer, S. B., Malo, J. L., Occupational asthma caused by aromatic herbs, *Allergy* 1996, *51*, 647 – 649.

[63] Armentia, A., Vega, J. M., Can inhalation of garlic dust cause asthma?, *Allergy* 1996, *51*, 137 – 138.

[64] Lybarger, J. A., Gallagher, J. S., Pulver, D. W., Litwin, A., *et al.,* Occupational asthma induced by inhalation and ingestion of garlic, *J. Allergy Clin. Immunol.* 1982, *69*, 448 – 454.

[65] Alvarez, M. S., Jacobs, S., Jiang, S. B., Brancaccio, R. R., *et al.*, Photocontact allergy to diallydisulfide, *Am. J. Contact Dermat.* 2003, *14*, 161 – 165.

[66] Scheman, A., Gupta, S., Photoallergic contact dermatitis from diallyl disulfide, *Contact Dermatitis* 2001, *45*, 179.

[67] McGovern, T. W., LaWarre, S., Botanical briefs: garlic-*Allium sativum*, *Cutis* 2001, *67*, 193 – 194.

[68] Parish, R. A., McIntire, S., Heimbach, D. M., Garlic burns: a naturopathic remedy gone awry, *Pediatr. Emerg. Care* 1987, *3*, 258 – 260.

[69] Kaplan, B., Schewach-Millet, M., Yorav, S., Factitial dermatitis induced by application of garlic, *Int. J. Dermatol*. 1990, *29*, 75 – 76.

[70] Lee, T. Y., Lam, T. H., Contact dermatitis due to topical treatment with garlic in Hong Kong. *Contact Dermatitis* 1991, *24*, 193 – 196.

[71] Garty, B. Z., Garlic burns, *Pediatrics* 1993, *91*, 658 – 659.

[72] Canduela, V., Mongil, I., Carrascosa, M., Docio, S., *et al*., Garlic: always good for the health?, *Br. J. Dermatol.* 1995, *132*, 161 – 162.

[73] Roberge, R. J., Leckey, R., Spence, R., Krenzelok, E. J., Garlic burns of the breast, *Am. J. Emerg. Med.* 1997, *15,* 548.

[74] Hallel-Halevy, D., Zlotogorski, A., Grunwald, M. H., Halevy, S., Multifaceted dermatitis artefacta caused by garlic, *J. Eur. Acad. Dermatol. Venereol*. 1997, *9*, 185 – 187.

[75] Rafaat, M., Leung, A. K., Garlic burns, *Pediatr. Dermatol.* 2000, *17*, 475 – 476.

[76] Hviid, K., Alsbjorn, B., "Burns" caused by local application of garlic, *Ugeskr. Laeger* 2000, *162*, 6853 – 6854.

[77] Farrell, A. M., Staughton, R. C., Garlic burns mimicking herpes zoster, *Lancet* 1996*, 347*, 1195.

[78] Baruchin, A. M., Sagi, A., Yoffe, B., Ronen, M., Garlic burns, *Burns* 2001, *27*, 781 – 782.

[79] Lachter, J., Babich, J. P., Brookman, J. C., Factor, A. Y., Garlic: a way out of work, *Mil. Med.* 2003, *168*, 499 – 500.

[80] Dietz, D. M., Varcelotti, J. R., Stahlfeld, K. R., Garlic burns: a not-so-rare complication of a naturopathic remedy?, *Burns* 2004, *30*, 612 – 613.

[81] Friedman, T., Shalom, A., Westreich, M., Self-inflicted garlic burns: our experience and literature review, *Int. J. Dermatol.* 2006, *45*, 1161 – 1163.

[82] Ackermann, R. T., Mulrow, C. D., Ramirez, G., Gardner, C. D. *et al.*, Garlic shows promise for improving some cardiovascular risk factors, *Arch. Intern. Med*. 2001, *161*, 813 – 824.

[83] Ang-Lee, M. K., Moss, J., Yuan, C. S., Herbal medicines and perioperative care, *JAMA* 2001, *286*, 208 – 216.

[84] Rose, K. D., Croissant, P. D., Parliament, C. F., Levin, M. B., Spontaneous spinal epidural hematoma with associated platelet dysfunction from excessive garlic ingestion: a case report, *Neurosurgery* 1990, *26*, 880 – 882.

[85] Burnham, B. E., Garlic as a possible risk for postoperative bleeding, *Plast. Reconstr. Surg.* 1995, *95*, 213.

[86] German, K., Kumar, U., Blackford, H. N., Garlic and the risk of TURP bleeding. *Br. J. Urol*. 1995, *76,* 518.

[87] Carden, S. M., Good, W. V., Carden, P. A., Good, R. M., Garlic and the strabismus surgeon, *Clin. Experiment Ophthalmol.* 2002, *30*, 303 – 304.

[88] Desai, H. G., Kalro, R. H., Choksi, A. P., Effect of ginger & garlic on DNA content of gastric aspirate, *Indian J. Med. Res.* 1990, *92,*139 – 141.

[89] Hoshino, T., Kashimoto, N., Kasuga, S., Effects of garlic preparations on the gastrointestinal mucosa, *J. Nutr.* 2001, *131*, 1109S – 1113S.

[90] Yuncu, M., Eralp, A., Celik, A., Effect of aged garlic extract against methotrexate-induced damage to the small intestine in rats, *Phytother. Res*. 2006, *20*, 504 – 510.

[91] Rana, S. V., Pal, R., Vaiphei, K., Singh, K., Garlic hepatotoxicity: safe dose of garlic, *Trop. Gastroenterol*. 2006, *27*, 26 – 30.

[92] Gupta, M. K., Mittal, S. R., Mathur, A. K., Bhan, A. K., Garlic – the other side of the coin, *Int. J. Cardiol.* 1993, *38*, 333.

[93] Benes, J., Prerovsky, K., Rehurek, L., Kase, F., Garlic food allergy with symptoms of Meniere's disease, *Cas. Lek. Cesk.* 1966, *105*, 825 – 827.

[94] Park, J. J., Lee, J., Kim, M. A., Back, S. K., *et al.,* Induction of total insensitivity to capsaicin and hypersensitivity to garlic extract in human by decreased expression of TRPV1, *Neurosci. Lett*. 2007, *411*, 87 – 91.

[95] Marcus, D. M., Snodgrass, W. R., Do no harm: avoidance of herbal medicines during pregnancy, *Obstet. Gynecol*. 2005, *105*, 1119 – 1122.

[96] Meher, S., Duley, L., Garlic for preventing pre-eclampsia and its complications, *Cochrane Database Syst Rev.* 2006, *3*, CD006065.

[97] 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. Obstet. Gynecol. Reprod. Biol.* 2001, *99*, 201 – 206.

[98] Mennella, J. A., Beauchamp, G. K., Maternal diet alters the sensory qualities of human milk and the nursling's behaviour, *Pediatrics* 1991, *88*, 737 – 744.

[99] Mennella, J. A., Beauchamp, G. K., The effects of repeated exposure to garlic-flavored milk on the nursling's behaviour, *Pediatr. Res*. 1993, *34*, 805 – 808.

[100] Mennella, J. A., Johnson, A., Beauchamp, G. K., Garlic ingestion by pregnant women alters the odor of amniotic fluid, *Chem. Senses* 1995, *20*, 207 – 209.

[101] Snell, S. B., Garlic on the baby's breath, *Lancet* 1973, *2*, 43.

[102] Izzo, A. A., Herb-drug interactions: an overview of the clinical evidence. *Fundam. Clin. Pharmacol*. 2005, *19*, 1 – 16.

[103] Izzo, A. A., Di Carlo, G., Borrelli, F., Ernst, E., Cardiovascular pharmacotherapy and herbal medicines: the risk of drug interaction. *Int. J. Cardiol*. 2005, *98*, 1 – 14.

[104] Izzo, A. A., Borrelli, F., Capasso, R., Herbal medicine: the dangers of drug interaction. *Trends Pharmacol. Sci*. 2002, *23*, 358 – 391.

[105] Gurley, B. J., Gardner, S. F., Hubbard, M. A., Williams, D. K., *et al.*, Clinical assessment of effects of botanical supplementation on cytochrome P450 phenotypes in the elderly: St John's wort, garlic oil, Panax ginseng and Ginkgo biloba, *Drugs Aging* 2005, *22*, 525 – 539.

[106] Markowitz, J. S., Devane, C. L., Chavin, K. D., Taylor, R. M., *et al*., Effects of garlic (*Allium sativum* L.) supplementation on cytochrome P450 2D6 and 3A4 activity in healthy volunteers, *Clin. Pharmacol. Ther.* 2003, *74*, 170 – 177.

[107] Cox, M. C., Low, J., Lee, J., Walshe, J., *et al.,* Influence of garlic (*Allium sativum*) on the pharmacokinetics of docetaxel, *Clin. Cancer Res*. 2006, *12*, 4636 – 4640.

[108] Greenblatt, D. J., Leigh-Pemberton, R. A., von Moltke, L. L., *In vitro* interactions of water-soluble garlic components with human cytochromes p450, *J. Nutr*. 2006, *136*, 806S – 809S.

[109] Lin, J. H., Yamazaki, M., Clinical relevance of P-glycoprotein in drug therapy, *Drug Metab. Rev.* 2003, *35*, 417 – 454.

[110] Zhou, S., Lim, L. Y., Chowbay, B., Herbal modulation of P-glycoprotein. *Drug Metab. Rev.* 2004, *36*, 57 – 104.

[111] Foster, B. C., Foster, M. S., Vandenhoek, S., Krantis, A., *et al*., An *in vitro* evaluation of human cytochrome P450 3A4 and P-glycoprotein inhibition by garlic, *J. Pharm. Pharm. Sci*. 2001, *4,* 176 – 84.

[112] Saw, J. T., Bahari, M. B., Ang, H. H., Lim, Y. H., Potential drug-herb interaction with antiplatelet/anticoagulant drugs. *Complement. Ther. Clin. Pract.* 2006, *12*, 236 – 241.

[113] Lee, L. S., Andrade, A. S., Flexner, C., Interactions between natural health products and antiretroviral drugs: pharmacokinetic and pharmacodynamic effects, *Clin. Infect. Dis*. 2006, *43*, 1052 – 1059.

[114] Sunter, W. H., Warfarin and garlic, *Pharm. J.* 1991, *246*, 772.

[115] Tattelman, E., Health effects of garlic, *Am. Fam. Physician.* 2005, *72*, 103 – 106.

[116] Pathak, A., Leger, P., Bagheri, H., Senard, J. M., *et al.*, Garlic interaction with fluindione: a case report, *Therapie* 2003, *58,* 380 – 381.

[117] Macan, H., Uykimpang, R., Alconcel, M., Takasu, J., *et al.*, Aged garlic extract may be safe for patients on warfarin therapy, *J. Nutr.* 2006, *136*, 793S – 795S.

[118] No author listed, HIV patients taking antiretrovirals should avoid garlic, St. John's wort. Other health products were fine, *AIDS Alert* 2006, *21*, 21 – 22.

[119] Piscitelli, S. C., Burstein, A. H., Welden, N., Gallicano, K. D., The effect of garlic supplements on the pharmacokinetics of saquinavir, *Clin. Infect. Dis.* 2002, *34,* 234 – 238.

[120] Gallicano, K., Foster, B., Choudhri, S., Effect of short-term administration of garlic supplements on single-dose ritonavir pharmacokinetics in healthy volunteers, *Br. J. Clin. Pharmacol*. 2003, *55*, 199 – 202.

[121] Laroche, M., Choudhuri, S., Gallicano, K., Foster, B., Severe gastrointestinal toxicity with concomitant ingestion of ritonavir and garlic, *Can. J. Infect. Dis*. 1998, *9*, 471P.

[122] Aslam, M., Stockley, I. H., Interaction between curry ingredient (karela) and drug (chlorpropamide), *Lancet* 1979, *1*, 607.

[123] Gwilt, P. R., Lear, C. L., Tempero, M. A., Birt, D. D., *et al.*, The effect of garlic extract on human metabolism of acetaminophen, *Cancer Epidemiol. Biomarkers Prev.* 1994, *3*, 155 – 160.

[124] Jabbari, A., Argani, H., Ghorbanihaghjo, A., Mahdavi, R., Comparison between swallowing and chewing of garlic on levels of serum lipids, cyclosporine, creatinine and lipid peroxidation in Renal Transplant Recipients, *Lipids Health Dis*. 2005, *4*, 11.

