Inflammation and Native American medicine: the role of botanicals[1–3]

Andrea T Borchers, Carl L Keen, Judy S Stern, and M Eric Gershwin

ABSTRACT There is a growing interest in medicinal botanicals as part of complementary medicine in the United States. In particular, both physicians and consumers are becoming aware of the use of herbals by Native American societies; many botanicals sold today as dietary supplements in the United States were used by Native Americans for similar purposes. Yet, these supplements represent only a small number of the >2500 different plant species from vascular taxa, and >2800 species from all taxa, known to have been prized for their medicinal properties by the indigenous inhabitants of the North American continent. We review some of the studies of the immunomodulatory activities of botanicals used by native peoples of North America, the bioactive constituents responsible for those activities, and the mechanisms by which these constituents might modulate the immune system. We focus particularly on 3 species of purple coneflower (*Echinacea*) because of the widespread use of purple coneflower in the United States to boost immunity and prevent upper respiratory infections. Seven of the 10 most common botanicals sold in the United States were used extensively by Native Americans. However, there are very few data to support such use and even less information about drug toxicity or interactions. *Am J Clin Nutr* 2000;72:339–47.

KEY WORDS Ethnobiology, *Echinacea*, Native Americans, medical botanicals, review, herbal supplements

INTRODUCTION

Of the 10 top-selling herbal dietary supplements in the United States today, 7 were used by Native Americans (**Table 1**). Numerous other widely sold herbal supplements, such as black cohosh (*Cimicifuga racemosa*), blue cohosh (*Caulophyllum thalictroides*), elderberry (*Sambucus* species), and juniper (*Juniperus communis*), were used extensively by indigenous North American peoples. Some pharmaceuticals were originally discovered in the course of investigations of botanicals that were used by Native Americans for medicinal purposes. Examples are taxol, obtained from *Taxus brevifolia* (Pacific yew tree), and etoposide phosphate, a derivative of podophyllotoxin, which is a constituent of *Podophyllum peltatum* (May apple or American mandrake) (6, 7). Both are currently used for the treatment of various malignancies.

Plants play an important role in the medical practices of many, if not all, Native American peoples. Thus, plants are used not only in the diagnostic process, but also in the physical and ritual purification procedures that commonly precede ceremonies and in the act of healing itself. Of the >17 000 plant species that constitute the North American flora, >2500 members of the vascular taxa and >2800 of all taxa were used—and to some extent continue to be used—for medicinal purposes by various Native American societies (8). The gathering of information about the use of particular plants as medicine has been in progress for at least a century. The resulting data were compiled in book form in 1986 (9) and, more recently, in an Internet database (http://www.umd.umich.edu/cgi-bin/herb). Yet, ethnobotanists continue to uncover additional medicinal plants and uses of the plants already included in these databases (10–13).

Specific uses of medicinal plants by Native Americans have been reported and, interestingly, the same plant parts were often used by many different tribes in diverse areas of North America (**Table 2**). Analysis of the plants used as medicines by the original North American residents showed that the choice of medicinal botanicals was by no means random, but highly selective, as evidenced by the extensive use of some plant families and the virtual avoidance of others (8, 14). Several lines of evidence suggest that Native Americans took botanicals as medicine in the sense that Western science uses that term (15–17). For example, Native Americans used different plant parts for the treatment of various ailments (9), combined several botanicals for specific therapeutic purposes, and recognized toxic plants both as actual poisons and for medicinal purposes (3, 6, 15–17). However, we should emphasize that a spiritual component is also involved in the use of plants for the treatment of particular symptoms, because it is the power, the "spirit," of the plant that is believed to have the therapeutic effect (18).

For a plant to have "power," certain rules have to be observed in collecting the plant. There is surprising agreement among the

[1] From the Department of Nutrition, the Division of Rheumatology/Allergy and Clinical Immunology, the University of California, Davis.

[2] Supported by the National Institutes of Health (grant AI37627).

[3] Reprints not available. Address correspondence to ME Gershwin, Division of Rheumatology/Allergy and Clinical Immunology, University of California at Davis, TB 192, School of Medicine, Davis, CA 95616. E-mail: megershwin@ucdavis.edu.

Received November 10, 1999.

Accepted for publication January 19, 2000.

TABLE 1
The 10 top-selling botanicals in the United States, their uses by Native Americans, and their current uses[1]

Common name (Latin names)	Family	Sales ($ million)	Native American peoples who used the botanical	Native American indications	Current marketed indications
Ginkgo (*Ginkgo biloba*)	Ginkgoaceae	90	None	Not used	Memory and circulation
Ginseng (*Panax quinquefolius*, *Panax ginseng*, *Eleutherococcus senticosus*)	Araliaceae	86	(*P. quinquefolius* only) Cherokee, Creek, Delaware, Fox, Houma, Iroquois, Menominee, Mohegan, Pawnee, Penobscot, Potawatomi	Tonic, expectorant; for fevers, tuberculosis, asthma, and rheumatism; as a strengthener of mental powers	Immune function and stress
Garlic (*Allium sativum*)	Liliaceae	71	Cherokee	Stimulant, carminative, diuretic, expectorant, mild cathartic; for scurvy, asthma, and prevention of worms	Cardiovascular health and cholesterol lowering
Echinacea (*Echinacea purpurea*, *Echinacea angustifolia*, *Echinacea pallida*)	Asteraceae (Compositae)	49[2]	Cheyenne, Choctaw, Dakota, Delaware, Fox Kiowa, Montana, Omaha Pawnee, Ponca, Sioux, Winnebago	Pain relief; for coughs and sore throats, fevers, smallpox, mumps, measles, rheumatism, and arthritis; antidote for poisons and venoms	Immune function
Goldenseal (*Hydrastis canadensis*)	Ranunculaceae		Cherokee, Iroquois, Micmac	Tonic; for fever, whooping cough, and pneumonia	Immune function
St John's wort (*Hypericum perforatum*)	Hyperiaceae (Guttiferae)	48	Cherokee, Iroquois, Montagnais	For fever, coughs, and bowel complaints	Antidepressant
Saw palmetto (*Serenoa repens*)	Palmacea	18	None	Not used	Prostate health
Grape seed extract (*Vitis vinifera*)	Vitaceae	10	None	Not used	Antioxidant status
Evening primrose (*Oenothera biennis*)	Onagraceae	7	Cherokee, Iroquois, Ojibwa, Potawatomi	For premenstrual and menstrual pain, obesity, and bowel pains	Antioxidant status; premenstrual and menstrual pain
Cranberry (*Vaccinium macrocarpon*)	Ericaceae	6	Montagnais	For pleurisy	Health of urinary tract

[1] From references 1–5.
[2] Echinacea and goldenseal combined.

instructions reported from such geographically and culturally distinct tribes as the Iroquois of the Northeast and the Salishan of the Northwest (Vancouver Island). In both tribes, the importance of collecting plants in the morning is stressed, tree bark is to be taken from the eastern side of the tree, an offering of tobacco is to be made (11, 18), and prayers need to be said (16, 18). Such details regarding the collection procedure or, perhaps more important, the precise plant part used and the method of its preparation, are not always reported. This lack of information and the fact that medicinal use of plants by North America's indigenous residents commonly, if not always, transcended the mere physical contributes to the paucity of literature dealing with their medicinal properties.

Despite the availability of many of these botanicals in health food stores and, to an increasing extent, in supermarkets and pharmacies, scientific research regarding efficacy and safety is limited. Most medicinal botanicals have not been investigated to any great extent, and rarely has the focus of such research been specifically on medicinal botanicals used by Native Americans. Fortunately, however, some of the species used medicinally by Native Americans are also native to other parts of the world (eg, *Sambucus nigra*, *Sambucus racemosa*, and *J. communis*); others were introduced to European settlers by indigenous North American populations and have subsequently become popular in Europe [eg, *Echinacea* species (19) and *Lobelia inflata* (20)]. Intentionally or accidentally, settlers from other continents, in turn, brought some of their native botanicals, resulting in the eventual use of some foreign species by Native Americans (eg, *Urtica dioica* and *Tanacetum vulgare*). Thus, what little research exists on species used by original North American inhabitants predominantly comes from other countries where the same species were used, often for the same therapeutic purposes as those reported by Native Americans. However, even in plants grown within the same vicinity, differences in the amounts and ratios of chemical constituents, and thus of biological activity, will arise, depending on environmental conditions (21); the time of harvest, storage, and processing and the extraction procedure will introduce further variability (22, 23).

Plants with antiinflammatory activities

Research on botanicals used by indigenous populations has generally been confined to in vitro screenings of individual plants or their constituents for their antibacterial, antiviral, or antiinflammatory activities (24–27). The fact that a botanical was traditionally used for wound healing, fever, infection, edema, or rheumatic disease is taken as an indicator that the plant should be tested for its antiinflammatory properties (26). Although several in vitro assays can be used to test for antiinflammatory activities (28), most screening procedures include inhibition of cyclooxygenase and 5-lipoxygenase. These 2 enzymes are central to the pathways producing thromboxanes, prostaglandins, and leukotrienes. A list of several whole-plant extracts and isolated chemical components that have an inhibitory effect on one or both of these enzymes is provided in **Table 3**. Because different

TABLE 2
Selected plants and their uses by Native Americans[1]

Genus and species and part used	Indication	Societies that used the plant
Echinacea angustifolia		Cheyenne, Dakota, Fox, Kiowa, Montana Indians, Omaha, Pawnee, Ponca, Teton Sioux, and Winnebago
Infusion of leaves and roots	Taken for sore mouth, gums, or throat	
Plant	Antidote for many poisons and venoms	
Root	Antidote for snake bites; used in medicine for stomach cramps and bowel pain	
Ground roots	Chewed for coughs and sore throat	
Smashed roots	Applied as poultice to snake bites, stings, and septic diseases	
Juice	Used to wash burns and to relieve pain	
Plant	Used in smoke treatment for distemper of horses	
E. pallida		Cheyenne and Dakota
Decoction of roots	Taken for rheumatism and arthritis, smallpox, mumps, and measles; taken as vermifuge; used as a wash for burns and fever	
Roots	Chewed for colds	
Poultice of roots	Applied to inflammation	
Plant	Antidote for snake bites	
E. purpurea Moench		Choctaw and Delaware-Okl
Root	Chewed for cough and dyspepsia	
Tincture of root	For cough and dyspepsia	
Infusion of root	Taken for gonorrhea	
Urtica dioica L.		Chehalis, Cherokee, Cowlitz, Iroquois, Klallam, Kwakiutl, Lummi, Ojibwa, Potawatomi, Quileute, Quinault, Samish, Shuswap, Shagit, Shokomish, Snohomish, Squaxin, Swinomish, Tainarna, and Wet'suwet'en
Whole stalk	Used to whip person with rheumatism or paralysis	
Infusion of stalks	Rubbed on body for soreness and stiffness	
Infusion of nettles or crushed leaves or tips of plants	Taken before or during childbirth	
Infusion of roots	Taken for treatment of intermittent fever	
Infusion of pounded roots	Taken for rheumatism	
Decoction of stems and roots	Used as sweatbath for rheumatism	
Boiled rhizomes	Used as a general medicine	

[1] From references 9 and 12.

assay systems were used in the various studies, a direct comparison of the results is not appropriate. Of the plants listed in Table 3, purple coneflower (*Echinacea* species) and stinging nettle (*U. dioica*), are discussed below. For the remaining plants, what little additional research exists on them is presented in the available detail.

Sanguinarine (13-methyl[1,3]benzodioxolo[5,6-*c*]-1,3-dioxolo[4,5-*i*]phenanthridinium) is found in the root of *Sanguinaria canadensis* (bloodroot), a plant from the family of Papaveraceae that was used extensively by numerous Native American societies for blood tonification and purification, pain relief, wound healing, fevers, and numerous other purposes (9). The use of a medicinal botanical as a tonic usually indicates that the botanical has the ability to enhance certain immune responses. It is uncertain what is meant by "blood purification" in terms of modern medicine. In vitro, sanguinarine suppressed human peripheral blood neutrophil function, including chemotaxis, adhesion, oxidative burst, degranulation, and phagocytosis, and was nontoxic at all concentrations tested (35). Sanguinarine also strongly inhibited the activation of nuclear transcription factor κB (NF-κB), which is involved in the induction of numerous proinflammatory mediators (36). Sanguinarine suppressed NF-κB activation by preventing phosphorylation and degradation of inhibitory κB-α, which prevents entry of NF-κB into the nucleus.

Various preparations of *Hamamelis virginiana* (witch hazel; Hamamelidaceae family) were taken by Native Americans for pain relief, colds, and fevers (9). A crude alcohol and water extract of *H. virginiana*, as well as fractions in which the hamamelitannin content was reduced by ultrafiltration, were assessed for their antiinflammatory activities in several in vitro and in vivo experimental systems (37). In vitro, elastase, a proteolytic enzyme participating in the inflammatory response, was inhibited most potently by the fraction containing the highest concentration of hamamelitannin, and this fraction exhibited the strongest antioxidant activity. Contrasting with this, and also with the finding that hamamelitannin inhibited 5-lipoxygenase activity at very low concentrations (31) (Table 3), partial removal of hamamelitannin by ultrafiltration resulted in a stronger inhibition of croton oil–induced ear edema (37). Oral pretreatment with an ethanolic extract of the leaves of *H. virginiana*, before a carrageenan injection, did not prevent paw edema in rats but reduced the arthritic paw swelling induced with Freund's adjuvant, although to a lesser extent than did *Polygonum bistorta*, another Native American medicinal botanical (38). In the only clinical trials of the antiinflammatory effects of *H. virginiana*, preparations of this botanical were applied topically rather than administered orally (39). In 2 such trials, *H. virginiana* was found to have a mild suppressive effect on ultraviolet light–induced erythema and itching (39, 40), whereas a similar preparation was no more effective than was the drug-free vehicle in relieving atopic eczema (41). Whether oral ingestion of *H. virginiana* has greater effectiveness than does topical application remains to be addressed in animal models of inflammation and possibly in humans.

S. nigra (black elder; Caprifoliaceae family) is one of many *Sambucus* species used by Native Americans, mostly for rheumatism and fever (9). A methanol, and particularly a butanol

TABLE 3
Antiinflammatory botanicals that inhibit cyclooxygenase (COX) and 5-lipoxygenase (5-LOX)[1]

Plant	Extraction procedure (concentration tested)	Plant constituent	Reference	COX inhibition	5-LOX inhibition
Achillea millefolium	Cold water extract of herb (0.2 g/L)	Alkamides (50 μmol/L)	26	21%	—
			29	37%	None
Echinacea angustifolia	*N*-hexane extract of roots (50 mg/L)	Individual root alkamides (50 μmol/L)	29	62%	82%
			29	≤75%	≤82%
Echinacea purpurea		Alkamide fraction from roots (50 μmol/L)	30	ND	92%
Hamamelis virginiana		Hamamelitannin	31	ND	IC_{50} = 1.0 μmol/L
Juniperus communis	Cold water extract of fruit (0.2 g/L)		26	55%	—
Ledum palustre	Cold water extract of herb (0.2 g/L)		26	50%	—
Picea abies	Cold water extract of shots (0.2 g/L)		26	55%	—
Polygonum aviculare	Cold water extract of herb (0.2 g/L)		26	52%	—
Sanguinaria canadensis L.		Sanguinarine	32	—	IC_{50} = 0.4 μmol/L
Tanacetum vulgare		Parthenolide	33	IC_{50} = 6 μmol/L	IC_{50} = 12 μmol/L
Urtica dioica	80% MeOH extraction of leaves		34	IC_{50} = 92 mg/L	None
		Caffeic malic acid		IC_{50} = 38 mg/L	IC_{50} = 83 mg/L
	Cold water extraction of herb (0.2 g/L)		26	None	—

[1] IC_{50}, half-maximal inhibitory concentration.

and a chloroform, extract of *S. nigra* leaves, but not flowers, significantly inhibited lipopolysaccharide (LPS)-induced synthesis of tumor necrosis factor α (TNF-α) by human peripheral blood mononuclear cells but had minimal effect on interleukin (IL)-1α and IL-1β production (42). Oral administration of an aqueous extract of the aerial parts of *S. nigra* before a carrageenan injection significantly inhibited hind-paw edema in mice (27). A standardized extract of the berries of the black elder, which also contains raspberry extract and citric acid, inhibited viral replication of several strains of influenza viruses in vitro and was subsequently tested in vivo (43). In this double-blind, placebo-controlled study completed by 27 patients, the same extract with added glucose and honey, taken orally for 3 d after the onset of influenza virus B infection, was associated with significantly better relief of symptoms and faster recovery in the treated than in the placebo group (43). Viral antibody titers tended to be higher in the extract-treated group than in the placebo group, suggesting that this botanical extract, possibly in addition to exerting direct antiviral activity, stimulated host immune responses. To our knowledge, this was the only double-blind, placebo-controlled clinical trial to date that used elderberry extract. Although the study was limited by its small sample size, its promising results seem to warrant further in vitro and in vivo studies of elderberry preparations.

Echinacea species (purple coneflower; Compositae family)

E. angustifolia, the narrow-leafed purple coneflower, has long been used by Native Americans for pain relief and wound treatment, as an antidote against various poisons, and for symptoms associated with the common cold (Table 1) (3, 9). It was introduced by Native Americans to European settlers, who subsequently took what they thought was *E. angustifolia* back to Europe. It turned out, however, that the species introduced in Europe was *E. purpurea*, another native American plant used for medicinal purposes by the Choctaw and Delaware (9, 19). *E. purpurea* has since become one of the most popular medicinal botanicals in Europe and the United States (19). For medicinal purposes, besides *E. purpurea* and *E. angustifolia*, a third species, *E. pallida*, is commonly used.

What the American consumer calls *Echinacea* can be any one of the 3 above-mentioned species or a combination of 2 or even of all 3 of them, which should of course be indicated on the label. Furthermore, many *Echinacea* preparations, including one of the best-known European brands that has been used in numerous studies (Echinacin; Biomed, Düsendorf, Switzerland), are extracts of both root and above-ground parts, whereas in other instances the root alone or the above-ground parts alone are used. There are substantial differences in the chemical compositions and the biological activities not only between different *Echinacea* species, but also between their roots and aerial parts (44–46). It is noteworthy that *E. purpurea* does not contain echinacoside, the substance used frequently for standardizing *E. angustifolia* and *E. pallida* extracts (47). Further differences arise from the extraction procedure. For example, the polysaccharides to which many of the stimulatory effects of *Echinacea* species on the nonspecific immune system have been attributed are likely to be present in aqueous, but not in alcoholic, extracts (47). In addition, in the United States, *Echinacea* is often sold in combination with goldenseal (*Hydrastis canadensis*); combinations with other medicinal botanicals are common here and in Europe.

Echinacea is one of 12 commonly used herbs that physicians need to be aware of and knowledgeable about (48). At least 3 different species of *Echinacea* are sold under that name, yet the literature is often reviewed without regard to what particular species

was used. Moreover, differences arising from different extraction procedures, solvents, and plant parts used are ignored, and little distinction is made between data obtained with purified polysaccharides and those obtained with crude extracts.

In vitro, the phagocytosis of yeast particles by human granulocytes was stimulated by commercial extracts of both *E. angustifolia* and *E. purpurea* (not further characterized; 49). In the same assay system, ethanolic root extracts of *E. purpurea* stimulated phagocytosis to a greater extent than did *E. angustifolia* or *E. pallida* (44). In contrast, a widely available commercial extract of both roots and aerial parts of *E. purpurea* significantly decreased the chemiluminescence (phagocytosis) of human granulocytes at a high concentration (1:1 dilution), and the increase seen with a 1:100 dilution was not significant (50). These results might be attributable to experimental or procedural problems, as suggested by the fact that incubation of granulocytes with phorbol myristate acetate, a known inducer of phagocytosis, did not result in an increase in phagocytotic activity. In addition, cell viability was not assessed and might have been reduced after incubation with the high concentration of this *Echinacea* extract. However, others also reported that a high concentration of an ethanolic extract of *E. purpurea* suppressed, rather than enhanced, phagocytosis (51). Human macrophages incubated in vitro with a lyophilized and reconstituted fresh-pressed juice or a reconstituted dried juice of the above-ground parts of *E. purpurea*, harvested at the peak of flowering, produced the cytokines TNF-α, IL-1, and IL-10 at concentrations comparable with, or higher than, those seen with LPS stimulation; IL-6 production was higher than in controls, but lower than that obtained with LPS (52).

A purified polysaccharide from *E. purpurea* augmented the phagocytosis of yeast particles or opsonized zymosan by human granulocytes by 23% and 34%, respectively (53). Incubation of human macrophages with a purified polysaccharide from *E. purpurea* cell culture induced the production of TNF-α, IL-1, and IL-6. In addition, this polysaccharide increased the motility of human polymorphonuclear cells (PMNs) and their cytotoxic activity against staphylococci and stimulated the proliferation of human lymphocytes (54).

Both natural killer activity and antibody-dependent cell cytotoxicity were higher after treatment with an *E. purpurea*/RPMI homogenate than in untreated controls in peripheral blood mononuclear cells isolated from healthy subjects or patients with chronic fatigue syndrome or AIDS (55). It was not specified whether the "fresh herbs" used for the homogenate included roots or flowers.

In vivo, ethanolic root extracts of *E. purpurea*, *E. pallida*, and *E. angustifolia* all significantly increased the phagocytic activity of liver and spleen macrophages in mice treated 3 times daily for 2 days by gavage (47). *E. purpurea* root extract was more effective than were root extracts from either of the other species. However, an extract from the aerial parts of *E. purpurea* stimulated phagocytosis to a much lesser extent than did *E. pallida* or *E. angustifolia* (44).

Intravenous treatment of mice with polysaccharides isolated from *E. purpurea* cell culture significantly increased the survival rate of healthy and immunosuppressed mice injected with lethal doses of *Candida albicans* or *Listeria monocytogenes* (56, 57). Because protection against *C. albicans* and *L. monocytogenes* is thought to be mediated mostly by PMNs and macrophages, respectively, these findings provide further indications that polysaccharides are at least partially responsible for the stimulation of the nonadaptive immune responses observed with various *Echinacea* extracts.

In humans, an alcohol extract of *E. purpurea* roots administered intravenously or orally resulted in a significant increase in PMN phagocytic activity (51, 58). However, this was not a consistent finding of clinical studies with various *Echinacea* preparations (59). Oral ingestion of an extract containing *E. angustifolia*, *Eupatorium perfoliatum*, and *Thuja occidentalis* by 23 cancer patients for 4 wk reportedly had no effect on the concentrations of the 6 cytokines measured in whole-blood cell cultures (60). Methodologic problems might largely account for this lack of effect. No attempt was made to equalize the number of cells used per assay per patient, and the cytokines were measured only in phytohemagglutinin- or pokeweed mitogen–stimulated, but not in unstimulated, cells and only after 48 and 96 h of culture. However, in contrast with the results obtained in vitro, intravenous injection of a polysaccharide from *E. purpurea* also did not significantly increase the concentrations of TNF-α or IL-1β or increase IFN activity in human serum or plasma, although monocytes and PMNs were induced to migrate into the peripheral blood (54).

Among the specific uses of *Echinacea* species reported, the Kiowa chewed ground roots of *E. angustifolia* for coughs and sore throats, the Cheyenne chewed roots of *E. pallida* for colds or took infusions of leaves and roots for sore mouth and throat, and the Choctaw chewed roots of *E. purpurea* or made a tincture of it as a cough remedy (9). It is this particular indication of *Echinacea* preparations as a cold remedy that was tested in numerous clinical trials. In a placebo-controlled, double-blind study with 180 patients with upper respiratory infections, patients given the higher (900 mg/d) dosage of an ethanolic extract from the root of *E. purpurea* experienced significantly fewer and milder symptoms of shorter duration than did patients treated with placebo or the lower dosage (450 mg/d) (61). Another placebo-controlled, double-blind clinical study involved 303 volunteers taking a liquid extract containing mainly *E. angustifolia* (as well as smaller amounts of *Eupatorium perfoliatum* and *Baptisia tinctoria*) and 306 volunteers receiving placebo (62). Treatment with this combination of botanicals was effective in diminishing the frequency of upper respiratory infections when administered prophylactically. A recent placebo-controlled, double-blind study with an ethanolic extract of *E. angustifolia* or *E. purpurea* roots showed only a trend toward a reduced risk of upper respiratory infections (63), although it is questionable whether time until onset was an appropriate outcome measure (63). In addition to the studies mentioned above, several clinical trials were performed with various *Echinacea* preparations, but many were not rigorously controlled or were confounded by the fact that preparations containing botanicals besides *Echinacea* species were used (59).

E. purpurea extracts or isolated polysaccharides were neither toxic nor mutagenic when tested in vitro and in vivo, in mice as well as in humans (64, 65). In humans, paleness, slight and transient tachychardia, and equally transient influenza-like symptoms were the most serious adverse effects reported after intravenous injection of an *E. purpurea* extract (51), whereas oral ingestion of an *E. purpurea* extract produced only slightly more adverse effects than did placebo. In at least one study, *E. angustifolia* tended to be associated with more adverse effects than were either *E. purpurea* or placebo, and the adverse effect profile was the same as with *E. purpurea* (63), including headache, nausea, and fatigue (62).

However, plant extracts can cause allergic reactions. Recently, a case of anaphylaxis associated with the consump-

tion of a supplement containing a whole-plant extract of *E. angustifolia* and root extract of *E. purpurea* was reported (66). However, from the tests performed, a clear causal relation between the plant extracts and subsequent anaphylaxis could not be established. Rather, as has been suggested (67), it is possible that another ingredient of the *Echinacea*-containing preparation or of one of the numerous other supplements consumed by the patient were responsible. Included with the case report were the findings that a considerable percentage (19%) of patients with asthma and allergic rhinitis exhibited cross-reactivity to *Echinacea* extract (66). However, note that reactivity was not defined. An inappropriately chosen threshold of reactivity might account for the fact that, instead of the thousands of cases of *Echinacea*-induced anaphylaxis one would have expected to see over the past decade (67) on the basis of Mullins' findings (66), this was one of the first reports of such an occurrence in the literature. Thus, although the possibility of allergic reactions to *Echinacea* cannot be ruled out, the information summarized in the preceding paragraph indicates that, overall, *Echinacea* is a safe and well-tolerated medicinal botanical.

Native Americans used *Echinacea* species extensively for the treatment of colds and for alleviation of the symptoms associated with them, such as sore throat, cough, and fever. Evidence has been accumulating from in vitro and in vivo studies that *Echinacea* species indeed contain bioactive substances capable of stimulating nonadaptive immunity and of helping to prevent and allow patients to more quickly overcome upper respiratory infections. Note, however, that at this point it is not clear to what extent the results of in vitro studies, particularly those conducted with isolated polysaccharides, translate to in vivo situations. Furthermore, the lack of dose-response data from most clinical studies constitutes a serious shortcoming of the existing database on *Echinacea* species. In addition, the use of many different *Echinacea* preparations of undefined or poorly defined chemical compositions in the various studies makes comparisons of the results impossible and severely limits reproducibility. A team of researchers who have worked extensively with various *Echinacea* species, therefore, has long urged the use of HPLC fingerprints to document the exact chemical composition of an extract to enable correlation of specific chemical constituents with observed immunomodulatory activities and to obtain reproducible results (44, 47, 68).

Urtica dioica (stinging nettle; Urticaceae family)

Although *U. dioica* is a native of Europe and Asia (2), its extensive use by Native American societies throughout North America (9, 12; Table 2) suggests that the plant and its medicinal use spread rapidly after its introduction. Various parts of the stinging nettle (*U. dioica*) were administered externally and internally by numerous Native American societies for a variety of purposes, including as a general tonic (ie, what we would now consider an immunostimulant) and as a treatment for fevers and rheumatism (Table 2).

In vitro, by using whole blood from healthy volunteers, a commercial ethanolic extract of *U. dioica*, designated as IDS23, inhibited LPS-induced release of TNF-α and IL-1β but had no effect on the secretion of these cytokines when added to the culture medium in the absence of LPS (69). Inhibition was minimal at concentrations <2.5 g/L. It is unlikely that such a high concentration could be achieved in vivo. When known constituents of *U. dioica* extract, such as caffeic acid, caffeic malic acid, chlorogenic acid, rutin, and quercetin, were tested individually, none inhibited the synthesis of TNF-α or IL-1β. In the same study, *U. dioica* extract stimulated the production of IL-6 to the same extent as did LPS, and this effect was not further augmented by the combination of these 2 agents.

Preincubation with IDS23 or IDS23/1, the water-soluble fraction of IDS23, inhibited activation of NF-κB induced by incubating HeLa or L929 cells with TNF-α, Jurkat cells with phorbol myristate acetate, or MonoMac6 cells with LPS (70). The binding of NF-κB to DNA was inhibited considerably more strongly after preincubation with IDS23/1 than with IDS23. IDS23/1 did not interfere directly with the DNA binding process itself but rather prevented the degradation of the inhibitory molecule IκB-α, which binds to NF-κB in the cytosol and prevents its entry into the nucleus. Another transcription factor, AP-1, was inhibited by IDS23/1, but only partially. Rheumatoid arthritis is an inflammatory disease of joints; cytokines, particularly TNF-α and IL-1, and other mediators of inflammation are strongly implicated in its pathogenesis (71, 72). Both NF-κB and AP-1, in turn, play a central role in the induction of these proinflammatory cytokines and other mediators. The activity of NF-κB and AP-1 is upregulated in rheumatic synovia, in which transcription factors are thought to participate in various inflammatory and joint destructive processes (73–75). Thus, the results of these in vitro studies provide some indication that the Quileute and Tainarna tribes might have derived some benefit when they used infusions of *U. dioica* as an antirheumatic (9).

When healthy volunteers ingested capsules containing 335 mg IDS23/1 twice daily for 3 wk, the concentrations of TNF-α, IL-1β, IL-4, IL-6, and IL-10 produced in cultures of whole blood all remained below the detection limit (≥7 pg/L) (76). However, LPS-stimulated concentrations of TNF-α and IL-1β were slightly but significantly reduced after 7 d and further reduced after 21 d of IDS23/1 treatment compared with baseline. Addition of IDS23/1 to these whole-blood cultures further inhibited the LPS-induced synthesis of these 2 cytokines, leading the authors to propose that the optimal concentration of biologically active constituents had not been reached. It remains to be established which component or components of *U. dioica* exert the cytokine inhibitory effect observed in vitro and whether such components remain intact during digestion and reach the bloodstream in a fully biologically active state. The suppression of cytokine synthesis in response to inflammatory stimuli constitutes one mechanism by which *U. dioica* might ameliorate rheumatic disorders. If confirmed in vivo, the ability of *U. dioica* to inhibit other inflammatory processes, such as cyclooxygenase activity (Table 3) and NF-κB and possibly AP-1 activation, would also be expected to have beneficial effects in rheumatic diseases. Thus, science is beginning to validate the Native American concept that *U. dioica* is a valuable antirheumatic agent. However, the data available to date are rather limited and, though promising, await confirmation in experimental models and in clinical trials, if appropriate.

Urtica dioica agglutinin

U. dioica agglutinin (UDA) is a lectin isolated from the rhizome of the stinging nettle. In vitro, it is a murine T cell–specific mitogen with characteristics that are kinetically and functionally distinct from those of concanavalin A (Con A), another mitogen specific for T cells (77, 78). The lectin moiety of UDA recognizes specific carbohydrate structures present on major histocompatibility complex class II molecules, and this binding event results in clonal expansion of T cells expressing Vβ8.3 within 3 d (79), particularly of the Jb1.1, Jb1.6, and Jb2.7 subpopulations (80).

Such selective expansion was also observed among peripheral T cells in vivo after intravenous injection of UDA into Balb/c mice and was followed by anergy and deletion via apoptosis of mature Vβ8.3$^+$ T lymphocytes (81). The percentage of Vβ8.3$^+$ T cells was not fully restored to pre–UDA-treatment concentrations, even after 2 mo. In contrast with peripheral T cells, Vβ8.3$^+$ thymocytes did not undergo clonal expansion after intravenous injection of UDA (82). Furthermore, the total number of thymocytes decreased only slightly (25%) between 2 and 8 d after the administration of UDA, and the proliferative response of thymocytes from UDA-treated animals to in vitro restimulation with UDA was ≈4-fold lower than at baseline but was restored to almost normal values after 8 d.

A role for T cells bearing the Vβ8 receptor has been suggested in the pathogenesis of autoimmune diseases in humans (83) and in animal models (84–86). MRL-*lpr/lpr* is a mutant mouse strain lacking the Fas protein, which plays a central role in apoptosis. Such mice spontaneously develop many of the symptoms found in the human autoimmune disease, systemic lupus erythematosus (SLE). A CD4$^+$ T cell clone expressing Vβ8.3-Db1.1 and Jb1.1 elements was expanded in MRL-*lpr/lpr*, but not MRL$^{+/+}$, mice, suggesting that it contributed to the pathogenesis of SLE-like disease in the mutant strain (87). Treatment of MRL-*lpr/lpr* mice with intravenous injections of 100 μg UDA every other week from 6 wk to 6 mo of age resulted in the specific and sustained deletion of Vβ8.3$^+$ T cells accompanied by an absence of clinical signs of SLE, a reduction of glomerulonephritis, and a significant delay in the enlargement of lymph nodes compared with phosphate buffered saline–treated controls in both male and female animals (88). Interestingly, autoantibody production remained low in UDA-treated female MRL-*lpr/lpr* mice but was not affected in male mice. Despite the promising nature of the data reviewed above, more studies are needed before clinical trials can even be considered.

CONCLUSION

The consumption of botanical supplements in the United States has been increasing at a rapid rate and this trend is expected to continue. In many cases, the original indications of the putative beneficial effects of botanical supplements appear to have come from their use by Native Americans. Yet, scientific research is still confined to only a handful of the hundreds of substances sold in health food stores.

As this review shows, most available research is still confined to in vitro investigations. Only a few studies on the effects of Native American medicinal botanicals have been conducted in experimental animals, and there are even fewer reports of clinical trials. Nonetheless, what little scientific data have been gathered tend to confirm that many of the plant species contain bioactive constituents that are effective in treating the very ailments for which they were used by Native Americans. Particularly noteworthy are the indications that some of these medicinal botanicals might be useful in the treatment of chronic inflammatory diseases such as rheumatoid arthritis and SLE. The therapies currently available for both of these conditions are often quite ineffective and are almost invariably accompanied by serious adverse effects. It would, therefore, be highly desirable to find less toxic alternatives, and some medicinal botanicals might be candidates for such alternatives.

Note, however, that the safety of medicinal botanicals has only rarely been investigated, particularly with respect to long-term use and to drug interactions. Instead, much of the current research appears to focus on attempts to isolate and characterize bioactive principles. However, it should by now be clear that isolated chemical constituents of plant extracts seldom have the same effect as does the complex mixture of bioactive molecules present in whole-plant (or plant part) extracts. In view of the increasing popularity of botanical supplements, new scientific approaches for investigating these supplements need to be developed to allow research to move away from the reductionist principles that have been applied to their study so far.

REFERENCES

1. Scimone A, Scimone A. US sees the green in herbal supplements. Chem Market Rep 1998;254:FR3–4.
2. Thomson WAR. Medicines from the earth: a guide to healing plants. New York: Harper & Row, 1983.
3. Foster S, Duke JA. A field guide to medicinal plants: eastern and central North America. Boston: Houghton Mifflin Company, 1990.
4. Tierra M. The way of herbs. New York: Pocket Books, 1990.
5. Duke JA. The green pharmacy. Emmaus, PA: Rodale Press, 1997.
6. Blumenthal M. New world plants; new world drugs. Allergy Proc 1992;13:345–52.
7. Schacter L. Etoposide phosphate: what, why, where, and how? Semin Oncol 1996;23:1–7.
8. Moerman DE. An analysis of the food plants and drug plants of native North America. J Ethnopharmacol 1996;52:1–22.
9. Moerman DE. Medicinal plants of North America. Ann Arbor, MI: Museum of Anthropology, University of Michigan, 1986.
10. Johnson Gottesfeld LM, Anderson B. Gitksan traditional medicine: herbs and healing. J Ethnobiol 1988;8:13–33.
11. Turner NJ, Hebda RJ. Contemporary use of bark for medicine by two Salishan native elders of Southeast Vancouver Island, Canada. J Ethnopharmacol 1990;29:59–72.
12. Johnson Gottesfeld LM. Wet'suwet'en ethnobotany: traditional plant uses. J Ethnobiol 1994;14:185–200.
13. Ritch-Krc EM, Thomas S, Turner NJ, Towers GHN. Carrier herbal medicine: traditional and contemporary plant use. J Ethnopharmacol 1996;52:85–94.
14. Moerman DE. The medicinal flora of native North America: an analysis. J Ethnopharmacol 1991;31:1–42.
15. Reichard GA. Navaho religion: a study of symbolism. Princeton, NJ: Princeton University Press, 1990.
16. Vogel VJ. American Indian medicine: University of Oklahoma Press, 1970.
17. Arnason T. Use of plants for food and medicine by native peoples of eastern Canada. Can J Bot 1981;59:2189–325.
18. Herrick JW. Iroquois medical botany. Syracuse, NY: Syracuse University Press, 1995.
19. Hobbs C. Echinacea: a literature review. Botany, history, chemistry, pharmacology, toxicology, and clinical uses. Herbalgram 1994;33: 35–48.
20. Schwarz H-D. 100 Jahre Lobelin. Z Phytother 1990;11:159–60.
21. Orvis KS, Goldman IL. Relationship between antiplatelet activity and sulfur fertility in hydroponic and field-grown onions (*Allium cepa*). Hort Sci 1997;32:523 (abstr).
22. Weber ND, Andersen DO, North JA, Murray BK, Lawson LD, Hughes BG. In vitro virucidal effects of *Allium sativum* (garlic) extract and compounds. Planta Med 1992;58:417–23.
23. Goldman IL. Strength of onion-induced human antiplatelet activity is associated with plant development. Hort Sci 1997;32:523 (abstr).
24. McCutcheon AR, Ellis SM, Hancock REW, Towers GHN. Antibiotic screening of medicinal plants of the British Columbian native peoples. J Ethnopharmacol 1992;37:213–23.
25. McCutcheon AR, Roberts TE, Gibbons E, et al. Antiviral screening of British Columbian medicinal plants. J Ethnopharmacol 1995;49: 101–10.

26. Tunón H, Olavsdotter C, Bohlin L. Evaluation of anti-inflammatory activity of some Swedish medicinal plants. Inhibition of prostaglandin biosynthesis and PAF-induced exocytosis. J Ethnopharmacol 1995; 48:61–76.
27. Yesilada E, Sezik E. Screening of some Turkish medicinal plants used in the treatment of rheumatoid arthritis and inflammatory diseases for their anti-inflammatory activities. Planta Med 1990;56:659.
28. Wagner H. Search for new plant constituents with potential antiphlogistic and antiallergic activity. Planta Med 1989;55:235–41.
29. Müller-Jakic B, Breu W, Pröbstle A, Redl K, Greger H, Bauer R. In vitro inhibition of cyclooxygenase and 5-lipoxygenase by alkamides from *Echinacea* and *Achillea* species. Planta Med 1994;60:37–40.
30. Wagner H, Breu W, Willer F, Wierer M, Remiger P, Schwenker G. In vitro inhibition of arachidonate metabolism by some alkamides and prenylated phenols. Planta Med 1989;55:566–7.
31. Hartisch C, Kolodziej H, von Bruchhausen F. Dual inhibitory activities of tannins from *Hamamelis virginiana* and related polyphenols on 5-lipoxygenase and lyso-PAF:acetyl-CoA acetyltransferase. Planta Med 1997;63:106–10.
32. Vavrecková C, Gawlik I, Müller K. Benzophenanthridine alkaloids of *Chelidonium majus*; I. Inhibition of 5- and 12-lipoxygenase by a non-redox mechanism. Planta Med 1996;62:397–401.
33. Sumner H, Salan U, Knight DW, Hoult JRS. Inhibition of 5-lipoxygenase and cyclo-oxygenase in leukocytes by feverfew. Involvement of sesquiterpene lactones and other components. Biochem Pharmacol 1992;43:2313–20.
34. Obertreis B, Giller K, Teucher T, Behnke B, Schmitz H. Antiphlogistische Effekte von Extractum *Urticae dioicae* foliorum im Vergleich zu kaffeoyläpfelsäure. (Antiphlogistic effects of *Urtica dioica* leaf extract compared to caffeic malic acid.) Arzneimittelforschung 1996;46:52–6.
35. Agarwal S, Reynolds MA, Pou S, Peterson DE, Charon JA, Suzuki JB. The effect of sanguinarine on human peripheral blood neutrophil viability and functions. Oral Microbiol Immunol 1991;6:51–61.
36. Chaturvedi MM, Kumar A, Darnay BG, Chainy GBN, Agarwal S, Aggarwal BB. Sanguinarine (pseudochelerythrine) is a potent inhibitor of NF-κB activation, IκBα phosphorylation, and degradation. J Biol Chem 1997;272:30129–34.
37. Erdelmeier CAJ, Cinatl J Jr, Rabenau H, Doerr HW, Biber A, Koch E. Antiviral and antiphlogistic activities of *Hamamelis virginiana* bark. Planta Med 1996;62:241–5.
38. Duwiejua M, Zeitlin IJ, Waterman PG, Gray AI. Anti-inflammatory activity of *Polygonum bistorta*, *Guaiacum officinale* and *Hamamelis virginiana* in rats. J Pharm Pharmacol 1994;46:286–90.
39. Hughes-Formella BJ, Bohnsack K, Rippke F, et al. Anti-inflammatory effect of hamamelis lotion in a UVB erythema test. Dermatology 1998;196:316–22.
40. Korting HC, Schafer-Korting M, Hart H, Laux P, Schmid M. Anti-inflammatory activity of hamamelis distillate applied topically to the skin. Influence of vehicle and dose. Eur J Clin Pharmacol 1993;44:315–8.
41. Korting HC, Schafer-Korting M, Klovekorn W, Klovekorn G, Martin C, Laux P. Comparative efficacy of hamamelis distillate and hydrocortisone cream in atopic eczema. Eur J Clin Pharmacol 1995;48:461–5.
42. Yesilada E, Üstün O, Sezik E, Takaishi Y, Ono Y, Honda G. Inhibitory effects of Turkish folk remedies on inflammatory cytokines: interleukin-1α, interleukin-1β and tumor necrosis factor α. J Ethnopharmacol 1997;58:59–73.
43. Zakay-Rones Z, Varsano N, Zlotnik M, et al. Inhibition of several strains of influenza virus in vitro and reduction of symptoms by an elderberry extract (*Sambucus nigra* L.) during an outbreak of influenza B Panama. J Altern Complement Med 1995;1:361–9.
44. Bauer R, Remiger P, Jurcic K, Wagner H. Beeinflussung der Phagozytose-aktivität durch *Echinacea*-Extrakte. (Effects of *Echinacea* extracts on phagocytic activity.) Z Phytotherapie 1989;10:43–8 (in German).
45. Bauer R, Remiger P. TLC and HPLC analysis of alkamides in *Echinacea* drugs. Planta Med 1989;55:367–71.
46. Perry NB, van Klink JW, Burgess EJ, Parmenter GA. Alkamide levels in *Echinacea purpurea*: a rapid analytical method revealing differences among roots, rhizomes, stems, leaves and flowers. Planta Med 1997;63:58–62.
47. Bauer R, Jurcic K, Puhlmann J, Wagner H. Immunologische In-vivo- und In-vitro-Untersuchungen mit Echinacea-Extrakten. (Immunological in vivo and in vitro examinations of Echinacea extracts.) Arzneimittelforschung 1988;38:276–81 (in German).
48. O'Hara MA, Kiefer D, Farrell K, Kemper K. A review of 12 commonly used medicinal herbs. Arch Fam Med 1998;7:523–36.
49. Tympner K-D. Der immunbiologische Wirkungsnachweis von Pflanzenextrakten. (The demonstration of immunobiological effectiveness of plant extracts.). Z Angewandte Phytother 1981;5:181–4 (in German).
50. Gaisbauer M, Schleich T, Stickl HA, Wilczek I. Untersuchungen zum Einfluß von *Echinacea purpurea* Moench auf die Phagozytose von Granulozyten mittels Messung der Chemilumineszenz. (The effect of *Echinacea purpurea* Moench on the phagocytosis in granulocytes measured by chemiluminescence.) Arzneim-Forsch/Drug Res 1990;40:594–8 (in German).
51. Jurcic K, Melchart D, Holzmann M, et al. Zwei Probandenstudien zur Stimulierung der Granulozyten-Phagozytose durch *Echinacea*-extrakt-haltige präparate. (Two clinical studies on the stimulation of granulocyte phagocytosis by preparations containing *Echinacea*.) Z Phytother 1989;10:67–70.
52. Burger RA, Torres AR, Warren RP, Caldwell VD, Hughes BG. Echinacea-induced cytokine production by human macrophages. Int J Immunopharmacol 1997;19:371–9.
53. Wagner H, Proksch A, Vollmar A, Kreutzkamp B, Bauer J. In-vitro-Phagozytose-Stimulierung durch isolierte Pflanzenstoffe gemessen im Phagozytose-Chemilumineszenz-(CL)-Modell. (In vitro phagocytosis stimulation by isolated plant materials in a chemoluminescence-phagocytosis model.) Planta Med 1985;2:139–44 (in German).
54. Roesler J, Emmendörffer A, Steinmüller C, Luettig B, Wagner H, Lohmann-Matthes M-L. Application of purified polysaccharides from cell cultures of the plant *Echinacea purpurea* to test subjects mediates activation of the phagocytic system. Int J Immunopharmacol 1991;13:931–41.
55. See DM, Broumand N, Sahl L, Tilles JG. In vitro effects of echinacea and ginseng on natural killer and antibody-dependent cell cytotoxicity in healthy subjects and chronic fatigue syndrome or acquired immunodeficiency syndrome patients. Immunopharmacology 1997;35:229–35.
56. Steinmüller C, Roesler J, Gröttrup E, Franke G, Wagner H, Lohmann-Matthes M-L. Polysaccharides isolated from plant cell cultures of *Echinacea purpurea* enhance the resistance of immunosuppressed mice against systemic infections with *Candida albicans* and *Listeria monocytogenes*. Int J Immunopharmacol 1993;15:605–14.
57. Roesler J, Steinmüller C, Kinderlein A, Emmendörffer A, Wagner H, Lohmann-Matthes M-L. Application of purified polysaccharides from cell cultures of the plant *Echinacea purpurea* to mice mediates protection against systemic infections with *Listeria monocytogenes* and *Candida albicans*. Int J Immunopharmacol 1991;13:27–37.
58. Möse JR. Zur Wirkung von Echinacin auf Phagozytoseaktivität und natural killer cells. (On the effect of Echinacin on phagocytic activity and natural killer cells.) Medwelt 1983;51/52:1463–7 (in German).
59. Melchart D, Linde K, Worku F, et al. Results of five randomized studies on the immunomodulatory activity of preparations of Echinacea. J Altern Complement Med 1995;1:145–60.
60. Elsässer-Beile U, Willenbacher W, Bartsch HH, Gallati H, Schulte Mönting J, von Kleist S. Cytokine production in leukocyte cultures during therapy with Echinacea extract. J Clin Lab Anal 1996;10: 441–5.
61. Bräunig B, Dorn M, Knick E. *Echinaceae purpureae* radix: zur Stärkung der körpereigenen Abwehr bei grippalen Infekten. (Echinacea purpurea radix: for strengthening host immunity in respiratory infections.) Z Phytother 1992;13:7–13 (in German).

62. Schmidt U, Albrecht M, Schenk N. Pflanzliches Immunstimulans senkt Häufigkeit grippaler Infekte. (A plant-derived immunostimulant reduces the frequency of upper respiratory infections.) Natur Ganzheits Medizin 1990;3:277–81 (in German).
63. Melchart D, Walther E, Linde K, Brandmaier R, Lersch C. Echinacea root extracts for the prevention of upper respiratory tract infections. Arch Fam Med 1998;7:541–5.
64. Mengs U, Clare CB, Poiley JA. Toxicity of *Echinacea purpurea*. Arzneimittelforschung 1991;41:1076–81.
65. Schimmer O, Abel G, Behninger C. Untersuchungen zur Gentoxischen Potenz eines neutralen Polysaccharids aus *Echinacea*-Gewebekulturen in menschlichen Lymphozytenkulturen. (Investigations of the genotoxic potential of a neutral polysaccharide from *Echinacea* tissue cultures in cultures of human lymphocytes.) Z Phytother 1989;10:39–42.
66. Mullins RJ. Echinacea-associated anaphylaxis. Med J Aust 1998; 168:170–1.
67. Myers SP, Wohlmuth H. Echinacea-associated anaphylaxis. Med J Aust 1998;168:583–4.
68. Bauer R, Khan IA, Wagner H. Neue Möglichkeiten zur Standardisierung von Echinacea-Extrakten. (New possibilities for standardization of Echinacea extracts.) Sci Pharm 1986;54:145 (abstr) (in German).
69. Obertreis B, Ruttkowski T, Teucher T, Behnke B, Schmitz H. Ex-vivo in-vitro inhibition of lipopolysaccharide stimulated tumor necrosis factor-α and interleukin-1β secretion in human whole blood by extractum *Urticae dioicae* foliorum. Arzneimittelforschung 1996;46:389–94.
70. Riehemann K, Behnke B, Schulze-Osthoff K. Plant extracts from stinging nettle (*Urtica dioica*), an antirheumatic remedy, inhibit the proinflammatory transcription factor NF-κB. FEBS Lett 1999;442: 89–94.
71. Feldmann M, Brennan FM, Maini RN. Rheumatoid arthritis. Cell 1996;85:307–10.
72. Feldmann M, Brennan FM, Maini RN. Role of cytokines in rheumatoid arthritis. Annu Rev Immunol 1996;14:397–440.
73. Marok R, Winyard PG, Coumbe A, et al. Activation of the transcription factor nuclear factor-κB in human inflamed synovial tissue. Arthritis Rheum 1996;39:583–91.
74. Shiozawa S, Shimizu K, Tanaka K, Hino K. Studies on the contribution of c-fos/AP-1 to arthritic joint destruction. J Clin Invest 1997;99:1210–6.
75. Miyazawa K, Mori A, Yamamoto K, Okudaira H. Constitutive transcription of the human interleukin-6 gene by rheumatoid synoviocytes. Spontaneous activation of NF-κB and CBF1. Am J Pathol 1998;152:793–803.
76. Teucher T, Obertreis B, Ruttkowski T, Schmitz H. Zytokin-Sekretion im Vollblut gesunder Probanden nach oraler Einnahme eines *Urtica dioica* L.-Blattextraktes. (Cytokine secretion in whole blood of healthy volunteers after oral ingestion of an *Urtica dioica* L. leaf extract.) Arzneimittelforschung 1996;46:906–10.
77. Le Moal MA, Truffa-Bachi P. *Urtica dioica* agglutinin, a new mitogen for murine T lymphocytes: unaltered interleukin-1 production but late interleukin 2-mediated proliferation. Cell Immunol 1988; 115:24–35.
78. Le Moal MA, Colle J-H, Galelli A, Truffa-Bachi P. Mouse T-lymphocyte activation by *Urtica dioica* agglutinin. II. Original pattern of cell activation and cytokine production induced by UDA. Res Immunol 1992;143:701–9.
79. Galelli A, Truffa-Bachi P. *Urtica dioica* agglutinin. A superantigenic lectin from stinging nettle rhizome. J Immunol 1993;151: 1821–31.
80. Musette P, Galelli A, Truffa-Bachi P, Peumans W, Kourilsky P, Gachelin G. The Jβ segment of the T cell receptor contributes to the Vβ-specific T cell expansion caused by staphylococcal enterotoxin B and *Urtica dioica* superantigens. Eur J Immunol 1996;26:618–22.
81. Galelli A, Delcourt M, Wagner M-C, Peumans W, Truffa-Bachi P. Selective expansion followed by profound deletion of mature Vβ8.3$^+$ T cells in vivo after exposure to the superantigenic lectin *Urtica dioica* agglutinin. J Immunol 1995;154:2600–11.
82. Delcourt M, Peumans WJ, Wagner M-C, Truffa-Bachi P. Vβ-specific deletion of mature thymocytes induced by plant superantigen *Urtica dioica* agglutinin. Cell Immunol 1996;168:158–64.
83. Thompson SD, Murray KJ, Grom AA, Passo MH, Choi E, Glass DN. Comparative sequence analysis of the human T cell receptor β chain in juvenile rheumatoid arthritis and juvenile spondylarthropathies. Arthritis Rheum 1998;41:482–97.
84. Robinson CP, Cornelius J, Bounous DE, Yamamoto H, Humphreys-Beher MG, Peck AB. Characterization of the changing lymphocyte populations and cytokine expression in the exocrine tissues of autoimmune NOD mice. Autoimmunity 1998;27:29–44.
85. Suzuki M, Cheng KC, Krug MS, Yoo TJ. Successful prevention of retrocochlear hearing loss in murine experimental allergic encephalomyelitis with T cell receptor Vβ8-specific antibody. Ann Otol Rhinol Laryngol 1998;107:917–27.
86. Goldman-Brezinski S, Brezinski K, Zhang X-M, et al. Effects of oral tolerance induction by myelin basic protein on Vβ8$^+$ Lewis rat T cells. J Neurosci Res 1998;51:67–75.
87. Musette P, Pannetier C, Gachelin G, Kourilsky P. The expansion of a CD4$^+$ T cell population bearing a distinctive β chain in MRL *lpr/lpr* mice suggests a role for the fas protein in peripheral T cell selection. Eur J Immunol 1994;24:2761–6.
88. Musette P, Galelli A, Chabre H, et al. *Urtica dioica* agglutinin, a Vβ8.3-specific superantigen, prevents the development of the systemic lupus erythematosus-like pathology of MRL *lpr/lpr* mice. Eur J Immunol 1996;26:1707–11.