CONTENTS

PART I—
LEGAL/REGULATORY ASPECTS OF HERBAL PRODUCTS

cal methods, funded by government or the private sector, would add to the knowledge base being compiled by the Cochrane Collaboration. Until then, patients and health care professionals must use caution in the "wild west" world of herbal products.

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cial laboratory that analyzes kidney stones found that 200 out of 166,466, or 0.064% of stones analyzed by that laboratory, contained either ephedrine or pseudoephedrine. Unfortunately, the analytic technique used could not distinguish ephedrine from pseudoephedrine, and because pseudoephedrine is used so much more widely than ephedrine, it seems that the risk of renal calculus associated with ephedrine use must be quite small.

Direct toxicity, with altered renal function and/or demonstrable kidney lesions, has never been demonstrated. Urinary retention, occurring as a consequence of drug overdose, has rarely been reported (Glidden and DiBona, 1977;

Lindberg, 1988). The FDA and Commission E both have warned against the possibility of urinary retention in patients with prostatic enlargement, but the theoretical basis for this concern is unclear, and, in any case, retention in patients with prostate disease has not been reported.

Ephedrine and most of its enantiomers are excreted unchanged in the urine (although small amounts are oxidized in the liver to norephedrine and norpseudoephedrine, both CNS stimulants). In patients with diminished renal function, these drugs may accumulate and cause serious toxicity. None of the enantiomers are easily removed by dialysis, and treatment remains supportive, using pharmacologic antagonists to counter the α- and β-adrenergic effects of these drugs (Lyon and Tuney, 1996). Because excretion is pH dependent, patients with renal tubular acidosis are also at risk (Prate et al., 1980).

The FDA reports having received a number of accounts of hematuria after use of ephedra-based products. No such cases have appeared in the peer reviewed literature, and review of the reports published by the FDA shows that all of the affected individuals were taking multiple remedies. There is no question that some herbal medicines cause interstitial nephritis as well as other renal pathologies. For example, a cluster of more than 100 cases of interstitial nephritis was reported from Belgium in 1992. All of the cases involved young women who had been prescribed an herbal remedy for weight loss. Renal biopsies from these women disclosed acellular, interstitial fibrosis, often with precancerous transformation of the urinary tract epithelia. Many of these same women were also found to have aortic valve disease. Epidemiologic investigation disclosed that the renal injury was a result of the inadvertent substitution of *Stephnania tetrandra* with *Aristolochia fangji*, an herb known to contain aristilochic acid, a potent carcinogen. The valvular damage may have been a consequence of the fenfluramine and diethylpropion that had also been added to the mixture. It seems extremely unlikely that ephedrine was in any way associated with the hematuria reported in the FDA ADRs.

1.7.3 Cardiovascular Diseases

Ephedrine and pseudoephedrine share properties with cocaine and with the amphetamines because they: (1) stimulate β-receptors directly and (2) also cause the increased release of norepinephrine. Chronic exposure to abnormally high levels of circulating catecholamines can damage the heart. This is certainly the case with cocaine and methamphetamine (Karch et al., 1995; Karch, 1999), but ephedrine-related cardiomyopathy is an extremely rare occurrence, occurring only in individuals who take massive amounts of drug for prolonged periods of time.

The literature contains three case reports describing heart failure in ephedrine users; one was a 35-yr-old asthmatic taking 4000 mg of ephedrine per day and "liberal doses of prednisolone" for 14 yr. Another involved a woman who had been abusing ephedrine (300–600 mg/d) for 10 yr, and a third case, involving a 28-yr-old, cigarette smoking, 321-pound woman taking 2000 mg of ephedrine every day for 8 yr (To et al., 1980; Gaultieri, 1996; Schafers et al., 1998). The difficulty in interpreting these reports is that histologic findings were not described and angiography was not performed, making the diagnosis of cardiomyopathy impossible to prove.

Similar considerations apply to the relationship (if any) between myocardial infarction and ephedrine use. There have been scattered reports of pseudoephedrine-associated hypertension (Mahini, 1986), coronary artery spasm (Weiner et al., 1990), cardiomyopathy (To et al., 1980), and intracranial hemorrhage in association with ephedrine and pseudoephedrine overdose (Rutstein, 1963; Loizou et al., 1982; Wooten et al., 1983; Nadeau, 1984; Stoessl et al., 1985; Bruno et al., 1993), but the incidence seems to be much lower with ephedrine than with other agents such as phenylpropanolamine, and there is a paucity of autopsy studies. More often than not, toxicology results were not even recorded, and the victims were known to have long-term histories of polydrug use (Bruno et al., 1993). There are no case reports in the peer review literature linking ephedrine, phenylpropanolamine (although case reports linking phenylpropanolamine and stroke were once common), or pseudoephedrine to myocardial infarction. Toxicology tests were not performed in any of the three cases listed in the FDA monograph, and those cases were, in any event, so poorly documented that no conclusions are possible.

Cardiac arrhythmia is known as a complication of catecholamine excess (Lermann et al., 1999), and chronic exposure to high levels of catecholamines can induce a type of myocardial fibrosis that favors arrhythmias, but a linkage with ephedrine and its isomers has never been shown. The literature contains one case report (Weesner et al., 1982). The report described arrhythmias occur-

ing to the Commission, use is contraindicated in patients with high blood pressure, glaucoma, "impaired circulation of the cerebrum, adenoma of the prostate with residual urine accumulation, pheochromocytoma, and thyrotoxicosis." "Anxiety and restlessness" are also considered contraindications (Blumenthal, 1998). Ephedra is regulated as a dietary supplement in the United States. The FDA has proposed a dosage limit of 8 mg every 6 h, and a daily maximum dose of 24 mg (Anonymous 1997).

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Chapter 2—
Kava

Shawn Reeder and Melanie Johns Cupp

Piper methysticum, kava-kava, awa, kew, tonga (Anonymous, 1996), kawa, yaqona, sakau (Norton and Ruze, 1994), ava, ava pepper, intoxicating pepper (Heiligenstein and Guenther, 1998)

2.1 History and Traditional Uses

Kava is a term used to describe both *Piper methysticum* and the preparation made from its dried rhizome and root (Anonymous, 1996). This South Pacific plant is a robust, branching, perennial shrub with heart-shaped, green, pointed leaves (Singh, 1992) that grow up to 28 cm long and flower spikes that grow up to 9 cm long (Anonymous, 1996). The shrub grows best in warm, humid conditions with lots of sunlight, at altitudes of 150–300 m above sea level (Singh, 1992), where it forms dense thickets (Norton and Ruze, 1994). Kava reproduces vegetatively, without fruit or seeds, usually under cultivation (Norton and Ruze, 1994). There are reports of up to 72 varieties of the kava plant which differ in appearance, and chemical analysis has shown differences in their composition as well which may lead to differences in physiologic activity (Singh, 1992). Kava has been described in the European literature since the early 1600s when it was taken there by the Dutch explorers LeMaire and Schouten, who had acquired it while seeking new passages across the Pacific (Norton and Ruze, 1994). Captain James Cook was the first to describe the use of kava during the religious and cultural ceremonies of the people of the South Sea Islands, where it was, and still is, prepared as a beverage and consumed for its intoxicating, calming effects that promote sociability (Norton and Ruze, 1994). Thus, kava is used for the purposes that Western society uses alcohol,

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A study in rats using radiolabeled EGb 761 revealed a bioavailability of at least 60% (Kleijnen and Knipschild, 1992). Peak blood concentrations occurred at 1.5 h. At 3 h, the highest radioactivity was measured in the stomach and small intestine, indicating that these are the sites of absorption.

3.7.2 Distribution

Rat studies using radiolabeled EGb 761 have revealed that the extract follows a two-compartment model of distribution (Kleijnen and Knipschild, 1992). The radiolabeled extract was distributed into glandular and neuronal tissues, as well as the eyes.

The volumes of distribution of ginkgolide A, ginkgolide B, and bilobalide are 40–60 L, 60–100 L, and 170 L, respectively (Kleijnen and Knipschild, 1992).

3.7.3 Metabolism/Elimination

The half-life of the flavonol glycosides administered as the product LI 1370 is 2–4 h (Kleijnen and Knipschild, 1992). Similar results were obtained using 80 mg of the product EGb 761; half-lives of ginkgolides A and B were 4 h and 6 h, respectively. The half-life of bilobalide was 3 h after administration of 120 mg of this extract. Similar results were reported in another study (Fourtillan et al., 1995) using this same product; mean halflives of ginkgolide A, ginkgolide B, and bilobalide were 4.5 h, 10.57 h, and 3.21 h, respectively.

A study in rats using radiolabeled EGb 761 reveled a half-life of 4.5 h, with elimination following first-order (linear) kinetics (Kleijnen and Knipschild, 1992).

Approximately 70% of ginkgolide A, 50% of ginkgolide B, and 30% of bilobalide is excreted unchanged in the urine (Kleijnen and Knipschild, 1992). Metabolites isolated from human urine after administration of EGb include a 4-hydroxybenzoic acid conjugate, 4-hydroxyhippuric acid, 3methoxy-4-hydroxyhippuric acid, 3,4-dihydroxybenzoic acid, 4-hydroxybenzoic acid, hippuric acid, and 3-methoxy-4-hydroxybenzoic acid (vanillic acid) (Pietta et al., 1997). In accord with previous data, these metabolites accounted for <30% of the administered EGb dose. Metabolites were not detectable in blood samples.

3.8 Chemical Analysis

Identification and chemical analysis can be found in the National Formulary (USP, 1998).

cyclokessyl acetate, guaiane-type sesquiterpenoids, also exhibited antidepressant activity. Kanokonol, kessyl glycol, and kessyl glycol diacetate, valeranetype sesquiterpenoids, did not exhibit an effect.

A 30% ethanol extract of the Japanese valerian root ("Hokkai-Kisso") extract (4.1 g/kg and 5.7 g/kg) and imipramine (20 mg/kg) also demonstrated statistically significant antidepressant effects compared to placebo as measured by the forced swimming test in rats (Sakamoto et al., 1992). As in the Oshima study, kessyl glycol diacetate exhibited no antidepressant activity in the forced swimming test. Because the forced swimming test can be affected by stimulants, anticholinergics, and antihistamines as well as antidepressants, the effect of the valerian extract on reserpine-induced hypothermia, a test for antidepressant activity and inhibition of neuronal reuptake of monoamines, was measured. Both valerian (11.2 g/kg) and imipramine (20 mg/kg) reversed reserpine-induced hypothermia, suggesting that the antidepressant effect of valerian is due to reuptake of monoamine neurotransmitters, as with conventional antidepressants.

4.4.2 Musculoskeletal Effects

(*See also* Section 4.4.1 for a discussion of the possible mechanisms of musculoskeletal effects.)

Isovaltrate and valtrate (valepotriates) and valeronone, an essential oil component, isolated from *Valeriana edulis* ssp. *procera* Meyer (Valeriana "mexicana") caused suppression of rhythmic contractions in guinea pig ileum in vivo at a dose of 20 mg/kg administered intravenously via the jugular vein. The investigators also demonstrated that the same compounds as well as dihydrovaltrate isolated from the same valerian species produced relaxation of carbachol-stimulated guinea pig ileum preparations in vitro. They concluded that these compounds have a musculotropic action in concentrations from 10^{-5}. to 10^{-4} *M* (Hazelhoff et al., 1982).

4.4.3 Reproduction

There has been a theoretical concern with regard to pregnant women taking valerian because of possible effects on uterine contractions (Combest, 1997), but no problems were noted in three cases of intentional overdose with 2–5 g of valerian during wk 3–10 of pregnancy (Czeizel et al., 1997). A mentally retarded child was born to a woman who overdosed on valerian 3 g, phenobarbital, glutethamide, amobarbital, and promethazine at 20 wk gestation, but this same woman delivered a mentally retarded child 2 yr later after an overdose attempt with glutethamide, amobarbital, and promethazine (Czeizel et al., 1988).

would be expected to have at least an additive effect with barbiturates, alcohol, benzodiazepines, and other CNS depressants.

Also *see* Chapter 5, St. John's wort, section 5.6 Drug Interactions.

4.7 Chemical Analysis

Isolation and identification of the essential oil components valeranone, valerenal, valerenic acid and isoeugenyl-isovalerate (Hazelhoff et al., 1979a; Hendriks et al., 1981) and the valepotriates valtrate, isovaltrate, and didrovaltrate (Hazelhoff et al., 1979b; Tittel and Wagner, 1978; Tittel et al., 1978).

4.8 Regulatory Status

Valerian was included as an official drug in the *US Pharmacopeia* until 1936 and in the *National Formulary* until 1946. Currently, the USP advisory panel does not recommend valerian's use owing to lack of adequate scientific evidence and conflicting study results. They encourage further research (USP, 1998). Valerian is generally recognized as safe (GRAS) as a food and beverage flavoring by the FDA (Anonymous, 1991). The German Commission E has approved valerian as a sleep-promoting and calmative agent to be used in the treatment of unrest and sleep disturbances caused by anxiety (Blumenthal, 1998). In Australia, valerian is acceptable as an active ingredient in the "listed products" category of the *Therapeutic Goods Administration.* In Belgium, subterranean parts, powder extract, and tincture are allowed for use as traditional tranquilizers. The Health Protection Branch of Health Canada allows products containing valerian as a single agent in the form of crude dried root in tablets, capsules, powders, extracts, tinctures, drops, or tea bags intended for use as sleeping aids and sedatives. In the United Kingdom, valerian is included on the General Sales List of the Medicines Control Agency and is allowed in "traditional herbal remedies" as a sedative to promote natural sleep (USP, 1998).

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Chapter 5—
St. John's Wort

John T. Schwarz and Melanie Johns Cupp

Hypericum perforatum, goat weed, klamath weed, rosin rose, amber touch and heal, tipton weed (Bradshaw et al. 1998); blutdkraut, Johnswort, qian ceng lou, Sankt Hans urt, St. Jan's kraut, St. Johnswort, toutsaine, tupfelhartheu, walpurgiskraut, zweiroboij, amber, chassediable, corazoncillo, hardhay, hartheu, herbe de millepertuis, herrgottsblut, hexenkraut, hierba de San Juan, hipericon, hypericum, iperico, Johannesort, pelatro, perforata, Johannisblut, Johanniskraut (USP, 1998a)

5.1 History and Traditional Uses

Hypericum is a perennial aromatic shrub with bright yellow flowers that bloom from June to September (Wincor and Gutierrez, 1997). The flowers are said to be at their brightest and most abundant around June 24th, the day traditionally believed to be the birthday of John the Baptist. The plant is native to Europe and can also be found in the United States and Canada. It grows in the dry ground of fields, roadsides, and woods.

Historically, St. John's wort has been used to treat neurologic and psychiatric disturbances (anxiety, insomnia, bed-wetting, irritability, migraine, excitability, exhaustion, fibrositis, hysteria, neuralgia, and sciatica), gastritis, gout, hemorrhage, pulmonary disorders, and rheumatism, and has been used as a diuretic (USP, 1998a). Some form of the herb have been used topically as an astringent and to treat blisters, burns cuts, hemorrhoids, inflammation, insect bites, itching, redness, sunburn, and wounds.

5.2 Current Promoted Uses

St. John's wort is promoted for treatment of mood disorders, particularly depression, and promotion of emotional well being. It has also been promoted

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in combination with ma huang (ephedra) for weight loss, but use of such products has been discouraged by the FDA (USP, 1998a).

5.3 Products Available

Most commercially available preparations of hypericum in the United States are dried alcoholic extracts in a solid oral dosage form. Other preparations include the dried herb or liquid extracts. The following is a list of a few of the available formulations:

Movana®—tablet containing 0.3% hypericin extract (300 mg)

Kira®—tablet containing 0.3% hypericin extract (300 mg)

Dr. Art Ulene's Herbal Formulas®—capsule containing 150 mg of hypericin

Nature's Fingerprint®—500-mg capsule and 300-mg tablet containing extract

NaturaLife®—grain alcohol extract (250 mg of hypericin/mL)

Celestial Seasoning®—capsule containing 0.3% hypericin extract (300 mg) with

Siberian ginseng, vitamins B_6, B_3, B_{12}, zinc, and folic acid

One A Day®—tablet with 225 mg of hypericin and 100 mg of kava kava

Harmonex®—450 mg of hypericin from a flower extract and 90 mg ginseng

Sundown®Herbals—300 mg of hypericin with ginkgo biloba, ginseng, and ginger

5.4 Pharmacologic/Toxicologic Effects

5.4.1 Neurological Effects

Many studies have been done comparing St. John's wort to placebo or to tricyclic antidepressants (Linde et al., 1996). However, problems with inclusion criteria, diagnostic criteria, antidepressant dosing, and study duration do not permit definitive conclusions about the safety and efficacy of St. John's wort for treatment of depression.

Studies indicate that St. John's wort may be effective in treating depression (Linde et al., 1996). However, the exact chemical entity that causes this effect and the mechanism of action is unknown. St. John's wort contains compounds from several chemical classes. These include naphthodianthrones (hypericin, pseudohypericin, protopseudohypericin, cyclopseudohypericin), flavonoids (quercetin, hyperosid, quercitrin, isoquercitrin, campherol, rutin, luteolin, and 13-II8-biapigenin), ethereal oil, phenol carbonic acids (e.g., chlorogenic acid), procyanidins, 1,3,6,7-tetrahydroxyxanthone, and hyperforin. Of these, hyperforin, the hypericins, and tetrahydroxyxanthone are characteristic of St. John's wort, while the other constituents are found in many plants (Wagner and Bladt, 1994). Interestingly, melatonin, a human pineal gland hormone, has been identified in St. John's wort flower and leaf at concentrations of 4.39 µg/g and 1.75 µg/g, respectively (Murch et al., 1997), but its role in the pharmacological effects of St. John's wort have yet to be investigated.

Chapter 6—
Chamomile

Melanie Johns Cup

Matricaria chamomile (L.) (German chamomile, Hungarian chamomile, genuine chamomile), *Anthemis nobilis* (English chamomile, Roman chamomile, common chamomile); sometimes called *Chamaemelum nobile* (L.) (Anonymous, 1991)

6.1 History and Traditional Uses

Chamomile has been used medicinally since ancient Rome for its purported sedative, antispasmodic, and antirheumatic effects (Anonymous, 1991).

6.2 Current Promoted Uses

Chamomile is used topically to treat a variety of inflammatory conditions involving the mouth, skin, respiratory tract (via inhalation), and gastrointestinal tract. It is also used internally as a gastrointestinal antispasmodic and antiinflammatory (Blumenthal, 1998). Chamomile is purported to have sedative, hypnotic, analgesic, and immunostimulant effects (Yamada et al., 1996).

6.3 Products Available

The flowers of M. *chamomilla* and A. *nobilis* are used in teas and extracts (Anonymous, 1991). Chamomile oil is used in aromatherapy (Yamada et al., 1996).

6.4 Pharmacologic/Toxicologic Effects

6.4.1 Neurologic Effects

The effects of chamomile oil vapor were studied in ovariectomized rats, which served as an experimental menopausal model (Yamada et al., 1996).

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she developed urticaria, laryngeal edema, tachycardia, and hypotension. Intravenous fluids, corticosteroids, and antihistamines were administered. Fortyfour minutes after enema administration, a cesarean delivery was performed. The uterus was atonic and bloodless. The newborn had an Apgar score of 0, and a pH of 6.85. Although initially responding to sodium bicarbonate, the newborn died the next day after suffering a tonic-clonic seizure. The woman suffered a hematoma of the abdominal wall, a bleeding gastric ulcer, paralytic ileus, and sepsis, but recovered with laparogastrotomy and a 3-wk course of antibiotics. Skin prick tests were negative for latex, glycerol, and common airborne allergens. A skin prick test with Kamillosan® was postitive, and immunoglobulin E (IgE) specific for chamomile was detected by radioallergosorbent test (RAST). Although the extraction of dried chamomile plants for the production of Kamillosan® yields a low amount of protein in the product, it is apparently enough to trigger anaphylaxis when the product is applied to a large area of the colonic mucosa. The investigators attempted to identify the protein responsible for antibody production using electrophoresis (Jensen-Jarolim et al., 1998).

Anaphylaxis to chamomile tea has also been reported (Benner and Lee, 1973; Casterline, 1980). A 35-yr-old woman experienced abdominal cramps, tongue "thickness," a tight sensation in her throat, angioedema of the lips and eyes, diffuse itching, and a full sensation in her ears after a few sips of chamomile tea. Her symptoms resolved over 1-–2 h after treatment with diphenhydramine and a corticosteroid. A scratch test with chamomile produced a large wheal-and-flare with pseudopod formation. She had a history of ragweed hay fever and a strong positive reaction to ragweed on skin testing. Five of 15 additional patients with a history of positive reactions to ragweed developed positive skin test reactions to chamomile tea. These patients were not challenged with chamomile tea orally because of the risk of anaphylaxis (Benner and Lee, 1973).

In another case report (Casterline, 1980), a 54-yr-old woman experienced generalized hives, upper airway obstruction, and pharyngeal edema 20 min after drinking a cup of chamomile tea and taking two aspirin tablets. She was treated with epinephrine and diphenhydramine in the emergency room with complete symptom resolution. The patient had no history of aspirin allergy, but reported mild seasonal allergic rhinitis. Total IgE was elevated, and RAST was 2+ for ragweed. Graded oral aspirin challenges produced no immediate or delayed reaction.

In addition to being used as a beverage, chamomile tea is used as an eye wash to treat conjuctivitis and other ocular conditions. Seven patients ages 21–51 suffered conjunctivitis after eye washing with chamomile tea. The reactions were immediate, and two patients suffered angioedema of the eyelid. One required emergency treatment with epinephrine. All had histories of seasonal

also showed that a crude polysaccharide extract of E. purpurea also increased macrophage cytotoxicity toward tumor cells and increased macrophage IL-1 production (Stimpel et al., 1984). Echinacea polysaccharide effects on T-cells and B-cells were limited (Luettig et al., 1989; Stimpel et al., 1984).

7.4.2 Antimicrobial/Antiviral Effects

A study assessed ability of an echinacea extract to enhance natural killer cell activity against K562 cells and antibody-dependent cellular cytotoxicity (ADCC) against human herpesvirus infected H9 cells (See et al., 1997). Dried, ground preparations of fresh echinacea were homogenized and filtered to produce an extract that was added in increasing concentrations to peripheral blood mononuclear cells from patients with AIDS, chronic fatigue syndrome (CFS), and healthy volunteers. CFS and AIDS patients were excluded from the study if they were taking corticosteroids, colony-stimulating factors, interleukins, interferons, or cancer chemotherapy. Echinacea extract enhanced the cytotoxicity of natural killer cells, and increased activity against cells infected with human herpesvirus 6 (HH6) in all three groups at concentrations of at least 0.1 µg/mL and 1 µg/mL, respectively.

The ability of an oral echinacea preparation to prolong the time to onset of an upper respiratory infection was compared to that of placebo in 302 volunteers from an industrial plant and several military institutions (Melchart et al., 1998). Volunteers were administered either placebo or 50 drops (2 mL) twice daily of 30% ethanol in water extract of *E. angustifolia* or *E. purpurea*, providing approx 200 mg of echinacea daily for 12 wk. Although patients felt they had benefited from echinacea ($p = 0.04$), there was no difference among the three groups in regard to time to the first upper respiratory infection, the main outcome measure. A second outcome measure, the number of patients in each group who developed at least one infection, was not different to a statistically significant degree.

Another study (Grimm and Muller, 1999) also examined the efficacy of echinacea in preventing colds and upper respiratory infections, but used a different preparation. The preparation used in this study was fluid extract of Echinacea purpurea herb juice expressed from whole flowering *E. purpurea* (without the roots) in a 22% alcohol solution. This preparation was identical to Echinacin-Liquidum, a German product. This study was unique because patients were enrolled only if they had a history of more than three colds or respiratory infections in the preceding year. One hundred and eight patients were randomized to receive 4 mL twice daily of study drug or identical placebo for 8 wk. The primary outcome measures were the incidence and severity of colds during the study period. Medical history, physical exam, and hemato-

Chapter 9—
Garlic

James Allman and Melanie Johns Cupp

Allium sativum, Allii sativi bulbus, knoblauch (Blumenthal, 1998)

9.1 History and Traditional Uses

Over the centuries, garlic has been used to ward off vampires, demons, witches, and evil beings; as an aphrodisiac to improve performance and desire; and as a cure-all for everything from athlete's foot to hemorrhoids and cancer (Tyler, 1993).

9.2 Current Promoted Uses

Garlic is promoted to lower cholesterol and blood pressure, delay atherosclerotic processes, prevent heart attack and stroke, improve circulation, and prevent cancer.

9.3 Products Available

Centrum® Herbals "Garlic" capsules, 300 mg

Herbscience® Garlic, 600 mg caplet

Kwai®, 600 µg of allicin (300 mg of dried garlic, 10 mg tablets (*see* detailed description below)

Kyolic® Aged Garlic Extract™ 1500 mg caplets

Nature Made® Extra Strength Odor-controlled garlic, 500 mg

Nature Made® Garlic Oil, 500-mg softgel

Nature Made® Odorless Garlic, 500-mg tablets

Nature Made® High Potency Garlic Oil, 1500-mg softgels

Nature's Resource® Garlic Powder, 180-mg enteric coated tablets

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9.4 Pharmacologic/Toxicologic Effects

9.4.1 Cardiovascular Effects

Warshafsky et al. (1993) completed a meta-analysis using Medline (1966–1991) to collect all randomized, placebo-controlled trials that tested the effectiveness of oral garlic preparations in lowering cholesterol in humans. Inclusion criteria included trials in which at least 75% of participants had elevated cholesterol levels, defined as 5.17 mmol/L (200 mg/dL). Studies were excluded if they did not contain enough data to compute effect size. Of the 28 studies found, all but five were excluded. Four of the five studies claimed to be double-blinded. All five used parallel group design. Three of the studies used Kwai® powder tablets in doses of 600, 800, and 900 mg/d. One study used 1000 mg (4 mL) of Kyolic® aqueous extract per day and the other study used 700 mg of spray-dried powder per day. None of the studies included dietary restrictions on subjects participating. The authors concluded that total cholesterol levels decreased by a statistically significant ($p < 0.001$), yet clinically small, 9% compared to placebo, in patients given the equivalent of half a clove per day. Several more recent studies have confirmed the results of this meta-analysis.

Berthold et al. (1998) performed a double-blind, randomized, placebocontrolled, crossover trial to examine the effects of garlic oil on serum lipoproteins, cholesterol absorption, or cholesterol synthesis. The product used was an enteric coated preparation (Tegra®, Hermes, Arzneimittel GmbH, Munich Germany) of steam-distilled garlic oil. The daily dosage corresponded to 4–5 g of fresh garlic cloves, or 4000 U of allicin equivalents per day. Diallyl disulfide (>30%) and diallyl trisulfide (>25%) were assumed to be the active ingredients. Twenty-six patients with moderately high cholesterol (240–338 mg/dL) and triglyceride (<265 mg/dL) were recruited through the local newspaper. Subjects had not taken any lipid-lowering agents within the prior 8 wk; however, some subjects were taking antihypertensive medication, hormone replacement therapy, or thyroid hormones. Subjects were allowed to eat their "normal" diets throughout the study, but could not eat any additional garlic. Twenty-five subjects finished the 12-wk study, with one subject dropping out because of scheduling conflicts. Garlic oil did not affect any of the parameters studied.

Similar results have been obtained with garlic powder. Isaacsohn et al. (1998) conducted a randomized, double-blinded, placebo-controlled study that concluded that 900 mg/d of Kwai® garlic powder tablets (*see* Section 9.3) for 12 wk was ineffective in lowering cholesterol. The 50 subjects (28 garlic treatment, 22 placebo) recruited from a lipid clinic were also instructed on the National Cholesterol Education Program Step 1 Diet or other low-fat diet. Dietary compliance was measured using the Food Record Rating (FRR) Score.

9.4.2. Gastrointestinal Effects

Garlic was effective against castor oil induced diarrhea, and relieved abdominal distension/discomfort, belching, and flatulence in 30 patients (Ross, 1998).

Small doses of garlic are purported to increase the tone of smooth muscle in the gastrointestinal tract, while large doses decrease such actions (Tyler, 1993). An ethanol—chloroform extract of fresh bulb antagonized acetylcholine and prostaglandin E induced rat fundus smooth muscle contraction at a concentration of 0.002 mg/mL; however, an ethanol extract of fresh garlic bulb caused rat fundus smooth muscle stimulation at a concentration of 0.016 mg/mL (Ross, 1998).

The gastrointestinal side effects of garlic extracts and commercially available products are described in Section 9.4.1.

9.4.3 Antimicrobial Activity

Therapy of cryptococcal meningitis with a combination of oral and parenteral garlic has been reported to produce a 69% cure rate. Garlic has also been claimed to suppress oropharyugeal or vaginal candidia colonization, clear Candida cystistis in diabetics or patients with Foley catheters, cure dermatophytic infections, and treat systemic aspergillosis. Based on these reports, and the in vitro activity of garlic extracts against bacteria and fungi, Caporaso, Smith, and Eng (1983) studied the antifungal activity of human urine and serum from five volunteers who had consumed a 10–15 mL of fresh extract of garlic. The contents of a 1500 mg garlic extract capsule distributed by the Windmill Natural Vitamin Co. (Morton Grove, IL) was also assayed for antifungal activity. Several yeasts (*Candida sp., Cryptococcus sp.*) and mycelial fungi species (*Aspergillus sp., Mucor pusillus, and Rhizopus sp.*) were tested. All the yeast and mycelial fungi species except *C. glabrata* and *R. arrhizus* were susceptible to the garlic extract at a 1:100 dilution or greater. Similar results were obtained with urine samples from the volunteers. When serum the human volunteers was used, susceptibility dropped significantly, only serum samples taken at 30 and 60 min postingestion were active against the yeasts. The commercial preparation did not exhibit antifungal activity. Because an in vitro study suggests that allicin is the antifungal component of garlic (Barone and Tansey, 1977), the authors postulated that their results were due to instability of allicin at the relatively high pH of human serum ex vivo, binding of allicin to serum protein, inactivation of allicin in serum, or rapid distribution of allicin out of the vascular compartment into body tissues. Clinical use of oral garlic extracts for purposes of treating fungal infections appears to be limited because the gastrointestinal tolerance of the amount of garlic extract used in this study was

9.6 Drug Interactions

There are no documented drug interactions, but garlic's antiplatelet effect might be dangerous in patients taking warfarin or antiplatelet agents such as aspirin, clopidogrel, ticlopidine, or dipyridamole.

9.7 Pharmacokinetics/Toxicokinetics

9.7.1 Absorption

The bioavailability of the garlic component S-allyl-L-cysteine (SAC) was 64.1%, 76.6%, and 98.2% in rats after oral administration of 12.5 mg/kg, 25 mg/kg, and 50 mg/kg, respectively. Bioavailability was 103% in mice and 87.2% in dogs. SAC is rapidly absorbed from the gastrointestinal tract, with a peak plasma concentration occurring at 0.25 h in dogs, 0.5 h at doses of 12.5 mg/kg and 25 mg/kg in rats, and at 1 h in rats administered 50 mg/kg (Nagae et al., 1994).

9.7.2 Distribution

Egen-Schwind and colleagues (1992) found that 1,2-vinyl dithiin, a component of oily preparations of garlic, accumulates in fatty tissues, while 1,3vinyl dithiin is more hydrophilic and is rapidly eliminated from serum, kidney, and fat tissue. The latter compound was detected in rat liver over the first 24 h after administration, while 1,2-vinyl dithiin was not. Both 1,3-vinyl dithiin and 1,2-vinyl dithiin were detected in the serum, kidney, and fat.

In rats, mice, and dogs, SAC is distributed mainly in the liver, kidney, and plasma (Nagae et al., 1994). In rats, SAC levels are highest in the kidney, and plasma and tissue levels peak 15–30 min after oral administration.

Garlic apparently distributes into human amniotic fluid and breast milk. Ten women were given placebo or garlic oil capsules 45 min prior to routine amniotic fluid sampling. Four of the five amniotic fluid samples from the women who had ingested garlic were judged by a blinded panel to have a stronger and more garlic-like odor than a paired amniotic fluid sample from a woman in the placebo group (Mennella et al., 1995). Ingestion of garlic for 3 d by nursing women decreased the infants' feeding time compared to infants of mothers who had taken placebo (Mennella and Beauchamp, 1993).

9.7.3 Metabolism/Elimination

De Rooij et al. (1996) conducted a study to evaluate the urinary excretion ofM-acetyl-S-allyl-L-cysteine (allylmercapturic acid, ALMA). The importance of this study lies in the use of ALMA as a biomarker for occupational exposure

excreted in the urine in rats as *N*-acetyl-SAC, and <1% of the dose is excreted as unchanged SAC in the urine and bile. In mice both SAC (16.5%) and the *N*-acetylated metabolite (7.2%) are excreted in the urine, while in dogs <1% of the dose was found in the urine as either SAC or *N*-acetyl-SAC. The half-life of SAC in rats ranges from 1.49 h with an intravenous dose of 12.5 mg/kg to 2.33 h with an oral dose of 50 mg/kg. In mice, the half-life of SAC is 0.77 h when given orally and 0.43 h for intravenous administration, and in dogs approx 10 h after either oral or intravenous administration (Nagae et al., 1994).

9.8 Analysis of Biofluids

Jandke and Spiteller (1987) performed GC-MS to analyze urine samples obtained after ingestion of garlic and onions. *N*-acetyl-*S*-(2-carboxypropyl) cysteine, *N*-acetyl-*S*-allyl-L-cysteine (ALMA, allylmercapturic acid), and hexahydrohippuric acid were identified. De Rooij and colleagues (1996) also used GC-MS to identify ALMA in human urine. Gas chromatographic sulfur selective analysis with a flame photometric detector as well as mass selective analysis was performed. Sulfur selective detection was approx 10 times less sensitive than GC-MS in selective ion monitoring (SIM) mode. The vinyl dithiins, found in oily garlic preparations, were detected in rat serum, kidney, fat, and liver using GC-MS (Egen-Schwind et al, 1992). Details of these analyses can be obtained from the cited references.

9.9 Regulatory Status

Garlic is approved in Germany as a nonprescription drug. The oil, extract, and oleo resin have been deemed generally recognized as safe (GRAS) as food substances by the FDA, and garlic is also regulated as a dietary supplement in the United States. In Canada garlic is approved as a food supplement; garlic is on the general sale list in the United Kingdom; in France it is accepted for the treatment of minor circulatory disorders; and in Sweden it is classified as a natural product (Blumenthal, 1997).

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and paws to induce arthritis in treatment rats. Rats were randomized to receive 33 mg/kg of ingwerol (ginger oil obtained by steam distillation of dried ginger root), 33 mg/kg of eugenol (a component of clove oil purported to have antiinflammatory activity), or normal saline orally for 26 d, beginning just prior to the induction of arthritis. Compared to normal saline, both treatments were effective in decreasing both knee and paw swelling.

10.4.3 Use in Migraine

A case reported the use of ginger for the prevention of migraines (Mustafa and Srivastava, 1990). A 42-yr-old woman suffered migraine with aura for 10 yr once or twice every 2 or 3 mo. Because the frequency and duration of migraine increased, the patient was prescribed 500–600 mg of powdered ginger to be taken at the onset of aura, then every 4 h for the next 3–4 d. The patient reported some relief within 30 min of the first dose. Then she added uncooked fresh ginger to her diet. In a 13-mo period, she reported only six migraines. These results should be confirmed in a double-blind, controlled trial.

10.4.4 Cardiovascular Effects

In vitro studies of gingerol using canine cardiac tissue and rabbit skeletal muscle demonstrated Ca^{2+}-ATPase activation in the cardiac and skeletal sarcoplasmic reticulum (SR) (Kobayashi et al., 1987). Gingerol (3–30 μ*M*) increased Ca^{2+}-ATPase pumping rate in a dose-dependent manner. A 100-fold dilution with fresh saline solution of 30 μ*M* gingerol completely reversed Ca^{2+}-ATPase activation. The investigators concluded that gingerol may be a useful pharmacologic tool in the study of regulatory mechanisms of the SR Ca^{2+} pumping systems, and their effect on muscle contractility.

Another in vitro study examined the effect of 6-, 8-, and 10-gingerol on isolated left atria of guinea pigs (Shoji et al., 1982). The study found the gingerols had a dose-dependent positive inotropic effect that was evident at doses as low as 1×10^{-5}, 2×10^{-6}, and 3×10^{-5} g/mL for 6-, 8-, and 10-gingerol, respectively. Thus, 8-gingerol was the most potent gingerol in regard to cardiotonic activity.

In vitro, aqueous ginger extract has dose-dependent antithromboxane synthetase activity that correlates with its ability to inhibit aggregation of human platelets in response to ADP, collagen, and epinephrine (Srivastava, 1984). However, this may not be clinically significant; inhibition of platelet aggregation has been demonstrated in humans only after consumption of 5 g of raw ginger daily for 1 wk (Srivastava, 1989). A single 2-g dose of dried ginger did not affect platelet function (Lumb, 1994).

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Kava Root extract (30% kavalactones)

Kavatrol™ 200 mg

Nature's Resource™
Kava Kava 150 mg

Cranberry Juice Concentrate

Nature's Resource™
Cranberry 405 mg

Feverfew Leaf

Nature's Resource™
Feverfew
380 mg

Saw Palmetto Berry Extract

Nature's Resource™
Saw Palmetto
(at least 45% fatty acids and sterols)
80 mg

Propalmex®
Saw palmetto
(85-95% free fatty acids and phytosterols)
160 mg

Quanterra™
Prostate 160 mg

Pumpkin seed oil extract
(85-95% free fatty acids)
40 mg

Zinc (as zinc gluconate)
7.5 mg

St. John's Wort Extract (0.3% hypericin)

Kira™ (WS® 5572) 300 mg
from upper parts of flowers and leaves

Quanterra™
Emotional Balance
(LI 160 WS) 300 mg
(aerial part, dried extract)

Celestial Seasonings®
St. John's Wort 300 mg

Alterra™ 450 mg
(extended-release tablet)

Movanna™ (WS-5572)
(from flowers and leaves)
300 mg

Harmonex™
St. John's wort extract
(flower) 450 mg
Siberian ginseng extract (root)
(0.8% eleutherosides) 90 mg

Ginkgo Biloba Leaf Extract

Quanaterra™
Mental Sharpness
(EGb 761®) 60 mg

Ginkoba™ 40 mg

Ginkai™
(LI 1370) 50 mg
(25% ginkgo flavonoids and 6% terpenoids)

Ginsana® is available in the United States in softgel capsules and chewy squares. The capsules are green because chlorophyll is added. Other brands of ginseng are most commonly available in capsule or tablet form and are usually brown. Dosage strengths normally range between 50 mg and 300 mg of panax ginseng extract per capsule or tablet. Also, several combination products are available. For example, Ginkogin® is a combination of panax ginseng, ginkgo biloba, and garlic. There are other types of ginseng on the market including Siberian, Brazilian, and Indian ginseng. These are not of the genus *Panax* and do not contain ginsenosides (Tyler, 1997).

12.4 Pharmacologic/Toxicologic Effects

12.4.1 Endocrine Effects

Panax ginseng may exert hypoglycemic effects possibly by accelerating hepatic lipogenesis and increasing glycogen storage (Yokozawa et al., 1975; Oshima et al., 1985; Sotaniemi et al., 1995). In a study of 36 newly diagnosed type II diabetics, ginseng at a dose of 200 mg daily exerted a statistically significant benefit on glycosylated hemoglobin (HbA_{1c}) compared to 100 mg of ginseng daily or placebo after 8 wk of therapy, and patients receiving 100 mg of ginseng had smaller mean fasting blood glucose levels than patients taking 200 mg of ginseng or placebo (Sotaniemi et al., 1995). The actual difference among the mean HbA_{1c} in the three groups was small; the 200-mg ginseng group had a mean glycosylated hemoglobin of 6% vs 6.5% for the 100-mg ginseng and placebo groups. Likewise, the actual difference among mean fasting blood glucose in the three groups was small; the mean fasting blood glucose was 7.7 mmol/L for the 100-mg ginseng group, 7.4 mmol/L for the 200-mg ginseng group, and 8.3 mmol/L for the placebo group at the end of the study. The observed differences might be attributed to differences in body weight among the three groups. The small study sample limits the generalizability of these results.

All the ginsenosides (saponins) so tested have shown anti-fatigue actions in mice (Kaku et al., 1975). This may reflect the purported "adaptogenic" action of ginseng, which can be defined as an increase in resistance to stresses and is thought to be secondary to normalization of body processes through regulation of the production of various hormones (Awang, 1998).

Ginseng appears to have a modulating effect on the hypothalamic-pituitary-adrenal axis by inducing secretion of adrenocorticotropic hormone (ACTH) from the anterior pituitary to increase plasma cortisol (Hiai et al., 1979; Fulder, 1981), perhaps accounting for improvement in 11 quality of life measurements in a large double-blind study using ginseng extract G115 (Caso Marasco et al., 1996).

14.4.3 Respiratory Effects

An uncontrolled study (Christophe et al., 1994) in patients with cystic fibrosis demonstrated an increase in vital capacity after 4 wk of supplementation with 1500 mg of borage oil (330 mg of GLA) daily. AA content of serum phospholipids was increased, although they would be expected to decrease based on results of other studies. AA, DGLA, and linoleic acid content of cholesterol esters also increased.

14.4.4 Carcinogenicity

Although other members of the Boraginaceae family contain hepatocarcinogenic pyrrolizidine alkaloids, there are no reports of similar compounds in common borage (Anonymous, 1992).

14.4.5 Hematologic Effects

GLA at a dose of 5.23 g provided as borage oil for 42 d in male volunteers increased platelet phospholipid DGLA (Barre and Holub, 1992), but borage oil at doses of 3 g/d has been shown not to affect human platelet aggregation (Bard et al., 1997).

14.4.6 Effects in Diabetic Neuropathy

Dietary supplementation with 1% borage oil and other GLA-containing oils ameliorated diminished motor and sensory nerve conduction velocity in diabetic rats, but efficacy did not correlate with GLA content of the various oils (Dines et al., 1996).

14.4.7 Cardiovascular Effects

Dietary borage oil decreased blood pressure in both spontaneously hypertensive and normotensive rats via an unknown mechanism. Cholesterol levels and activity of β-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase were increased (Engler et al., 1992).

A diet supplemented with GLA and eicosapentaenoic acids improved oxygen delivery by decreasing vascular resistance and increasing cardiac index in endotoxin-induced lung injury in pigs. This mechanism is thought to involve attenuation of endotoxin-induced thromboxane B_2 synthesis (Murray et al., 1995). A study (Mancuso et al., 1997) in endotoxic rats demonstrated that in addition to attenuation of thromboxane B2 production, production of leukotriene B_4, leukotriene C_4/D_4, and $PGF_{1\alpha}$, as well as neutrophil accumulation, was attenuated. Lung phospholipid concentrations of AA were decreased and DGLA was increased.

Cardiovascular effects have also been demonstrated in humans. Borage oil at a dose of 4.5 mL/d for 4 wk in nine normotensive volunteers augmented

Chapter 16—
Chaparral

Kim Melgarejo and Melanie Johns Cupp

Larrea tridentata Coville, synonymous with *L. divaricata* Cav. and *L. mexicana* Moric (Tyler, 1993), *L. glutinosa* Englem, creosote bush, greaseweed, hediondilla (Anonymous, 1993); *L. nitida, L. ameghinoi, L. cuneifolia* (Leonforte, 1986)

16.1 History and Traditional Uses

Chaparral is a broad term that describes any thicket of wild shrubs and dwarf trees, but chaparral, the herb, is known more specifically by the names listed above (Tyler, 1993). Chaparral is able to survive the arid deserts of the United States and Mexico. The shrub is a branched bush that grows to 9 ft in height. Its bilobed leaves have a resinous feel and strong smell (Anonymous, 1993). This olive-green bush was used medicinally by Native Americans. Chaparral purportedly possesses analgesic, expectorant, emetic, diuretic, and antiinflammatory properties, and has been used in the treatment of arthritis, colds, tuberculosis, and cancer. It has also been used as a hair tonic and as an antidote for LSD flashbacks (Tyler, 1993). Tea made from boiled leaves has been used to treat sexually transmitted diseases and intestinal cramps, and to stimulate urination. The leaves were soaked in water to produce an extract used as a bath for rheumatism and chicken pox. The dried powdered leaves were used as a dusting powder for sores, and were mixed with badger oil to make an ointment used on burns to aid new skin formation (Waller and Gisvold, 1945).

Nordihydroguaiaretic acid (NDGA), purported by the active constituent of chaparral, was first isolated in 1945 (Waller and Gisvold, 1945). NDGA was used as a food antioxidant from 1945 to 1967, in products such as lards, oils, candies, baking mixes, frozen foods, vitamins, and pharmaceuticals at levels of 0.01–0.02% (Smart et al., 1969).

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after she began taking chaparral. Clinical presentation varied. Chief complaints in most patients included fatigue, right upper quadrant pain, dark urine, light stools, nausea, and diarrhea. A few patients also reported anorexia, weight loss, fever, and itching. Most patients had acute hepatitis characterized by jaundice, increases in serum levels of alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, total bilirubin, γ-glutamyltransferase, and lactate dehydrogenase. Liver biopsy was performed on three patients, revealing acute cholangitis with cholestasis, acute cholestasis with cholestasis and cirrhosis, and subacute cholangitis with cholestasis and cirrhosis. Five of seven patients who underwent abdominal ultrasound had evidence of a thickened gallbladder. Three of these patients had gallstones as revealed on ultrasound or computed tomography (CT). An exploratory laparotomy was performed in one patient, revealing ascites and a nodular liver. T-tube cholangiography showed nonfilling of the gallbladder, but no evidence of biliary disease. Endoscopic retrograde cholangiopancreatography (ERCP) revealed narrowed intrahepatic bile ducts in one of the two patients in whom it was performed. The authors of the review concluded that cumulative dose, but not duration of use, appears to be a risk factor for chaparral-induced hepatotoxicity. In addition, they state that hepatotoxic drugs or viruses might predispose patients to chaparral-associated hepatotoxicity. Four of these 13 cases (Anonymous, 1992; Alderman et al., 1994; Gordon et al., 1995) were previously reported in the medical literature, and are described in the following paragraphs.

Two of the cases included in the review by Sheikh and colleagues were first reported by the Centers for Disease Control (CDC) in 1992 (Anonymous, 1992). A 42-yr-old man was evaluated for jaundice and icteric sclera after consuming three 500-mg capsules of chaparral per day for the previous 6 wk. Past medical history included no unusual dietary practices, no alcohol for the past 3 yr, and no exposure to hepatotoxins. On physical exam, the liver was palpated 3 cm below the right costal margin. Upper abdominal ultrasound was normal. Lab findings were negative for hepatitis A, B, and C, cytomegalovirus (CMV), and Epstein-Barr virus (EBV). Serum chemistry revealed total bilirubin of 16.6 mg/dL (normal is 0–0.5 mg/dL), alkaline phosphatase of 133 U/L (normal is is 0–135 U/L), γ-glutamyltranspeptidase (GGT) of 158 U/L (normal is 0–32 U/L), aspartate aminotransferase (AST) of 1077 U/L (normal is 0–48 U/L), and lactate dehydrogenase (LDH) of 405 U/L (normal is 0–225 U/L). He was diagnosed as having hepatic dysfunction secondary to chaparral ingestion. Twenty-six days after discontinuing the herb, his LFTs had returned to normal (Anonymous, 1992).

Another patient sought medical advice after having experienced right upper quadrant pain and jaundice for 4 wk. This 41-yr-old woman had con-

in the two largest cysts. The microscopic cysts were ringed by flattened epithelial cells and appeared to originate as dilatations and outpouchings of the Bowman's capsule and the proximal and distal tubules. Most were glomerular and at the same stage of development. With questioning the patient admitted to consuming three to four cups daily of chaparral tea for a 3 mo period approx 18 mo prior to presentation. On postsurgical follow-up of almost 2 yr, serum creatinine stabilized at 1.7 mg/dL, and periodic renal ultrasound revealed no changes in the right kidney (Smith et al., 1994).

Sixteen cases of contact dermatitis have been attributed to chaparral or NDGA (Sheikh et al., 1997). In a case series of acute dermatitis caused by exposure to chaparral (Leonforte, 1986), six men developed dermatitis from exposure to chaparral as a bath additive; from using chaparral to make a fire for a barbecue; and through occupational exposure. Clinical presentation included scales, erythema, pruritus, edema, vesicles, and papules. An elevated white blood cell count and eosinophilia were noted in one patient. Biopsy, performed in one patient, revealed suprabasal, multiloculated blisters containing a net of fibrin, neutrophils, eosinophils, and mononuclear cells. An inflammatory infiltrate and congested capillaries were seen at the base of the dermis. Patch test to chaparral leaves was positive in the four patients in whom it was performed. Although the clinical presentation suggested a photodermatitis in four patients, a photopatch test was negative in another patient in whom it was performed.

In one of the cases reviewed by Sheikh and colleagues, a patient developed a generalized urticarial rash, nausea, and abdominal pain after ingestion of chaparral, but had been taking chaparral for 1 yr, had a history of allergies, and was also taking naproxen and ketorolac. Miscellaneous adverse effects associated with chaparral use include sudden unilateral loss of vision, tachycardia, electrolyte abnormalities with cardiac arrest, and syncopal episodes (Sheikh et al., 1997).

16.6 Drug Interactions

Although drug interactions with chaparral have not been reported, NDGA is an inhibitor of CYP450 microsomal enzymes in vitro (Capraville et al., 1988; Agarwal et al., 1991). Its ability to inhibit drug metabolizing isoforms of CYP450 in vivo remains to be seen.

16.7 Pharmacokinetics

In rats, NDGA is metabolized in the lower third of the ileum and cecum to its *o*-quinone metabolite. It is absorbed into the bloodstream, is filtered by the glomeruli, then reabsorbed and retained by the proximal tubule epithelial cells

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by the liver by dehydrogenation to highly reactive, electrophilic pyrrole-like compounds capable of binding to tissues (Mattocks, 1968). Molecular characteristics of those PAs that are metabolized to reactive metabolites include lipid solubility, allowing access to the hepatic microsomal enzymes; ester groups, which act as highly reactive alkylating groups; branching chains, which interfere with ester hydrolysis to nontoxic metabolites (Mattocks, 1981); and the presence of a double bond in the five-membered ring structure of the molecule (Frei et al., 1992). PAs present in coltsfoot that are metabolized to reactive metabolites that covalently bind to hepatic, renal, and pulmonary macromolecules such as DNA and RNA include senecionine and seneciphylline (Eastman et al., 1982). Senkirkine, another PA present in coltsfoot, has been shown to be hepatotoxic in rats (Schoental, 1970). Tussiglione, discussed in Sections 17.4.1 and 17.4.2, does not have the molecular features that would predict hepatotoxicity (Li and Wang, 1988).

The risk of hepatotoxicity from PA consumption is likely dependent upon dose and individual characteristics (Kumana et al., 1985). For example, female rats appear to be more susceptible to PA toxicity than male rats (Candrian et al., 1985).

17.4.5 Carcinogenicity/Genotoxicity

Dried coltsfoot flowers fed to rats induced hemangioendothelial carcinoma (Hirono et al., 1976). These observations prompted further carcinogenicity studies of the PAs. The PA senkirkine has proved to be carcinogenic, causing nonmalignant liver cell adenomas in rats (Hirono et al., 1979). Proliferation of intrahepatic bile ducts and oval cells, blood lagoons, and cirrhosis was found, even in rats that did not develop tumors. Senkirkine and senecionine were shown to be genotoxic carcinogens based on studies showing damage to DNA in rodent hepatocytes (Mori et al., 1985). Dried flower stalks of *Petasites japonicus*, a kind of coltsfoot found in Japan, fed to rats induced liver cell adenoma, hepatocellular carcinoma, and hemangioendothelial sarcoma of the liver, which appeared as soft, hemorrhagic nodules (Hirono et al., 1973). Petasitenine, a PA found in *Petasites japonicus* Maxim, was later isolated and given to rats (Hirono et al., 1978). Liver cell necrosis, hemorrhage, bile duct proliferation, liver cell adenomas, and hemangioendothelial sarcomas appearing as multicentric hemorrhagic nodules were documented. One rat had metastasis of hemangioendothelial sarcoma to the lung.

In a study (Candrian et al., 1985) using radiolabeled senecionine and seneciphylline, the ability of senecionine to bind to liver DNA in female rats was four times higher than that in males, suggesting that females are more susceptible to the carcinogenic effects of these compounds.

continued taking the tea. The third patient continued to take the tea for an additional 16 d, against medical advice, and ultimately died of hepatic failure, gastrointestinal hemorrhage, and portal hypertension despite treatment with diuretics and paracentesis. The fourth patient discontinued the tea after 21 d because she developed a rash. When evaluated 77 d later, she was found to have mild hepatomegaly only. Pertinent initial laboratory values for the four patients included normal serum albumin in all four. The patient who later died presented with an elevated bilirubin of 55 μmol/L (normal is < 26 μmol/L), which increased to 402 mmol/L after 12 d. Bilirubin was within normal limits in the other three patients. AST and ALT were initially elevated (52–232 U/L) in all but the fourth patient, and decreased over time in all but the patient who died, in which they increased slightly. An elevated prothrombin time (PT) ratio of 1.2, which increased to 1.7 after 12 d, was documented in the patient who later died. Ultrasonography revealed hepatomegaly with patent hepatic and portal veins, even in the two patients who had portal hypertension, reflecting the short duration of the disease. Liver biopsy was performed on all four patients, and in all four cases the histologic features of venoocclusive disease were evident. The biopsy from the patient who eventually died showed areas of intense centrilobular sinusoidal dilatation with hemorrhage, cell atrophy, and necrosis. Intimal edema and loose fibrosis significantly narrowed many central and sublobular hepatic veins. Liver biopsies from two of the three patients who survived were similar, but congestion and liver cell changes in the centrilobular zone were not as severe. The liver biopsy from the patient who discontinued the tea after only 3 wk revealed only slight residual sclerosis of some of the sublobular veins with dilatation of the feeding venules. Postmortem examination of the patient who died revealed a slightly enlarged liver with "nutmeg" appearance and reverse lobulation, extensive centrilobular hemorrhagic necrosis, and scarring around severely narrowed, sclerotic sublobular and central veins. Other findings included 3 L of ascitic fluid, esophageal varices, and bloody mucus in the stomach.

The tea consumed by these four women was analyzed using spectrophotometry after reaction with Ehrlich's reagent revealed unsaturated PAs that were determined to be senecionine and the corresponding N-oxide in concentrations of 0.42 mg/g and 1.4 mg/g, respectively. The leaves were determined to be from the family Compositae, to which coltsfoot belongs, although their exact identity could not be determined because of their chopped condition. Cumulative doses of these alkaloids were calculated to be 1350 mg over 45 d for one patient, 1380 mg over 46 d for the patient who died, 570 mg over 19 d for another patient, and 630 mg over 21 d for the patient with the mildest symptoms. The cumulative dose was 15 mg/kg in the patient who exhibited mild symptoms, while the mean cumulative dose was 18 mg/kg in the other three patients.

in absolute ethanol, centrifuged, and shaken with a modified Ehrlich reagent (3 g of 4-dimethylaminobenzaldehyde in 60 mL of absolute ethanol and 40 mL of 14% methanolic boron trifluoride). Modification of the reagent with acid is required to overcome tissue buffering activity. The mixture is heated for 1–2 min at 80–95°C and then the reagent is decanted and exchanged with new ethanol. Ehrlich reagent gives a mauve color in the presence of tissue samples containing PA metabolites. Demonstration of PA metabolites in the liver by color change can be accomplished by making thin liver slices, fixing them with alcohol, heating for a few minutes in Ehrlich reagent, then replacing the reagent with clean ethanol. Because PA metabolites are highly bound to tissues, Ehrlich reagent works for fresh tissues that have been frozen, ethanol-fixed slices, ethanolic homogenates that are 2 wk old, and perhaps even on older tissues. Ehrlich reagent will also give a mauve color when added to urine containing pyrrolizidine metabolites. Quantification of PAs and metabolites can be done using spectrophotometry (Mattocks, 1968; Kumana et al., 1985). PAs in herbal products can also be quantified using this method (Kumana et al., 1985).

TLC analysis of PAs (Sharma et al., 1965; Mattocks, 1967; Mattocks, 1986) and their N-oxides (Mattocks, 1967) has been described. Seneciphylline and its N-oxide metabolite have been detected in herbs using TLC, fast atom bombardment mass spectrometry, NMR spectrometry, gas chromatographymass spectroscopy (GC-MS), and co-chromatography (thin-layer and gas chromatography) (Speri et al., 1995). Senkirkine was detected in dried, milled flowers using GC-MS (Hirono et al., 1976). Alternatively, senkirkine can be extracted from the milled buds (Roekemoer and Warren, 1951), then its melting point, TLC, and infrared (IR) spectrum can be compared to an authentic sample (Hirono et al., 1979). Boiling point, melting point, retention time (R_T) for gas chromatography, and retention factor (R_F) for TLC have been published for senecionine, seneciphylline, and senkirkine, along with procedural details of these analyses (Chalmers et al., 1965).

High-performance liquid chromatography (HPLC) was used to measure seneciphylline and senecionine in rat lung, liver, and kidney (Candrian et al., 1985). Details of HPLC detection of these compounds using a reversed-phase styrene-divinylbenzene resin column and Schoeffel SF-770 detector set at 220 nm have been described (Ramsdell and Buhler, 1981). Metabolites of senecionine in rat urine have been detected using HPLC and mass spectrometry (Estep et al., 1990a).

77.9 Regulatory Status

The German Commission E recommends limiting the use of coltsfoot leaf to 4–6 wk per year. Furthermore, the daily dosage of PAs with the 1,2-unsatur-

Chapter 18—
Comfrey

David Burch and Melanie Johns Cupp

Symphytum officinale (L.), *S. tuberosum*, *Sympytum* × *uplandicum* Nyman (Russian comfrey, a hybrid of *S. officinale* and *S. asperum*) (Anonymous, 1995), *Symphytum asperum* Lepech (prickly comfrey) (USP, 1998), boneset, knitback, knitbone (Awang, 1987), consound, common comfrey, blackwort, bruisewort, slippery root, yalluc, gum plant, consolida, ass ear (Grieve, 1971)

18.1 History and Traditional Uses

Comfrey is a perennial herb that has a thick root and white, hairy, branching stems (Leung, 1980). The plant is native to Europe and Asia and grows to about 1 m high (Leung, 1980). Over the past 2000 yr, people from all over the world have been using comfrey to heal their ailments. Comfrey use was first documented by the ancient Romans and Greeks (Wiesner, 1984). Around 200 AD, the Greek physician Dioscorides praised the therapeutic uses of comfrey in his book *Materia Medico*, and coined the genus name *Symphytum* from the Greek word *syuphuo*, which means "to make to grow together." During the Middle Ages, comfrey in the form of an external poultice became popular for healing broken bones (Awang, 1987). It was during this time that comfrey received its nicknames such as boneset, knitbone, and knitback. As the popularity of comfrey grew over the centuries so did its indications for use. Comfrey has been used to treat respiratory problems (bronchitis, catarrh, hemoptysis, pleurisy, whooping cough), gastrointestinal diseases (cholecystitis, colitis, dysentery, diarrhea, ulcers, hematemesis), metorrhagia, phlebitis, and tonsillitis (USP, 1998). Comfrey has also been touted for its nutritional value; it has been considered a good source of protein and vitamin B_{12}, which is unusual for a plant.

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18.4.1 Gastrointestinal Effects

In an in vitro study using rat gastric tissue, researchers showed that an extract of 10 mg of dried comfrey leaves (*S. officinale*) homogenized in 1 mL of Kreb's solution increased the release of prostaglandin $F_{2\alpha}$ and 6-keto-prostaglandin $F_{1\alpha}$ (Stamford and Tavares, 1983). As numerous prostaglandins have been found to protect the gastric mucosa, there may be a biologic basis for use of comfrey as a treatment for peptic ulcers.

18.4.2 Hepatotoxicity

Commercial comfrey is usually derived from the leaves or roots of *Symphytum officinale* (common comfrey) (USP, 1998). However, some products are derived from *Symphytum x uplandicum* Nyman (Russian comfrey) or *Symphytum asperum* Lepech (prickly comfrey), which appear to be more toxic than common comfrey (Anonymous, 1998). Russian comfrey and prickly comfrey contain a very toxic pyrrolizidine alkaloid (PA) called echimidine that common comfrey does not contain (Tyler, 1994). Although common comfrey does not contain echimidine, it does contain other hepatotoxic PAs. These alkaloids include 7-acetylintermedine, 7-acetyllycopsamine, their unacetylated precursors, and symphytine (Tyler, 1993).

These PAs can cause hepatic venoocclusive disease with zonal or focal hemorrhagic hepatic necrosis, damage to the endothelium of the central and sublobular veins, hepatocyte swelling, biliary hyperplasia, and marked fibrosis (Abbott, 1988). These alkaloids can also cause pulmonary fibrosis (Svoboda and Reddy, 1972).

Several studies in rats have shown liver damage caused by comfrey. In one study (Yeong et al., 1991), three groups of mice received different doses of PAs derived from the fresh roots and leaves of *Symphytum x uplandicum* Nyman (Russian comfrey). A single dose of 200 mg/kg was given to group I rats, a dose of 100 mg/kg three times a week was given to group II rats, and dose of 50 mg/kg three times a week for 3 wk was given to group III rats. All of the rats developed dose-dependent liver damage evident by light and electron microscopy. Group I rats showed swelling of hepatocytes and hemorrhagic necrosis of perivenular cells with preservation of sinusoidal walls and endothelial cells. Group I rats also developed noticeable extravasation of red blood cells. Group II and III rats had similar changes but with more severe necrosis. Loss of sinusoidal lining cells and disruption of hepatocyte cellular margins was found in both group II and group III rats. All of these histologic changes are indicative of hepatic venoocclusive disease caused by PAs.

Another study examined the activity of various hepatic drug-metabolizing enzymes in liver homogenates of three groups of six male Long-Evans rats fed

venular fibrosis surrounded atrophic hepatocytes, and had replaced necrotic hepatocytes. Portal tracts were mildly fibrotic, and a few scattered glycogenated nuclei were seen. She was diagnosed with hepatic venoocclusive disease attributed to comfrey consumption. A repeat liver biopsy 20 mo later showed dense fibrosis of portal tracts with proliferating bile ductules and minimal inflammatory cells. Areas of collapse also contained proliferating bile ductules and isolated hepatocytes. Thin, fibrous septa compressed by regenerating nodules radiated from small, occluded terminal hepatic venules. Most of the terminal hepatic venules were patent, although some had thickened walls. The bile ducts were unremarkable.

In another case report (Yeong et al., 1990), a 23-yr-old man was diagnosed with venoocclusive disease. Symptoms began 1–2 wk after ingestion of four to five comfrey leaves each day for 1–2 wk. He presented with a 3-mo history of flulike symptoms followed by malaise and night sweats, and a 3-wk history of abdominal distension and peripheral edema. He was hypoalbuminemic (22 g/L) with a bilirubin of 28 µmol/L, markedly elevated alkaline phosphatase (475 U/L,) glutamyl transferase of 99 U/L, and aspartate transferase markedly elevated (365 U/L). The prothrombin time (PT) ratio was 1.4, partial thromboplastin time (PTT) was 38 s, and platelet count was mildly decreased (148×10^9/L). Two tricut liver biopsies on two separate occasions showed centrilobular hemorrhagic necrosis and platelet plugging of the central and sublobular veins. Sinusoidal dilatation and congestion was also evident. Cellular infiltrate in the necrotic areas consisted of fibroblasts, lymphocytes, and macrophages. Liver angiography revealed luminal narrowing in the small hepatic vein radicles associated with nonhomogeneous filling of the hepatic sinusoids. Hepatic venous wedge pressure was elevated at 30 mm Hg. The main hepatic veins and portal vein were patent. The lumen of the inferior vena cava was narrowed by the enlarged liver. He later died of liver failure attributed to comfrey-induced hepatic venoocclusive disease. Contributing factors included ingestion of young comfrey leaves, which have a relatively high alkaloid content, and the protein-deficient diet that the young man had followed for the 4 yr preceding his death.

In the first published case of venoocclusive disease associated with consumption of a comfrey-containing preparation, a 49-yr-old woman presented with swelling of the abdomen and extremities that had begun 4 mo prior. Liver biopsy showed centrilobular necrosis and congestion. During hepatic venography, a wedge pressure of 23 mm Hg and a corrected sinusoidal pressure of 17 mm Hg were recorded, suggesting moderate portal hypertension. No outflow obstruction in the vena cava or hepatic veins was appreciated. The smaller hepatic venules were seen to be nearly obliterated on films taken during bal-

loon distention of one of the intrahepatic venous tributaries. The patient's condition required placement of a side-to-side portacaval shunt. During surgery, portal pressures and postshunt preportal pressure confirmed postsinusoidal block.There was no evidence of a hypercoagulable state or outlet obstruction, and the patient had not been taking any medications; however, the patient had, for the 6 mo prior to presentation, consumed approx 1 quart per day of a tea known as MU-16, and had taken two comfrey-pepsin pills with meach meal for the past 4 mo. Other food supplements taken by the patient included vitamins C, K, E, A, and B complex; calcium, magnesium, zinc, iron, lecithin, sterotrophic adrenal bovine extract, and approx 3 cups of chamomile tea per week. After analyzing the MU-16 tea and comfrey-pepsin pills for PAs and pyrrolizidine *N*-oxides, the investigators calculated that the patient had consumed 14.1 µg/kg/d pyrrolizidines from the capsules, and 0.49–1.45 µg/kg/d from the tea (Ridker et al., 1985).

Comfrey tea from a particular distributor in Britain was found to be contaminated with the anticholinergic *Atropa belladonna* (deadly nightshade) (Anonymous, 1983). Three patients experienced anticholinergic symptoms including hallucinations, erythema, thirst (Galizia, 1983), light-headedness, agitation, confusion, difficulty in urination, dry mouth, sinus tachycardia, dilated pupils, and warm dry skin (Routledge and Spriggs, 1989) after drinking comfrey tea. In these case reports, belladonna was not definitively identified as the contaminant, but the tea consumed by one patient was found to contain atropine at a concentration of 0.014% (Routledge and Spriggs, 1989).

18.6 Drug Interactions

A study involving rats showed that phenobarbital induces the metabolism of PAs to their lethal metabolites (Lafranconi and Huxtable, 1984). The USP recognizes this as a possible drug interaction and also suggests that patients on any medications avoid taking comfrey (USP, 1998).

18.7 Pharmacokinetics/Toxicokinetics

18.7.1 Absorption

Comfrey is absorbed through the skin as well as the gastrointestinal tract (Abbott, 1988). A experiment conducted by Swiss researchers on rats showed that 0.1–0.4% of the dermal dose of 194 mg of alkaloid *N*-oxides/kg (extracted from the roots of Polish *S. officinale*) was absorbed and was recovered in urine within 48 h (Brauchli et al., 1982).

continuation of the product, the patient's LFTs and liver histology normalized over the next 9 mo. The hepatotoxicity experienced by this woman was attributed to the mistletoe component of the product because no record of toxic reactions to kelp, motherwort, or scullcap were found. Although the same was true of mistletoe, the authors believed mistletoe to contain several potential hepatotoxins.

There is currently no experimental data that document liver toxicity of scullcap (Larrey, 1997). Studies of scullcap products available in the United Kingdom in the early 1980s revealed that some products contained a species of *Teucrium* in place of scullcap (Phillipson and Anderson 1984, Anonymous, 1985). The genus *Teucrium* is of the same family (Lamiaceae) as scullcap but is associated with hepatotoxicity. Several cases of liver toxicity and injury have been associated with *Teucrium chamaedrys* (Germander) in France, where it has been used as an herbal weight loss product (Larrey et al., 1992).

In light of these facts, it is important be aware of the toxicities of other herbs that may be included in scullcap products. It is difficult to attribute hepatotoxicity to scullcap because it has not been reported with products containing only scullcap. Be aware that many herbal products contain multiple ingredients, and some ingredients may not even be listed on the label. For example, scullcap is often formulated with valerian (Foster, 1998). Perhaps an interaction between scullcap and other herbs is responsible for some of the cases of hepatotoxicity.

19.6 Chemical Analysis

Flavonoid content of scullcap hot water extract has been determined using HPLC with a UV detector (Nagai et al., 1989b).

Interestingly, melatonin, the human pineal gland hormone, has been detected in scullcap at a concentration of 0.09 µg/g (Murch et al., 1997).

19.7 Regulatory Status

Scullcap is approved as a nonprescription medication in Canada and is on the General Sales List in the United Kingdom. *Scutellaria baicalensis* can be found in the Japanese Pharmacopoeia (Anonymous, 1998b). The drug is not regulated in France. In the United States, scullcap is regulated as a dietary supplement, and has been classified as an "Herb of Undefined Safety" by the FDA (Duke, 1985). A scullcap monograph was listed in the United States Pharmacopoeia from 1863 to 1916 but is currently not included (Tyler, 1993). Scullcap is not listed in the German Commission E monographs.

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20.6 Pharmacokinetics/Toxicokinetics

20.6.1 Absorption

Glycyrrhizin (glycyrrhizic acid) is biotransformed in the large intestine to the active glycyrrhetinic acid (glycyrrhetic acid) by the glucuronidase activity of anaerobic bacteria in the large intestine (Hattori et al., 1983; Gunnarsdottir and Johannesson, 1997). Absorption is independent of dose (Krahenbuhl et al., 1994b), but the bioavailability of glycyrrhetic acid in plasma has been found to be greater after ingestion of pure glycyrrhizic acid than after ingestion of licorice (Cantelli-Forti, 1994). In one human study, the mean C_{max} of glycyrrhetic acid after ingestion of 200 mg of glycyrrhizic acid in licorice was 794 ng/mL (range 466–1636 mg/mL), occurring at a mean T_{max} of 13 h (range 8–30 h) (Gunnarsdottir and Johannesson, 1997).

20.6.2 Distribution

Glycyrrhizic acid, when administered intravenously, has been found to have a volume of distribution of approx 80 mL/kg, and is undetectable in plasma after oral administration (Yamamura et al., 1992). The likely reason for this latter finding is biotransformation by intestinal bacteria, as mentioned in the previous section. After oral administration of 500 mg, 1000 mg, and 1500 mg of glycyrrhetinic acid, volume of distribution was calculated to be 2300 mL/kg, 3100 mL/kg, and 3800 mL/kg, respectively (Krahenbuhl et al., 1994a).

20.6.3 Metabolism/Elimination

The elimination half-life of glycyrrhizic acid after intravenous administration is 3.5 h, and is independent of the dose in human studies (Yamamura et al., 1992).

As mentioned in the preceding discussion of absorption, glycyrrhetinic acid is the active principle after oral administration owing to cleavage of two glucuronic acid moieties from glycyrrhizic acid by intestinal flora (Hattori et al., 1983; Hattori et al., 1989; Krahenbuhl et al., 1994b). The elimination half-life of glycyrrhetinic acid in humans was found to be 11.5 h after a dose of 100 mg, and 38.7 h after a dose of 1500 mg. The terminal half-life could not be calculated after a dose of 500 mg. This dose-dependent elimination likely reflects extensive tissue binding and has been hypothesized be the reason toxicity may take weeks to resolve after cessation of chronic licorice ingestion (Krahenbuhl et al., 1994b). Urinary elimination of glycyrrhetinic acid is negligible; rat studies suggest the majority of its elimination is achieved through elimination of glucuronide or sulfate conjugates in the bile. Human studies suggest that enterohepatic recirculation occurs (Krahenbuhl et al., 1994a)

20.6.4 Analysis of Biofluids

The presence of glycyrrhizin (glycyrrhizin acid) and glycyrrhetinic acid in biological fluids and tissue can be determined through high-performance liquid chromatography (HPLC), thin-layer chromatography (TLC) (Parke et al., 1963), enzyme immunoassay (Kanaoka et al., 1988a), radioimmunoassay (Kanaoka et al., 1988b), and gas chromatography-selected ion monitoring (Itoh et al., 1985). Most pharmacokinetic studies have been performed using HPLC; thus, Krahenbuhl and colleagues have written a review of HPLC methods of bioanalysis of glycyrrhizin and glycyrrhetinic acid. These compounds are readily extracted using methanol, acetonitrile, chloroform, or acetoacetate—*n*-heptane with or without prior addition of inorganic salts. These extracts can be used directly for HPLC. Determination of urine and bile concentrations can be difficult owing to the presence of interfering endogenous compounds. Extraction using a combination of ion-pairing with organic solvent extraction or with solid-phase extraction using C 18 columns is more time consuming than direct solvent extraction, but recovery is in excess of 90% (Krahenbuhl et al., 1994b). The latter technique has been described for detection in plasma using commercially available 18-β-glycyrrhetinic acid as the internal standard and the use of a Bond Elut C2 (ethy1) extraction column to minimize the amount of organic solvent required (Russel et al., 1998).

A micellar electrokinetic chromatographic technique for determining glycyrrhizin and glycyrrhetinic acid in human plasma and urine has limits of detection of glycyrrhizin in urine and plasma of 1.6 µg/mL and 0.8 µg/mL, respectively, and limits of 2 µg/mL and 1 µg/mL for glycyrrhetinic acid in urine and plasma (Wang et al., 1998). In contrast, an HPLC technique has been described with a limit of detection of both compounds in plasma of 0.1 µg/mL (de Groot and Koops, 1988).

20.7 Regulatory Status

Licorice is approved by the German Commission E to treat peptic ulcer, in doses of 200–600 mg glycyrrhizin daily (Blumenthal, 1998). They also recommend that treatment not exceed 6 wk because of the known side effects of licorice. It is recommended that patients with cardiovascular or renal disease use licorice only under the care of a physician. Patients prone to potassium deficiency are also advised not use licorice.

In the United States licorice is regulated as a dietary supplement (Blumenthal, 1997). It is Generally Recognized as Safe (GRAS) (Blumenthal, 1997), a designation that refers only to its use as a food additive.

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with water. He was sent home 2 h later where he experienced vomiting every hour. The vomiting ceased at 2:00 AM when he drank an ounce of diluted brandy. He experienced diarrhea and a bitter taste for 48 h.

21.5 Pharmacokinetics/Toxicokinetics

Pokeweed is absorbed in the gastrointestinal tract and through abrasions on the skin (Lewis and Smith, 1979).

21.6 Chemical Analysis

Pharmacologically/toxicologically important components of the plant include triterpenoid saponins (phytolaccosides) (Woo et al., 1978), mitogenic lectins (Kino et al., 1995), and pokeweed antiviral protein (PAP) (Myers et al., 1995). Isolation of lectins A, B, and C from pokeroot using Q-Sepharose column chromatography followed by gel filtration on a Sephadex G-75 column, hydrophobic chromatography using a Butyl-Toyopearl column, FPLC on a Mono-Q column, and sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) have been described (Kino et al., 1995). Phytolaccosides A, B, D, E, and G have also been isolated from pokeweed root using chromatographic techniques (Woo et al., 1978)

21.7 Regulatory Status

In 1979, the Herb Trade Association recommended that members should stop selling pokeroot as an herbal food or beverage, and that except for the immature leaves, all pokeweed products should be withdrawn from sale in the United States (Lewis and Smith, 1979).

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Aloe, 100 mg, is commonly available in the United States in combination with 150 mg of cascara sagrada in a product called Nature's Remedy®. It is a brown, round tablet with the logo "NR."

Aloe vera is the source of two products that have different content. Aloe gel, also called aloe vera gel, mucilage, or (incorrectly) aloe juice, is the thin, clear jelly obtained by crushing the cells in the parenchymal tissue found inside the leaves (Tyler, 1993; Swan son, 1995). The gel is used in cosmetics and topical products (Swanson, 1995). Although this gel does not contain laxative anthraquinones, contamination can occur, so a cathartic effect might occur if the gel is used internally (Tyler, 1993). Contents of the gel include glucomannan, a polysaccharide thought to possess emollient properties (Anonymous, 1992); bradykinase and an antiprostaglandin agent, which are thought to be responsible for the gel's antiinflammatory activity; and magnesium lactate, which is purported to block histamine release (Natow, 1986). Whether these substances are stable during storage is controversial (Tyler, 1993).

The aloe latex or aloe juice is obtained from the yellow latex of pericyclic cells found beneath the epidermis (Swanson, 1995). It is dried to yield a solid material called "aloe" that contains anthraquinones (Leung, 1980). The specific constituents of the latex include barbaloin, which is metabolized to the laxative aloe-emodin (Leung, 1980; Blumenthal, 1998), iso-barbaloin, chrysophanic acid (Leung, 1980), and aloin (Blumenthal, 1998). The term "aloin" also refers to a crystalline, concentrated form of the dried latex (aloe).

The term "aloe vera gel extract" sometimes is used to refer to the pulverized leaves, rather than to an actual extract (Leung, 1980). Two preparations that may contain only minimal amounts of aloe include "aloe extract," which may be highly diluted, and "reconstituted aloe vera," which is prepared from a powder or liquid concentrate (Tyler, 1993). Preparations that list "aloe" as an ingredient, but not near the top of the ingredient list, probably contain very little aloe (Tyler, 1993). One author (Swanson, 1995) found a product labeled "100% pure aloe vera," with an asterisk referring to small print reading "plus emollients, stabilizers, and preservatives to ensure potency and efficacy."

24.4 Pharmacologic/Toxicologic Effects

24.4.1 Gastrointestinal Effects

See also Sections 25.4.2 and 25.4.3 for additional pertinent information.

Twelve patients with peptic ulcers treated with aloe gel emulsion and "as needed" Pro-Banthine showed a clinical recovery and no relapse 1 yr later (Blitz et al., 1963). The results of this study are controversial, as researchers did not

The affected area was a 4 cm by 8 cm desquamated area that oozed serous fluid. The patient reported severe itching and burning sensations in the area, and had to wear gloves to bed to prevent scratching. The dermatitis had failed treatment with boric acid, phenol in olive oil, ichthyol, a 5% mercurial ointment, and zinc oxide. She was then treated with fresh whole aloe leaf which ceased the burning and itching and resulted in complete skin healing over a period of 5 wk.

Two studies published a few years after this case report supported the observations of Collins and Collins. One investigator demonstrated that 1 g of fresh aloe gel applied for 14 d promoted complete healing in 10 of 28 rats that had received 4000 rads. of x-ray radiation in divided doses. Only 5 rats treated with saline showed marked improvement (Rowe, 1940). A later study found that fresh aloe gel applied twice a day for 3–4 wk improved healing in rats that had received 4000 rads. of x-ray radiation in a single dose. Partially decomposed gel was effective as well, but the fresh rind, aqueous extracts of the dried rind, and an ointment made of dried aloe were not effective. Fresh rind was also used to treat a patient with a chronic x-ray reaction of 7 mo duration, also with negative results (Rowe et al., 1941). Another animal study showed that acemannan wound dressing gel applied to mice that had received 30–47.5 Gy radiation produced a lower peak skin reaction to the radiation than no treatment, K-Y jelly, or Aquaphor ointment (Roberts and Travis, 1995). It was determined that the wound dressing gel was most effective if treatment began immediately after radiation and was continued for at least 2 wk. However, an ointment consisting of 2 drams of powdered aloe, mineral oil, and white petrolatum applied twice daily to irradiated rats for 3 wk did not result in increased rate of healing. In a phase III study, aloe gel from *A. barbadensis* was no more effective than placebo in preventing radiation-induced dermatitis in women receiving breast or chest wall irradiation (Williams et al., 1996). This result prompted a study of no treatment vs aloe gel, which also showed no benefit. Allergic reactions to aloe were reported in three patients. Results of animal studies might not be reproduced in humans because the experimentally produced reactions are of the acute type, rather than the chronic reactions studied in humans (Rowe et al., 1941).

A study in mice exposed to ultraviolet radiation found that aloe vera gel does not act to stimulate DNA repair after exposure nor does it act as a sunscreen; however, it was shown to prevent UV-radiation-induced suppression of immune response for 24 h after sun exposure (Strickland et al., 1994).

Aloe vera cream was shown to improve tissue survival by 24% in the experimental rabbit-ear frostbite model (Miller and Koltai, 1995). Combination with systemic pentoxifylline showed 30% improvement. Some hospitals

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administration of Agiolax® containing 378 µg of "potential" aloe-emodin (free aloe-emodin plus aloe-emodin in the form of dianthrone sennosides and monoanthrone glucosides) and Sennatin® containing 400 µg of "potential" aloeemodin, plasma levels of aloe-emodin were below the limit of detection (0.5 ng/mL). The average rhein C_{max} was 43.8 ng/mL after the first dose of Sennatin® and 49.6 ng/mL after the fourth dose, with T_{max} occurring 11.3 h and 9.7 h after the first and fourth doses, respectively. This time course corresponds to the time required for the sennosides to be transported to the colon, where intestinal flora metabolize the sennosides, releasing free rhein. An additional small peak in plasma concentration was noted 1–3 h after administration, corresponding to absorption of free rhein in the formulation. For Agiolax®, the average C_{max} was 65.1 ng/mL after the first dose, and 81.8 ng/mL after the fourth dose. These peak plasma concentrations occurred 3.4 h and 4.9 h after the first and fourth doses. Maximal rhein concentrations thus appear much earlier after Agiolax® administration compared to Sennatin®, reflecting a higher amount of free rhein in the former preparation (Krumbiegel and Schulz, 1993).

25.5.2 Distribution

Although lactating mothers have reported milk discoloration and laxative effect in breast-fed infants while taking senna (Curry, 1986), 15 mg of sennosides administered to 20 lactating women for 3 d resulted in rhein concentrations of < 10 ng/mL in the breast milk in 94% of the women (Faber, 1988). Breast-fed infants showed no signs of laxative exposure. Data in monkeys reflect these findings (Cameron et al., 1988).

25.5.3 Metabolism/Elimination

Intestinal flora metabolizes the sennosides, releasing free rhein that is subsequently absorbed. The half-life of rhein is approx 7 h (Krumbiegel and Schulz, 1993). Chrysophanic acid is excreted in urine and colors acidic urine yellowish-brown and alkaline urine reddish-violet (Curry, 1986).

25.6 Chemical Analysis

Determination of sennoside content can be achieved spectrophotometrically, or via HPLC (Christ et al, 1978; Lainonen et al., 1988). There is also a USP monograph (USP, 1999) that details the chemical analysis of senna.

25.7 Analysis of Biofluids

Determination of human plasma levels of aloe-emodin and rhein using HPLC with a fluorometric detector has been described (Krumbiegel and Schulz, 1993).

Specific products containing cascara sagrada include concentrated milk of magnesia-cascara (cascara sagrada equivalent to 1 mL of aromatic fluid extract per teaspoon of milk of magnesia), Kondremul® with Cascara (220 mg per teaspoon of mineral oil). Nature's Remedy® Natural Vegetable Laxative Tablets (150 mg of cascara sagrada and 100 mg of aloe in a brown, round, filmcoated tablet with the logo "NR").

26.4 Pharmacologic/Toxicologic Effects

26.4.1 Gastrointestinal Effects

The primary active ingredients of cascara sagrada include cascarosides A, B, C, and D, but barbaloin, chrysaloin, chryophanol, emodin, and aloe-emodin are also present (Tyler, 1994; Anonymous, 1996). The anthrone glucofrangulin is present in the cortex of the European species *Rhamni frangula* (De Witte, 1993). As with senna and aloe constituents, these anthrones produce an active secretion of water and electrolytes within the lumen of the small intestine. In addition, the anthrones inhibit absorption of water and electrolytes from the large intestine. This causes an increase in the volume of bowel contents, and strengthens the dilatation pressure in the intestine to stimulate peristalsis (Anonymous, 1996).

The use of fresh bark, which contains free anthrones, may cause severe vomiting, intestinal cramping, and possibly spasms (Anonymous, 1996). Therefore, the bark requires either storage for at least 1 yr before use or artificial conversion by heat to allow oxidation of the harsh laxative constituents, the emodin glycosides (anthrones), to less active monomeric forms (Tyler, 1994; Anonymous, 1996).

See also Section 25.4.2 for information on effects of chronic laxative use.

26.4.2 Nutritional and Metabolic Effects

See Section 25.4.3.

26.4.3 Carcinogenicity/Mutagenicity/Genotoxicity

2-Hydroxyemodin, ω-hydroxyemodin, and aloe-emodin, metabolites of the cascara sagrada constituents emodin and chrysophanol, appear to be genotoxic (Mueller et al., 1998).

See also a Sections 25.4.1 for additional information on emodin and aloeemodin, and Section 24.4.2 for general information on the association between anthranoid laxative use and colorectal cancer.

Osthole, a coumarin derivative found in the root, and ferulic acid, a volatile oil component, have been shown to inhibit platelet function (Gao and Chen, 1988; Hoult and Paya, 1996). A dong quai root preparation administered intravenously was also shown to prolong prothrombin time in humans (Mei et al., 1991).

27.4.4 Immunologic Effects/Antineoplastic Activity/Antimicrobial Activity

Selective inhibition of experimentally induced immunoglobulin E (IgE) production has been demonstrated with aqueous extracts of dong quai (Sung et al., 1982). Thus, the herb may prove useful in the treatment and/or the prevention of allergic symptoms. However, a polysaccharide isolated from dong quai has been demonstrated to have an immunostimulant effect, and to have an antitumor effect in murine models, (Choy et al., 1994). Thus, it may prove to have efficacy in the treatment of cancer. The coumarins found in dong quai purportedly stimulate macrophages, enhancing phagocytosis. Other immunostimulatory actions include possible B-lymphocyte mitogenic activity, complement activation, interferon production (Walker et al., 1998), and interleukin-2 production (Chen, 1994). Dong quai may have activity against both Gram-negative and Gram-positive bacteria (Walker et al., 1998).

27.4.5 Anti-Inflammatory Activity

Ferulic acid, a phenolic compound of dong quai, was found to exert analgesic and anti-inflammatory activity in both the early and late phases of the inflammatory process in laboratory animals (Ozaki, 1992). The analgesic action is said to be 1.7 times greater than that of aspirin (Walker et al., 1998). Histamine-mediated inflammation is not affected by dong quai (Sung et al., 1982).

27.4.6 Dermatological Effects

Dong quai has been used in the treatment of eczema, neurodermic dermatitis, and psoriasis in Chinese medicine (Huang, 1993). Psoralen and bergapten, two of the furocoumarins found in dong quai, are photoreactive and have the potential to cause severe photodermatitis. Psoralens induce skin melanization in the presence of light and have been employed in the treatment of skin depigmentation and psoriasis (Ivie, 1981). The risk of phototoxicity in humans from ingestion of dong quai has not been characterized.

27.4.7 Carcinogenicity

As noted previously, the furocoumarins, psoralen and bergapten, can induce photosensitization. These agents are also photocarcinogenic, and muta-

Chapter 28—
Cat's Claw

Melissa Dawn Bostic and Melanie Johns Cupp

Uncaria tomentosa, Uncaria guianensis, Uncaria gambir, una de gato, life-giving vine of Peru, samento (Anonymous, 1996)

28.1 History and Traditional Uses

Cat's claw is a twining woody vine with small, sharp thorns at the base of each pair of leaves that help the vine cling to trees, allowing it to grow up to 100 ft high (Giesler and Jones, 1998). These sharp thorns resemble the claws on the paw of a cat, thus the origin of the plant's common name. The genus *Uncaria* is found throughout the tropics, mainly in Asia and South America. It has a long history of use in South America as an antiinflammatory, antirheumatic, and contraceptive. It is also traditionally used to treat gastrointestinal ulcers, tumors, gonorrhea, dysentery, various skin problems, cancers of the female genitourinary tract, and intestinal disorders. Native South Americans also use cat's claw to "cleanse the kidneys" and treat bone pain. An Asian species, *Uncaria gambir,* is used as a tanning agent, an astringent, and an antidiarrheal (Anonymous, 1996). The stem, bark, roots, and leaves are all used medicinally (Giesler and Jones, 1998).

28.2 Current Promoted Uses

A case report of a cancer patient in Austria who underwent a miraculous recovery helped bring attention to cat's claw in the 1970s (Giesler and Jones, 1998). Some European reports that it is useful in the treatment of AIDS when used in combination with zidovudine (AZT), as well as the purported useful-

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