SCIENCE AND SOCIETY

Complementary and alternative medicine: assessing the evidence for immunological benefits

Martin H. Goldrosen and Stephen E. Straus

Abstract | With words such as AIDS, allergy and autoimmunity embedded in the popular lexicon, we often equate health with the precision and the tenor of responses to allergens and microorganisms. This leads many people to seek their own solutions to sustain, restore or even boost their immune competence, hoping to live more comfortably and longer. Here, we consider the social and clinical contexts in which these promises of enhanced immunity are pursued through popular practices known as complementary and alternative medicine and the evidence that supports these.

Complementary and alternative medicine (CAM) consists of diverse clinical interventions that are popular yet not embraced by conventional medicine because there is insufficient proof that they are safe and effective. Complementary interventions are used together with conventional treatments, whereas alternative interventions are used instead of them. In 1998, the National Center for Complementary and Alternative Medicine (NCCAM) was established by the US Congress at the National Institutes of Health (Bethesda, United States) to rigorously investigate popular CAM modalities to determine which are beneficial and worthy of further consideration for mainstream practice[1]. Among the many CAM approaches that warrant careful investigation are those that claim to sustain, restore or boost immunity. Here, we discuss who uses CAM, the social, ethical and legal issues regarding its use, the benefits versus the risks, the complexities of carrying out clinical research with CAM therapeutic modalities, and the implications of these therapies. In particular, we discuss these issues in the context of the immune system.

Use of CAM

When originally developing its research strategies and priorities, NCCAM reviewed more than 800 types of CAM practice, including many with potential immunological effects. These can be grouped into five main domains: biologically based approaches, manipulative and body-based therapies, mind–body interventions, energy therapies and alternative medical systems (FIG. 1). There is little overlap between the therapeutic modalities in different domains, with the exception of the alternative medical systems, which draw on therapies from the other four domains. For example, AYURVEDA (see Glossary), the traditional system of medicine in India, addresses conditions of the mind, body and spirit through the use of diet, exercise, MEDITATION, HERBS, MASSAGE, YOGA and exposure to sunlight.

The prevalence of the use of CAM throughout developed countries ranges from 9% of individuals to 65% (REFS 2,3). This variation results from the disparity in definitions of CAM, the selection of therapies assessed, the method of survey used and the period of CAM use. By one often-cited estimate, between 1990 and 1997, visits to CAM practitioners in the United States increased from 427 million to 629 million, thereby exceeding the number of visits to all primary-care physicians by 243 million[4]. In the most recent and comprehensive survey of CAM use[3], CAM was most often used to treat back pain or back problems, head or chest colds, neck pain or neck problems, joint pain or stiffness, and anxiety or depression. The ten most common CAM therapies used during the previous year were prayer for one's own health (used by 43.0% of individuals), prayer by others for one's own health (24.4%), natural products (18.9%), deep-breathing exercises (11.6%), participation in a prayer group for one's own health (9.6%), meditation (7.6%), CHIROPRACTIC care (7.5%), yoga (5.1%), massage (5.0%) and diet-based therapies (3.5%)[3]. CAM use was more prevalent among women, older adults and those with higher educational attainment (more than 16 years of schooling)[3,5].

There are several reasons why CAM therapies are popular. CAM practitioners aim not only to treat the physical and biochemical manifestations of illness but also to consider the nutritional, emotional, social and spiritual context in which the illness arises. The use of body-based techniques and mind–body interventions is comforting and can reduce stress. Furthermore, numerous CAM products can be purchased at health-food shops and supermarkets and, as natural substances that have often been used for centuries, they claim to be effective yet safer than drugs. CAM places patients in control of their own health.

Regulation of CAM

The average consumer, however, does not understand how CAM products are regulated. In the United States, in general, DIETARY SUPPLEMENTS are regulated by the Food and Drug Administration (FDA) as foods, not as drugs, in accordance with the Dietary Supplement Health and Education Act of 1994 (DSHEA)[114]. Whereas drugs must be approved by the FDA as being safe and

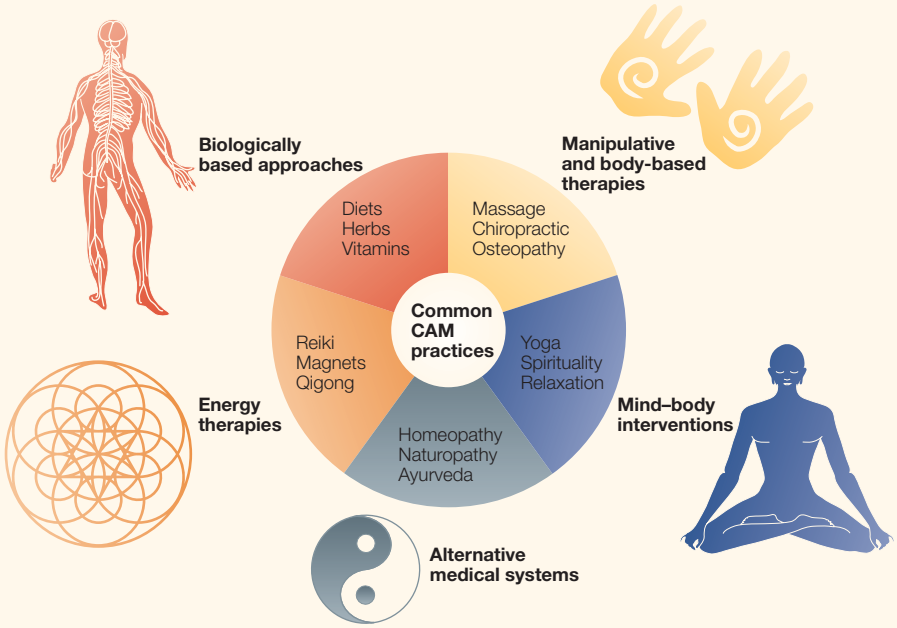

Figure 1 | **CAM domains and some of the most common examples.** Biologically based complementary and alternative medicine (CAM) approaches include herbal medicines, 'megadoses' of vitamins and SPECIAL DIETS[107], such as those proposed by Drs Atkins[108] and Ornish[109]. Manipulative and body-based therapies include methods that involve manipulation and/or movement of the body, such as massage, chiropractic and osteopathy. Mind–body interventions use various techniques that are designed to facilitate the capacity of the mind to affect bodily function and symptoms, including yoga, prayer, meditation, spirituality and guided imagery. Energy therapies are intended to affect energy fields (biofields) that purportedly surround and penetrate the human body, using REIKI and therapeutic touch. Alternatively, energy therapies can involve the unconventional use of ELECTROMAGNETIC FIELDS, such as pulsed fields, magnetic fields, or alternating- or direct-current fields. Alternative medical systems involve complete systems of theory and practice that have evolved independently of, and often before, the conventional biomedical approach. Many of these are traditional systems of medicine that are practised by individual cultures throughout the world, such as traditional Chinese medicine (of which acupuncture is a principal component) and Ayurvedic medicine from India, but they also include the more-modern Western approaches that are applied in HOMEOPATHY and naturopathy.

effective before they can be sold to treat or prevent specific diseases, the FDA is not authorized to evaluate the safety or efficacy of dietary supplements before their marketing. However, the FDA can ban the sale of supplements that are shown to be unsafe, and it did so recently for the first time, for products containing ephedra (*Ephedra sinica*) — a Chinese herb used for weight loss and athletic-performance enhancement. As was evident from the prolonged efforts of the FDA to curtail the use of ephedra, it is difficult to prove that such products are unsafe. Whereas manufacturers of drugs must report adverse drug events to the FDA after a drug has been marketed, manufacturers of dietary supplements are not required to collect or file such reports. Furthermore, under the DSHEA regulations, manufacturers of dietary supplements can claim that their products maintain the normal 'structure or function' of bodily systems, but they cannot claim that they treat or prevent diseases. For example, a herbal manufacturer needs no proof to claim that its products maintain a healthy immune system or healthy joints. However, a manufacturer cannot claim that its products treat states of immune deficiency or arthritis, even though the distinctions between these sets of claims could be subtle.

Consumers in the United States spend nearly $20 billion each year on dietary supplements that do not require a prescription, and they must rely on the manufacturers to provide truthful and non-misleading information regarding the safety and benefit of their products. Surveys have shown that 59% of Americans believe that the FDA regulates dietary supplements in the same manner as drugs because they are often sold next to over-the-counter medications[6]. Although the DSHEA legislation affords the public unfettered access to thousands of dietary supplements, some people have proposed that public health would be better served if the FDA required at least evidence of product safety before sale[7].

Many other countries regulate dietary supplements more stringently[8]. For example, in most countries of the European Union, HERBAL MEDICINES are sold in pharmacies as licensed non-prescription or prescription medicines. The sale of herbal medicinal products is allowed without the requirement to carry out specific clinical studies provided that their safety and efficacy are supported by common experience accrued through long-standing use. The quality aspect of the medicinal product is independent of its traditional use, so no derogation can be made with regard to the necessary physiochemical, biological and microbiological tests. Moreover, in 2002, the European Union defined the upper limits of safe levels of VITAMINS and minerals, and required products that could exceed these levels to carry explicit warnings[9]. There is no similar requirement in the United States.

Risks of CAM use

Using CAM can have risks. Most importantly, it could distract patients from pursuing well-established treatments. However, the authors of a survey published in 1997 reported that only 4.4% of respondents relied solely on alternative therapies[4]. So, most individuals are not turning away from conventional medicine but use unconventional approaches as complements to conventional ones[10]. Unfortunately, until recently, only 40% of patients disclosed their use of CAM therapies to physicians[4]. This could have serious consequences because several herbal medicines can have harmful effects and others can markedly alter the metabolism of conventional drugs. For example, aristolochia (*Aristolochia fangchi*), a Chinese herb incorporated in a weight-reducing product in error, is associated with genitourinary cancers[11]; the anxiolytic herb kava (*Piper methysticum*) is associated with hepatic failure[12]; and ephedra is associated with strokes[13].

St John's wort (*Hypericum perforatum*), which is widely used for the treatment of depression, upregulates the expression of several cytochrome oxidases (such as CYP3A); together, these affect the metabolism of more than half of all conventional drugs[14], including the HIV-protease inhibitor indinavir[15], the topoisomerase inhibitor irinotecan (used in multi-drug treatment of solid tumors)[16,17] and the potent immunosuppressant drug cyclosporine (used to reduce the risk of transplant rejection)[18,19]. Taking St John's wort extract in combination with a low-dose oral contraceptive increased intracyclic bleeding episodes, thereby increasing the risk of unintended pregnancies[20,21].

Box 1 | **Challenges of conducting clinical trials of CAM**

- Use of a multiple-modality complex intervention, rather than a single intervention, in some forms of complementary and alternative medicine (CAM).
- Development of a specific individualized treatment for each patient that often focuses on the symptoms of the disease rather than on one main pathology.
- Finding appropriate placebos or shams for manipulative and body-based interventions.
- Accruing, randomizing and retaining patients with strong opinions favouring or rejecting CAM.
- Availability of standardized and well-characterized herbal preparations.

Clinical trials of CAM

BOX 1 summarizes the complexities of carrying out clinical trials to verify the safety and efficacy of CAM modalities[22]. Despite these difficulties, NCCAM has been able to support well-designed randomized clinical trials of CAM treatments. Ongoing trials include the following: a comparison of a NATUROPATHIC TREATMENT, a TRADITIONAL CHINESE MEDICINE treatment and a conventional treatment for women with temporomandibular-joint disease; a large study of acupuncture for the treatment of osteoarthritis; and many studies of individual dietary supplements for the prevention or treatment of diseases. The status of NCCAM's ongoing phase III clinical trials is shown in TABLE 1.

The decision to undertake each of these trials was based on the following: the importance of the disease to public health, the quality of the preliminary data, the availability of a well-characterized intervention, the extent of public use and the cost of doing the research[22]. It is notable that CAM approaches for which the main target is the immune system are not represented on this list, because the existing data for such interventions do not currently warrant phase III trials. Here, we summarize what is known about these approaches from the limited studies that have been carried out.

CAM and immunity

Among the many mechanisms by which CAM approaches are claimed to function, their purported effects on immunity resonate with the contemporary appreciation that health depends considerably on immune competence. Even before the concept of an immune system was articulated, vitalistic practitioners, such as naturopathic physicians, maintained that disease should be treated by stimulating the ability of the body to heal itself rather than by treating symptoms. Now, we know that infections and cancers can result from a loss of 'optimal' immune surveillance. In addition, at present, although the aetiologies for some disorders, such as multiple sclerosis and sarcoidosis, remain unproven, they are nonetheless best understood in immunological terms. Moreover, popular literature is rife with speculations that debilitating fatigue, behavioural disorders and many other disorders could be immunologically mediated: for examples, see the Chronic Fatigue and Immune Dysfunction Syndrome Association of America and The Autism Autoimmunity Project in the Online links box. So, the appeal of CAM approaches that claim to alter immunity can be readily understood. But, do these claims engender unjustified optimism or might some of them have a basis in fact?

There are numerous publications describing the therapeutic efficacy of CAM modalities that are thought to mediate their effects through the immune system, all reporting varying degrees of evidence. In FIG. 2, the hierarchy of available evidence is characterized; it ranges from anecdotes and case studies to large randomized clinical trials. TABLE 2 summarizes selected interventions that have been associated with meaningful clinical changes in small and large randomized trials. In this article, we carefully evaluate the immune changes that are induced by these selected CAM modalities. The emphasis is mainly on dietary interventions, because the clinical data for some of these are the most compelling. For other CAM approaches that are not directly addressed here, there is minimal objective evidence for beneficial immunological or clinical effects.

Dietary supplements

Dietary supplements are consumed in a formulation containing a predetermined dose (such as in capsule form) and include vitamins, minerals, essential fatty acids, herbal medicines, amino acids and enzymes. Nutraceuticals are dietary supplements that deliver a concentrated form of a presumed bioactive agent from a food, are presented in a non-food matrix and are used to enhance health in dosages that exceed those that could be obtained from normal foods[7]. A subset of dietary supplements functions as immunostimulatory nutrients because they have the potential to modulate the activity of the immune system[23]. Among them, the most studied are vitamins A and E, the mineral zinc and omega-3 polyunsaturated fatty acids (PUFAs).

Vitamins. Oxidative stress occurs when there is an imbalance between the generation of free radicals by reactive-oxygen species and the level of endogenous anti-oxidants in cells and tissues. The consequences of oxidative stress might include the development of degenerative disorders, such as cancer, cardiovascular disease and ageing (with its attendant immune senescence)[24,25]. Higher organisms have evolved various endogenous defence mechanisms to prevent the generation of reactive-oxygen species. For example, catalase and glutathione peroxidase decompose the hydrogen peroxide that is involved in the killing of microorganisms[23]. Dietary supplements such as vitamin E can provide an essential exogenous source of anti-oxidants.

Table 1 | **Some ongoing, large phase III trials of CAM modalities**

CAM approach	Disease/condition	Status of trial
Acupuncture	Osteoarthritis	Study completed; data being analysed
Glucosamine chondroitin sulphate	Osteoarthritis	Enrolment completed; studies ongoing
Vitamin E	Prostate cancer	Enrolment completed; study ongoing
Shark cartilage	Lung cancer	Enrolment ongoing; study ongoing
St John's wort (*Hypericum perforatum*)	Minor depression	Recruitment ongoing
EDTA-chelation therapy	Coronary-artery disease	Recruitment ongoing
Saw palmetto (*Serenoa repens*)	Benign prostate hypertrophy	Final protocol developed in 2004

CAM, complementary and alternative medicine; EDTA, ethylenediaminetetraacetic acid.

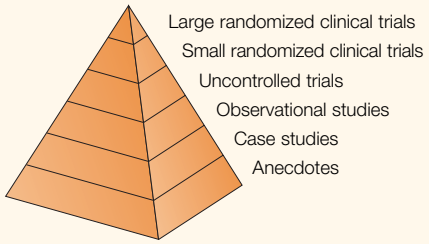

Figure 2 | **Hierarchy of evidence.** Information regarding the efficacy and safety of any clinical approach, including those of complementary and alternative medicine, spans a continuum that ranges from anecdotes and retrospective studies to small randomized, controlled trials (phase II clinical trials) and large randomized, controlled trials (phase III clinical trials).

Vitamin E (α-tocopherol) is fat soluble and functions as an anti-oxidant and free-radical scavenger in cell membranes by blocking the peroxidation of PUFAs[26–28]. So, vitamin E protects cell-membrane lipids from peroxidation. A deficiency in vitamin E is associated with decreased T-cell and B-cell mitogenesis[29], interleukin-2 (IL-2) production, natural killer (NK)-cell activity[30] and neutrophil phagocytosis in both rats and humans. Conversely, supplementation with vitamin E increases T-cell mitogenesis, IL-2 production[31] and NK-cell activity[32] in rats, as well as T-cell and B-cell mitogenesis[33] and antibody production[34] in mice.

Vitamin E deficiency is exacerbated in elderly people who are malnourished[35]. Supplementation of elderly individuals with pharmacological doses of vitamin E augments their immune responses. Specifically, vitamin E has been shown to increase delayed-type hypersensitivity (DTH) responses in elderly individuals, with 200 mg each day having the maximal effect[36]. The 200 mg dose also increased antibody responses after vaccination with hepatitis-B-virus surface antigen, tetanus toxoid or pneumococcal polysaccharides. Recently, Meydani and co-workers reported on a randomized, double-blinded, placebo-controlled trial of 617 people of 65 years of age or more who were given 200 international units (IU) of vitamin E each day for 1 year[37]. Supplementation with 200 IU of vitamin E each day did not have a significant effect on the incidence of lower respiratory-tract infections in elderly nursing-home residents. However, the authors observed a protective effect of vitamin E supplementation on upper respiratory-tract infections (particularly the common cold) that merits further investigation.

The risks of contracting some infectious diseases are increased in the setting of vitamin deficiency. The evidence for this is strongest for vitamin A (retinol)[25]. In turn, infectious diseases can then precipitate or exacerbate vitamin deficiencies by promoting decreased food intake[38], impairing nutrient absorption[39] and causing direct nutrient loss in sweat, stools and urine[40]. Vitamin A deficiency broadly impairs innate immunity by reducing the function of neutrophils, macrophages and NK cells[41,42]. In addition, vitamin A deficiency inhibits antibody responses directed by T helper 2 (T_H2) cells[43] and impedes the normal regeneration of mucosal barriers that are damaged by viral infection[25].

Large community-based studies have shown that vitamin A deficiency is associated with a markedly increased risk of child mortality[44]. Worldwide, ~10% of the vitamin-A-deficient children who die are infected with measles virus, often complicated by bacterial pneumonia. Supplementation with high doses of vitamin A improves recovery from measles by decreasing both the duration of

Table 2 | **Some CAM modalities that might mediate their effects through the immune system**

CAM intervention	CAM domain	Level of evidence	Condition	Dose	Subjects	Observation	Reference
Vitamin A	Biological (dietary supplement)	Meta-analysis of 12 randomized clinical trials	Vitamin-A-deficient children	50,000 IU per day	NA	30% reduction in childhood mortality	45
Vitamin E	Biological (dietary supplement)	Small randomized clinical trial	Healthy elderly people (>65 years)	200 mg per day	88	Increase in clinically relevant immunity	36
Zinc	Biological (dietary supplement)	Large randomized clinical trial	Zinc-deficient children	10 mg per day	579	26% reduction in childhood diarrhoea	56
Omega-3 PUFA	Biological (dietary supplement)	Large randomized clinical trial	Patients surviving myocardial infarction	1,000 mg per day omega-3 PUFA	11,323	45% reduction in sudden cardiac death	68
Echinacea	Biological (herbal product)	Small randomized clinical trial	Common cold	5 ml per day *Echinacea purpurea* extract*	80	Reduction in rhinorrhoea from 9 to 6 days	79
Thunder God vine	Biological (herbal product)	Small randomized clinical trial	Rheumatoid arthritis	360 mg per day for 20 weeks	35	66% of patients had a 20% reduction in disease severity	83
Lactobacillus casei GG	Biological (probiotic)	Small randomized clinical trial	Childhood rotaviral diarrhoea	3×10^9 colony-forming units	100	Reduction in diarrhoea from 6 to 3 days	90
T'ai chi	Mind–body	Small randomized clinical trial	Shingles (varicella-zoster virus infection)	15-week intervention, 45 sessions	36	50% increase in varicella-zoster-virus-specific immunity	103
Hypnosis	Mind–body	Small randomized clinical trial	Genital herpes (herpes-simplex virus infection)	6 weeks of self-hypnosis	21	50% reduction in herpes-simplex virus recurrence	104

*Negative results were obtained using a different echinacea preparation (see text for details). CAM, complementary and alternative medicine; IU, international units; NA, not applicable; PUFA, polyunsaturated fatty acids.

illness and its overall mortality rate[44,45]. Moreover, in compelling studies of this inexpensive intervention, vitamin A supplements were shown to significantly reduce overall early-childhood mortality from measles by 30% (REF. 45). It is therefore recommended that vitamin A be given to all children suffering from measles, regardless of whether they are deficient in vitamin A[46]. It is less clear whether supplementation with vitamin A improves morbidity and mortality caused by other infections, and the benefits of vitamin A in terms of measles do not justify universal supplementation. Furthermore, modest adverse effects, such as exacerbation of the inflammatory process and worsening of clinical symptoms and signs, were noticed in children with bacterial pneumonia who were given high doses of vitamin A[47].

Vitamin A might be useful for treating patients with specific immunodeficiency states. For example, in one small study of patients with common variable immunodeficiency, decreased serum levels of vitamin A were observed[48]. Vitamin A supplementation of these patients resulted in a significant increase in CD40-stimulated production of IgG, serum levels of IgA and phytohaemagglutinin-induced proliferation of peripheral-blood mononuclear cells[48]. Several studies also found that low serum concentrations of vitamin A correlate with HIV-associated disease severity and progression[49]. However, researchers studying the effects of vitamin A supplementation on the maternal–fetal transmission of HIV have reported conflicting findings[50,51].

Minerals. Zinc is a cofactor for many enzymatic reactions. Patients with acrodermatitis enteropathica — an autosomal recessive disorder attributed to a defect in zinc metabolism — suffer from T-cell dysfunction and diarrhoea, and are more susceptible to viral, bacterial and fungal infections[52,53]. In humans, zinc deficiency is associated with a decreased number of lymphoid precursors and impaired activity of T_H1 cells, as manifested by decreased production of interferon-γ (IFN-γ), IL-2 and tumour-necrosis factor (TNF), but it has no effect on the production of IL-4, IL-6 or IL-10 (REFS 50,54).

There is growing evidence that zinc deficiency is a clinically important problem. In some studies of malnourished children, supplementation with zinc decreased the incidence of diarrhoea by more than 50% (REF. 55). In other studies, supplementation with zinc was effective for the treatment of diarrhoea in undernourished children only when it was begun within the first 4 days of illness[56]. Zinc has also been evaluated for both the prevention and treatment of viral colds, with conflicting results being reported[57].

Even in developed countries, malnutrition can be prevalent in elderly people, further impairing an already senescent immune system and increasing the risk and severity of infections. Supplementation of malnourished older adults with zinc enhances DTH responses and increases lymphocyte numbers and NK-cell activity[58]. However, it is unclear whether supplementation with zinc results in a reduced number of infections, because studies evaluating zinc were carried out in combination with supplementation with other trace elements. For example, studies of elderly people who are malnourished have shown a clinical benefit from supplementation with zinc in combination with selenium, with or without vitamins A, C and E. During 2 years of supplementation, individuals who received the two trace elements alone or in combination with the vitamins had significantly fewer infectious events compared with patients who were administered a placebo or vitamins alone[59].

It should be noted, however, that excessive zinc intake impairs immune responses[60], indicating the importance of dose regulation of dietary supplements. A high zinc intake can result in depletion of copper, and copper deficiency by itself impairs immune function. Copper is required for the proper structure and function of cytochrome C oxidases in the mitochondrial electron-transport chain of immune cells[61].

From the available studies, no consensus has been reached regarding the implications of vitamin and mineral supplementation for the general population. At present, dietary-supplement manufacturers and some authorities are pressing for universal supplementation. Other leading authorities do not consider that the evidence justifies supplementation for all healthy people who have normal diets.

Essential fatty acids. The PUFA content of immune cells varies according to the cell type and the lipid fraction examined. Typically, the phospholipid portion of human peripheral-blood mononuclear cells comprises 15–25% arachidonic acid (an omega-6 PUFA) and only 0.1–0.8% eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) and omega-3 PUFAs[62,63]. Arachidonic acid gives rise to the eicosanoid family of inflammatory mediators (prostaglandins, leukotrienes and related metabolites), which are involved in increasing the intensity and duration of inflammatory and immune responses.

Ingestion of fish oils — a good source of omega-3 PUFAs — decreases the amount of arachidonic acid in the cell membrane that is available for eicosanoid production and thereby decreases inflammation[62,63]. Additional anti-inflammatory effects of omega-3 PUFAs are elicited by eicosanoid-independent mechanisms that involve downstream intracellular-signalling pathways. In animals and humans, ingestion of fish oils decreases generation of reactive-oxygen species, production of TNF, IL-1 and IL-6 (REF. 64), proliferation of lymphocytes and release of IL-2 and IFN-γ[65]. So, supplementation of the diet with high levels of fish oils has a potent anti-inflammatory effect but impairs neutrophil, monocyte and lymphocyte responses. The impairment of immune function could be ameliorated without restoring the inflammatory response by taking 200 mg of vitamin E each day[63,66].

Recently, the Agency for Healthcare Research and Quality in the United States evaluated the effects of omega-3 PUFAs on cardiovascular disease, in which inflammation has a central role[67]. The anti-inflammatory effects of omega-3 fatty acids might contribute to their beneficial cardiac effects. On the basis of 39 studies, the report concludes that the consumption of omega-3 PUFAs, fish or fish oil reduces mortality from all causes and reduces the incidence of various outcomes of cardiovascular disease, such as sudden death, cardiac death and myocardial infarction. For example, among 11,323 patients surviving myocardial infarction, there was a 45% reduction in sudden cardiac death in the group of patients given 1 g of fish-oil-derived omega-3 PUFAs each day[68].

Several trials have assessed the impact of dietary supplementation with fish oils on chronic inflammatory disorders, such as rheumatoid arthritis[69], Crohn's disease[70], asthma[71,72] and IgA nephropathy[73]. In some of these studies, lower levels of leukotriene B_4, IL-1 and C-reactive protein were observed. Reduced symptoms were also observed in these small-scale clinical trials of fish-oil supplementation, with the strongest evidence for rheumatoid arthritis[69]. It is unclear from these studies what the optimal dose of fish oil is and whether there is any benefit of using different omega-3 PUFAs in combination.

Herbal medicines. Herbal products were the mainstay of indigenous medical practices for millennia and remain the only widely available treatments in some countries[8]. Also, it is estimated that approximately half of all pharmaceuticals are derived from natural products[74], including morphine, digitalis, quinine,

Table 3 | **Some herbal products that modulate immune responses**

Common name	Latin name	Active components	Plant sources	Common uses	Immune effects	Reference
Cat's claw	*Uncaria tomentosa*	Indole alkaloids	Root	Immune stimulant	Increases lymphocyte proliferation	110
Curcumin (turmeric)	*Curcuma longa*	Curcuminoids	Rhizomes	Anti-inflammatory	Inhibits production of pro-inflammatory cytokines	111
Echinacea	*Echinacea purpurea*, *Echinacea angustifolia* and *Echinacea pallida*	Echinacosides	Root, shoots and leaves	Against common cold and influenza	Extract of *E. purpurea* results in the production of pro-inflammatory cytokines	77
Ginseng	*Panax ginseng*, *Panax quinquefolium* and *Eleutherococcus senticosus*	Ginsengosides	Root	General tonic	*P. ginseng* induces the production of pro-inflammatory cytokines	112
Marijuana	*Cannabis sativa*	Cannabinoids	Leaves and flowers	Narcotic	Suppresses the cell-mediated immune response by induction of apoptosis	113
Thunder God vine	*Tripterygium wilfordii* Hook F	Terpenoids (di-, tri- and sesquiwilfortrine)	Root	Anti-inflammatory	Inhibits production of pro-inflammatory cytokines	81

vincristine, taxol and artemisinin. Today, herbal products remain popular, even among people who also use pharmaceuticals. TABLE 3 lists several herbal products that have been shown to modulate the immune response in the following ways: stimulation of the immune response (Cat's claw); inhibition of the immune response (marijuana); induction of pro-inflammatory cytokine production (echinacea and ginseng); and inhibition of pro-inflammatory cytokine production (curcumin and Thunder God vine).

Clinical trials of echinacea highlight the complexity of studies of herbal products. Three different species of *Echinacea* (*Echinacea angustifolia*, *E. purpurea* and *E. pallida*) are used for medicinal purposes and marketed as echinacea[75]. Preparations are made from roots, above-ground parts (stems, leaves and flowers) or a mixture of both. Furthermore, some preparations of echinacea are aqueous extracts, whereas others are alcoholic extracts. Differences between the species, the soil in which the plants are cultivated, the parts of the plant used and the extraction procedures can result in substantial differences in chemical composition and biological activity[76].

Immunological studies of echinacea have used aqueous or alcoholic extracts, as well as purified polysaccharides — the compounds thought to be responsible for the non-specific immune stimulatory effects of echinacea. Both extracts of echinacea and purified polysaccharides were shown to stimulate phagocytosis by animal and human neutrophils *in vitro*[75]. Human macrophages that were exposed *in vitro* to commercial preparations of echinacea released substantially more TNF, IL-1, IL-6 and IL-10 — a pattern that is consistent with that of activated macrophages[77]. Despite these reproducible *in vitro* activities, it has been difficult to confirm in placebo-controlled trials that echinacea extracts have salutary effects on the common cold[78]. Whereas echinacea has not proven to be effective in preventing the common cold, conflicting results have been observed in trials designed to treat the common cold. A reduction in median duration of illness (6 days compared with 9 days for those taking the placebo) was observed in a double-blinded, placebo-controlled trial of 80 adults with early symptoms of the common cold who were given 5 ml of pressed juice from fresh-flowering *E. purpurea* twice daily for 10 days[79]. By contrast, no benefit was observed in a placebo-controlled trial of 148 students with early cold symptoms who were given a mixture of unrefined *E. purpurea* herb (25%) and root (25%) and *E. angustifolia* root (50%) taken in 1 g doses six times on the first day of illness and three times on each subsequent day of illness for up to 10 days[80].

Although herbal products such as echinacea can non-specifically enhance immune activities, other herbal products can inhibit them. For example, Thunder God vine (*Tripterygium wilfordii* Hook F), which has been used in traditional Chinese medicine for more than two centuries, has both immunosuppressive and anti-inflammatory effects[81,82]. It contains triptolide and related diterpenoid components. Triptolide inhibits the proliferation of T cells by preventing transcription of the gene encoding IL-2 in response to antigenic and mitogenic stimulation. Triptolide also inhibits the production of pro-inflammatory cytokines and mediators, including TNF, IL-1, IL-6, IL-8 and prostaglandin E_2. In animal models, triptolide prolongs allograft survival and inhibits graft-versus-host disease[81]. Thousands of patients in China with autoimmune and inflammatory diseases, particularly rheumatoid arthritis, have been treated with triptolide[82]. The first small randomized, placebo-controlled trial of triptolide showed a significant dose-dependent response in patients with rheumatoid arthritis[83]. However, in larger, uncontrolled studies, triptolide was observed to have renal, cardiac, haematopoietic and reproductive toxicities[81,82].

Probiotics. The health benefits of fermented foods have been recognized since ancient times, although the mediators of fermentation — bacteria and yeast — were only identified in the nineteenth century. Today, food supplements that contain live microorganisms (in the form of capsules, powders, enriched yoghurts and milks) are commonly consumed to treat gastrointestinal and urogenital-tract infections[84]; these are known as probiotics, derived from the Greek words meaning 'for life'. *Lactobacillus* and *Bifidobacterium* species are the most frequently used in probiotics. Multiple mechanisms are postulated to explain their actions, including the following: reduction of lactose

Glossary

AYURVEDA
The traditional Indian system of medicine. Ayurvedic (meaning 'science of life') medicine is a comprehensive system that places equal emphasis on the body, mind and spirit, and it strives to restore the innate harmony of the individual.

BIOFEEDBACK
A process for monitoring a body function (such as breathing, heart rate or blood pressure) and altering the function through relaxation or imagery.

CHIROPRACTIC
A system of treatment that is based on the relationship between structure (mainly of the spine) and function, and how that relationship affects the preservation and restoration of health.

DIETARY SUPPLEMENTS
Products that contain one or more ingredients (such as vitamins, minerals and herbs) that are intended to supplement the diet, are intended for human use and are in the form of a tablet, capsule, powder or another preparation that is not a conventional food.

ELECTROMAGNETIC FIELDS
Magnetic fields can be used therapeutically to create a static force on the body for the purpose of relieving pain.

HERBAL MEDICINES
Individual herbs or mixtures of herbs that are used for therapeutic value.

HERBS
Plants or plant products that produce or contain chemicals that act on the body.

HOMEOPATHY
A Western system of medicine that is based on the principle that 'like cures like' — that is, the same substance that in large doses produces the symptoms of an illness cures it when administered in very small doses. Homeopathic physicians believe that the more dilute the remedy, the greater its potency. Therefore, homeopaths treat illness by using small doses of specially prepared plant extracts and minerals to stimulate the defence mechanisms and healing processes of the body.

HYPNOSIS
An alternative state of consciousness in which the attention of an individual is focused away from the present reality and towards particular images, thoughts, perceptions, feelings, motivations, sensations, behaviours or any combination of these.

MASSAGE
The manipulation of the soft tissues of the body to normalize them.

MEDITATION
A self-directed method for relaxing the body and calming the mind. The practitioner makes a concentrated effort to focus on a single thought to still the inclination of the mind to mull over the many demands and details of daily life.

NATUROPATHIC TREATMENT
A system of treatment that views disease as a manifestation of alterations in the processes by which the body naturally heals itself. It emphasizes restoration of health, as well as treatment of disease. Naturopathic physicians use an array of healing practices, including diet and clinical nutrition, homeopathy, acupuncture and herbal medicine.

QIGONG
A component of traditional Chinese medicine that combines movement, meditation and the regulation of breathing to enhance the flow of vital energy (qi, pronounced chi) in the body, to improve blood circulation and to enhance immune function.

REIKI
Means 'universal life energy' in Japanese. It is based on the belief that, by channelling spiritual energy through the practitioner, the spirit is healed, and the spirit, in turn, heals the physical body.

SPECIAL DIETS
Diet therapies that are believed to prevent and/or control illness and/or promote health, such as those proposed by Drs Atkins and Ornish.

SPIRITUALITY
An inner sense of something greater than oneself. Recognition of a meaning to existence that transcends one's immediate circumstances.

TRADITIONAL CHINESE MEDICINE
A system of treatment that emphasizes the proper balance or disturbances of qi (vital energy) in health and disease, respectively. Traditional Chinese medicine consists of a group of techniques and methods, including acupuncture, herbal medicine, oriental massage and qigong (a form of energy therapy).

VISUAL IMAGERY
A flow of thoughts that includes sensory qualities such as smell, touch, hearing, taste, motion and images.

VITAMINS
A general term for various unrelated organic substances that occur in many foods in small amounts and that are required for the normal metabolic functioning of the body.

YOGA
An ancient system of practices originating in India. It is aimed at integrating mind, body and spirit to enhance health and well-being. There are many different forms of yoga. Hatha yoga — the most widely practised form of yoga in the Western world — uses specific postures and breathing exercises.

content in milk products by β-galactosidase (which is produced by *Lactobacillus* spp.); release of antimicrobial agents, such as organic acids, free fatty acids, ammonia, hydrogen peroxide and bacteriocins[85]; competition for the ecological niche that would otherwise be occupied by pathogenic organisms[86]; and immunomodulation[87,88]. Importantly, probiotic bacteria can modulate the intestinal IgA response. For example, an increase in the number of IgA-secreting cells and the amount of rotavirus-specific IgA in the serum was observed in patients with rotaviral diarrhoea who were treated with *Lactobacillus casei* GG[89].

Probiotics have been evaluated as treatments for several conditions: diarrhoea in children and adults, atopic disease in children, inflammatory bowel disease and urogenital-tract infections. The strongest data are for the prevention and treatment of rotaviral diarrhoea in children, for which administration of *Lactobacillus* spp.-containing probiotics was associated with significant reductions in the duration and severity of the infection[90,91]. Furthermore, in a double-blinded, placebo-controlled trial, Kalliomaki and co-workers showed that ingestion of *L. casei* GG prevented atopic disease in children who were at high risk[92]. However, conflicting results were obtained in adults with traveller's diarrhoea[93,94]. The value of probiotics for the treatment of inflammatory bowel disease[95] and urogenital-tract infections[96] remains to be determined.

Mind–body approaches

Mind–body medicine focuses on interactions between the brain, mind, body and behaviour and the powerful ways in which emotional, mental, spiritual and behavioural factors can directly affect health. Mind–body medicine uses interventions such as relaxation, HYPNOSIS, VISUAL IMAGERY, meditation, yoga, BIOFEEDBACK, T'ai chi, QIGONG, SPIRITUALITY and prayer to promote health.

Numerous studies indicate that the psychological state of an individual influences many facets of health, including susceptibility to illness, outcomes of infection, general well-being and senescence[97]. Researchers in the field of psychoneuroimmunology have documented immune defects in association with several diseases and with stress[98]. However, most of these studies have been correlative, which thereby prevents statements of causality among identified psychological, immune and health outcomes.

Among the most compelling studies have been those by Cohen and colleagues[99], who looked at the relationship between psychological stress and resistance to infection. To evaluate this, they prospectively studied the association between psychological stress and the frequency of documented clinical colds among individuals who were intentionally exposed to respiratory viruses. They observed that psychological stress was associated in a dose-dependent manner with an increased risk of acute infectious respiratory illness and that this risk was attributable to increased rates of infection.

Psychological stress can affect immunity through the hypothalamic–pituitary–adrenal (HPA) axis and the sympathetic–adrenal medullary (SAM) axis[100]. Stress-induced activation of the HPA axis results in the release of neuroendocrine hormones, such as adrenocorticotropin, from the anterior pituitary gland. Adrenocorticotropin then circulates through the bloodstream to the adrenal glands, where it induces the release of glucocorticoids, which then bind receptors at the cell surface of lymphoid and myeloid cells[101]. Lymphoid cells can also respond to signals from the SAM axis that are activated by stress, because they have receptors for catecholamines, adrenaline and noradrenaline. Catecholamines induce changes in cellular trafficking, lymphocyte proliferation and antibody production. They also suppress the synthesis of IL-12 and increase the production of IL-10 (REF. 102). This shifts the tenor of cell-mediated immunity from T_H1-type to T_H2-type responses, which results in increased production of antibodies. It is hypothesized that this T_H2-type orientation could increase the risk of viral, fungal and mycobacterial infections.

Because powerful links between the brain and the immune system have evolved, this indicates a purpose and biological advantage for these links. Yet, research on the effects of specific interventions is in its infancy. For example, both the incidence and the severity of shingles (caused by reactivation of varicella-zoster virus, VZV) increase markedly with increasing age and in association with a decline in VZV-specific cell-mediated immunity. Instructing elderly individuals to practise T'ai Chi resulted in an increase in their VZV-specific cell-mediated immunity[103]. This is the first study to show that a behavioural intervention can influence a virus-specific cell-mediated immune response that is important in protection against symptomatic re-infection. Suggestive evidence also comes from hypnosis and conditioning trials. For example, the impact of self-hypnosis, relaxation and guided imagery were evaluated in 21 patients with recurring infection with genital herpes-simplex virus 2 (HSV2). In this small study, after 6 weeks of self-hypnosis using guided imagery, disease recurrence was reduced by almost 50% (REF. 104), which correlated with increased HSV-specific activity of NK cells.

A systematic review of the literature[105] revealed moderate evidence of efficacy for mind–body interventions such as relaxation, meditation, imagery, biofeedback and hypnosis for the treatment of coronary-artery disease, headaches, insomnia, incontinence and chronic lower-back pain. However, a meta-analysis of 85 trials revealed only modest evidence that these interventions can reliably alter an immune response[106].

Conclusions

The data regarding CAM approaches have mainly been obtained using *in vitro* assays, which have uncertain relevance to *in vivo* effects, and small *in vivo* studies in which the immunological effects observed could not be associated with meaningful clinical changes. The exceptions to this general conclusion are the data obtained from studies of individuals with a marked vitamin A or zinc deficiency, remediation of which increases immune responses and improves outcomes. The value of probiotics for the treatment of inflammatory bowel disease and urogenital-tract infections merits additional study, because current treatments are not always satisfactory. Probiotics alone or in combination with other agents might result in a useful therapy.

Mind–body therapies that purport to address psychoneuroimmunological circuits are another fertile area of research. Further progress will arise from studies that evaluate the impact of brain–body interactions on concurrent measures of immune parameters, disease progression, resistance to infection, and health and well-being. Moreover, studies of any of the CAM modalities will benefit from the use of newer and more powerful technologies. So far, studies have mainly relied on relatively simple and insensitive methodologies, such as phenotyping of lymphocytes and quantitation of antibody, proliferative or cytokine responses. Studies of brain correlates of behaviour and immunity using functional magnetic-resonance imaging and positron-emission tomography, and microarray analyses of the expression of genes that mediate immune and neuroendocrine responses, could prove sufficiently sensitive to identify more proximate and powerful contributors to health and to provide objective evidence (in the context of well-controlled trials) of the salutary effects of particular CAM or conventional interventions.

Martin H. Goldrosen is at the Office of Scientific Review, National Center for Complementary and Alternative Medicine, National Institutes of Health, Suite 401, 6707 Democracy Boulevard, Bethesda, Maryland 20817, USA.

Stephen E. Straus is at the Office of the Director, National Center for Complementary and Alternative Medicine, National Institutes of Health, Building 31, Room 2B11, 31 Center Drive, Bethesda, Maryland 20892-2182, USA.

Correspondence to S.E.S.
e-mail: strauss@nccam.nih.gov

doi:10.1038/nri1486

1. National Center for Complementary and Alternative Medicine. *Expanding Horizons of Healthcare: Five-Year Strategic Plan 2001–2005* (National Institutes of Health, Bethesda, 2000).
2. Ernst, E. Prevalence of use of complementary/alternative medicine: a systematic review. *Bull. World Health Organ.* **78**, 252–257 (2000).
3. Barnes, P. M., Powell-Griner, E., McFann, K. & Nahin, R. L. Complementary and alternative medicine use among adults: United States, 2002. *Adv. Data* **343**, 1–19 (2004).
4. Eisenberg, D. M. *et al*. Trends in alternative medicine use in the United States, 1990–1997: results of a follow-up national survey. *JAMA* **280**, 1569–1575 (1998).
5. Ni, H., Simile, C. & Hardy, A. M. Utilization of complementary and alternative medicine by United States adults: results from the 1999 National Health Interview Survey. *Med. Care* **40**, 353–358 (2002).
6. Harris Interactive. Widespread ignorance of regulation and labeling of vitamins, minerals and food supplements, according to a National Harris Interactive Survey. *Harris Interactive Health Care News* (Dec 2002). *Harris Interactive* [online], http://www.harrisinteractive.com/news/allnewsbydate.asp?NewsID=560
7. Zeisel, S. H. Regulation of 'nutraceuticals'. *Science* **285**, 1853–1855 (1999).
8. World Health Organization. *Regulatory Situation of Herbal Medicines: A Worldwide Review* (World Health Organization, Geneva, 1998).
9. European Parliament and the Council of the European Union. The approximation of the laws of the member states relating to food supplements directive (2002/46/EC). *Official J. Eur. Communities* L183/51 (10 Jun 2002).
10. Astin, J. A. Why patients use alternative medicine: results of a national study. *JAMA* **279**, 1548–1553 (1998).
11. Nortier, J. L. *et al*. Urothelial carcinoma associated with the use of a Chinese herb (*Aristolochia fangchi*). *N. Engl. J. Med.* **342**, 1686–1692 (2000).
12. Teschke, R. Kava, kavapyrones and toxic liver injury. *Z. Gastroenterol.* **41**, 395–404 (2003) (in German).
13. Chen, C., Biller, J., Willing, S. J. & Lopez, A. M. Ischemic stroke after using over the counter products containing ephedra. *J. Neurol. Sci.* **217**, 55–60 (2004).
14. Markowitz, J. S. *et al*. Effect of St John's wort on drug metabolism by induction of cytochrome P450 3A4 enzyme. *JAMA* **290**, 1500–1504 (2003).
15. Piscitelli, S. C., Burstein, A. H., Chaitt, D., Alfaro, R. M. & Falloon, J. Indinavir concentrations and St John's wort. *Lancet* **355**, 547–548 (2000).
16. Mathijssen, R. H., Verweij, J., de Bruijn, P., Loos, W. J. & Sparreboom, A. Effects of St. John's wort on irinotecan metabolism. *J. Natl Cancer Inst.* **94**, 1247–1249 (2002).
17. Mansky, P. J. & Straus, S. E. St. John's Wort: more implications for cancer patients. *J. Natl Cancer Inst.* **94**, 1187–1188 (2002).
18. Bauer, S. *et al*. Alterations in cyclosporin A pharmacokinetics and metabolism during treatment with St John's wort in renal transplant patients. *Br. J. Clin. Pharmacol.* **55**, 203–211 (2003).
19. Ernst, E. St John's wort supplements endanger the success of organ transplantation. *Arch. Surg.* **137**, 316–319 (2002).
20. Hall, S. D. *et al*. The interaction between St John's wort and an oral contraceptive. *Clin. Pharmacol. Ther.* **74**, 525–535 (2003).
21. Pfrunder, A. *et al*. Interaction of St John's wort with low-dose oral contraceptive therapy: a randomized controlled trial. *Br. J. Clin. Pharmacol.* **56**, 683–690 (2003).
22. Nahin, R. L. & Straus, S. E. Research into complementary and alternative medicine: problems and potential. *BMJ* **322**, 161–164 (2001).
23. Hughes, D. A. Dietary carotenoids and human immune function. *Nutrition* **17**, 823–827 (2001).
24. De la Fuente, M. Effects of antioxidants on immune system ageing. *Eur. J. Clin. Nutr.* **56** (Suppl. 3), S5–S8 (2002).
25. Stephensen, C. B. Vitamin A, infection, and immune function. *Annu. Rev. Nutr.* **21**, 167–192 (2001).
26. Moriguchi, S. & Muraga, M. Vitamin E and immunity. *Vitam. Horm.* **59**, 305–336 (2000).
27. Beharka, A., Redican, S., Leka, L. & Meydani, S. N. Vitamin E status and immune function. *Methods Enzymol.* **282**, 247–263 (1997).
28. Serafini, M. Dietary vitamin E and T cell-mediated function in the elderly: effectiveness and mechanism of action. *Int. J. Dev. Neurosci.* **18**, 401–410 (2000).

29. Langweiler, M., Schultz, R. D. & Sheffy, B. E. Effect of vitamin E deficiency on the proliferative response of canine lymphocytes. *Am. J. Vet. Res.* **42**, 1681–1685 (1981).
30. Meeker, H. C., Eskew, M. L., Scheuchenzuber, W., Scholz, R. W. & Zarkower, A. Antioxidant effects on cell-mediated immunity. *J. Leukoc. Biol.* **38**, 451–458 (1985).
31. Bendich, A., Gabriel, E. & Machlin, L. J. Dietary vitamin E requirement for optimum immune responses in the rat. *J. Nutr.* **116**, 675–681 (1986).
32. Moriguchi, S., Kobayashi, N. & Kishino, Y. High dietary intakes of vitamin E and cellular immune functions in rats. *J. Nutr.* **120**, 1096–1102 (1990).
33. Yasunaga, T., Kato, H., Ohgaki, K., Inamoto, T. & Hikasa, Y. Effect of vitamin E as an immunopotentiation agent for mice at optimal dosage and its toxicity at high dosage. *J. Nutr.* **112**, 1075–1084 (1982).
34. Tengerdy, R. P., Henzerling, R. H., Brown, G. L. & Mathias, M. M. Enhancement of the humoral immune response by vitamin E. *Int. Arch. Allergy Appl. Immunol.* **44**, 221–232 (1973).
35. High, K. P. Nutritional strategies to boost immunity and prevent infection in elderly individuals. *Clin. Infect. Dis.* **33**, 1892–1900 (2001).
36. Meydani, S. N. *et al*. Vitamin E supplementation and *in vivo* immune response in healthy elderly subjects. A randomized controlled trial. *JAMA* **277**, 1380–1386 (1997).
37. Meydani, S. N. *et al*. Vitamin E and respiratory tract infections in elderly nursing home residents: a randomized controlled trial. *JAMA* **292**, 828–836 (2004).
38. Martorell, R., Yarbrough,C., Yarbrough, S. & Klein, R. E. The impact of ordinary illnesses on the dietary intakes of malnourished children. *Am. J. Clin. Nutr.* **33**, 345–350 (1980).
39. Solomons, N. W. Pathways to the impairment of human nutritional status by gastrointestinal pathogens. *Parasitology* **107**, S19–S35 (1993).
40. Stephensen, C. B. *et al*. Vitamin A is excreted in the urine during acute infection. *Am. J. Clin. Nutr.* **60**, 388–392 (1994).
41. Wiedermann, U. *et al*. Vitamin A deficiency predisposes to *Staphylococcus aureus* infection. *Infect. Immun.* **64**, 209–214 (1996).
42. Dawson, H. D., Li, N. Q., DeCicco, K. L., Nibert, J. A. & Ross, A. C. Chronic marginal vitamin A status reduces natural killer cell number and function in aging Lewis rats. *J. Nutr.* **129**, 1510–1517 (1999).
43. Carman, J. A., Pond, L., Nashold, F., Wassom, D. L. & Hayes, C. E. Immunity to *Trichinella spiralis* infection in vitamin A-deficient mice. *J. Exp. Med.* **175**, 111–120 (1992).
44. Glasziou, P. P. & Mackerras, D. E. Vitamin A supplementation in infectious diseases: a meta-analysis. *BMJ* **306**, 366–370 (1993).
45. Fawzi, W. W., Chalmers, T. C., Herrera, M. G. & Mosteller, F. Vitamin A supplementation and child mortality. A meta-analysis. *JAMA* **269**, 898–903 (1993).
46. American Academy of Pediatrics Committee on Infectious Diseases. Vitamin A treatment of measles. *Pediatrics* **91**, 1014–1015 (1993).
47. Stephensen, C. B. *et al*. Adverse effects of high-dose vitamin A supplements in children hospitalized with pneumonia. *Pediatrics* [online], **101**, E3 (1998).
48. Aukrust, P. *et al*. Decreased vitamin A levels in common variable immunodeficiency: vitamin A supplementation *in vivo* enhances immunoglobulin production and downregulates inflammatory responses. *Eur. J. Clin. Invest.* **30**, 252–259 (2000).
49. Semba, R. D. Vitamin A and human immunodeficiency virus infection. *Proc. Nutr. Soc.* **56**, 459–469 (1997).
50. Coutsoudis, A., Pillay, K., Spooner, E., Kuhn, L. & Coovadia, H. M. Randomized trial testing the effect of vitamin A supplementation on pregnancy outcomes and early mother-to-child HIV-1 transmission in Durban, South Africa. South African Vitamin A Study Group. *AIDS* **13**, 1517–1524 (1999).
51. Fawzi, W. W. *et al*. Effect of providing vitamin supplements to human immunodeficiency virus-infected, lactating mothers on the child's morbidity and $CD4^+$ cell counts. *Clin. Infect. Dis.* **36**, 1053–1062 (2003).
52. Barnes, P. M. & Moynahan, E. J. Zinc deficiency in acrodermatitis enteropathica: multiple dietary intolerance treated with synthetic diet. *Proc. R. Soc. Med.* **66**, 327–329 (1973).
53. Zinc therapy of depressed cellular immunity in acrodermatitis enteropathica. *Nutr. Rev.* **39**, 168 (1981).
54. Beck, F. W., Prasad, A. S., Kaplan, J., Fitzgerald, J. T. & Brewer, G. J. Changes in cytokine production and T cell subpopulations in experimentally induced zinc-deficient humans. *Am. J. Physiol.* **272**, E1002–E1007 (1997).
55. Roy, S. K. *et al*. Randomised controlled trial of zinc supplementation in malnourished Bangladeshi children with acute diarrhoea. *Arch. Dis. Child.* **77**, 196–200 (1997).
56. Sazawal, S. *et al*. Zinc supplementation in young children with acute diarrhea in India. *N. Engl. J. Med.* **333**, 839–844 (1995).
57. Turner, R. B. & Cetnarowski, W. E. Effect of treatment with zinc gluconate or zinc acetate on experimental and natural colds. *Clin. Infect. Dis.* **31**, 1202–1208 (2000).
58. Prasad, A. S. *et al.* Zinc deficiency in elderly patients. *Nutrition* **9**, 218–224 (1993).
59. Girodon, F. *et al*. Effect of micronutrient supplementation on infection in institutionalized elderly subjects: a controlled trial. *Ann. Nutr. Metab.* **41**, 98–107 (1997).
60. Chandra, R. K. Excessive intake of zinc impairs immune responses. *JAMA* **252**, 1443–1446 (1984).
61. Failla, M. L. & Hopkins, R. G. Is low copper status immunosuppressive? *Nutr. Rev.* **56**, S59–S64 (1998).
62. Gibney, M. J. & Hunter, B. The effects of short- and long-term supplementation with fish oil on the incorporation of n-3 polyunsaturated fatty acids into cells of the immune system in healthy volunteers. *Eur. J. Clin. Nutr.* **47**, 255–259 (1993).
63. Yaqoob, P., Pala, H. S., Cortina-Borja, M., Newsholme, E. A. & Calder, P. C. Encapsulated fish oil enriched in α-tocopherol alters plasma phospholipid and mononuclear cell fatty acid compositions but not mononuclear cell functions. *Eur. J. Clin. Invest.* **30**, 260–274 (2000).
64. Blok, W. L. *et al*. Pro- and anti-inflammatory cytokines in healthy volunteers fed various doses of fish oil for 1 year. *Eur. J. Clin. Invest.* **27**, 1003–1008 (1997).
65. Meydani, S. N. *et al*. Oral (n-3) fatty acid supplementation suppresses cytokine production and lymphocyte proliferation: comparison between young and older women. *J. Nutr.* **121**, 547–555 (1991).
66. Kramer, T. R. *et al*. Increased vitamin E intake restores fish-oil-induced suppressed blastogenesis of mitogen-stimulated T lymphocytes. *Am. J. Clin. Nutr.* **54**, 896–902 (1991).
67. Wang, C. *et al*. *Effects of Omega-3 Fatty Acids on Cardiovascular Disease* Summary, Evidence report/technology assessment 94 (Agency for Healthcare Research and Quality, Rockville, 2004).
68. Marchioli, R. *et al*. Early protection against sudden death by n-3 polyunsaturated fatty acids after myocardial infarction: time-course analysis of the results of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-Prevenzione. *Circulation* **105**, 1897–1903 (2002).
69. Volker, D., Fitzgerald, P., Major, G. & Garg, M. Efficacy of fish oil concentrate in the treatment of rheumatoid arthritis. *J. Rheumatol.* **27**, 2343–2346 (2000).
70. Belluzzi, A. *et al*. Effect of an enteric-coated fish-oil preparation on relapses in Crohn's disease. *N. Engl. J. Med.* **334**, 1557–1560 (1996).
71. Broughton, K. S., Johnson, C. S., Pace, B. K., Liebman, M. & Kleppinger, K. M. Reduced asthma symptoms with n-3 fatty acid ingestion are related to 5-series leukotriene production. *Am. J. Clin. Nutr.* **65**, 1011–1017 (1997).
72. Villani, F., Comazzi, R., De Maria, P. & Galimberti, M. Effect of dietary supplementation with polyunsaturated fatty acids on bronchial hyperreactivity in subjects with seasonal asthma. *Respiration* **65**, 265–269 (1998).
73. Donadio, J. V. Jr, Bergstralh, E. J., Offord, K. P., Spencer, D. C. & Holley, K. E. A controlled trial of fish oil in IgA nephropathy. Mayo Nephrology Collaborative Group. *N. Engl. J. Med.* **331**, 1194–1199 (1994).
74. Newman, D. J., Cragg, G. M. & Snader, K. M. Natural products as sources of new drugs over the period 1981–2002. *J. Nat. Prod.* **66**, 1022–1037 (2003).
75. Borchers, A. T., Keen, C. L., Stern, J. S. & Gershwin, M. E. Inflammation and Native American medicine: the role of botanicals. *Am. J. Clin. Nutr.* **72**, 339–347 (2000).
76. Perry, N. B., Burgess, E. J. & Glennie, V. L. *Echinacea* standardization: analytical methods for phenolic compounds and typical levels in medicinal species. *J. Agric. Food Chem.* **49**, 1702–1706 (2001).
77. Burger, R. A., Torres, A. R., Warren, R. P., Caldwell, V. D. & Hughes, B. G. *Echinacea*-induced cytokine production by human macrophages. *Int. J. Immunopharmacol.* **19**, 371–379 (1997).
78. Berman, J. D. & Straus, S. E. in *Principles and Practices of Infectious Diseases* (eds Mandell, G., Bennett, J. E. & Dolin, R.) (Elsevier, Philadelphia, in the press).
79. Schulten, B., Bulitta, M., Ballering-Bruhl, B., Koster, U. & Schafer, M. Efficacy of *Echinacea purpurea* in patients with a common cold. A placebo-controlled, randomised, double-blind clinical trial. *Arzneimittelforschung* **51**, 563–568 (2001).
80. Barrett, B. P. *et al*. Treatment of the common cold with unrefined *Echinacea*. A randomized, double-blind, placebo-controlled trial. *Ann. Intern. Med.* **137**, 939–946 (2002).
81. Tao, X. & Lipsky, P. E. The Chinese anti-inflammatory and immunosuppressive herbal remedy *Tripterygium wilfordii* Hook F. *Rheum. Dis. Clin. North Am.* **26**, 29–50 (2000).
82. Chen, B. J. Triptolide, a novel immunosuppressive and anti-inflammatory agent purified from a Chinese herb *Tripterygium wilfordii* Hook F. *Leuk. Lymphoma* **42**, 253–265 (2001).
83. Tao, X., Younger, J., Fan, F. Z., Wang, B. & Lipsky, P. E. Benefit of an extract of *Tripterygium wilfordii* Hook F. in patients with rheumatoid arthritis: a double-blind, placebo-controlled study. *Arthritis Rheum.* **46**, 1735–1743 (2002).
84. Alvarez-Olmos, M. I. & Oberhelman, R. A. Probiotic agents and infectious diseases: a modern perspective on a traditional therapy. *Clin. Infect. Dis.* **32**, 1567–1576 (2001).
85. Silva, M., Jacobus, N. V., Deneke, C. & Gorbach, S. L. Antimicrobial substance from a human *Lactobacillus* strain. *Antimicrob. Agents Chemother.* **31**, 1231–1233 (1987).
86. Mack, D. R., Michail, S., Wei, S., McDougall, L. & Hollingsworth, M. A. Probiotics inhibit enteropathogenic *E. coli* adherence *in vitro* by inducing intestinal mucin gene expression. *Am. J. Physiol.* **276**, G941–G950 (1999).
87. Christensen, H. R., Frokiaer, H. & Pestka, J. J. Lactobacilli differentially modulate expression of cytokines and maturation surface markers in murine dendritic cells. *J. Immunol.* **168**, 171–178 (2002).
88. Gill, H. S., Rutherfurd, K. J. & Cross, M. L. Dietary probiotic supplementation enhances natural killer cell activity in the elderly: an investigation of age-related immunological changes. *J. Clin. Immunol.* **21**, 264–271 (2001).
89. Kaila, M. *et al*. Enhancement of the circulating antibody secreting cell response in human diarrhea by a human *Lactobacillus* strain. *Pediatr. Res.* **32**, 141–144 (1992).
90. Guarino, A., Canani, R. B., Spagnuolo, M. I., Albano, F. & Di Benedetto, L. Oral bacterial therapy reduces the duration of symptoms and of viral excretion in children with mild diarrhea. *J. Pediatr. Gastroenterol. Nutr.* **25**, 516–519 (1997).
91. Van Niel, C. W., Feudtner, C., Garrison, M. M. & Christakis, D. A. *Lactobacillus* therapy for acute infectious diarrhea in children: a meta-analysis. *Pediatrics* **109**, 678–684 (2002).
92. Kalliomaki, M. *et al*. Probiotics in primary prevention of atopic disease: a randomised placebo-controlled trial. *Lancet* **357**, 1076–1079 (2001).
93. Buydens, P. & Debeuckelaere, S. Efficacy of SF 68 in the treatment of acute diarrhea. A placebo-controlled trial. *Scand. J. Gastroenterol.* **31**, 887–891 (1996).
94. Oksanen, P. J. *et al*. Prevention of travellers' diarrhoea by *Lactobacillus* GG. *Ann. Med.* **22**, 53–56 (1990).
95. Fedorak, R. N. & Madsen, K. L. Probiotics and the management of inflammatory bowel disease. *Inflamm. Bowel Dis.* **10**, 286–299 (2004).
96. Reid, G. *et al*. Oral use of *Lactobacillus rhamnosus* GR-1 and *L. fermentum* RC-14 significantly alters vaginal flora: randomized, placebo-controlled trial in 64 healthy women. *FEMS Immunol. Med. Microbiol.* **20**, 131–134 (2003).
97. Evans, P., Hucklebridge, F. & Chow, A. *Mind, Immunity and Health: The Science of Psychoneuroimmunology* (Free Association Books, London, 2000).
98. Kiecolt-Glaser, J. K., McGuire, L., Robles, T. F. & Glaser, R. Psychoneuroimmunology and psychosomatic medicine: back to the future. *Psychosom. Med.* **64**, 15–28 (2002).
99. Cohen, S., Tyrrell, D. A. & Smith, A. P. Psychological stress and susceptibility to the common cold. *N. Engl. J. Med.* **325**, 606–612 (1991).
100. Yang, E. V. & Glaser, R. Stress-associated immunomodulation and its implications for responses to vaccination. *Expert Rev. Vaccines* **1**, 453–459 (2002).
101. Eskandari, F. & Sternberg, E. M. Neural–immune interactions in health and disease. *Ann. NY Acad. Sci.* **966**, 20–27 (2002).

102. Elenkov, I. J., Papanicolaou, D. A., Wilder, R. L. & Chrousos, G. P. Modulatory effects of glucocorticoids and catecholamines on human interleukin-12 and interleukin-10 production: clinical implications. *Proc. Assoc. Am. Physicians* **108**, 374–381 (1996).
103. Irwin, M. R., Pike, J. L., Cole, J. C. & Oxman, M. N. Effects of a behavioral intervention, Tai Chi Chih, on varicella-zoster virus specific immunity and health functioning in older adults. *Psychosom. Med.* **65**, 824–830 (2003).
104. Gruzelier, J. H. A review of the impact of hypnosis, relaxation, guided imagery and individual differences on aspects of immunity and health. *Stress* **5**, 147–163 (2002).
105. Astin, J. A., Shapiro, S. L., Eisenberg, D. M. & Forys, K. L. Mind–body medicine: state of the science, implications for practice. *J. Am. Board Fam. Pract.* **16**, 131–147 (2003).
106. Miller, G. E. & Cohen, S. Psychological interventions and the immune system: a meta-analytic review and critique. *Health Psychol.* **20**, 47–63 (2001).
107. Anderson, J. W., Konz, E. C. & Jenkins, D. J. Health advantages and disadvantages of weight-reducing diets: a computer analysis and critical review. *J. Am. Coll. Nutr.* **19**, 578–590 (2000).
108. Foster, G. D. *et al*. A randomized trial of a low-carbohydrate diet for obesity. *N. Engl. J. Med.* **348**, 2082–2090 (2003).
109. Ornish, D. *Dr. Dean Ornish's Program for Reversing Heart Disease* (Ballantine Books, New York, 2004).
110. Sheng, Y., Bryngelsson, C. & Pero, R. W. Enhanced DNA repair, immune function and reduced toxicity of C-MED-100, a novel aqueous extract from *Uncaria tomentosa*. *J. Ethnopharmacol.* **69**, 115–126 (2000).
111. Chan, M. M. Inhibition of tumor necrosis factor by curcumin, a phytochemical. *Biochem. Pharmacol.* **49**, 1551–1556 (1995).
112. Nakaya, T. A., Kita, M., Kuriyama, H., Iwakura, Y. & Imanishi, J. *Panax ginseng* induces production of proinflammatory cytokines via Toll-like receptor. *J. Interferon Cytokine Res.* **24**, 93–100 (2004).
113. McKallip, R. J., Lombard, C., Martin, B. R., Nagarkatti, M. & Nagarkatti, P. S. Δ^9-tetrahydrocannabinol-induced apoptosis in the thymus and spleen as a mechanism of immunosuppression *in vitro* and *in vivo*. *J. Pharmacol. Exp. Ther.* **302**, 451–465 (2002).
114. United States Congress. Dietary Supplement Health and Education Act (Public Law 103-417; codified at US congress 287C-11) (25 Oct 1994). *Food and Drug Administration* [online], http://www.fda.gov/opacom/laws/dshea.html

Acknowledgements
We acknowledge the assistance of C. Pontzer for proof-reading the manuscript.

Competing interests statement
The authors declare no competing financial interests.

Online links

DATABASES
The following terms in this article are linked online to:
Entrez Gene:
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene
C-reactive protein | IFN-γ | IL-1 | IL-2 | IL-4 | IL-6 | IL-8 | IL-10 | IL-12 | TNF

FURTHER INFORMATION
National Center for Complementary and Alternative Medicine: http://nccam.nih.gov
Chronic Fatigue and Immune Dysfunction Syndrome Association of America: http://www.cfids.org
The Autism Autoimmunity Project:
http://www.autismautoimmunityproject.org
Access to this interactive links box is free online.

ONLINE CORRESPONDENCE
Nature Reviews Immunology publishes items of correspondence online. Such contributions are published at the discretion of the Editors and can be subject to peer review. Correspondence should be no longer than 500 words with up to 15 references and should represent a scholarly attempt to comment on a specific Review or Perspective article that has been published in the journal. To view correspondence, please go to our homepage and select the link to Correspondence or use the URL indicated below.

The following correspondence has recently been published:

Processed switch-region transcripts and retrotranscripts as possible generators of heteroduplex 'R-loop' targets for AID-deamination
Steele, E. J.
http://www.nature.com/nri/archive/correspondence.html
This correspondence relates to the article

CLASS-SWITCH RECOMBINATION: INTERPLAY OF TRANSCRIPTION, DNA DEAMINATION AND DNA REPAIR
Chaudhuri, J. and Alt, F. W.
Nature Reviews Immunology **4**, 541–552 (2004).

César Milstein and the discovery of monoclonal antibodies
Karpas, A.
http://www.nature.com/nri/archive/correspondence.html

A witness is not a judge
Alkan, S. S.
http://www.nature.com/nri/archive/correspondence.html
This correspondence relates to the article

MONOCLONAL ANTIBODIES: THE STORY OF A DISCOVERY THAT REVOLUTIONIZED SCIENCE AND MEDICINE
Alkan, S. S.
Nature Reviews Immunology **4**, 153–156 (2004).