4 Respiratory System

4.1 Cold Syndrome (Flulike Infection)

A cold (common cold, upper respiratory infection, flulike infection) is a benign catarrhal inflammation of the upper and middle respiratory tract caused by a viral infection. It may present as rhinitis, pharyngitis, laryngitis, laryngotracheobronchitis, or less commonly as sinusitis or tracheobronchitis.

4.1.1 Risk Factors

It is widely believed that people are more likely to contract a cold after being exposed to low temperatures – hence the popular term for the disease. Yet experiments under controlled conditions have failed to prove that lowering the body temperature induces colds or even increases susceptibility to a rhinoviral infection. Nevertheless, there is ample evidence to support a link between exposure to cold and a decreased resistance to infection. In one study, for example, the incidence of colds among crew members on modern, air-conditioned cargo ships was almost twice that seen in workers on non-air-conditioned ships of the same line traveling the same route (Schwaar, 1976). The most likely explanation is that workers on the air-conditioned vessels were exposed to greater and more frequent ambient temperature changes, especially in tropical regions.

Experiments have shown that cooling of the feet is associated with a transient, reflex fall in the temperature of the oral, pharyngeal, and tracheal mucosae (Demling et al., 1956; Pollmann, 1987; Schmidt and Kairies, 1932). The partial restriction of blood flow, leading to cooling of the mucous membranes and a local decrease in mucosal resistance, could promote invasion by pathogenic organisms already adherent to the mucosal surfaces (see Sect.4.1.2).

Whether the infection will incite a symptomatic illness or will be successfully combated with no overt symptomatology depends on preexisting nonspecific host defense mechanisms as well as the condition of the mucosa, the mucosal blood flow, the thickness and condition of the epithelium, the thickness and composition of the mucous layer, the local concentration of antibodies and interferon, the commensal flora colonizing the mucosae, the replication factors in the host cells, and the virulence of the pathogenic microorganisms. Every viral infection impairs the mucociliary clearance mechanism of the upper respiratory tract, paving the way for the bacterial

V. Schulz et al., *Rational Phytotherapy*

invasion of areas normally free of bacteria, such as the paranasal sinuses, middle ear, and tracheobronchial tree (Germer, 1985).

4.1.2 Viruses and Host Defenses

All told, there are about a dozen different groups of viruses with more than 150 serotypes that have a demonstrable association with upper respiratory infections. The viruses, that show a predilection for the respiratory mucosa include rhinoviruses, coronaviruses, respiratory syncytial (RS) viruses, adenoviruses, and parainfluenza viruses.

The confinement of rhinoviruses to the surfaces of the upper airways is due in part to the very limited temperature range that is optimum for their growth (Mims, 1976): they proliferate well at 33°C, the temperature of the nasal epithelium, and less well at the normal body temperature of 37°C. In theory, inhaling hot steam (which may contain essential oils, Sect.4.2.2.2) could alter the temperature milieu of the nasal mucosa and make it less hospitable to viruses. There is still no experimental proof of this hypothesis, however.

In evaluating the efficacy of immunostimulants (Chap.9), it is helpful to review the strategy that has emerged in the conflict between cold viruses and specific host immune responses during the course of their joint evolution. There are two mechanisms by which cold viruses attempt to evade host defenses:

- By very rapid proliferation combined with a very short incubation period of 1–2 days. The host organism needs 5–7 days to produce specific antibodies, and usually the infection has already run its course by the time the host has mounted a specific response (Fig.4.1).
- By antigenic variations that constantly generate new viral types, delaying and weakening the primary response of the immune system.

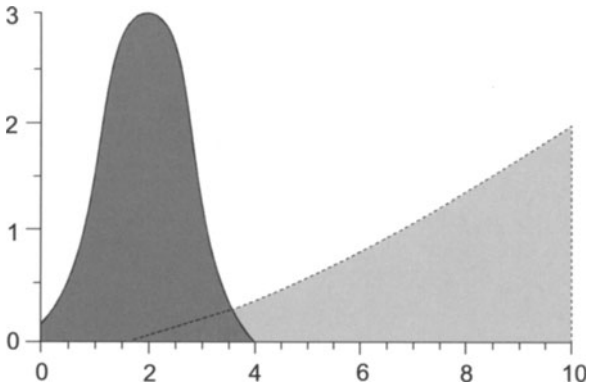

Fig. 4.1. Immune response to an upper respiratory viral infection. Through rapid proliferation, the infecting viruses evade much of the immune response. Dark area: proliferation of viruses; light area: host immune response (antibody formation).

It is likely that interferon plays a major role in the active host defenses against cold viruses. It has been shown that interferon can protect the organism within a few hours after the onset of an infection (Jork, 1979). When a cell is invaded by viruses, it responds by releasing interferon for several hours prior to its own destruction. The interferon from the doomed cell travels to healthy neighboring cells by diffusion, and its interaction with the cells confers absolute protection from viruses for about a 24-h period. It has not yet been proven that this interferon induction mechanism actually checks the cold viruses. There are no known cases in which a congenital defect of interferon production would allow observation of the progress of a cold in a human body unprotected by interferon. Nor are there any suitable animal models in which the effects of interferon could be selectively eliminated for experimental purposes. The mechanism of action of interferon suggests that its anti-viral activity is protective and not curative. Clinical studies with human leukocyte interferon support this view, showing that intranasally applied interferon protects against respiratory viral infection (Merigan et al., 1973). There have been no reports of curative effects.

4.2 General Phytotherapeutic Measures

Herbal remedies can make a significant contribution to the relief of cold symptoms. Remedies should be selected that do not further compromise the mucociliary clearance mechanism of the upper respiratory tract. Disruption of this mechanism by the viral infection, can promote the bacterial invasion of normally germ-free areas (paranasal sinuses, inner ear, tracheal mucosa). If bacterial complications arise, herbal medications can be administered as an adjunct to antibiotic therapy.

4.2.1 Teas for Cold Relief

A proven and recommended home remedy for the initial stages of a cold (scratchy throat, malaise) consists of hot teas and gradient foot baths (starting at about 33°C and increasing the water temperature over a 20-min period according to tolerance) followed by warm bed rest to promote diaphoresis. Teas made from elder flowers, linden flowers, and meadowsweet flowers are particularly recommended for colds. Willow bark is also a component in many tea formulas (see Sect.4.2.1.5).

4.2.1.1 Elder Flowers

Elder flowers are derived from *Sambucus nigra* (Fig.4.2), a deciduous shrub that is widely distributed in Europe and central Asia. The flowering tops, which are flat compound cymes, are gathered, dried, and separated by sifting into individual flowers and peduncles and pedicels. These latter are then discarded. A crude drug of lower quality is made by drying and cutting the

Fig. 4.2. Cymes of *Sambucus nigra*.

flowering tops, without separating the flowers from the peduncles and pedicels. Elder flowers have a faint, distinctive odor, an initially sweet taste, and an acrid aftertaste. It has not been proven that elder flowers contain diaphoretic principles. Elder flower tea is prepared as follows according to the German Standard Registration: pour boiling water (150 Ml) over about 2 teaspoons (3 g) of dried elder flowers, steep for 5 min, and strain; drink 1–2 cups very hot.

4.2.1.2 Linden Flowers

Linden flowers are derived from two species of linden tree that are native to Europe and are often planted ornamentally along city streets: the early blooming summer linden (*Tilia platyphyllos*, Fig.4.3) and the winter linden *(Tilia cordata)*, which blooms about 2 weeks later. The crude drug from both species is made by gathering and drying the fully developed, whole flowering tops including the bracts.

Dried linden flowers have a pleasant, distinctive odor different from that of the fresh blossoms. They have pleasant, faintly sweet, mucilaginous taste.

The pleasant taste is based on the interaction of astringent tannins (about 2%) with mucilage and aromatics. However, the flowers have not been shown to have constituents with a specific diaphoretic action. The diaphoretic effect of linden flower tea (like that of elder flower tea) is based at least partly on the heat of the liquid itself combined with warm bed rest. It should be noted that the response to thermal stimuli follows a marked diurnal pat-

Fig. 4.3. Drooping cymes of the linden (*Tilia platyphyllos*).

tern. Hildebrandt et al. (1954) found that heat applied in the morning had little or no effect, while heat applied in the afternoon and evening induced profuse sweating.

4.2.1.3 Meadowsweet Flowers

The crude drug consists of the dried flowers of *Filipendula ulmaria* (formerly *Spiraea ulmaria*), an herbaceous perennial of the Rosaceae family native to northern Europe. The dried herb consists mostly of brownish yellow petals accompanied by numerous unopened buds. Commercial herb of good quality has a faint odor of methylsalicylate and a bitter, astringent taste. Meadowsweet flowers contain 0.5% flavonol glycosides, mostly quercetin-4′-glucoside (spiraeoside). The astringent taste is due to the presence of tannins. Hexahydroxydiphenic acid esters of glucose have been identified as components of the tannin fraction. The aromatic fraction consists of salicylaldehyde, phenylethyl alcohol, anisaldehyde, and methylsalicylate (methyl ester of salicylic acid).

Meadowsweet flowers are used in the form of a tea infusion, either alone or mixed with other tea herbs, in the supportive therapy of colds. Infusions contain only trace amounts of salicylates, so meadowsweet tea is considered an aromatic remedy rather than a salicylate medication.

4.2.1.4 Willow Bark and Salicylates

The treatment of inflammatory disorders with salicin-containing plant extracts was known to the physicians of ancient Greece. Dioscorides (ca. 50 AD), in his book *De Materia Medica* recommended willow bark preparations as a remedy for gout and other inflammatory joint diseases, suggesting that it be taken "with some pepper and wine." Extracts from parts of the willow tree (*Salix* species) were also used in medieval folk medicine for their pain-relieving and fever-reducing properties. In 1829, the French pharmacist. Leroux isolated the glycoside salicin as the active principle in these extracts. Six years later the German chemist Löwig was the first to synthesize salicylic acid. Because he had extracted the parent compound, salicylaldehyde, from plants of the genus *Spiraea*, he named the product spiric acid. This name later became the root for aspirin (*a-* acetyl, *-spir-* spiric acid, *-in* suffix), first marketed in 1896. Acetylsalicylic acid is better tolerated than salicylic acid and has made salicin-containing plant drugs obsolete.

The following calculation illustrates the problems posed by the continued use of willow bark preparations: A single aspirin dose of at least 500 mg is necessary for effective analgesia. Allowing for differences in molecular weights, 500 mg of aspirin is equivalent to 794 mg of salicin – an amount contained in no less than 88 g of willow bark. Moreover, when the powdered herb is used, salicin is not released quantitatively. As far as orthodox scientific medicine is concerned, willow bark is purely of historical interest today.

Willow bark is indicated in phytotherapy for "febrile diseases, rheumatic complaints, and headache" according to the Commission E monograph of 1992. Accordingly, the herb is a common ingredient in diaphoretic and antirheumatic teas. The source plant, identified simply as willow bark, has not been specifically defined. Various *Salix* species and varieties with a high salicin content are used, most notably *Salix alba* (white willow), *Salix fragilis* (brittle willow), and *Salix purpurea* (purple willow). In addition to salicin, willow bark contains 8–20% tannins. Presumably, the bitter taste and known irritant effect of tannins on the gastric mucosa would limit the use of higher doses in the form of powdered herb or infusions.

4.2.1.5 Tea Formulas

Indications: Febrile upper respiratory infections in which diaphoresis is desired. *Preparation and dosing guidelines:* Pour boiling water (about 150 mL) over 1 tablespoon or 1–2 teaspoons of the dried herb, cover and steep for about 10 min, and strain. Drink one fresh cup several times daily.

Directions to patient: Take 1–2 teaspoonsful per cup (about 150 mL) as an infusion several times daily.

Diaphoretic tea according to DRF (German Prescription Formula Index)

Rx	Elder flowers	
	Linden flowers	aa 25.0
	Mix to make tea	
	Directions (see above)	

Diaphoretic tea according to Meyer Camberg

Rx	Linden flowers	
	Elder flowers	aa 30.0
	Chamomile flowers	40.0
	Mix to make tea	
	Directions (see above)	

Diaphoretic tea in Swiss Pharmacopeia 6

Rx	Linden flowers	40.0
	Elder flowers	30.0
	Peppermint leaves	20.0
	Pilocarpus leaves	10.0
	Mix to make tea	
	Directions (see above)	

Cold-relief tea I according to German Standard Registration

Rx	Linden flowers	30.0
	Elder flowers	30.0
	Meadowsweet flowers	20.0
	Rose hips	20.0
	Mix to make tea	
	Directions (see above)	

Cold-relief tea IV according to German Standard Registration

Rx	Willow bark	35.0
	Elder flowers	30.0
	Thyme	20.0
	Rose hips	5.0
	Licorice root	5.0
	Mallow flowers	5.0
	Mix to make tea	
	Directions (see above)	

Diaphoretic tea according to Suppl. Vol.6 (German Pharmacopeia)

Rx	Willow bark	20.0
	Birch leaves	20.0
	Elder flowers	20.0
	Linden flowers	20.0
	Meadowsweet flowers	10.0
	Chamomile flowers	0.5
	Pilocarpus leaves	0.5
	Mix to make tea	
	Directions (see above)	

4.2.2
Essential Oils

There is much empirical evidence to show that essential plant oils such as peppermint oil and eucalyptus oil are beneficial for subjective complaints involving the nasopharynx, particularly nasal airway obstruction. Surprisingly, rhinomanometric measurements after menthol inhalation showed no objective change in nasal airflow, which seem to contradict general experience. But when a patient with a stuffy nose has the sensation of being able to breathe more easily after inhaling peppermint oil and is able to sleep better after this therapy, the response must be characterized as something more than a placebo effect (Eccles et al., 1988).

Two controlled clinical studies were carried out in a total of 160 patients to test the efficacy and tolerance of a multicomponent essential oil distillate in the treatment of common cold symptoms. Control groups received ethanol solvent or a placebo, and the tests were blinded by adding orange and vanilla aroma to all the test preparations. Five subjective symptoms were scored by the physician during a 7-day treatment period. A steady decline in mean scores was observed for the symptoms of general malaise, headache and body aches, sore throat, and swallowing difficulties. This decline was significantly greater in the oil-treated group than in the controls. The oil distillate and placebo were equivalent in their effects on the symptoms of cough, hoarseness, and runny nose. These descriptive results were confirmed and differentiated by a statistical factor analysis that included local pharyngeal findings in addition to subjective symptoms (Schneider, 1997). Essential oils for topical application are available in various forms: nasal ointments, nosedrops, aerosol inhalants, steam inhalants, or as an ingredient of lozenges, troches, or gargles.

4.2.2.1
Nasal Ointments and Nosedrops

Menthol, camphor, and essential oils are lipophilic substances that, when processed into medicines, can be incorporated only into lipophilic bases. White petroleum jelly or lanolin alcohols are used for nasal ointments, and fatty plant oils are used for nosedrops. As a rule, rhinologic medications should not disrupt the normal protective functions of the nasal mucosa. Hydrophilic preparations are preferable in this regard as they do not disrupt the normal function of the ciliary apparatus. Fatty preparations have two serious disadvantages: they do not mix with the nasal mucous so they do not make adequate contact with the mucosa, and the high viscosity of hydrophobic bases can significantly retard ciliary motion.

The effect of menthol on the nasal mucosa appears to depend on the concentration. Higher concentrations (>5%), which generally are not used, cause local irritation. According to Nöller (1967), the application of menthol to the nasal mucosa elicits a two-phase response: an initial phase lasting about 30 min in which the nasal air passage becomes constricted or even obstructed, followed by a period of improved nasal airflow. Despite the initial, objective increase in mucosal swelling, test subjects consistently report a pleasant,

cooling sensation and a feeling of being able to breath more easily. This purely subjective improvement in rhinitis-associated complaints by menthol application may relate partly to the action of menthol on temperature and pain receptors (Bromm, 1995; Göbel, 1995). Cold, fresh air has a similar effect on nasal stuffiness, most noticeable on walking outdoors from a heated room (Fox, 1977).

The effects of camphor and eucalyptus oil are similar to those of menthol. Detailed investigations (Burrow et al., 1983; Eccles and Jones, 1987, 1988) showed that all three substances stimulate the cold receptors in the nasal mucosa and lead to subjective improvement of complaints, despite the fact that there is no measurable decongestant effect. The absence of this effect is advantageous, however, when one considers that the inflammatory response is a natural process and that suppressing it could delay or prolong recovery.

Interestingly, Bromm et al. (1995) and Göbel et al. (1995) found significant differences between the effects of peppermint oil (main component: menthol) and eucalyptus oil (main component: cineol) on temperature and pain receptors when applied topically to the scalp.

In summary, the local application of peppermint oil and eucalyptus oil can significantly improve subjective nasal stuffiness without compromising natural host defenses. So far, no comparable studies have been done on other essential oils contained in cold remedies. The anhydrous bases used in many formulations (fatty oils, petroleum jellies, paraffins) are incompatible with normal functioning of the ciliary apparatus. Ciliary motion is not hampered by dosage forms that deliver the active ingredient to the mucosa through inhalation (chest rubs, cold balsams, inhalant solutions, nasal sprays) (see Sect.4.2.2.2).

Camphor, menthol, and other medications that contain highly aromatic substances or their essential oils should not be applied to the face and especially the nasal region of infants and children under 2 years of age due to the risk of glottic spasm and respiratory arrest.

4.2.2.2 Inhalation Therapy

Essential oils reach the nasal mucosa in much lower concentration when administered by inhalation than when applied topically. Unfortunately, no studies have yet been published on the effects of inhaled essential oils on the nasal mucosa. It is conceivable, for example, that small amounts of essential oils reaching the mucosa could actually stimulate ciliary motion rather than suppress it. In one clinical study, the inhalation of cineol led to significant improvement in ciliary clearance in patients with chronic obstructive bronchitis (Dorow, 1989). Extrapolating observations on the expectorant effects of inhaled alcohol (Boyd and Sheppard, 1970) on the nasal mucosa suggests that essential oils could stimulate the flow of secretions. The fact that secretions inhibit drying of the nasal mucosa is important because mucosal dryness can seriously disable the ciliary apparatus. For this reason, keeping the mucosae moist is perhaps the most important supportive measure in the management of colds.

Two basic methods are available for administering essential oils by inhalation: steam inhalation and dry inhalation. Steam inhalation is a simple, effective method when applied by any of three techniques:

- simmering chamomile, peppermint leaves, or anise in a pot and inhaling the rising vapors while the head is covered with a towel (head steam bath);
- adding 1 teaspoon of lemon balm spirit to a steam vaporizer; chamomile extracts and other products containing essential oils can also be used;
- taking a hot bath to which a bath salt containing essential oils has been added.

Inhalation devices can be purchased and used for dry inhalation, but a simpler method is to place several drops of peppermint oil on a handkerchief or on the pillow near the head at bedtime and inhale the vapors through the nose. Several breaths should be enough to produce a sensation of easier breathing. As menthol stimulates the cold receptors in the nasal mucosa, it intensifies the patient's sensation and awareness of air streaming through the nose. This is a subjective response that need not be accompanied by an objective change in the nasal air passage (Burrow et al., 1983; Eccles et al., 1987, 1988). Meanwhile, it is a physiological fact that thermoregulation is linked to vasoregulation, i.e., cold stimuli tend to induce vasoconstriction. Therefore, it may be hypothesized that essential oils, by activating cold receptors in the nose, can induce reflex vasoconstriction and thus exert a decongestive effect (Leiber, 1967). Hamann and Bonkowsky (1987) supported this hypothesis by demonstrating objective improvement in the nasal airway.

Risks and contraindications to the topical use of essential oils should be noted. In particular, various mint oils, including peppermint oil, should not be used in the facial region of infants and small children, especially near the nose, due to the risk of inducing reflex respiratory arrest. Spruce needle oil, pine needle oil, and turpentine oil may exacerbate bronchial spasms in asthmatics and in patients with whooping cough.

4.2.2.3 Lozenges, Troches, and Gargles

Lozenges, troches, and gargles are used to soothe local inflammation in the mouth and throat and inhibit the urge to cough.

The cough accompanying a common cold may develop as a result of nasal airway obstruction. As the pharyngeal mucosa dries out, the cough receptors in the throat become more irritable. Even in the absence of objective clinical studies, it is reasonable to assume that lozenges, by promoting the flow of saliva, can keep the mucosa moist and indirectly quiet the cough.

A major ingredient of throat lozenges is sugar, which may be in the form of sucrose, corn syrup, glucose, maltose, fructose, or the substitutes sorbitol and xylitol.

Troches differ from ordinary tablets in their significantly longer dissolving time, achieved by omitting the disintegrants and forming the troches under

much higher pressure. Another difference is that the troche masks the taste of the drug substance itself (e.g., plant mucilage). Besides the sugars, essential oils also serve as flavor correctives and thus perform a dual function.

Gum lozenges derive their name from their content of the raw material gum arabic. The base consists of sugar, gum arabic, and possibly other hydrocolloids. The liquid mass is mixed with solid drug substances, plant extracts, and essential oils and formed by pouring into molds. Essential oils may be the only medicinal substances that are incorporated into cough drops and gum lozenges. The most important essential oils are anise oil, eucalyptus oil, fennel oil, menthol, peppermint oil, thyme oil, and tolu balsam (Table 4.1).

Cough drops and gum lozenges are held in the mouth for 20–30 min while they dissolve. One function of the essential oils in them is to impart a pleasant flavor that stimulates salivation. The increased salivation promotes more frequent reflex swallowing, although voluntary swallowing is also useful for suppressing an imminent urge to cough.

Gargling involves taking a fluid into the mouth without swallowing it and holding it suspended in the throat by forcing air through it while exhaling. Gargling exerts a massaging action that is mostly confined to the pharyngeal ring and largely spares the tonsils. Thus, gargles are indicated for inflammatory diseases of the oropharynx and have two essential functions: to cleanse

Table 4.1. Essential oils commonly used in cough remedies.

Essential oil (Latin name)	Source	Main constituents	Sensory qualities
Anise oil (Anisi aetheroleum)	Ripe fruits of *Pimpinella anisum* (aniseseed)	90% *trans*-Anethole	Spicy odor of anise; sweet taste.
Eucalyptus oil (Eucalypti aetheroleum)	Fresh leaves of *Eucalyptus* species that contain cineol	70% Cineole (=eucalyptol)	Camphor-like odor; taste is initially acrid, then cooling.
Fennel oil (Foeniculi aetheroleum)	Ripe fruits of sweet fennel, *Foeniculum vulgare var, vulgare*	50–70% trans-Anethole, 10–23% fenchone	Odor similar to anise; taste is initially sweet, then becomes bitter and camphor-like.
Peppermint oil (Menthae piperitae aetheroleum)	Flowering tops of *Mentha piperita* (peppermint)	40–55% Menthol, 10% esters of menthol, 10–35% menthone	Pale yellowish liquid with the pleasant, refreshing odor of the peppermint plant; taste is initially acrid, then cooling.
Thyme oil (Thymi aetheroleum)	Fresh flowering tops of *Thymus vulgaris* (thyme)	30–70% Thymol, 3–15% carvacrol	Colorless liquid that gradually turns red; has a phenolic (medicinal) smell and acrid taste.
Tolu balsam (Balsamum tolutanum)	Balsamic resin seeps from the damaged bark *Myroxylon balsamum*	Esters of benzoic and cinnamic acid (not well analyzed)	Doughy, reddish-brown mass with an odor reminiscent of vanilla; has a somewhat bitter, acrid taste.

Two basic methods are available for administering essential oils by inhalation: steam inhalation and dry inhalation. Steam inhalation is a simple, effective method when applied by any of three techniques:

- simmering chamomile, peppermint leaves, or anise in a pot and inhaling the rising vapors while the head is covered with a towel (head steam bath);
- adding 1 teaspoon of lemon balm spirit to a steam vaporizer; chamomile extracts and other products containing essential oils can also be used;
- taking a hot bath to which a bath salt containing essential oils has been added.

Inhalation devices can be purchased and used for dry inhalation, but a simpler method is to place several drops of peppermint oil on a handkerchief or on the pillow near the head at bedtime and inhale the vapors through the nose. Several breaths should be enough to produce a sensation of easier breathing. As menthol stimulates the cold receptors in the nasal mucosa, it intensifies the patient's sensation and awareness of air streaming through the nose. This is a subjective response that need not be accompanied by an objective change in the nasal air passage (Burrow et al., 1983; Eccles et al., 1987, 1988). Meanwhile, it is a physiological fact that thermoregulation is linked to vasoregulation, i.e., cold stimuli tend to induce vasoconstriction. Therefore, it may be hypothesized that essential oils, by activating cold receptors in the nose, can induce reflex vasoconstriction and thus exert a decongestive effect (Leiber, 1967). Hamann and Bonkowsky (1987) supported this hypothesis by demonstrating objective improvement in the nasal airway.

Risks and contraindications to the topical use of essential oils should be noted. In particular, various mint oils, including peppermint oil, should not be used in the facial region of infants and small children, especially near the nose, due to the risk of inducing reflex respiratory arrest. Spruce needle oil, pine needle oil, and turpentine oil may exacerbate bronchial spasms in asthmatics and in patients with whooping cough.

4.2.2.3 Lozenges, Troches, and Gargles

Lozenges, troches, and gargles are used to soothe local inflammation in the mouth and throat and inhibit the urge to cough.

The cough accompanying a common cold may develop as a result of nasal airway obstruction. As the pharyngeal mucosa dries out, the cough receptors in the throat become more irritable. Even in the absence of objective clinical studies, it is reasonable to assume that lozenges, by promoting the flow of saliva, can keep the mucosa moist and indirectly quiet the cough.

A major ingredient of throat lozenges is sugar, which may be in the form of sucrose, corn syrup, glucose, maltose, fructose, or the substitutes sorbitol and xylitol.

Troches differ from ordinary tablets in their significantly longer dissolving time, achieved by omitting the disintegrants and forming the troches under

mucilages in plants can inhibit cough by forming a protective coating that shields the mucosal surface from irritants (Kurz, 1989). This effect is limited to the pharynx, however, since plant mucilages probably are not absorbed as macromolecules and thus cannot reach the tracheobronchial mucosa following oral administration. Mucilaginous herbs have not known adverse effects, although coltsfoot leaves may be contraindicated due to their content of pyrrolizidines (hence the omission of this herb from Table 4.2). While it is true that the content of potentially carcinogenic pyrrolizidine alkaloids is very low, implying a very small risk, it is always possible that products may contain varieties of coltsfoot leaves that have a higher alkaloid content or are mixed with butterbur leaves *(Petasites hybridus),* which contain pyrrolizidine alkaloids. It should be added that since cultivated varieties of coltsfoot have become available, it is no longer necessary to gather the plant in the wild (Kopp et al., 1997). Other available mucilaginous herbs include mallow leaves and Iceland moss. "Immunomodulating" effects have also been ascribed to polysaccharides isolated from Iceland moss (Ingolfsdottir et al., 1998).

The antitussive efficacy and tolerance of an English plantain preparation were tested in an observational study of 593 patients with acute respiratory infections and bronchitis. The average duration of treatment was 10 days, and the patients ranged from 6 to 70 years of age. Therapeutic efficacy was rated by taking 13 separate scores and adding them to get a total score. The total score decreased by 65% during the observation period, and the partial scores for cough symptoms and chest discomfort declined by 70–80%. Only seven of the 593 patients reported adverse reactions, including five cases of diarrhea. None of the patients found the side effects serious enough to discontinue the therapy. Separating the patients into seven different age groups showed an approximately equal response at all age levels (Kraft, 1997).

Besides containing mucilaginous herbs to reduce local irritation, most cough-soothing tea mixtures also contain herbs that serve as odor and flavor correctives. Thus, antitussive teas have basically the same composition as bronchial teas, and both are often referred to collectively as cough and bronchial teas. Formulas for these teas are listed in Sect. 4.4.5.

4.3.2 Essential Oils in Cough Remedies

Throat lozenges and other intraoral cough remedies may contain essential plant oils singly or in combination with other medicinal agents. Anise oil, eucalyptus oil, fennel oil, menthol, peppermint oil, thyme oil, and tolu balsam are commonly used (Table 4.1). The function of the essential oils is to produce a pleasing taste sensation that stimulates the production and secretion of saliva, which in turn activates the swallowing reflex. Voluntary swallowing can also suppress an impending cough. Lozenges and cough drops can aid patients in their efforts at voluntarily controlling the urge to cough (Walther, 1979).

Table 4.2. Mucilaginous herbs used in teas or lozenges to soothe coughs and sore throat.

Herb (Latin name)	Source plant (family)	Constituents	Preparation
Marshmallow root (Althaeae radix)	*Althaea officinalis* (Malvaceae)	5-10% Mucilage	2-5% Infusion or cold-water maceration (1-2 teaspoons/150 mL)
Iceland moss (Lichen islandicus)	*Cetraria ericetorum* and *C.islandica* (Parmeliaceae)	About 50% mucilage of glucan type, including lichenin as the main component	1-2% Infusion (1-2 teaspoons/150 mL)
Mullein flowers (Verbasci flos)	*Verbascum densiflorum* and *V.phlomoides* (Scrophulariaceae)	3% Mucilage of unknown structural type	1-2% Infusion (3-4 teaspoons/150 mL)
Mallow leaf (Malvae folium)	*Malva sylvestris* and *M.neglecta* (Malvaceae)	About 8% mucilage of unknown tertiary structure; arabinose, glucose, galactose, and galacturonic acid also occur as basic components	2-3% Infusion (3-4 teaspoons/150 mL)
Mallow flowers (Malvae flos)	*Malva sylvestris ssp. mauritaniana* (Malvaceae)	About 10% mucilage as in mallow leaves	2% Infusion (2 teaspoons/150 mL)
Plantain (Plantaginis lanceolatae herba)	*Plantago lanceolata* (Plantaginaceae)	About 6% mucilage, including a rhamnogalacturonan, an arabinogalactan, and a glucomannan; iridoid glycrosides including 1-2% aucubin	2% Infusion (3-4 teaspoons/150 mL)

4.3.3 Ephedra

The crude drug consists of the dried, young stems of *Ephedra sinica* and other Ephedra species that contain ephedrine, such as *E. equisetina* and *E. intermedia*. Ephedra species are herbaceous perennials (family Ephedraceae) that grow to a height of 1 m and resemble horsetail. Ephedra tops contain up to 2% alkaloids with (–) ephedrine as the principal alkaloid.

Preparations made from ephedra stems exert the peripheral vasoconstricting, bronchodilating, and central stimulatory actions of ephedrine. Whole herb extracts reportedly have a less pronounced hypertensive action than pure (–)-ephedrine (*Brit Herb Pharmacopoeia* 1983, p 83).

Coughing induced by stimulation of the tracheal or bronchial mucosa in anesthetized animals is suppressed by ephedra extracts (Hosoya, 1985) much as it is suppressed by ephedrine itself (0.01 mg/kg b.w.). This suppression of the cough reflex results from the bronchodilating action of ephedrine, although a pronounced antitussive effect is obtained even in nonasthmatic subjects (Aviado, 1972). One disadvantage is that ephedrine lacks an expec-

torant action and has even been shown to reduce airway secretions in laboratory animals.

The indications for ephedra preparations are mild forms of airway disease, especially those resulting from spastic disorders. A single dose of ephedra extract should deliver 15–30 mg of alkaloids, calculated as ephedrine. The maximum daily dose for adults is 300 mg total alkaloids calculated as ephedrine. The maximum daily dose for children is 2 mg/kg body weight. Today ephedrine is usually administered in pure form rather than as one component of a whole plant extract. Potential adverse effects are palpitations, blood pressure elevation, sleeplessness, anorexia, and urinary difficulties.

Conditions that would contraindicate ephedra preparations or limit their use are hypertension, thyrotoxicosis, pheochromocytoma, narrow-angle glaucoma, and prostatic adenoma with urinary retention.

In the United States, the central-nervous-system stimulation effects of ephedra preparations are often potentiated by the addition of caffeine-containing botanicals. Such combination products have frequently been used on a chronic basis to promote weight loss or to enhance athletic performance. Very high doses of these products have also been employed, especially by teenagers, as euphoriants or intoxicants, so-called legal highs. It is estimated that 15 billion doses of ephedra-containing products were consumed in the United States during 1998.

As of 1999, the Food and Drug Administration (FDA) had recorded more than 2000 adverse events attributed to ephedra, but these were not evaluated as to degree of seriousness. All events resulting in illness or injury apparently associated with an ephedra product were listed. Of these, 29 deaths supposedly associated with ephedra or ephedrine were included. The validity of these figures has recently been questioned by a Congressional committee (Skinner, 1999).

In 1995 and 1996, the FDA held two meetings of an expert advisory group to make recommendations regarding the continued marketability of ephedra products. As a result of these deliberations, the agency proposed, in 1997, the following rules: prohibit the marketing of dietary supplements (non-drug products) containing 8 mg or more of ephedrine [sic] alkaloids per serving with a maximum daily dosage of 24 mg; require label statements instructing consumers not to use the product for more than 7 days; prohibit the use of ephedrine alkaloids with caffeine or herbs containing caffeine; prohibit labeling claims that require long-term intake to achieve the purported effect; require a statement that "taking more than the recommended serving may result in heart attack, stroke, seizure, or death." Because of industry objections, these rules were never implemented. Whether they ever will be remains in doubt (Huck, 1999). In the meantime, several states have imposed restrictions on ephedra sales.

There are no laws or regulations in the United States that provide for the quality assurance of any herbal product. These are technically sold not as drugs but as dietary supplements, a food category. This creates problems that become especially severe with potent herbs such as ephedra because the consumer cannot rely upon the label to reflect accurately the activity of the product.

Several analytical studies have shown that wide variations often exist between labeled and actual amounts of acive constituents. In the case of ephedra preparations, total alkaloid content has been shown to vary between 0% to more than 150% of label claim. If herbs were regulated as drugs are in the U.S., such discrepancies would almost certainly result in the products being designated as misbranded and would necessitate their recall by the manufacturer.

Because the health problems associated with long-term consumption of ephedra preparations have received widespread publicity, many persons are reluctant to utilize products containing it. Consequently, some manufacturers have substituted *Sida cordifolia* (family Malvaceae), an ancient Ayurvedic remedy, for ephedra. Its seeds contain about 0.3% of an alkaloid mixture of which ephedrine is the principal constituent. So, the activity is exxentially the same as ephedra, but this is not recognized by the uninformed consumer.

There is also concern in the U.S. that clandestine chemists may use ephedra as a starting material for the synthesis of illegal designer drugs, such as methamphetamine. Although possible, it is not likely because of the difficulty in separating the product from accompanying plant material. A much more likely starting material is pseudoephedrine which is readily available in pure form. Large-scale sales of that alkaloid are now monitored by the Drug Enforcement Agency (Maltz, 1996).

4.4 Herbal Expectorants

4.4.1 Mechanisms of Action

Often in practical use a strict distinction cannot be drawn between antitussives (Sect.4.3) and expectorants. Mucus in the bronchi stimulates soughing, so expectorants produce an indirect antitussive effect. Conversely, vigorous coughing intensifies the secretion of mucus, so antitussives can reduce excess mucus production (Kurz, 1989). According to their pharmacologic definition, expectorants are agents that can influence the consistency, formation, and transport of bronchial secretions.

Herbal expectorants have been used on an empirical basis for centuries. They are believed to act by three mechanisms: a reduction of mucus viscosity (owing partly to the water content of tea preparations), a gastropulmonary reflex mechanism, and the liquefaction of secretions, which is accomplished mainly by direct effects of the essential oils on the bronchial glands (Ziment, 1985).

4.4.1.1 Reduction of Mucus Viscosity by Water

The ability of expectorants to reduce mucus viscosity is due at least partly to the fluid that is ingested with certain preparations. This particularly applies to many bronchial teas, 3 or more liters of which may be consumed daily in

a palatable form without causing undesired pharmacologic effects (like those of caffeine in caffeinated beverages).

The quantity of water administered by inhalation is very small by comparison. With a standard regimen of 20 min of inhalation 3 or 4 times daily, water aerosols should have no impact on mucociliary clearance. Thus, inhaled water would appear ineffectual for hydrating airway secretions or altering their rheologic properties (Medici, 1980).

Although animal experiments have failed to confirm the efficacy of increased water intake in liquefying airway secretions (Irwin et al., 1977), this is widely acknowledged to be one of the most important benefits of expectorant medications (Nolte, 1980; Dorow, 1984; Endres and Ferlinz, 1988).

4.4.1.2 Neural Mechanism Based on the Gastropulmonary Reflex

It is known that irritation of the upper digestive tract induces vomiting as afferent impulses are relayed to the vomiting center from visceral sensory fibers in the gastric mucosa. Vomiting starts with increased salivation and a feeling of nausea. Reflex expectorants are administered in a dose sufficient to induce a preliminary stage in which a thin, watery secretion is produced in the goblet cells and in the bronchial glands.

All substances that induce vomiting when taken in large amounts can act as expectorants when taken in a smaller dose (1/10 of the emetic dose). The prototype for this drug action is emetine, an alkaloid obtained from ipecac root. The saponin-containing herbs may have a comparable mechanism of action (see Sect.4.4.2). Reflex expectorants include acrid-tasting spices that irritate the gastric mucosa and induce nausea when taken in large doses. Spices such as long pepper, cubeb, ginger, and curcuma are common ingredients of cough remedies in traditional Indian and Chinese medicine. Onions and garlic, cooked in milk, are used in European folk medicine as mucolytic agents to help clear congested airways.

4.4.1.3 Liquefaction of Secretions by Direct Action on the Bronchial Glands

Bronchomucotropic agents (Ziment, 1985) directly stimulate the bronchial glands and increase their activity. These agents may be inhaled externally or administered orally for subsequent excretion (and action) via the bronchial tree. Essential oils and aromatic herbs have bronchomucotropic properties.

A study of the direct actions of the terpene preparation Ozothin (see Sect.4.4.3) on the bronchial glands showed that this agent selectively stimulates the serous glands but depresses the function of the mucous glands. The net result of these actions is a liquefaction of bronchial secretions (Lorenz and Ferlinz, 1985).

Ethyl alcohol is an effective expectorant when inhaled in low concentrations (Boyd and Sheppard, 1969) and is classified as a mucotropic agent.

Like the essential oils, alcohol acts as a local irritant, but its overall action is probably based partly on its surfactant properties, i.e., its ability to alter surface tension.

A solution of essential oils in ethanol, rather than essential oils alone, can be added to a steam vaporizer in order to utilize the expectorant effects of both substances (e.g., a tablespoon of citronella spirit or the compound spirit described in German Pharmacopeia 6). The ethanol dose in these spirits, at about 4 g, is too small to produce central alcohol effects in adults.

4.4.2 Saponin-Containing Herbs

Saponins are glycosidic plant constituents with a terpenoid agylcone component. They are like detergents in their tendency to form a durable foam when shaken with water. Saponins have an acrid and/or bitter taste and are irritating to mucous membranes. In finely powdered form, saponins cause sneezing, eye inflammation, and lacrimation. In addition to their surfactant properties, saponins alter the permeability of all biologic membranes. Higher concentrations entering the blood or tissues have a generally toxic effect on cells. Due to their polar nature, saponins are only sparingly absorbed from the gastrointestinal tract so they usually produce no systemic effects when administered orally. Their expectorant action is thought to be mediated by the gastric mucosa, which reflexly stimulates mucous glands in the bronchi via parasympathetic sensory pathways. Higher doses of saponin-containing expectorants cause stomach upset, nausea, and vomiting.

The saponin-containing herbs that are most commonly used as expectorants are listed in Table 4.3. The list does not include licorice root. The glycyrrhizin contained in licorice root is often classified as a saponin, and its chemical composition would support this. But licorice does not have all the biologic and pharmacologic properties that are characteristic of saponins. As a result, licorice root and its preparations are not included in the class of reflex expectorants. This mechanism by which glycyrrhizin exerts its expectorant action requires further study. In any case, licorice and licorice extracts are useful as flavor correctives in teas and cough syrups.

Some combination products contain preparations from *Gypsophila* species as their saponin component. These plants are perennial herbs or subshrubs that prefer a dry climate (e.g., tall gypsophyll). Gypsophila-derived saponin is a complex chemical mixture. It is the standard saponin used to determine the hemolytic index as described in pharmacy texts.

Small amounts of saponins are also contained in grindelia, a tincture of which is a component of several combination products. The aerial parts of *Grindelia* species, native to the southwestern U.S., are gathered during the flowering season and dried to make the crude drug, which also contains 0.3% volatile oil. Grindelia is believed to act as an expectorant, although relevant pharmacologic studies have not been performed. The only saponin-containing herb that is widely prescribed as a single-herb preparation (see Table A2) is ivy (*Hedera helix*, Fig. 4.4). The 1988 Commission E monograph states that ivy leaves are for use in the treatment of catarrhal disorders of the

Table 4.3. Saponin-containing herbs that are used as expectorants.

Herb (Latin name)	Source plant (family)	Type of saponin	Remarks
Ivy leaf (Hederae folium)	*Hedera helix* (Araliaceae)	Neutral bis-desmosides, termed hederacosides, with oleanolic and 28-hydroxyoleanolic acid as aglycone; also hederin type of monodesmosides; total saponin content 3-6%	Not used as an infusion. Extracts used in drug products, with daily dose equal to 0.3 g of crude drug. Fresh leaves can cause skin irritation; the contact allergen is falcarinol, an aliphatic C_{17} alcohol with acetylene bonds
Primula root (Primulae radix)	*Primula veris* and/or *P.elatior* (Primulaceae)	Monodesmosidic triterpene saponins (5-10%), including the principal saponin primulic acid A	Used as an infusion or tincture, with daily dose equal to 1 g of crude drug.
Soap bark (Quillajae cortex)	*Quillaja saponaria* (Rosaceae)	Triterpene saponins (10%)	Single dose of 0.2 g of crude drug corresponds to 10 g of decoction (2%) or 1.0 g of tincture
Senega snakeroot (Polygalae radix)	*Polygala senega* (Polygalaceae)	6-10% Bisdesmosidic triterpene saponins	Single dose of 1 g of crude drug corresponds to 20 g of decoction (5%) or 2.5 g of tincture (1:5)

Fig. 4.4. Ivy (*Hedera helix*).

upper respiratory tract and in the symptomatic treatment of chronic inflammatory bronchial diseases. The average recommended daily dose is 0.3 g of the dried herb or an equivalent dose of extract. Four controlled studies in patients with chronic obstructive bronchitis have demonstrated the therapeutic efficacy of a water-ethanol extract (30% ethanol, herb-to-extract ratio 5–7:1, brand name Prospan) in adults (Meyer-Wegener et al., 1993) as well as children (Gulyas et al., 1997; Mansfeld et al., 1997, 1998). One of these studies was a prospective double-blind study in 99 women and men 25–70 years of age diagnosed with chronic obstructive bronchitis. Four week's treatment with a daily dose of approximately 60 mg of ivy extract (equivalent to about 400 mg of the crude drug) was compared with 90 mg of ambroxol. The key parameters for rating therapeutic efficacy were the spirometrically measured vital capacity and one-second forced expiratory volume, chest auscultation, and a global efficacy rating by the physician. The two pharmacotherapies were rated as equally effective in all test criteria, with no statistically significant differences. Seven patients taking the ivy extract and six patients taking ambroxol reported adverse reactions, but only one patient (taking ambroxol) had to drop out because of side effects (Meyer-Wegener et al., 1993).

A water-ethanol solution of the same extract was tested in a randomized double-blind placebo-controlled crossover study in 24 children 4–12 years of age with bronchial asthma. The protocol consisted of treatment periods of 3 days alternating with washout periods of 3–5 days. The daily dose of ivy extract was 35 mg, equivalent to 210 mg of the crude drug. All medications were taken and all measurements were performed at the same time of day. The main test parameter was airway resistance. Secondary parameters were intrathoracic gas volume, residual volume, and several other spirometric parameters. Children treated with the ivy extract showed statistically significant and clinically relevant improvements, especially in airway resistance and intrathoracic gas volume, compared with the placebo-treated controls (Mansfeld et al., 1998).

The same group of authors performed another randomized crossover study in 26 hospitalized children 5–11 years of age comparing the efficacy of the alcohol-based solution taken orally and the extract administered in suppository form. The orally and rectally administered extracts were equivalent in their effects when given in a dose ratio of approximately 1:5 (Mansfeld et al., 1997). Another double-blind crossover study investigated the dose equivalence of an alcohol-free juice preparation and the water-ethanol solution in 25 children 10–16 years of age. Surprisingly, it was found that the water-ethanol solution was approximately 2.5 times more effective than the alcohol-free juice preparation (Gulyas et al., 1997). In an observational study of 113 children of both sexes, the juice preparation produced no adverse effects when taken over a period of 3–4 weeks (Lässig et al., 1996).

In a controlled multicenter study, 761 private physicians tested a combination product containing 60 mg of cowslip root *(Primula veris)* extract and 160 mg of thyme *(Thymus vulgaris)* extract in a total of 7783 patients with acute bronchitis. More than 2000 of the patients were children under 12 years of age. A total of 4629 patients took the herbal combination product for 10

days, and 3154 patients took reference drugs, mainly *N*-acetylcysteine and ambroxol, for an equal period. Using a standard rating scale, the physicians and the patients rated the signs and symptoms at the beginning and end of the 10-day treatment period. Statistical analysis showed that the herbal combination product was marginally better than *N*-acetylcysteine and ambroxol in its efficacy and was significantly better in its tolerance. This positive outcome occurred equally in the subgroups of children and adults (Ernst et al., 1997).

4.4.3 Essential Oils as Expectorants

The principal essential oils that are used as expectorants are reviewed in Table 4.4. These oils cannot be strictly differentiated from essential oils that are used as antitussives (Table 4.1). The essential oils are well absorbed after oral administration and are partially excreted via the lungs. As the exhaled molecules pass through the bronchial tree, they can act on the bronchial mucosa to stimulate the serous glandular cells and ciliated epithelium.

Irritation of the mucous membranes is a property shared by all essential oils. Even trace amounts that have little or no detectable odor can exert demonstrable local effects on mucosal surfaces (Boyd and Sheppard, 1970a). The specificity of the effects of essential oils is demonstrated by studies with Ozothin, a turpentine oil that has been purified with oxidants. Chemically,

Table 4.4. Essential oils that are used as expectorants in inhalants, cold ointments, or capsules. See also Table 4.1.

Essential oil (Latin name)	Source plant (family)	Main constituents	Remarks
Spruce-needle oil (Piceae aetheroleum)	*Pinus exelsa*, *Abies species* (Pinaceae)	20-40% Bornyl acetate along with α- and β-pinene and β-phellandrene	
Cajuput oil (Cajuputi aetheroleum rectificatum)	Leaves of *Melaleuca* species (Myrtaceae)	65% Cineole (=eucalyptol)	Reminiscent of eucalyptus oil (see Table 4.1)
Pine-needle oil (Pini aetheroleum)	*Pinus silvestris* (Pinaceae)	80% Monoterpene hydrocarbons, including α-pinene and 3-carene	
Myrtol	Exact botanical origin unknown	Mainly cineole (=eucalyptol), α-pinene and limonene	
Niaouli oil	*Melaleuca viridiflora* (Myrtaceae)	Like cajuput oil; principal constituent cineole (=eucalyptol)	
Rectified turpentine oil (Terebinthinae aether oleum rectificatum)	*Pinus palustris* and other *P.*species (Pinaceae)	90% Monoterpene hydrocarbons: α- and β-pinene	Starting material is the tree trunk gum turpentine.
Citronella oil (Citronellae aetheroleum)	*Cymbopogon winterianus* and *C.nardus* (Poaceae)	Monoterpene alcohols such as geraniol, nerol, and corresponding aldehydes such as citral and citronellal	Often sold under the name of lemon grass oil or Indian grass oil.

Ozothin represents a mixture of monoterpene alcohols, aldehydes, and ketones, most notably verbenol, verbenone, myrtenol, myrtenal, and pinocarveol. Its actions can be summarized as follows:

- stimulates serous bronchial gland function and suppresses mucous glandular cell activity following i.v. administration (Bauer, 1973);
- reduces surface tension (surfactant effect) (Zänker and Blümel, 1983);
- improves mucociliary activity and tracheobronchial clearance in concentrations of 10^{-7} g/mL or higher (Iravani, 1972).

Controlled clinical studies have been done to test the efficacy of certain medicinal products containing essential oils. A placebo-controlled double-blind study was done in patients with chronic obstructive bronchitis who were being managed with theophylline and a beta-adrenergic drug. This regimen was supplemented by treatment with an ointment containing menthol, camphor, eucalyptus oil, and conifer oil as its active ingredients. Statistical analysis showed that this regimen was significantly better than a placebo-supplemented regimen in terms of objective parameters (pulmonary function, quantify of sputum) as well as subjective parameters (cough, breathing difficulties, lung sounds) (Linsenmann and Swoboda, 1986). Placebo-controlled double-blind studies in patients with acute tracheobronchitis showed improved mucolysis following the administration of essential oils in capsule form (containing anethole, cineole, and dwarf pine needle oil) compared with a placebo (Stafunsky et al., 1989; Linsemann et al., 1989). Another study in patients with chronic obstructive airway disease showed that an orally administered combination of pine oil, lemon oil, and cineole was effective as ambroxol in increasing mucociliary clearance (Dorow et al., 1987).

When stimulus-response relationships are present, ordinary dose-response relationships hold only within a limited range. The expectorant action of essential oils is subject to a marked reversal effect in which very low doses are mucotropic (stimulate bronchial gland activity) while higher doses are inhibitory. This was first shown experimentally for citral and geraniol (Boyd and Sheppard, 1970.

Adverse effects and allergic reactions (type IV) are known to occur with essential oils. Inhalation can provoke bronchospasms, particularly in children and asthmatics. This danger can be reduced by placing the vaporizer farther from the patient and gradually increasing the inhaled concentration by moving the device progressively closer (Kurz, 1989).

Besides the familiar essential oil preparations listed in Tables 4.1 and 4.4, saxifrage root (*Pimpinella saxifraga*) is also considered an aromatic herb, and its preparations are found in several combination products. It contains 0.4–0.6% volatile oil with isoeugenol esters as a characteristic component.

4.4.3.1 Dosage Forms

Bronchial teas. There is no strict dividing line between antitussive teas and bronchial teas (see Sect.4.3.1). Also, the efficacy of antitussive and bronchial teas is based only in part on specific pharmacodynamic actions. An essential

part of any expectorant therapy is increased fluid intake; this measure, plus humidification of the air, helps keep bronchial secretions in a relatively nonviscid state and prevents drying of the mucous membranes. About 2–3 L of water should be consumed daily, except in cases where fluid intake is restricted due to heart failure or impaired renal function.

Oral dosage forms. Coated tablet, capsules, and drops allow for accurate dosing. They also permit the use of extracts that contain nonvolatile components.

Inhalations. These agents are administered by steam inhalation. The simplest method is to place about 1 L of water in a pan, bring it to a boil, let it cool slightly, and add the prescribed amount of agent to the hot water. The patient bends over the vessel and inhales the rising vapors as deeply as possible. A towel should be draped over the head and vessel to ensure that the essential oils in the inhalation do not evaporate too quickly. Since the water temperature falls rapidly, an adequate amount of steam is obtained only initially. Commercial steam vaporizers will keep the inhalation solution at a high temperature for a longer period.

Physically, the steam consists of water-saturated air mixed with essential oil vapors and possibly alcohol vapors, depending on the temperature of the medium. The gradient between the temperature in the water vessel and the temperature of the body will cause part of the rising steam to condense. The concentrations of water vapor and volatile medicinal agents (essential oils, ethyl alcohol) that reach the airways depend on the local partial vapor pressure at body temperature, with lower concentrations occurring in the lower respiratory tract. This is probably not a disadvantage with essential oils, however, since low concentrations exert a stronger mucotropic action than higher ones (the "reversal effect"). Boyd and Sheppard (1970) note that the rising vapors should have a barely perceptible odor.

Percutaneous application. Most medications classified as chest rubs or cold balsams are ointments; some are oil- or paraffin-base solutions that incorporate essential oils. The designated amount is applied to the skin of the chest and back. As lipophilic compounds, portions of the oils penetrate the skin, enter the circulation, and reach the bronchial mucosa. As unknown percentage evaporates on the warm skin and is inhaled.

Bath salts and oils. Essential oils are available in several forms for adding to bathwater: bath salts, bath oils, and essences (i.e., essential oils without other additives). The very large surface area of exposed skin allows for more extensive absorption and distribution than chest rubs. Portions of the absorbed essential oil components are excreted via the lungs, producing an expectorant action in the bronchial tree. The percutaneously absorbed and exhaled doses are further supplemented by the inhalation of essential oils from the air over the bathwater.

Observations in aromatherapy (Jackson, 1989) are consistent with the dose-response relationship found in experimental animals (Boyd and Sheppard, 1970) and support the value of moderate dosing. Just 7–9 drops of essential oil, equivalent to about 150–200 mg, is recommended for a whole bath consisting of about 30 L water.

Favorite essential bath oils for respiratory tract diseases are eucalyptus oil, pine needle oil, spruce needle oil, thyme oil, and cypress oil.

4.4.3.2 Cineole (Eucalyptol)

Approximately 70% of eucalyptus oil is cineole (Table 4.1). Cineole is an ambiguous term, referring either to the pure chemical substance that is isolated from cineole-containing eucalyptus oils by fractional crystallization or distillation, or to the commercial medication known as cineol. The pharmaceutical product has a cineole content of only 80–90% and is produced simply by treating eucalyptus oils with lye. This yields a clear, colorless liquid with a camphor-like odor and a pungent, cooling taste.

Cineole has antispasmodic, secretagogic, secretolytic, rubefacient (antimicrobial), and fungicidal properties. Experiments with cineole inhalation in rabbits showed that it exerts a surfactant-like action by reducing surface tension (Zänker et al., 1984).

Römmelt et al. (1988) investigated the pharmacokinetics of 1,8-cineole following 10 min exposure to a terpene-containing ointment (9.17% cineole) administered by steam inhalation. The C_{max} in the venous blood following alveolar absorption was 200 ng/mL; the half-life was 35.8 min. Concentrations as low as 10 ng/mL were associated with an increase in ciliary frequency.

As for adverse effects, rare instances of stomach upset have been reported following the internal use of cineole, and external use occasionally causes hypersensitivity reactions of the skin. The LD_{50} in rats is 3480 mg/kg b.w. Cineole has a wide therapeutic range, and there have been almost no reports of cineole toxicity. Patel and Wiggins (1980) reported one case of medicinal poisoning with eucalyptus oil.

The usual therapeutic dose for adult patients is 0.3–0.6 g cineole daily.

4.4.3.3 Myrtol

Myrtol, an essential oil with a pleasant odor reminiscent of turpentine oil and eucalyptus oil, is a component of a drug product that has the following manufacturer-listed ingredients: not less than 25% lemonene, 25% cineole, and 6.7% (+)-α-pinene.

There is no information in the pharmaceutical literature on the botanical origin of the ingredients.

The chemical composition of myrtol suggests that its actions, adverse effects, and toxicologic properties are very similar to those of cineole and eucalyptus oil. No data are available on the pharmacokinetics of myrtol after oral administration. It is reasonable to assume that the monoterpenes of myrtol are rapidly absorbed from the gastrointestinal tract and that maximum blood levels are reached in 1–2 h. Some of the absorbed cineole and other monoterpenes are excreted via the lungs, a pathway that again brings them into contact with the bronchial mucosa.

4.4.3.4
Anise Oil and Anethole

Anise oil as described in German Pharmacopeia 9 is the essential oil obtained from the ripe fruits (often called seeds) of *Pimpinella anisum* (family Apiaceae, Fig.4.5) or *Illicium verum* (family Illiciaceae). The principal component (80–90%) of anise oil is anethole which is obtained from anise oil by freezing.

Anise oil is a clear, colorless liquid with a spicy odor and a sweet, aromatic taste that solidifies to a white crystalline mass when refrigerated. Anethole forms white crystals that melt at 20–22°C.

The expectorant effects of anise oil and anethole are presumably based on their ability to stimulate the ciliary activity of the bronchial epithelium. Moreover, antispasmodic and antibacterial actions have been demonstrated in vitro.

Anethole is rapidly absorbed from the gastrointestinal tract of healthy subjects and is just as rapidly eliminated with the urine (54–69%) and expired

Fig. 4.5. Anise (*Pimpinella anisum*).

air (13–17%). Its principal metabolite is 4-methoxyhippuric acid (approximately 56%); additional metabolites are 4-methoxybenzoic acid and three other metabolites that have yet to be identified (Caldwell and Sutton, 1988; Sangister et al., 1987). Changing the dose does not alter the pattern of metabolite distribution in humans, contrary to findings in the mouse and rat (Sangister et al., 1984). These results do not support the assumption based on animal experiments that higher doses of anethole in humans could block the enzyme system responsible for its degradation.

Adverse effects consist of occasional allergic skin reactions (Opdyke, 1973). The LD_{50} in different animal species (rat, mouse, guinea pig) ranges from 2090 to 3050 mg/kg b.w. for trans-anethole. The *cis* derivative is at least 15 times more toxic. At present there are no regulations specifying a maximum allowable content of *cis*-anethole in anethole or anise oil. Animal studies have refuted speculations about a carcinogenic effect (Drinkwater et al., 1976; Miller et al., 1983; Newberne et al., 1989; Truhaut et al., 1989).

The indications for the internal and external use of anise oil and anethole are catarrhal diseases of the upper respiratory tract. The recommended and single oral dose is 0.1 g (4 drops) for anise oil. It should be taken in diluted form.

4.4.4 Licorice Root

Licorice root consists of the dried rhizome and roots of *Glycyrrhiza glabra* (family Fabaceae). The genus name *Glycyrrhiza* is derived from the ancient Greek word for licorice (Gr. Glykos sweet + rhiza root), which was later latinized to liquiritia and eventually modified to licorice.

The cut, dried herb consists of rough, fibrous, yellowish segments having a somewhat vermiform appearance. Licorice has a faint but characteristic odor and a sweet taste. It contains at least 4% glycyrrhizin, which is a mixture of the potassium and calcium salts of glycyrrhizic acid.

Licorice root and its preparations are proven expectorants that have mucolytic and secretagogic properties. It is also postulated that glycyrrhizin, like saponins and emetine, increases the bronchial secretion and transport of mucus via a reflex pathway originating in the stomach (Schmid, 1983). This mechanism presumes that glycyrrhizin causes local irritation of the mucosa, but glycyrrhizin does not appear to have this property; indeed, its value in the treatment of peptic ulcers is based on its soothing, demulcent effect on the gastric mucosa.

Perhaps licorice root preparations are more correctly regarded as antitussive agents rather than mycolytics, comparable to the sugar in cough syrups and cough drops. Sweet-tasting substances can influence the urge to cough, and voluntary swallowing can suppress an impending cough. Syrups, teas sweetened with honey or sugar, sweet cough syrups, and cough drops stimulate salivation and elicit more frequent reflex swallowing (Walther, 1979). The indirect antitussive effect of licorice root preparations may involve a degree of central suppression. Glycyrrhizic acid produced an antitussive action comparable to that of codeine when administered to laboratory ani-

mals (Anderson and Smith, 1961); further studies are needed to confirm this finding.

Licorice root preparations are useful as flavor correctives in medications that contain bad-tasting or nausea-inducing drug substances. The sweet taste of licorice is due entirely to glycyrrhizin, not to its aglycone, glycyrrhizic acid. Glycyrrhizin is 50 times sweeter than sugar (f_{sac}=50) meaning that the concentration of an aqueous glycyrrhizin solution is equivalent in sweetness to a solution containing 50 times that amount of sugar.

Adverse effects are not a problem when licorice is properly used. Overdosing can lead to a toxic condition that is clinically similar to primary aldosteronism. Martindale (1982) described the case of a 53-year-old man who had eaten 700 g of licorice in one week and developed aldosteronism manifested by cardiac complaints, hypertension, edema, headache, and general weakness. Another man was hospitalized for similar complaints after eating 70 g of licorice sticks daily for a period of two months.

The usual therapeutic dose is 1–2 g of dried licorice root, or equivalent amounts of its preparations, taken three times daily.

4.4.5 Suggested Formulations

Ipecac novum infusion according to DRF (German Prescription Formula Index)

Rx	Ipecac root infusion	0.5:170.0
	Ammonium chloride	5.0
	Anise spirit (5%)	5.0
	Marshmallow syrup	to make 200.0
	Directions: Take 1 tablespoonful every 2 h. Shake before using.	

Explanations: Ipecac root is emetic when given in the proper dosage, owing to its content of the alkaloids emetine and cephaeline. The expectorant dose is one-fifth of the emetic dose. Ipecac, like ammonium chloride, belongs tot he class of reflex bronchomucolytics.

Ammonium chloride is a colorless, odorless, crystalline substance with a strong salty taste. The ammonium ion has been recognized as an expectorant for centuries. Presumably it increases bronchial mucus secretion reflexly via the vagus nerve by irritating the gastric mucosa. Marshmallow syrup functions mainly as a flavor corrective. Some effort may be needed to find a pharmacist who is willing to compound a complex individual prescription. An alternative is to prescribe ipecac root in the form of a tincture.

Rx	Ipecac tincture	20.0 mL
	Directions: Take 10–20 drops with some liquid 3–5 times daily.	

Tea Formulas

Indications: bronchitis symptoms and catarrhal diseases of the upper respiratory tract.

Preparation and directions: Pour boiling water (about 150 mL) over 1 tablespoon of tea, cover and steep for about 10 min, and pass through a tea

strainer. Drink one cup of freshly brewed tea slowly several times daily, preferably while the tea is still hot.

Antitussive tea according to German Standard Registration

Rx	Marshmallow root	25.0
	Fennelseed	10.0
	Iceland moss	10.0
	English plantain	15.0
	Licorice root	10.0
	Thyme	30.0
	Directions (see above)	

Chest tea according to German Pharmacopeia 6*)

Rx	Marshmallow root	40.0
	Marshmallow leaves	20.0
	Licorice root	15.0
	Mullein flowers	10.0
	Violet root	5.0
	Aniseseed, crushed	10.0
	Directions (see above)	

Chest tea according to Swiss Pharmacopeia 6*)

Rx	Marshmallow root	10.0
	Licorice root	10.0
	Marshmallow leaves	10.0
	Mullein flowers	15.0
	Cornflower	5.0
	Helichrysum flowers	10.0
	Mallow flowers	10.0
	Aniseseed, crushed	15.0
	Senega root	10.0
	Wild thyme flowers	10.0

Cough and bronchial tea I according to German Standard Registration

Rx	Fennelseed	10.0
	English plantain	25.0
	Licorice root	25.0
	Thyme	20.0
	Marshmallow leaves	5.0
	Cornflower	5.0
	Mallow flowers	5.0
	Primrose flowers	5.0

Cough and bronchial tea Ii according to German Standard Registration

Rx	Aniseseed	10.0
	Linden flowers	40.0
	Thyme	20.0
	Iceland moss	5.0
	Mallow flowers	5.0
	Primrose flowers	5.0
	Heartsease	5.0

Pectoral tea according to Hager (1893)*)

Rx	Marshmallow leaves	20.0
	Nettle leaves	10.0
	Horsetail	10.0
	English plantain	5.0
	Mallow flowers	5.0
	Linden flowers	5.0
	Fennelseed, crushed	5.0
	Mullein flowers	2.5
	Fenugreek seeds, crushed	2.5

*) Original formula modified by substituting marshmallow leaves for coltsfoot leaves.

4.5 Phytotherapy of Sinusitis

First among the 100 most commonly prescribed herbal medications in Germany (see Appendix) is a combination product, Sinupret, approved by Commission E in 1994 for use in the treatment of "acute and chronic inflammations of the paranasal sinuses." A liquid form of the product has been available since 1934, and the coated tablet was introduced in 1968. The active ingredient in the tablet is a mixture of five powdered herbs: 6 mg of gentian root and 18 mg each of primrose flowers, sorrel, elder flowers, and European vervain. The liquid preparation contains a water-and-alcohol extract from the same herbs, also in proportions of 1:3:3:3:3. The Commission E monographs on these five herbs state that their actions are chiefly mucolytic, so Sinupret comes under the official heading of herbal expectorants.

A doctoral dissertation (März, 1998) cites more than a dozen pharmacologic and toxicologic studies dealing with the combination product. Of the 12 controlled clinical therapeutic studies, 4 compared Sinupret with a placebo (Table 4.5) and 8 compared it with reference drugs (ambroxol, myrtol, acetylcysteine, and bromhexine).

In the study by Neubauer (1994) in Table 4.5, there was an average difference of only 17% between the outcomes with Sinupret versus a placebo in patients on a basic regimen of antibiotics and decongestant nosedrops. In the common indications for phytotherapy, it is not unusual to find high success rates with placebos resulting in a relatively small difference between the placebo-treated and herb-treated groups (see Sect. 1.5.6 and Fig. 1.6). But since three of the four placebo-controlled studies showed a statistically significant superiority of the true drug, and two other double-blind studies showed equal or better efficacy and tolerance compared with ambroxol, it is reasonable to conclude that the product is effective for the approved indication, even if the fixed combination of five herbal powders is difficult to justify and does not conform to the dosages used in traditional herbal medicine (Sect. 1.5.4). The safety of the product has been well documented by toxicologic studies (März, 1998) and by observational experience. The incidence of mild side effects reported in a recent study was less than 1% (Ernst et al., 1997).

Table 4.5. Double-blind studies comparing Sinupret (S) with a placebo (P). The comparison of the statistical results is based on the number of patients in the first two studies and on the percentage of patients in the last study.

First author, year	Number of cases (n)	Indication	Duration of treatment (days)	Study criteria: statistical result
Richstein, 1980	31	Chronic sinusitis	7	Headache: "relieved" + "improved" S vs. P = 12 vs.6 ($p = 0.03$); X-ray findings: S vs. P $p = 0.035$
Lechler, 1986	39	Acute sinusitis (adolescent asthmatics)	?	X-ray findings: "normal" + "improved" S vs. P = 16 vs. 9 ($p<0.05$)
Berghorn, 1991	139	Acute sinusitis	14	Total symptom score: outcome tended to be better with S than P, but difference was not statistically significant.
Neubauer, 1994	177	Acute sinusitis (160), chronic sinusitis (17)	14	X-ray findings: "normal" + "improved" S vs. P = 87% vs. 70% ($p<0.05$). Patient self-rating "relieved" + "improved", S vs. P = 96% vs. 75%.

4.6 Drug Products

The *Rote Liste 1998* lists well over 100 herbal products under the heading of Antitussives and Expectorants, consisting mostly of fixed combinations of active ingredients along with numerous products containing a single active ingredient (Tables 4.1–4.4). The 100 most commonly prescribed phytomedicines in Germany include 25 herbal antitussive-expectorants, consisting of 10 single-herb products and 15 combination products.

References

Anderson J, Smith WG (1961) The antitussive activity of glycyrrhetinic acid and its derivatives. J Pharm Pharmacol 13:396–404.

Aviado DM (1972) Antitussives with peripheral actions. In: Pharmacological principles of medical practice. The William & Wilkins Co, Baltimore, S. 405–407.

Bauer L. (1973) Die Feinstruktur der menschlichen Bronchialschleimhaut nach Behandlung mit Ozothin. Klein Wochenschr 51: 450–453.

Bionorica (1994) Sinupret Tropfen, Sinupret Dragees. Wissenschaftliche Dokumentation zu Klinik, Pharmakologie und Toxikologie.

Boyd EM, Sheppard E (1996) Expectorant action of inhaled alcohol. Arch Otolaryng 90: 138–143.

Boyd EM, Sheppard E (1970a) The effect of inhalation of ceitral and geraniol on the output and composition of respiratory tract fluid. Arch Intern Pharmacodyn Ther 188: 5–13.

Boyd EM, Sheppard E (1970b) Inhaled Anisaldehyde and respiratory tract fluid. Pharmacol 3: 345–352.

Bromm B, Scharein E, Darsow U, Ring J (1995) Effects of menthol and cold on histamine-induced itch and skin reactions in man. Neuroscience Lett 187:157–160.
Burrow A, Eccles R, Jones AS (1983) The effects of camphor, eucalyptus and menthol vapur on nasal resistance to airflow and nasal sensation. Acta Otolaryng (Stockholm) 96:157–161.
Caldwell J, Sutton JD (1988) Influence of dose size on the disposition of trans-[methoxy-^{14}C) anethole in human volunteers. Food Chem Tox 26: 87–91.
Demling I, Gromotka R, Bünte H (1956) Über den Einfluß peripherer Temperaturreize auf die Durchblutung der Nasen- und Zungenschleimhaut gesunder Versuchspersonen. Z Kreislaufforsch 48: 225–230.
Dorow P (1984) Pharmakotherapie der Atmungsorgane. In: Kuemmerle HP, Hitzenberger G, Spitzy KH (Hrsg) Klinische Pharmakologie, Kap IV–4.5, Ecomed, Landsberg München.
Dorow P, Weiss PH, Felix R, Schmutzler H (1987) Einfluß eines Sekretolytikums und einer Kombination von Pinen, Limonen und Cineol auf die mukoziliäre Clearance bei Patienten mit chronisch obstruktiver Atemwegserkrankung. Arzneim Forsch (Drug Res) 37: 1378–1381.
Dorow P (1989) Welchen Einfluß hat Cineol auf die mukoziliare Clearance? Therapiewoche 39: 2652–2654.
Drinkwater NR, Miller EC, Miller JA, Pitot HC (1976) Hepatocardinogenicity of estragole and 1'-hydroestragole in the mouse and mutagenicity of 1-acetoxystragole in bacteria. J Natl Canc Inst 57: 1323–1331.
Eccles R, Jones AS (1982) The effects of menthol on nasal resistance to airflow. J Laryngology Otology 97: 705–709.
Eccles R, Lancashire B, Tolley NS (1987) Experimental studies on nasal sensation of airflow. Acta Otolaryngol (Stockholm) 103: 303–306.
Eccles R, Morris S, Tolley NS (1988) The effects of nasal anaesthesia upon nasal sensation of airflow. Acta Otolaryngol (Stockholm) 106: 152–155.
Endres P, Ferlinz R (1988) Bronchitisches Syndrom. In: Riecker G (Hrsg) Therapie innerer Krankheiten. Springer, Berlin Heidelberg New York, S. 137–142.
Ernst E, März R, Sieder C (1997) Akute Bronchitis: Nutzen von Sinupret . Fortschritte der Medizin 115: 52–53.
Ernst E, März R, Sieder C (1997) A controlled multi-centre study of herbal versus synthetic secretolytic drugs for acute bronchitis. Phytomedicine 4: 287–293.
Fox N (1977) Effect of Camphor, Ecalyptol and Menthol on the vascular state of the mucos membrane. Arch Otolaryngol 6: 112–122.
Germer WD (1985) Erkältungskrankheit. In: Hornbostel H, Kaufmann W, Siegenthaler W (Hrsg) Innere Medizin in Praxis und Klinik. Thieme, Stuttgart, Band III S 1350–1353.
Göbel H, Schmidt G, Dworschak M, Stolze H, Heuss D (1995) Essential plant oils and headache mechanisms. Phytomedicine 2: 93–102.
Gulyas A, Repges R, Dethlefsen U (1997) Konsequente Therapie chronisch-obstruktiver Atemwegserkrankungen bei Kindern. Atemwegs- und Lungenkrankheiten. 23: 291–294.
Gysling E (1976) Behandlung häufiger Symptome. Leitfaden zur Pharmakotherapie. Huber, Bern Stuttgart Wien, S. 86.
Hahn HL (1987) Husten: Mechanismen, Pathophysiologie und Therapie. Dtsch Apoth Z 127 (Suppl 5): 3–26.
Hamann KF, Bonkowsky V (1987) Minzölwirkung auf die Nasenschleimhaut von Gesunden. Dtsch Apoth Z 125: 429–436.
Hildebrandt G, Engelbrecht P, Hildebrandt-Evers G (1954) Physiologische Grundlagen für eine tageszeitliche Ordnung der Schwitzprozeduren. Z Klein Med 152: 446–468.
Hosoya E (1985) Studies of the construction of prescription in ancient chinese medicine. In: Chang HM, Yeung HW, Tso WW, Koo A (Hrsg) Advances in chinese medicinal material research. World Scientific Publ, Singapore, S 73–94.
Huck P (1999) Revisting ephedra. Health Suppl Retailer 5(4): 22–25, 28, 30.
Ingólfsdóttir K, Jurcic K, Wagner H (1998) Immunomodulating polysaccharides from aqueous extracts of Cetraria islandica (Iceland moss). Phytomedicine 5: 333–339.

Iravani J (1972) Wirkung eines Broncholytikums auf die tracheobronchiale Reinigung. Arzneim Forsch (Drug Res) 22: 1744–1746.
Irwin RS, Rosen MJ, Bramann SS (1977) Cough, a comprehensive review. Arch Int Med 137: 1186–1191.
Jackson J (1989) Aromatherapie. Kabel Verlag, Hamburg: 175–177.
Jork K (1979) Erkältungskrankheiten – Pathomorphologie und Therapie. Medizin in unserer Zeit 3: 15–19.
Kopp B, Wawrosch C, Lebada R, Wiedenfeld H (1997) PA-freie Huflattichblätter. Deutsche Apotheker Zeitung 137: 4066–4069.
Kraft K (1997) Therapeutisches Profil eines Spitzwegerichkraut-Fluidextraktes bei akuten respiratorischen Erkrankungen im Kindes- und Erwachsenenalter. In: Loew D, Rietbrock N (Hrsg) Phytopharmaka III: Forschung und klinische Anwendung. Steinkopff Verlag, Darmstadt: 199–209.
Kurz H (1989) Antitussiva und Expektoranzien. Wissenschaftliche Verlagsgesellschaft Stuttgart.
Lässig W, Generlich H, Heydolph F, Paditz E (1996) Wirksamkeit und Verträglichkeit efeuhaltiger Hustenmittel. TW Pädiatrie 9: 489–491.
Leiber B (1967) Diskussionsbemerkung. In: Dost FH, Leiber B (Hrsg) Menthol and menthol-containing external remedies. Thieme, Stuttgart, S 22.
Linsenmann P, Swoboda M (1986) Therapeutischer Wert ätherischer Öle bei chronisch-obstruktiver Bronchitis. Therapiewoche 36: 1162–1166.
Linsenmann P, Hermat H, Swoboda M (1989) Therapeutischer Wert ätherischer Öle bei chronisch-obstruktiver Bronchitis. Atemw Lungenkrankh 15: 152–156.
Lorenz J, Ferlinz R (1985) Expektoranzien: Pathophysiologie und Therapie der Mukostase. Arzneimitteltherapie 3: 22–27.
Maltz GA (1996) New rule regulates sales of large amounts of pseudoephedrine. Pharm Today 2(9): 9.
März RW (1998) Evaluation of a Phytomedicine. Clinical, pharmacological and toxicological data of Sinupret. Dissertation University of Utrecht.
Mansfeld HJ, Höhre H, Repges R, Dethlefsen U (1997) Sekretolyse und Bronchospasmolyse. TW Pädiatrie 10: 155–157.
Mansfeld HJ, Höhre H, Repges R, Dethlefsen U (1998) Therapie des Asthma bronchiale mit Efeublätter–Trockenextrakt. Münchener Medizinische Wochenschrift 140: 26–30.
Martindale (1982) The Extrapharmacopoeia (Reynolds JEF der) The Pharmaceutical Press London, S 691.
Medici TC (1980) Expektorantien: sinnvoll oder sinnlos? Pharmakritik 2: 21–24.
Merigan TC, Hall TS, Reed SE, Tyrell DAJ (1973) Inhibition of respiratory virus infection by locally applied interferon. Lancet 1: 563–567.
Meyer–Wegener J, Liebscher K, Hettich M (1993) Efeu versus. Ambroxol bei chronischer Bronchitis. Zeitschrift für Allgemeinmedizin 68: 61–66.
Miller EC, Swanson AB, Phillips DH, Fletcher TL, Liem A, Miller JA (1983) Structure-activity studies of the carcinogenicities in the mouse and rat of some naturally occurring and synthetic alkylbenzene derivates related to safrole and estragole. Cancer Res 34: 1124–1134.
Mims CA (1976) Infektion und Abwehr. Auseinandersetzung zwischen Erreger und Makroorganismus. Witzstrock, Baden-Baden Köln New York, S. 35.
Neubauer N, März RW (1994) Placebo-controlled, randomized double-blind clinical trial with Sinupret sugar coated tablet on the basis of a therapy with antibiotics and decongestant nasal drops in acute sinusitis. Phytomedicine 1: 177–181.
Newberne PM, Carlton WW, Brown WR (1989) Histopathological evaluation of proliferative lesions in rats fed with trans-Anethol in chronic studies. Food Chem Tox 27: 21–26.
Nöller HG (1967) Elektronische Messungen an der Nasenschleimhaut unter Mentholwirkung. In: Menthol and menthol-containing external remedies. Thieme, Stuttgart: 146–153, 179.
Nolte D (1980) Expektoranzien, Mukolytika und Antitussiva. In: Nolte D (Hrsg) Asthma. Urban & Schwarzenberg, München Wien Baltimore: 155–159.

Pöllmann (1987) Temperaturänderungen der Schleimhaut des Mundes und des Rachens während kalter und warmer Fußbäder. Klein Wschr 65: 286.
Opdyke DLJ (1973) Food cosmet tocicol 11, 865, zitiert nach Leung AY Encyclopedia of common drugs and cosmetics. Wiley, Chichester Brisbane Toronto 1980, S 31–33.
Patel S, Wiggins J (1980) Eucalyptus oil poisoning. Arch Dis Childh 55: 405–406.
Römmelt H, Schnitzer W, Swoboda M, Senn E (1988) Pharmakokinetik ätherischer Öle nach Inhalation mit einer terpenhaltigen Salbe. Z Phytother 9: 14–16.
Sangister SA, Caldwell J, Schmith RL (1987) The metabolic desposition of methoxy-^{14}C-labelled trans-anethole, estragole und p-prophylanisole in human volunteers. Xenobioticy 17: 1223–1232.
Schmid W (1983) Geschälte Süßholzwurzel. In: Böhme H, Hartke K (Hrsg) Deutsche Arzneibuch 8. Ausgabe 1978, Kommentar 2., neubearb. Auflage, Wissenschaftliche Verlagsgesellschaft Stuttgart und Govi-Verlag Frankfurt: 798.
Schmidt P, Kairies A (1932) Über die Entstehung von Erkältungskatarrhen und eine Methode zur Bestimmung der Schleimhaut-Temperatur. Fischer Jena: 1–70.
Schneider B (1997) Statistische Analyse von Erkältungskrankheiten und ihre Bedeutung. In: loew D, Rietbrock N (Hrsg) Phytopharmaka III: Forschung und klinische Anwendung. Steinkopff Verlag, Darmstadt 81–90.
Schwaar J (1976) Klimaanlagen und Erkältungskrankheiten bei Schiffreisen in den Tropen. Umschau 76: 719–720.
Skinner W (1999) FDA flunks U.S. House hearings on ephedra. Nat Med Law 3(1): 1, 5–8.
Stafunsky M, Manteuffel GE, Swoboda M (1989) Therapie der akuten Tracheobronchitis mit ätherischen Ölen und mit Soleinhalationen – ein Doppelblindversuch. Z Phytother 10: 130–134.
Truhaut R, LeBourhis B, Attia M, Glomot R, Newman J, Caldwell J (1989) Chronic toxicity/carcinogenicity study of trans-anthole in rats. Food chem Tox 27: 11–20.
Walther H (1979) Klinische Pharmakologie. Grundlagen der Arzneimittelanwendung. Volk und Gesundheit, Berlin: 360–364.
Zänker KS, Blümel G (1983) Terpene-induced lowering of surface tension in vitro. In: A rationale for surfactant substitution. Resp Exp Med 182: 33–38.
Zänker KS, Blümel C, Probst J, Reiterer W (1984) Theoretical and experimental evidence for the action of terpens as modulators in lung function. Prog Resp Res 18: 302–304.
Ziment I (1985) Possible mechanism of action of traditional oriental drugs for bronchitis. In: Chang HM, Yeung HW, Tso WW, Koo A (Hrsg) Advances in chinese medicinal materials research. World Scientific Publ, Singapore: 193–202.