

Hypersensitivity Reactions to Complementary and Alternative Medicine Products

Maria Teresa Ventura^{1,*}, Marinella Viola², Gianfranco Calogiuri³, Francesco Gaeta², Oronzo Pesole³ and Antonino Romano^{2,4}

¹Department of Internal Medicine, Immunology and Infectious Diseases (MIDIM), University of Bari Medical School, Policlinico, Bari, Italy; ²Department of Internal Medicine and Geriatrics, UCSC, Allergy Unit, C.I. Columbus, Rome, Italy; ³⁴th Pneumology Division, Civil Hospital A. Galateo, S. Cesareo, Lecce, Italy IRCCS and ⁴Oasi Maria S.S., Troina, Italy

Abstract: Complementary and alternative medicine (CAM) is becoming increasingly popular, and is often used for treating hypersensitivity diseases. Virtually all alternative remedies can cause hypersensitivity reactions, but the most frequently involved ones are tea tree oil, members of the Compositae family, propolis, oils used in aromatherapy, substances responsible for photosensitization, and metal-containing compounds. The main target organ is skin, with manifestations ranging from contact dermatitis (the most common) to urticaria-angioedema, maculopapular eruptions, photosensitivity reactions, and the Stevens-Johnson syndrome. Other types of reactions are possible, including respiratory and anaphylactic ones. Different pathogenic mechanisms have been suggested for CAM product reactions, including immunologic ones. Basophils and mast cells participate in IgE-mediated reactions through the release of mediators like histamine and tryptase, whereas a T-cell-mediated pathogenic mechanism is involved in most delayed reactions, particularly contact dermatitis and maculopapular eruptions. Skin tests and serum specific IgE assays are carried out to diagnose immediate hypersensitivity reactions, while patch tests and lymphocyte transformation tests are usually performed to evaluate delayed hypersensitivity reactions.

Thus clinicians should know about the potential of CAM products for causing adverse reactions. Our study is aimed at highlighting the risk of hypersensitive reactions to CAM remedies on the basis of the numerous cases reported in the literature.

Because little is known about adverse reactions to CAM products, further systematic studies and an appropriate regulation by health authorities are necessary.

Key Words: Hypersensitivity reactions, herbal remedies, metals, contact dermatitis, patch tests, specific IgE.

INTRODUCTION

There is evidence of growing interest by the public in so-called complementary and alternative medicine (CAM).

The World Health Organization estimates that 80% of the population uses some form of CAM for health care and the predictions are that this rate will continue to increase in the future, thanks also to media reports, convincing advertisements, and Internet claims [1]. According to European estimates, the frequency of use ranges from 20% in the Netherlands to 49% in France [2]. A survey performed in the United States revealed that the general population's use of unconventional treatments rose from 33.8% to 42.1% between 1990 and 1997 [3]. This practice is also associated with considerable annual costs for individual patients, because it is largely paid 'out of pocket'; according to estimates, these costs amount to AU\$ 930 million in Australia [4], US\$ 13.7 billion in the US [5], and £1.6 billion in the UK [6].

The typical CAM user is a youngish (35-50 years) and well-educated individual with high socioeconomic status; women and subjects who exercise frequently are predominant [7]. They are motivated by the assumption that CAM is natural and therefore safe, devoid of side effects, and without unpleasant consequences [7]. These subjects are unsatisfied with the results of traditional medicine and find CAM to be more compatible with their own values, beliefs, and philosophical orientations toward health and life [8]. They use CAM to treat chronic non-life-threatening diseases, including hypersensitivity ones, which are especially important because they are increasingly prevalent [9]. A survey shows that one-third of hypersensitive patients uses a lengthy list of unconventional remedies [10], ranging from homeopathy to aromatherapy, phytotherapy, acupuncture, and many others.

Because of its significant social-economical impact, CAM can no longer be ignored by academia. Advocates of CAM products highlight their benefits and often point to the safety of natural, soft, or holistic approaches, but little is known about their possible side effects. Many of these are not reported in the medical literature for two important reasons: 1) most of the remedies are not under the strict regulation of the health authorities, so adverse reactions are not

*Address correspondence to this author at the Department of Internal Medicine, Immunology and Infectious Diseases (MIDIM), University of Bari Medical School, Policlinico, Piazza G. Cesare, 11, 70124 Bari, Italy; E-mail: mt.ventura@allergy.uniba.it

monitored as are those of conventional drugs; 2) alternative remedies are usually not prescribed by physicians, but are purchased directly by users, most of whom do not report adverse reactions to their general practitioners. In effect, a study carried out by interviewing 515 users of herbal remedies demonstrated that 134 responders (26%) would have consulted their general practitioners for a serious adverse reaction to a conventional over-the-counter (OTC) drug, but not for a similar adverse reaction to a herbal remedy, while 4 responders (0.8%) would have consulted their general practitioners for a serious adverse reaction to a herbal remedy, but not for a similar reaction to a conventional OTC drug [11].

Furthermore, looking at the literature, the majority of clinical trials are of low methodological quality, and thus difficult to interpret. A few studies have been performed in a rigorously controlled fashion, but most of their results are inconclusive [12]. Most studies of CAM-related adverse reactions are reports of single subjects who suffered hypersensitivity reactions, mechanical injuries, pharmacological interactions, infectious complications, organ toxicity, neoplastic lesions, or nutritional deficiencies [13].

In particular, our review examines the compounds most frequently responsible for hypersensitivity reactions. Considering that the number of such reactions to remedies containing substances like herbs or metals reported in the medical literature is too large to be comprehensively reviewed here, we provide only a few examples of each type of CAM with the related compounds, based on the most recent case reports and those with clinical significance (Table 1).

Table 1. List of Complementary and Alternative Medicine Products Most Involved in Hypersensitivity Reactions

Herbal products
- Tea tree oil - Orange oils (<i>Citrus bergamia</i>) - Oils for aromatherapy (lavender, jasmine, rosewood, lemon, citronella, cassia, ylang-ylang, clove) - Compositae family (<i>Arnica montana</i>, <i>Inula helenium</i>, chamomile, <i>Echinacea angustifolia</i>) - Cucurbitaceae family (<i>Ecbalium elaterium</i>) - Rutaceae family (<i>Citrus hystrix</i>) - <i>Rhus toxicodendron</i> - <i>Ginkgo biloba</i> - <i>Ophiopogonis japonicus</i> - <i>Hypericum perforatum</i> - <i>Psoralea corylifolia</i> - Other (<i>Polygala tenuifolia</i>, <i>Pfaffia paniculata</i>, <i>Glycyrrhiza glabra</i>)
Metal products
- Chromium - Nickel - Mercury
Other
- Propolis - Enzymes

HYPERSENSITIVITY REACTIONS

Pathogenic Mechanisms

The revised nomenclature for allergies [14], which is based on the mechanisms that initiate and mediate hypersensitivity reactions, classifies such reactions to drugs as either allergic or non-allergic. The former are mediated by immunologic mechanisms, either antibodies or cells; all other reactions should be referred to as non-allergic drug hypersensitivity. In addition, allergic reactions to drugs are classified as IgE-mediated or non-IgE-mediated; many of the latter are cell-mediated. In IgE-mediated reactions, the drug or drug metabolite reacts with IgE bound to the surface of mast cells and leads to the activation, degranulation, and release of mast-cell vasoactive mediators like histamine and tryptase. In cell-mediated allergic reactions, CD4⁺ and CD8⁺ T cells recognize drugs through their $\alpha\beta$ receptors in an MHC (major histocompatibility complex)-dependent way [15]. Drug-specific T cells generate inflammatory skin reactions through the release of various cytokines (e.g., interleukin-5, interferon) and chemokines (e.g., interleukin-8). Activation of T cells with a particular function leads to a specific clinical picture; for example, a large number of cytotoxic CD8⁺ T cells in the epidermis is associated with the formation of vesicles and bullae, whereas in maculopapular exanthemas, perforin- and granzyme B-positive CD4⁺ T cells kill activated keratinocytes.

Non-allergic hypersensitivity reactions to drugs may involve different pathogenic mechanisms, such as the capability of releasing mediators through a non-immunologic mechanism and the inhibitory effect on cyclooxygenase-1 of nonsteroidal anti-inflammatory compounds.

Causal Agents, Clinical Manifestations, and Allergologic Diagnosis

First of all, it must be said that the potential sensitizing capability of numerous CAM remedies cause mainly contact dermatitis and less frequently induce IgE-mediated reactions, such as anaphylactic, respiratory (rhinitis and/or asthma), or cutaneous ones (urticaria and/or angioedema). In addition to the last-mentioned reactions, skin – which seems to be the main target organ – is also interested by maculopapular exanthemas, photosensitivity reactions, toxic dermatosis, erythema-multiforme-like eruptions, and the Stevens-Johnson syndrome (SJS).

Herbal Remedies

With regard to contact dermatitis, little is known about the prevalence of hypersensitivity reactions to herbal remedies. In a recent study [16], 140 patients with contact dermatitis (21 high-risk subjects using botanical products and suspected of hypersensitivity to these substances and 119 control subjects without histories of using herbal products) were patch-tested with 47 botanical extracts. A significant positive reaction was found in 47.6% of the high-risk group and in 3.4% of the control group. The most common allergen, as observed in an earlier study [17], was tea tree oil (the distilled extract of *Melaleuca alternifolia*).

Since the first report in 1991 [18], contact dermatitis from tea tree oil hypersensitivity has been much described in

recent years because of its increasing use for purported antimicrobial and anti-inflammatory effects [18-27]. The oil is used in many cosmetics, personal care products (ointments, lotions, deodorants, sunscreen lotions), and household products (fabric softeners, cleansers, laundry detergents), as well as in a non-prescriptive medicament for treating various cutaneous diseases. Due to its volatile nature, this oil can cause airborne contact dermatitis, as described in a 40-year-old atopic man after inhalation of vapors from a hot aqueous solution containing the oil and used for treating bronchitis [20]. Additionally, systemic contact dermatitis has resulted from ingestion of the oil [21]. One case of linear IgA disease was precipitated by topical application of tea tree oil to an umbilical piercing [22]. Occupational cases have been seen in a beautician and a chiropract [23], as well as in an aromatherapist [24].

Despite the numerous reported cases, it is difficult to estimate a prevalence rate for hypersensitivity contact dermatitis from tea tree oil. According to an Australian study [25], it ranged from 2.9% to 4.8% in 219 healthy volunteers, against 4.3% to 7.2% in pre-exposed patients; on the other hand, a recent American study [26] found that only 0.5% of the 906 patients tested resulted positive to patch tests with tea tree oil. In evaluating these data, it must be considered that there are several different oils, which are extremely heterogeneous even when extracted from the same plant, with a wide range of chemical components implicated as allergens; furthermore, each oil changes over time as a result of contact with air, light, moisture, or heat, as well as after application, owing to the absorbent and metabolic properties of the human skin [27].

The second largest number of positive reactions in patients with cosmetic-induced dermatitis is due to Compositae [17].

The Compositae family, with its numerous and widespread allergens (mainly sesquiterpene lactones), is probably the most important allergenic plant family in Europe today [28, 29]. In a recent study [30], the frequency of Compositae hypersensitivity among patients with extrinsic atopic dermatitis has been estimated at 30%. The prevalence of sensitization is high for a few species, such as arnica (*Arnica montana*) and elecampane (*Inula helenium*), but low for most, especially the widely used German chamomile.

Arnica seems to have the highest prevalence of sensitization; in his survey, Hausen [31] lists more than 100 reported hypersensitivity reactions between 1844 and 1977. Further studies have confirmed the high arnica sensitizing potential, even if some authors have also highlighted its irritant capability.

The greatest risk of more widespread immunological responses is associated with the use of elecampane. An erythema-multiforme-like eruption was observed in a 31-year-old woman after a 'herbal bag' had been applied for back pain; patch tests with *Inula helenium* were positive, demonstrating the responsibility of this compound [32].

On the other hand, the risk of elicitation of dermatitis seems to be low for chamomile (in particular the German species), even though its extracts are widely used in herbal remedies and cosmetics and a cellular-mediated hypersensi-

tivity has been found in more than 50% of Compositae-sensitive patients in large European studies [28, 33]. Life-threatening reactions have even been associated with chamomile use [34], as reported in a 35-year-old nonatopic woman during labor [35]. She experienced an anaphylactic shock after an enema containing glycerol and Kamillosoan, an oily extract from chamomile flowers; this reaction resulted in asphyxia and death of the baby, as well as in laparogastrotomy with subsequent paralytic ileus and septic fever in the woman. Skin prick tests were positive to Kamillosoan and negative to latex, glycerol, and a standard series of inhalant allergens, including extracts from birch pollen. IgE specific for chamomile were detected by the Phadebas CAP system™ (Pharmacia, Uppsala, Sweden) (class = 2). Immunoblots identified the anaphylaxis-triggering allergen, which was a homologue of the birch pollen allergen Bet v 1. In fact, the patient's IgE were able to bind the 17-kd allergens in chamomile and Kamillosoan, as well as the major birch pollen allergen Bet v 1 with a molecular weight of 17 kd.

Severe adverse reactions, even if rare, are also associated with other members of the Compositae family, such as *Echinacea angustifolia*, used for treating symptoms of the common cold and pollen hypersensitivity. Mullins *et al.* [36] described 5 cases of adverse reactions (specifically, two anaphylactic ones, two asthmatic ones, and a maculopapular rash) following intake of commercial extracts from this plant; *Echinacea* hypersensitivity was confirmed by positive skin prick tests performed using a commercially available glycerinated extract and/or by radioallergosorbent testing (RAST) for specific IgE in four of these cases and by repeated spontaneous challenges in three of them. Furthermore, on the basis of 51 reports of adverse reactions to *Echinacea* reviewed by the Australian Adverse Drug Reactions Advisory Committee, the possibility of cross-reactivity between *Echinacea* and other environmental allergens due to the presence of hypersensitivity symptoms in patients never exposed to the former has been highlighted [36]. *Echinacea* is also associated with recurrent erythema nodosum, as described in a 41-year-old man after intake of a herbal product containing this plant [37].

Other important reactions involving skin have been reported after use of numerous other herbal remedies. A 45-year-old woman experienced a systemic dermatitis from application of a *Rhus toxicodendron* tincture followed by the oral introduction of the same substance for the treatment of herpes lesions [38]. Patch test performed with *Rhus toxicodendron* gave a positive result.

A diffuse maculopapular rash was described in a 66-year-old woman about a week after ingestion of a ginkgo biloba supplement [39]. The extract of this plant is used worldwide as a possible remedy for dementia and memory loss. It is also well known for causing hypersensitivity contact dermatitis; the ginkgo plant, in effect, contains potent allergens, such as ginkgolic acids, which is also structurally similar to the *Toxicodendron* ones, with possible cross-allergenicity.

A case of SJS was observed in a 66-year-old woman after the consumption of a so-called health drink containing the *ophiopogonis* tuber [42]. Lymphocyte stimulation tests and patch tests performed with the drink, as well as 5 other drugs, taken contemporaneously by the patient, were positive

only for the drink. All of the 13 components of the latter were individually patch tested, and only Mai-Meu-Dong-Tang (the dry root tuber of *Ophiopogon japonicus*) showed a positive reaction at the 72-hour reading. Although contrary to standard practice [40, 41], a provocation test was performed with the *ophiopogonis* tuber, inducing an erythematous reaction at one-hundredth of the original dose. Another patient, a 46-year-old man, experienced a SJS twice after the intake of the same tablets, which he had bought in a health food shop as a general tonic [43]. Each tablet contained extracts of red clover, burdock, queen's delight, poke root, prickly pear, ash, sassafras bark, and Passiflora.

An extensive phytophotodermatitis due to *Citrus hystrix* was reported in a 49-year-old man after application of a folk remedy recommended to relieve the discomfort of insect stings. *Citrus hystrix* is a member of the Rutaceae family; its fruit is not eaten fresh, but can be made into preserves or used as a spice for cooking, a hair shampoo, or a medicine. Psoralens – chemical compounds with photosensitizing action – have been isolated from species of citrus and other plants of the Rutaceae family, as well as from species of Umbelliferae, Moraceae, and Leguminosae [44].

Photosensitivity has always been considered a possible adverse effect of St John's Wort (*Hypericum perforatum*), a best-selling herbal antidepressant. Golsch *et al.* [45] reported a case of a 61-year-old patient who developed recurrent itchy erythematous lesions in light-exposed areas after taking St John's Wort-extract for 3 years. Routine patch testing did not reveal any significant reactions and photo-patch testing was negative. An additional case of photosensitivity after oral administration of St John's Wort was published later [46]. After reading a magazine article, a 35-year-old woman took 500 mg daily of ground St John's Wort for mild depression. Four weeks later, she started to feel a stinging pain on the skin of her face and the dorsum of her hand, exacerbated by exposure to the sun. On the basis of a neurological examination, a diagnosis of subacute toxic neuropathy was made. St John's Wort was withdrawn and the symptoms disappeared gradually.

Another case of acute photosensitivity following treatment with a herbal remedy relates to *Psoralea corylifolia* [47]. The patient had taken the herbal product in the form of a cream that he used to treat his long-standing vitiligo and subsequently experienced erythema in exposed areas. By excluding other causes, a diagnosis of photosensitivity due to *Psoralea corylifolia* was made. This diagnosis was subsequently confirmed through an inadvertent rechallenge. The herb, which is frequently used for vitiligo by Indians, contains psoralen, isopsoralen, and psoralidin.

Essential oils used for aromatherapy have repeatedly been implicated as a cause of photosensitization. Specifically, oil of bergamot, an extract from the rind of bergamot oranges (*Citrus bergamia*), has photosensitive and melanogenic properties because of the presence of psoralens, primarily bergapten (5-methoxypsoralen). Bullous skin lesions have been described in two women: the first one used bergamot oil and subsequently stayed outdoors for several hours on a sunny day, while the second one was exposed to aerosolized bergamot oil in a sauna and subsequent UVA radiation in a tanning salon [48]. These reports highlight the po-

tential health hazard related to the increasing use of aromatherapy. This practice consists in the use of essential oils topically (massage, bath, wet dressings), orally, or by inhalation (*via* vaporization) to promote physical and psychological well-being [49]. Essential oils are aromatic substances extracted from flowers, plants, and wood resins by a variety of methods, such as distillation or maceration. An interesting case of multiple sensitizations was described in a 65-year-old aromatherapist, who presented an eczema initially on her arms and upper trunk, and later on her legs, face, and hands [24]. Positive to 17 of the 20 patch-tested oils, she had probably been first sensitized to lemongrass oil used in aromatherapy, and later developed dermatitis from other essential oils, household cleansers, and sealing wax.

According to an American questionnaire-based study, the prevalence of hand dermatitis in massage therapists ranges from 15% of the subjects assessed by the self-reported method to 23% of those evaluated by the symptom-based one [50]. In addition, statistically significant independent risk factors for self-reported hand dermatitis included the use of aromatherapy products, such as massage oils, creams, or lotions, as well as a history of atopic dermatitis; an association with the female gender had been demonstrated in previous studies [51-54]. The most commonly involved oils, identified by patch testing, include not only the above-mentioned tea tree oil and orange oils (e.g., bergamot oil), but also lavender, jasmine, rosewood, lemon, citronella, cassia, ylang-ylang, and clove oils. In general, the most common responsible allergens are monoterpene and sesquiterpene hydrocarbons, monoterpene and sesquiterpene alcohols, esters, ethers, aldehydes, ketones, and oxides. Furthermore, the metabolism of products by the skin increases their sensitizing potential or, conversely, a mixture of several substances may reduce the sensitizing potential of each one.

IgE-mediated reactions, sometimes life-threatening, may also be elicited by plant-derived products, as demonstrated in a patient suffering from pollen-induced hypersensitivity rhinoconjunctivitis, who experienced anaphylaxis after eating a pollen mixture used as a health food [55]. An intranasal administration of *Ecballium elaterium* was responsible for severe uvular angioedema with life-threatening dyspnoea in a 54-year-old woman who suffered an acute maxillary sinusitis [56]. She took this folk remedy on her neighbor's advice because of the failure of an antibiotic and analgesic therapy. In the emergency room, the airway obstruction was detected by physical examination. The patient was treated with epinephrine and prednisolone, with the gradual resolution of the symptoms. *Ecballium elaterium* is a plant indigenous to the Mediterranean region, whose common name is squirting cucumber; the juice of its fruits is used in treating sinusitis and rhinitis. Kloutsos *et al.* [57] demonstrated that *Ecballium elaterium* hypersensitivity was not rare. In this study, 42 patients who had experienced adverse reactions (mainly uvula oedema) after drinking this juice were skin tested, with positive reactions to pollen weeds and various fruits of the Cucurbitaceae family.

The inhalation of different substances of plant origin for occupational reasons may also cause respiratory symptoms. The list of these responsible agents is continuously lengthening. A pharmacist developed asthma and rhinitis while

chopping 6 kinds of herbs [Chunkung (*Cnidii rhizoma*), Banha (*Pinellia ternata*), Sanyak (*Dioscorea radix*), Kang-whal (*Ostericum koreanum*), Danggui (*Angelica radix*), and Kunkang (*Zingiberis rhizoma*)] [58]. Allergologic examination revealed strong positive responses to prick tests with each herb, while serum-specific IgE antibodies were detected by an immuno enzymatic assay (ELISA) only for Chunkung, Banha, and Sanyak. An immunoblotting study using these extracts also showed specific IgE-binding components within the individual extracts. Broncho-provocation tests performed at decreasing dilutions of Danggui resulted positive at a 1:1,000 dilution, while basophil histamine release tests performed for Sanyak and Danggui were positive for the latter extract.

Three cases of asthma and rhinitis induced by Wonjj (*Polygala tenuifolia*) [59], Brazil ginseng (*Pfaffia paniculata*) [60], and liquorice roots (*Glycyrrhiza glabra*) [61] were observed, respectively, in a man and two women processing these herbal medicines. An IgE-mediated mechanism was demonstrated by performing skin prick tests, serological tests (ELISA and/or ELISA inhibition tests) and bronchial challenges with the suspected substances.

Propolis

Another important cause of hypersensitivity reactions is represented by propolis, a substance with strong adhesive properties, used by honeybees to seal crevices in the hive and to embalm dead invaders and other particles there in order to prevent their microbial decomposition. The major source of propolis is the resinous exudate of poplar buds collected by bees. More than 46 compounds have been found in this natural product; the main sensitizing agents seem to be 3-methyl-2-butenyl caffeate and phenylethyl caffeate. Contact dermatitis to propolis is not rare. Since the first written warnings on its sensitizing potential, dating back to 1887 [62], more than 250 cases of hypersensitivity contact dermatitis caused by propolis have been described. A few of these cases occurred in beekeepers due to direct [63, 64] or airborne [63] contact. Gulbahar *et al.* [64] reported a case of a 45-year-old nonatopic beekeeper who experienced hand dermatitis during honey collection. He insisted that the lesions occurred when he was stung by the honeybees and denied the role of propolis, because he was continuously wearing gloves while handling the hives. Skin biopsy showed psoriasiform contact dermatitis; skin prick tests (SPT) and specific IgE assays (Phadebas CAP system) with *Apis mellifera* were negative; patch tests performed using the European standard series and *Apis mellifera* SPT material were also negative. On the other hand, a patch test with propolis (10% petroleum) was positive. The patient then remembered that there had been a slight contact with propolis while he was taking off his gloves. He decided to quit working as a beekeeper and his hand lesions healed almost completely. Besides the sensitization of beekeepers, only a few other cases of occupational contact dermatitis have been reported: a forest worker and a farmer, who had contact with poplar trees while cutting branches [65]; an artist, who was molding with beeswax [66]; an instrument maker, who probably had contact with varnish containing propolis [67]; and a worker in a retail store, who probably had contact with varnish containing beeswax [68]. A fatal reaction was described in a 48-year-

old man after topical application of propolis used to treat acute pharyngitis [69]. Symptoms developed 6 hours after propolis application and increased rapidly until the patient experienced laryngeal edema and cardiac arrest. He was resuscitated twice, but died 50 days later, because of intractable sepsis complications.

Metals

Metal-containing products may cause hypersensitivity reactions, mainly cutaneous ones. A man experienced a severe exacerbation of his eczema after oral intake of a chromium-containing homeopathic drug (Pentackan Sinnabaun D4) prescribed as a hyposensitizing therapy for treating his chromium hypersensitivity [70]. Another patient, a 52-year-old female, developed contact dermatitis after neuroreflexotherapy with the implantation of staples on her lower back [71]. She displayed a positive patch test to nickel, one of the metallic components of the staples. An unusual case of baboon syndrome to mercury in a homeopathic drug was reported in a 5-year-old girl with a maculopapular eruption that started 24 hours after the intake of a single tablet of a mercury-containing homeopathic cough remedy [72]. Patch tests were positive to thimerosal and mercury.

Other Products

A 54-year-old female patient experienced an anaphylactic shock during administration of a third course of a non-regular enzyme preparations (Wobe-Mugos injections, Wobe-Mugos tablets, and Wobe-Mugos suppositories) for multiple sclerosis [73]. Later it was shown she had already experienced symptoms after the second injection.

CONCLUSION

The above data suggest that hypersensitivity reactions to CAM treatments are an important issue in medicine. CAM is certainly not as safe as its advocates claim, because a considerable risk of adverse effects, sometimes severe, exists. Clinicians should be aware that these remedies can cause hypersensitivity reactions with patterns similar to those to conventional drugs. Thus, it is important for clinicians to first ask patients about their use of such therapies – particularly as many of them would not normally provide such information – and then to inform them about the risk of adverse reactions. In effect, it has been shown that appropriate information reduces CAM use [74].

At present, not even a rough estimate of the incidence of such hypersensitivity reactions is possible, because systematic investigations are not available [75]. Most of the above evidence regards case reports, and thus it is likely that the hypersensitivity reactions summarized above represent merely the tip of an iceberg. Case reports included in this review originated from extensive literature searches on PubMed, followed by our selection. It is conceivable that this search strategy did not retrieve all cases recorded in the medical literature.

In addition, the reported data are not homogeneous. With such publications, it is often difficult to demonstrate a causal link between the treatment and the adverse reaction. This situation limits the conclusions that can be drawn from the

present review, thus highlighting the need for systematic research in this complex field.

More prospective, controlled studies focusing on adverse effects are required to assess the safety of many treatments still used without sound scientific evidence [76]. The criteria for determining the allergologic diagnosis of the adverse effects of unconventional treatments should be the same as those for conventional therapies; a given method should be chosen only if the adverse reactions are established, and the benefits outweighs the risks. This method avoids the biased results generated by comparing systems that properly monitor adverse reactions with others where such monitoring is almost totally absent.

ABBREVIATIONS

CAM	=	Complementary and alternative medicine
ELISA	=	Enzyme-linked immunosorbent assay
IgA	=	Immunoglobulin A
IgE	=	Immunoglobulin E
kd	=	Kilodalton
mg	=	Milligram
MHC	=	Major histocompatibility complex
OTC	=	Over-the-counter
RAST	=	Radioallergosorbent testing
SJS	=	Stevens-Johnson syndrome
SPT	=	Skin prick test
UV	=	Ultraviolet radiation

REFERENCES

References 77-79 are related articles recently published in *Current Pharmaceutical Design*.

- [1] Bielory L. 'Complementary and alternative medicine' population based studies: a growing focus on allergy and asthma. *Allergy* 2002; 57: 655-8.
- [2] Fisher P, Ward A. Complementary medicine in Europe. *BMJ* 1994; 309: 107-11.
- [3] Eisenberg DM, Davis RB, Ettner SL, Appel MS, Wilkey S, Van Rompay M, et al. Trends in alternative medicine use in United States, 1990-1997. *JAMA* 1998; 280: 1569-75.
- [4] MacLennan AH, Wilson DH, Taylor AW. Prevalence and cost of alternative medicine in Australia. *Lancet* 1996; 347: 569-73.
- [5] Eisenberg DM, Kessler RC, Foster C, Norlock FE, Calkins DR, Delbanco T. Unconventional medicine in the United States. *N Engl J Med* 1993; 328: 246-52.
- [6] Ernst E, White A. The BBC survey of the complementary medicine use in the UK. *Complement Ther Med* 2000; 8: 32-6.
- [7] Schäfer T, Riehle A, Wichmann H-E, Ring J. Alternative medicine in allergies – prevalence, patterns of use, and costs. *Allergy* 2002; 57: 694-700.
- [8] Astin JA. Why patients use alternative medicine: results of a national study. *JAMA* 1998; 279: 1548-53.
- [9] Bielory L. Complementary and alternative interventions in asthma, allergy, and immunology. *Ann Allergy Asthma Immunol* 2004; 93(2 Suppl 1): S45-S54.
- [10] Senna G, Passalacqua G, Crivellaro M, Bonadonna P, Gani F, Dorizzi R, et al. Unconventional medicine: a risk of undertreatment of allergic patients. *Allergy* 1999; 54: 1117-9.
- [11] Barnes J, Mills SY, Abbot NC, Willoughby M, Ernst E. Different standards for reporting ADRs to herbal remedies and conventional OTC medicines: face-to-face interviews with 515 users of herbal remedies. *Br J Clin Pharmacol* 1998; 45: 496-500.
- [12] Passalacqua G, Compalati E, Schiappoli M, Senna G. Complementary and alternative medicine for the treatment and diagnosis of asthma and allergic diseases. *Monaldi Arch Chest Dis* 2005; 63: 47-54.
- [13] Niggemann B, Grüber C. Side-effects of complementary and alternative medicine. *Allergy* 2003; 58: 707-16.
- [14] Johansson SG, Bieber T, Dahl R, Friedmann PS, Lanier BQ, Lockey RF, et al. Revised nomenclature for allergy for global use: Report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. *J Allergy Clin Immunol* 2004; 113: 832-6.
- [15] Pichler WJ. Delayed drug hypersensitivity reactions. *Ann Intern Med* 2003; 139: 683-93.
- [16] Simpson EL, Law SV, Storrs FJ. Prevalence of botanical extract allergy in patients with contact dermatitis. *Dermatitis* 2004; 15: 67-72.
- [17] Thomson KF, Wilkinson SM. Allergic contact dermatitis to plant extracts in patients with cosmetic dermatitis. *Br J Dermatol* 2000; 142: 84-8.
- [18] Apted JH. Contact dermatitis associated with the use of tea-tree oil. *Australas J Dermatol* 1991; 32: 177.
- [19] Knight TE, Hausen BM. Melaleuca oil (tea tree oil) dermatitis. *J Am Acad Dermatol* 1994; 30: 423-7.
- [20] de Groot AC. Airborne allergic contact dermatitis from tea tree oil. *Contact Dermatitis* 1996; 35: 304-5.
- [21] de Groot AC, Weyland JW. Systemic contact dermatitis from tea tree oil. *Contact Dermatitis* 1992; 27: 279-80.
- [22] Perret CM, Evans AV, Russel-Jones R. Tea tree oil dermatitis associated with linear IgA disease. *Clin Exp Dermatol* 2003; 28: 167-70.
- [23] van der Valk PG, de Groot AC, Bruynzeel DP, Coenraads PJ, Weijland JW. Allergic contact eczema due to 'tea tree' oil. *Ned Tijdschr Geneesk* 1994; 138: 823-5.
- [24] Selvaag E, Holm J-O, Thune P. Allergic contact dermatitis in an aroma therapist with multiple sensitizations to essential oils. *Contact Dermatitis* 1995; 33: 354-5.
- [25] Greig JE, Carson CF, Stuckey MS, Riley TV. Skin sensitivity testing for tea tree oil—a report for the Rural Industries Research and Development Corporation. Rural Industries Research and Development Corporation, Barton Act, Australia; 1999: report No. 99.
- [26] Pratt M. North American Contact Dermatitis Group, personal communication, January 11, 2004.
- [27] Crawford GH, Sciacca JR, James WD. Tea tree oil: cutaneous effects of the extracted oil of *Melaleuca alternifolia*. *Dermatitis* 2004; 15: 59-66.
- [28] Hausen BM. A 6-year experience with *Compositae mix*. *Am J Contact Dermatitis* 1996; 7: 94-9.
- [29] Paulsen E, Andersen KE, Hausen BM. An 8-year experience with routine SL mix patch testing supplemented with *Compositae mix* in Denmark. *Contact Dermatitis* 2001; 45: 29-35.
- [30] Jovanovic M, Poljacki M, Duran V, Vujanovic L, Sente R, Stojanovic S. Contact allergy to *Compositae* plants in patients with atopic dermatitis. *Med Pregl* 2004; 57: 209-18.
- [31] Hausen BM. Arnica allergy. *Hautarzt* 1980; 31: 10-7.
- [32] Mateo MP, Velasco M, Miquel FJ, de la Cuadra J. Erythema-multiforme-like eruption following contact dermatitis from sesquiterpene lactones in herbal medicine. *Contact Dermatitis* 1995; 33: 449-50.
- [33] Paulsen E, Andersen KE, Hausen BM. Sensitization and cross-reaction patterns in Danish *Compositae*-allergic patients. *Contact Dermatitis* 2001; 45: 197-204.
- [34] Subiza J, Subiza JL, Hinojosa M, Garcia R, Jerez M, Valdivieso R, et al. Anaphylactic reactions after the ingestion of chamomile tea: a study of cross-reactivity with other composite pollens. *J Allergy Clin Immunol* 1989; 84: 353-8.
- [35] Jensen-Jarolim E, Reider N, Fritsch R, Breiteneder H. Fatal outcome of anaphylaxis to camomile-containing enema during labor: a case study. *J Allergy Clin Immunol* 1998; 102: 1041-2.
- [36] Mullins RJ, Hedde R. Adverse reactions associated with echinacea: the Australian experience. *Ann Allergy Asthma Immunol* 2002; 88: 42-51.
- [37] Soon SL, Crawford RI. Recurrent erythema nodosum associated with Echinacea herbal therapy. *J Am Acad Dermatol* 2001; 44: 298-9.

- [38] Cardinali C, Francalanci S, Giomi B, Caproni M, Sertoli A, Fabbri P. Contact dermatitis from *Rhus toxicodendron* in a homeopathic remedy. *J Am Acad Dermatol* 2004; 50: 150-1.
- [39] Chiu AE, Lane AT, Kimball AB. Diffuse morbilliform eruption after consumption of ginkgo biloba supplement. *J Am Acad Dermatol* 2002; 46: 145-6.
- [40] Bernstein IL, Gruchalla RS, Lee RE, Nicklas RA, Dykewicz MS, Shepherd GM, *et al.* Disease management of drug hypersensitivity: A practice parameter. *Ann Allergy Asthma Immunol* 1999; 83: 665-700.
- [41] Aberer W, Bircher A, Romano A, Blanca M, Campi P, Fernandez J, *et al.* Drug provocation testing in the diagnosis of drug hypersensitivity reactions: general considerations. *Allergy* 2003; 58: 854-63.
- [42] Mochitomi Y, Inoue A, Kawabata H, Ishida S, Kanzaki T, Stevens-Johnson syndrome caused by a health drink (Eberu®) containing ophiopogonis tuber. *J Dermatol* 1998; 25: 662-5.
- [43] Monk B. Severe cutaneous reactions to alternative remedies. *BMJ* 1986; 293: 665-6.
- [44] Kou D, Ong CN. Phytophotodermatitis due to the application of *Citrus hystrix* as a folk remedy. *Br J Dermatol* 1999; 140: 737-8.
- [45] Golsch S, Vocks E, Rakoski J, Brockow K, Ring J. Reversible increase in photosensitivity to UV-B caused by *St. John's Wort* extract. *Hautarzt* 1997; 48: 249-52.
- [46] Bove GM. Acute neuropathy after exposure to sun in a patient treated with *St John's Wort*. *Lancet* 1998; 352: 1121-2.
- [47] Maurice PD, Cream JJ. The dangers of herbalism. *BMJ* 1989; 299: 1204.
- [48] Kaddu S, Kerl H, Wolf P. Accidental bullous phototoxic reactions to bergamot aromatherapy oil. *J Am Acad Dermatol* 2001; 45: 458-61.
- [49] Price S, Price L. Aromatherapy for health professionals. Edinburgh: Churchill Livingstone, 1995.
- [50] Crawford GH, Katz KA, Ellis E, James WD. Use of aromatherapy products and increased risk of hand dermatitis in massage therapists. *Arch Dermatol* 2004; 140: 991-6.
- [51] Kavli G, Forde OH. Hand dermatoses in Tromsø. *Contact Dermatitis* 1984; 10: 174-7.
- [52] Susitaival P, Husman L, Horsmanheimo M, Notkola V, Husman K. Prevalence of hand dermatoses among Finnish farmers. *Scand J Work Environ Health* 1994; 20: 206-12.
- [53] Singgih SI, Lantinga H, Nater JP, Woest TE, Kruijt-Gaspersz JA. Occupational hand dermatoses in hospital cleaning personnel. *Contact Dermatitis* 1986; 14: 14-9.
- [54] Meding B, Swanbeck G. Prevalence of hand eczema in an industrial city. *Br J Dermatol* 1987; 116: 627-34.
- [55] Crivellaro MA, Senna G, Riva G, Cislighi C, Falagiani P, Canonica GW, *et al.* Pollen mixture used as health food may be a harmful source of allergens. *J Investig Allergol Clin Immunol* 2000; 10: 310-1.
- [56] Eray O, Tuncok Y, Eray E, Gunerli A, Guven H. Severe uvular angioedema caused by intranasal administration of *Ecbalium elaterium*. *Vet Human Toxicol* 1999; 41: 376-8.
- [57] Kloutsos G, Balatsouras DG, Kaberos AC, Kandiloros D, Ferekidis E, Economou C. Upper airway edema resulting from use of *Ecbalium elaterium*. *Laryngoscope* 2001; 111: 1652-5.
- [58] Lee SK, Cho HK, Cho SH, Kim SS, Nahm DH, Park HS. Occupational asthma and rhinitis caused by multiple herbal agents in a pharmacist. *Ann Allergy Asthma Immunol* 2001; 86: 469-74.
- [59] Park HK, Jeon SG, Kim TB, Kang HR, Chang YS, Kim YK, *et al.* Occupational asthma and rhinitis induced by a herbal medicine, *Wonji (Polygala tenuifolia)*. *J Korean Med Sci* 2005; 20: 46-9.
- [60] Subiza J, Subiza JL, Escribano PM, Hinojosa M, Garcia R, Jerez M, *et al.* Occupational asthma caused by Brazil ginseng dust. *J Allergy Clin Immunol* 1991; 88: 731-6.
- [61] Cartier A, Malo JL, Labrecque M. Occupational asthma due to liquorice roots. *Allergy* 2002; 57: 863.
- [62] White JC. *Dermatitis venenata*. Boston: Cupples & Hurd 1887: 127-31.
- [63] Garrido Fernandez S, Arroabarren Aleman E, Garcia Figueroa BE, Goienetxe Fagoaga E, Olaguibel Rivera JM, Tabar Purroy AI. Direct and airborne contact dermatitis from propolis in beekeepers. *Contact Dermatitis* 2004; 50: 320-1.
- [64] Gulbahar O, Ozturk G, Erdem N, Kazandi AC, Kokuludag A. Psoriasisiform contact dermatitis due to propolis in a beekeeper. *Ann Allergy Asthma Immunol* 2005; 94: 509-11.
- [65] Winkler A. Dermatitis caused by resin of poplar. *Dermatol Wochenschr* 1956; 133: 81-7.
- [66] Camarasa G. Occupational dermatitis from beeswax. *Contact Dermatitis* 1975; 1: 124.
- [67] Monti M, Berti E, Carminati G, Cusini M. Occupational and cosmetic dermatitis from propolis. *Contact Dermatitis* 1983; 9: 163.
- [68] Downs A, Sansom J. Occupational contact dermatitis due to propolis. *Contact Dermatitis* 1998; 38: 359-60.
- [69] Hsu CY, Chiang WC, Weng TI, Chen WJ, Yuan A. Laryngeal edema and anaphylactic shock after topical propolis use for acute pharyngitis. *Am J Emerg Med* 2004; 22: 432-3.
- [70] van Ulsen J, Stolz E, van Joost TH. Chromate dermatitis from a homeopathic drug. *Contact Dermatitis* 1988; 18: 56-7.
- [71] Conde-Salazar L, Valks R, Malfeito JE, García C, Ledo S. Contact dermatitis from the staples of neuroreflexotherapy. *Contact Dermatitis* 2004; 51: 217-8.
- [72] Audicana M, Bernedo N, Gonzalez I, Muñoz E, Fernández E, Gastaminza G. An unusual case of baboon syndrome due to mercury present in a homeopathic medicine. *Contact Dermatitis* 2001; 45: 185.
- [73] de Smet PA, Pegt GW, Meyboom RH. Acute circulatory shock following administration of the non-regular enzyme preparation Wobe-Mugos. *Ned Tijdschr Geneeskde* 1991; 135: 2341-4.
- [74] Staab D, von Rueden U, Kehrt R, Erhart M, Wenninger K, Kamtsiuris P, *et al.* Evaluation of a parental training program for the management of childhood atopic dermatitis. *Pediatr Allergy Immunol* 2002; 13: 84-90.
- [75] Bork K. *Cutaneous Side-effects of Drugs*. Philadelphia: Saunders, 1988.
- [76] Ernst E. Serious adverse effects of unconventional therapies for children and adolescents: a systematic review of recent evidence. *Eur J Pediatr* 2003; 162: 72-80.
- [77] Cetkovic-Cvrlje M, Tibbles HE. Therapeutic potential of Janus kinase 3 (JAK3) inhibitors. *Curr Pharm Des* 2004; 10(15): 1767-84.
- [78] Johnston GA. GABA(A) receptor channel pharmacology. *Curr Pharm Des* 2005; 11(15): 1867-85.
- [79] Tsang SY, Xue H. Development of effective therapeutics targeting the GABAA receptor: naturally occurring alternatives. *Curr Pharm Des* 2004; 10(9): 1035-44.

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.