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Asian medicine

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HISTORY OF ASIAN MEDICINE SYSTEMS

Many medical systems have emerged from Asia over the centuries, including Unani, Siddha and Ayurveda. When looking in detail at these systems, obvious similarities exist—the main one being the holistic approach each of them takes in treating patients. However, differences arise when one looks at how the development of each system has been affected by non-Asian medical systems over the centuries.

Unani medicine

Unani can be literally translated from the Arabic language as meaning 'Greek', from the Arabic word for Greece: 'al-Yunaan'. As an alternative medicine, Unani has found favour in Asia, especially India. In India, Unani practitioners can practise as qualified doctors, as the Indian government approves their practice. The principles of Unani medicine are based on the teachings of Hippocrates, Galen and Avicenna, and are based on the four humours (elements: phlegm (*Balgham*), blood (*Dam*), yellow bile (*Safra*) and black bile (*Sauda*). Although the principles of Unani can be traced back to year AD 2 the knowledge and teachings of the medical system were not documented until AD 1025, when Hakim Ibn Sina (known as Avicenna in the West) wrote *The Canon of Medicine* in Persia. The development of Unani medicine, as documented in this medical encyclopaedia, was influenced by Greek and Islamic medicine, and also by the Indian medical teachings of Sushruta and Charaka, the main texts of Ayurvedic medicine; both systems are based on the theory of the presence of elements in the human body, and the balance of these elements determines the state of a person's health. Each person's unique mixture of these substances determines his or her temperament: a predominance of blood gives a sanguine temperament; a predominance of phlegm makes one phlegmatic; yellow bile, bilious (or choleric); and black bile, melancholic. In Unani medicine, many medicines are based on honey, which is considered to have healing properties. Real pearls and metal are also used in the making of Unani medicine based on the kind of ailment it is aimed to heal. In today's modern medical world, honey is often used in wound dressings to kill bacteria because the high sugar content causes movement of water from inside bacterial cells by osmosis, leading to massive dehydration and the eventual death of the infecting organisms.

Ayurveda

Ayurveda is the ancient and sacred (Hindu) system of health care, originating in India over 5000 years ago. It is purely Indian in origin and has not been influenced by other countries or their medical systems. The literal translation of the word 'Ayurveda' from two words in Sanskrit—*āyus*, meaning 'life principle' and *veda*, referring to a 'system of knowledge'—accurately portrays the complexity and depth into which this medical system goes. A more overreaching translation can be taken as 'The knowledge (or science) of life'. The *Charaka Samhita*—an ancient Indian Ayurvedic text on internal medicine defines 'life' as a 'combination of the body, sense organs, mind and soul, the factor responsible for preventing decay and death, which sustains the body over time, and guides the processes of rebirth' and is one of the earliest written texts of Ayurveda, dating back to about 300 BC (see Chattopadhyaya, Further reading). It is believed to be the oldest of three ancient treatises of Ayurveda and is central to the modern-day practice of Ayurvedic medicine. Ayurveda is concerned with measures to protect '*āyus*', which includes healthy living along with therapeutic measures that relate to physical, mental, social and spiritual harmony. It is also one among the few traditional systems of medicine to contain a sophisticated system of surgery (which is referred to as '*salya-chikitsa*'). In today's Western society, the

emergence of holistic health systems such as Ayurveda has led to the accommodation of modern science, especially in relation to the testing of medicines, in which research and adaptation are actively encouraged. Indeed, it is perfectly possible to evaluate Ayurvedic medicines using conventional clinical trials, and this is being carried out increasingly. At present, there are only a few Ayurvedic practitioners ('*vaid*') in the West, but the rapidly increasing popularity of more holistic approaches to health—where each patient is considered unique and therefore must be treated individually—has led to the emergence of schools of Ayurveda, Ayurvedic treatment centres and more Ayurvedic medicines being imported. This approach is in contrast to Western medicine where populations are generalized and 'normal' means what is applicable to the majority. Many ethnic populations from India and Pakistan continue to use their own traditional remedies while living in Europe, Australia or the US. Philosophically, Ayurveda has similarities with Traditional Chinese Medicine (TCM). The familiar *yin* and *yang*—the opposing life forces identified in TCM, can be likened to the three 'humours' of Ayurveda—the *tridosha*.

Siddha medicine

Siddha, from the Tamil word for 'achievements', is said to have been developed by eighteen siddhars (beings who have achieved a high degree of physical as well as spiritual perfection or enlightenment), led by the great Siddha Ayastiyar. Some of his works are still standard books of medicine and surgery in daily use among the Siddha medical practitioners of today. Siddha literature is written in Tamil and the medicine is practised largely in Tamil-speaking parts of India and abroad. Like Ayurvedic medicine, this system believes that all objects in the universe, including the human body, are composed of five basic elements: earth, water, fire, air and sky. Siddha medicine is largely therapeutic in nature, and is a form of treatment of disease using substances of all possible origins in a way that balances the possible harmful effects of each substance. The principles and doctrines of this system, both fundamental and applied, have a close similarity to Ayurveda. Additionally, this system also considers the human body as a conglomeration of three humours, seven basic tissues and the waste products of the body. As in both Unani and Ayurvedic medical systems, the equilibrium of humours is considered as a healthy state, and its disturbance or imbalance leads to disease or sickness. Ancient siddhars wrote their recipes on palm-leaves for the use of future generations, and details include preparations that are made mainly out of the parts of the plants and trees, such as leaves, bark, stem, root, etc., but also include mineral and some animal substances. The use of metals like gold, silver and iron powders in some preparations is a special feature of Siddha medicine, which claims it can detoxify metals to enable them to be used for stubborn diseases. The use of mercury in the Siddha medical system is well documented and not uncommon, so patients prescribed medicines containing purified mercury should be treated only by highly qualified practitioners of the art. Over the centuries, the system has developed a rich and unique treasure of drug knowledge in which use of metals and minerals is very much advocated. The depth of knowledge required by practitioners of Siddha medicine is summarized below:

- There are 25 varieties of water-soluble inorganic compounds called '*Uppu*'. These are different types of alkalis and salts.
- There are 64 varieties of mineral drugs that do not dissolve in water but emit vapours when burnt in a naked flame; 32 of these are naturally occurring and the remaining 32 are man-made.
- Seven drugs do not dissolve in water but emit vapour on heating.
- The system has classified separately classes of metals and alloys, which melt when heated and solidify on cooling. These include gold, silver, copper, tin, lead and iron, which are incinerated according to strict regulations and used in the preparation of medicines.
- There is a group of drugs that exhibit sublimation on heating (including mercury and its salts).
- Sulphur (insoluble in water) is also used in therapeutic diagnosis and in maintenance of health.
- In addition there are drugs obtained from animal sources.

Most medicines and remedies (often common herbs and foods) used in Unani medicine (and Siddha medicine to a lesser extent) are also used in Ayurveda. Whereas Unani was influenced by Islam and Siddha by Alchemy, Ayurveda is associated with Vedic culture, and is generally considered to be the most 'original' form of traditional Asian medicine. The *Materia medica* of all these medical systems consists of many herbs made into pills, syrups, confections and alcoholic extracts, and also some metals. These traditional systems are still practised in rural communities in India and Pakistan—much more so than in cities.

COMMON TERMS AND CONCEPTS USED IN AYURVEDA

Ayurveda is dealt with in more detail because it has influenced the other Asian systems of medicine and remains the philosophical base for them. It is becoming increasingly popular in the West, although the term 'Ayurveda' is often misused. For example, recent newspaper headlines in the US included statements such as:

> *Ayurveda continues to grow rapidly as one of the most important systems of mind–body medicine, natural healing and traditional medicine as the need for natural therapies, disease prevention and a more spiritual approach to life becomes ever more important in this ecological age.*

before going on to calculate the success of this 'eco-friendly science' in material terms—in 2007 the 'global herbal market' was worth US$120 billion, with Ayurvedic treatments and products accounting for 50% of the total (*The Hindu*, 27 October 2007). There can be no argument about the increasing popularity of Ayurveda—clinics and treatment centres exist thousands of miles from India, and the term 'Ayurvedic tourism' is now recognized in many holiday resorts. Unfortunately, the high-class beauty and pampering packages offered in such places are centuries away from the 'real' Ayurveda, and disappoint professional *vaids*, who consider the use of a holistic system of medicine, meant to diagnose and treat a whole person, being reduced to superficial treatments intended to focus on a single part of the body as a travesty.

Prana is known as the 'life energy' and activates both the body and mind in Ayurvedic medicinal systems. It is contained in the head and controls the main functions of the mind, including emotions, memory and thought. Additionally, *prana* kindles the bodily fire '*Agni*' and therefore controls the function of the heart and, via the bloodstream, other vital organs (*dhatus*).

Bhutas are the five basic elements of Ayurveda—ether (or space), air, fire, water and earth. They are seen as manifestations of energy and can be equated to the five senses of hearing, vision, touch, taste and smell. In turn, these senses are associated with a particular sense organ (or organs) of the body, which impact on other 'organs of activity' and result in actions being carried out by the body. Table 36.1 summarizes some of the associations between the bhutas and the activities they govern.

Tridosha are the three humours or basic forces that manifest in the human body. They are formed from the five *bhutas* and are known as *vata, pitta* and *kapha*. The *tridosha* govern all functions of the body and mind and, by understanding the relationship between them, a *vaid* may make a diagnosis of the disease affecting a patient. Table 36.2

Table 36.1 The effect of the *Bhutas* on body function.

Bhuta	Body sense	Sense organ	Organs of activity	Action
Ether	Hearing	Ear	Tongue, vocal chords	Speech
Air	Touch	Skin	Muscles, colon, urinary bladder, heart	Movement
Fire	Vision	Eyes	Feet, gastrointestinal system	Walking
Water	Taste	Tongue	Saliva, digestive secretions, blood, muscles	Movement
Earth	Smell	Nose	Tendons, muscles, bones	Stability

Table 36.2 The effect of the *tridosha* on body function.

Dosha	Bhutas	Systems of the body affected	Body activity controlled
Vata	Ether and air	Central nervous system	Breathing, motion, heart beat, nervous impulses
Pitta	Fire and water	Digestion, metabolism, endocrine function	Body temperature, energy levels
Kapha	Water and earth	Immune system, secretions	Wound healing, memory retention, production of secretions

Table 36.3 A summary of constitutional characteristics associated with different *dosha*.

Dosha	Body characteristics
Vata	Lean build, with cool, dry and occasionally rough skin. These types often have small dark eyes and dark, curly hair. They may have a poor appetite, but variable thirst and are often mentally restless. They have a tendency to be emotionally insecure and unpredictable, lots of nervous energy, a fast mode of speech and poor, often interrupted sleep patterns
Pitta	Tend towards a medium build, with soft, warm skin, sharp (often grey or green) eyes and fair, sometimes oily hair. They have a good appetite (sometimes excessive) and are often thirsty. They tend towards sharp, aggressively intelligent mentality, causing a short temper and irritability. They have a strong method of speech, a moderate exercise level, but require little sleep, as it is always very sound
Kapha	Can be overweight, with cool, slightly oily skin. These types often have big blue eyes and thick hair. Often they have a low appetite for food or liquids, and tend to have a calm, considerate mentality. Emotionally they are calm and acquisitive, and tend to think carefully before they speak. They have an aversion to exercise and tend to have deep and lengthy sleep patterns

summarizes how the *bhutas* combine to form each of the *dosha*, and how each *dosha* affects the human body.

It should be noted the *tridosha* govern basic human emotions such as fear, anger and greed, and are involved in more complex emotions such as empathy, compassion and love. It is thought that when the *tridosha* are in equilibrium, the body and mind are healthy and a sense of well-being exists within a person. It is difficult to draw similarities between this philosophy and modern science, but most readers will agree that a sense of well-being exists in most of us when we are rested, well-fed and exercised.

Prakruti is a description of the human constitution—the 'type' of person you are. It is believed the individual's *prakruti* is determined by the parents' *prakruti* at the time of conception. A *vaid* can analyse a patient's constitution by looking at how his or her *tridosha* combine. Most people are a combination of *dosha* elements, and can be described as *vata-pitta* or *pitta-kapha* for instance. Table 36.3 shows the *dosha* characteristics associated with different parts of the human constitution.

As well as the *vata, pitta* and *kapha* type of personalities, three attributes provide the basis for distinctions in human temperament, individual differences and psychological and moral dispositions. These basic attributes are *satva, rajas* and *tamas.* In brief, *satva* expresses essence, understanding, purity, clarity, compassion and love; *rajas* describes movement, aggressiveness and extroversion; and *tamas* manifests in ignorance, inertia, heaviness and dullness.

Agni is known as the 'digestive fire' and governs metabolic processes. It is essentially *pitta* in nature. *Agni* can become impaired by an imbalance in the *tridosha* and therefore affect metabolism. In these circumstances, food will not be digested or absorbed properly, and toxins will be produced in the intestines and may find their way into the circulation.

Ama are the waste products of the body—faeces, urine and sweat—and are the root cause of disease. Their appearance and properties can give many indications of the state of the *tridosha* and therefore health. For example, a patient suffering from a *pitta* disorder, such as fever or jaundice, may have dark urine. Additionally, substances such as coffee and tea, which stimulate urination, also aggravate *pitta* and render the urine dark yellow. If a patient has overactive *ama* production, the overcombustion of nutrients may occur, leading to *vata* disorders and emaciation (e.g. overactive thyroid).

Dhatus are the seven tissues or organs of which the human body is composed. Therefore any imbalance in the *tridosha* directly affects the *dhatus. Dhatus* are those substances that are retained in the body and always rejuvenated or replenished. The *dhatus* do not correspond to our definition of anatomy, but are more a tissue type than an individual organ. Table 36.4 provides an approximate relationship between *dhatus* and parts of the body.

Gunas Charaka, author of the *Charaka Samhita*, wrote that all material, both organic and inorganic, as well as thought and action, have 'attributes'—qualities that contain potential energy, while the actions with which they are associated express kinetic energy. This is possibly the first reference to the concept of potential and kinetic energy. *Vata, pitta* and *kapha* each have their own attributes, and substances having similar attributes will tend to aggravate the related bodily humour. Table 36.5 gives a brief summary of the three *gunas*.

Table 36.4 The Sanskrit name for each of the seven *dhatus* and the tissues or organs with which they are associated.

Dhatu	Associated organ or tissue
Rasa	Nutritional fluid: plasma
Rakta	Blood: life force
Mamsa	Muscles: cover bones
Meda	Adipose tissue: lubrication
Asthi	Bone: help to stand and walk
Majja	Bone marrow: nerve tissue nourishment
Shukra	Testes/ovaries: reproduction

Table 36.5 A summary of the three *Gunas* and their effects upon the body.

Guna	Definition	Effects
Sattva	Essence/subtle	Provision of necessary energy for the body without taxing it
Raja	Activity	Sensuality, sexuality, greed, avarice, fantasies, egotism
Tamas	Inertia/gross	Dullness, drowsiness, pessimism, lack of common sense, laziness, doubt

PRINCIPLES OF AYURVEDA

In addition to the in-depth analysis of a patient's *prakruti* that a *vaid* will undertake to diagnose the patient's ailment, astrological considerations and karma must also be considered. Finally a thorough medical examination, not dissimilar to that undertaken by a TCM practitioner, including the appearance of the tongue, properties of the urine, sweat, sputum and faeces will also be carried out. Once the *vaid* has ascertained the disease and the likely cause of the problem, a complex treatment regimen will be prescribed. As health can be maintained by taking steps to keep *vata-pitta-kapha* in balance through a proper diet, herbal treatment and exercise programme, this is likely to be the first line of action. The concepts governing the pharmacology, therapeutics and food preparation in Ayurveda are based on the action and reaction of the *gunas* to and upon one another. Through understanding of these *gunas*, the balance of the tridosha can be maintained. The diseases and disorders ascribed to *vata, pitta* and *kapha* are treated with the aid of medicines possessing the opposite attribute, to try and correct the deficiency or excess. Many of the medicines prescribed in Ayurvedic medicine are herbs and patients may have to take them as medicines (tinctures, inhalations, pills, capsules or powders) or by combining them into their diet in a prescribed fashion. Table 36.6 provides a brief summary of the herb types used to treat different *dosha*-related illnesses.

Rasayana—widely used herbs

Rasayana (literal translation 'longevity enhancer') are remedies considered to have diverse action and, therefore, affect many systems of the body leading to a positive effect on health—panaceas in other words. The most important are summarized in a Table 36.7 and are included in many recipes to strengthen the tissues of the body. In general, modern research has found them to have antioxidant, immunomodulating and various other activities.

Table 36.6 A summary of herb classes used to treat different *dosha*-related illnesses.

Dosha-related illness	Herbs types used
Vata	Sweet (*madhur*), sour (*amla*) or warm (*lavana*)
Pitta	Sweet (*madhur*), bitter (*katu*) or astringent and cooling (*kashaya*)
Kapha	Pungent (*tikta*), bitter (*katu*) or astringent and dry (*kashaya*)

Preparation of Ayurvedic medicines

In addition to the rasayanas, many other herbs are used in Ayurvedic medicines. Table 36.8 summarizes some of the best documented. Readers should consider that although documented clinical evidence for the activity of some of these herbs can be fairly scarce, practising *vaids* stress the importance of the *combinations* of the herbs—suggesting a synergistic effect between them. Indeed, the main principles that guide Ayurvedic medicinal formulation are: synergy, opposition, enhancement, protection and, as always in holistic systems, balance. Each of these principles is summarized below:

- *Synergy* is the enhancement of the effectiveness of herbs and minerals with similar or complementary action, when combined together.
- *Opposition* is the counterbalancing of an undesirable effect of a herb or mineral by adding another ingredient with the opposite action.
- *Enhancement* is the promotion of the efficacy of the main ingredient, by either increasing its activity or its absorption, by the addition of other ingredients to a formulation.
- *Protection* describes when the potential toxicity of a formula is reduced, by adding mild laxatives or diuretics that promote elimination.
- *Balance* describes when the antagonistic actions of different constituents of a formula are considered to counteract each other.

The preparation of Ayurvedic medicines follows the general Ayurvedic philosophy that emphasizes the whole; that is, substances are combined in such a way that their natural attributes synergistically enhance the action of the whole formula. Traditional formulae are often named, and may denote a specific combination of herbs and other products prepared in a prescribed way, or instead, for their major ingredient(s). In some instances, the name denotes the person who first devised the formula, the therapeutic action of the medicine, or the part of the plant used. For example, *Triphala* powder is a mixture of powders of three fruits—*amla, baheda* and *hirda*—whilst *Chyavanprash* is a semi-solid formulation named after a sage, '*Chyavan*', who first devised the formula.

Preparative methods

As discussed previously, single drugs are rarely used in Ayurvedic practice. The formulations usually contain heterogeneous mixtures of herbs and minerals that have undergone a complex process of purification and preparation. Traditional methods used to prepare Ayurvedic drugs are based on the principles of extraction, concentration and purification, and the choice of preparation method depends on the part of the plant to be used, on its condition (fresh or dried), and on the drug's expected use. For example, cold decoctions are preferred for conditions attributed to an excess of pitta. Table 36.9 gives a summary of some of the most common methods of preparation of herbal material used to produce Ayurvedic medicines. For a more extensive list of herbal ingredients of Asian medicine in general, covering 97 families of plants, see M. Aslam, in the 15th edition of this book, p. 471.

Table 36.7 Summarizing the Rasayana herbs most commonly used in Ayurvedic medicinal combinations.

Botanical name	Ayurvedic name	Medicinal use	Clinical evidence
Asparagus racemosa Indian asparagus	*Shatavari*	Tonic, rejuvenative, aphrodisiac, laxative, antispasmodic, antacid, diuretic, antitumor	Constituents isolated from the raw plant, showed increased white cell production in human bone marrow. (Kanitkar *et al., J. Res. Ind. Med.*, 1969; 32)
Emblica officinalis Indian gooseberry	*Amla*	Improves memory and intelligence, tonic, demulcent	*E. officinalis* can heal indomethacin-induced stomach ulceration in rats by their antioxidant action and ability to form mucus. (Bhattacharya *et al., J. Clin. Biochem. Nutr.,* 2007; **41**(2): 106–114)
Piper longum Indian long pepper	*Pimpli*	Antioxidant, digestive stimulant, carminative, expectorant, bronchodilator, anthelmintic, analgesic, circulatory stimulant, aphrodisiac	*In vitro* antioxidant activity of *Piper longum*. (Agbor *et al., J. Herb. Pharmacother.,* 2007; **7**(2): 49–64)
Terminalia chebula Ink nut Black myrobalan	*Haritaki*	Mild laxative, glucose regulator, tonic, alterative, adaptogen, hepatoprotective, antispasmodic, expectorant, antiasthmatic, antiviral and hypoglycaemic, haemorrhoids, dental caries, bleeding gums, ulcerated oral cavity	Chebulagic acid, isolated from *Terminalia chebula*, proved to be a reversible and non-competitive inhibitor of maltase, showing a use for chebulagic acid in managing type-2 diabetes. (Gao *et al., Biosci. Biotechnol. Biochem.*, 2008; **72**: 601–603)
Tinospora cordifolia Heart-leaved moonseed	*Guduchi*	Detoxifier, antioxidant, breaks down exogenous and endogenous toxins, improves comprehension, memory and recollection	Validation of therapeutic claims of *Tinospora cordifolia*: a review promotes regeneration of the liver against CCl_4 induced hepatotoxicity. (Panchabhai *et al., Phytother. Res.,* 2007; in press doi:10.1002/ptr.2347)
Withania somnifera Winter cherry	*Ashwagandha*	Analgesic, improves blood glucose control, sedative, rejuvenator, asthma, uterine sedative, relaxant and antispasmodic effects on intestinal, uterine, bronchial, tracheal and blood-vessel muscles	Increases cells capacity to utilise glucose. (Anwer *et al., Basic Clin. Pharmacol. Toxicol.,* 2008; doi:10.1111/j.1742)

Table 36.8 Some important herbs of Ayurveda and their uses.

Botanical name	Ayurvedic name	Effect on dosha	Medical use
Acorus calamus Sweet flag	*Vacha*	Pacifies *vata* and *kapha*	Nerve stimulant, digestive
Adhatoda vasica Malabar nut	*Vasaka*	Pacifies *pitta* and *kapha*	Respiratory disorders, fevers
Aegle marmelos Bengal quince	*Bael, Bel*	Promotes *pitta*	Reduces symptoms of dysentery, digestive, tonic
Andrographis paniculata King of bitters	*Kalmegh*	Pacifies *kapha* and *pitta*	Hepatoprotective properties, jaundice
Eclipta alba Trailing eclipta	*Bhringarajah*	Pacifies *kapha* and *pitta*	Skin and hair disorders
Embelia ribes Embelia	*Viranga*	Pacifies *kapha* and *vata*	Antihelmintic, contraceptive
Nigella sativa Black cumin	*Kalonji*	Pacifies *vata* and *kapha*	Digestive, antiseptic
Ocimum sanctum Sweet basil	*Tulsi*	Pacifies *kapha* and *vata*	Expectorant, febrifuge, immunomodulator
Phyllanthus niruri Stone breaker	*Bhumyamlaki*	Pacifies *kapha* and *pitta*	Diabetes, jaundice, liver protectant

Table 36.8 Some important herbs of Ayurveda and their uses. (Cont'd)

Botanical name	Ayurvedic name	Effect on dosha	Medical use
Picrorrhiza kurroa Kutki, yellow gentian	*Katurohini*	Pacifies *kapha* and *pitta*	Hepatoprotective, immunomodulator
Piper nigrum Black pepper	*Kalmirch*	Pacifies *vata* and *pitta*	Digestive, respiratory disorders
Swertia chirata Chiretta	*Chirayita*	Balances *tridosha*	Appetite stimulant, liver disorders
Terminalia arjuna Arjun myrobalan	*Arjuna*	Pacifies *pitta* and *kapha*	Heart tonic, angina, hypertension
Tribulus terrestris Caltrops	*Gokhru*	Pacifies *vata* and *pitta*	Digestive, diuretic, aphrodisiac

Table 36.9 Methods of preparing Ayurvedic medicines.

Formulation	Method of production
Juice *(Swaras)*	Cold-pressed plant juice
Powder *(Churna)*	Shade-dried, powdered plant material
Cold infusion (*Sita kasaya*)	Herb : water 1 : 6, macerated overnight and filtered
Hot infusion (*Phanta*)	Herb : water 1 : 4, steeped for a few minutes and filtered
Decoction (*Kathva*)	Herb : water 1 : 4 (or 8, 16 then reduced to 1 : 4) boiled
Poultice (*Kalka*)	Plant material pulped
Milk extract (*Ksira paka*)	Plant boiled in milk and filtered

Shodhana (purification) is the process by which toxic substances are purified; that is, rendered less toxic. For example, detoxification of mercury involves a drawn-out process of heating and cooling the mercury salt, grinding it and then suspending and re-suspending the substance in a variety of liquids. Specific products that facilitate the process are added at each stage of preparation and the instructions might call for the use of a specific vessel at different stages of preparation. The instructions can be so detailed, up to the point of stating from which direction the heat is to be applied. It is left to the experience of Ayurvedic practitioners to decide, at the conclusion of an appropriate purification process, that the toxic substances are no longer poisonous but therapeutic. From this brief summary, it can be seen that the classical Ayurvedic methods of preparation are complex and tedious, and that short-cuts in preparation may make a significant difference in the efficacy and safety of the resulting product. Because of this, it may be beyond the scope of the average scientific paper to exactly describe the method by which an herb is prepared, especially if a formula is used, which may go some way as to explaining why such problems exist in replicating the results of other researchers.

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Chinese herbs in the West

S. Y. Mills

Herbs are used for health care in China more than either Western drugs or acupuncture. If their use in other countries with Chinese influence is taken into account, they form probably the largest tradition of health care in the world.

There is now an increasing use of Chinese herbs outside China and Asia, notably in the USA and the UK. Interest has been expressed within medical circles at cases where the use of Chinese medicine appears to have had dramatic benefits. The following presents a summary of the current status of the use of Chinese herbalism in the West.

HISTORICAL BACKGROUND

Chinese herbal medicine has a strikingly persistent tradition, surviving cultural and dynastic revolutions, with classic texts being preserved as living guides for physicians up to the present day. The earliest known text was unearthed in Hunnan province and dates from the fourth century BC. It lists over 200 herbs, with instructions for 52 pharmaceutical preparations. In around 250 BC, a herbal compendium, the *Pen Tsao Ching* was written in the name of the legendary Emperor Shen Nung, who was said to have lived 5000 years previously. Other still widely used established classics include a commentary on the previous text, the *Shen Nung Pen Tsao Ching Chi Chu* from around the fifth century AD, and the *Hsin Hsiu Pen Tsao* (New Revised *Materia Medica*), written in AD 659. More recent texts include the sixteenth-century *Pen Tsao Kang Mu,* in 52 volumes and containing over 11 000 prescriptions.

In 1977, the Chinese government published a *materia medica* listing almost 6000 herbs and other pharmacological compounds of natural origin. In 1985, in their Drug Administration Law, 8800 patent herbal drugs were identified as requiring re-evaluation. In 1994, an Essential Drug List (of which about 50% would be covered by health insurance) contained almost 1700 herbal drugs.

THERAPEUTIC PRINCIPLES

The approach of traditional Chinese medicine (TCM) is significantly different from that of modern orthodox medicine. Without the modern technology that has allowed isolation of pathogens and pathologies, it developed strategies for understanding and correcting an illness from the broader experience of its impact and associations. There was less opportunity to focus on or directly treat a specific disease entity. Rather, traditional medicine sought to avert adverse influences and to promote normal healthy function so as to help the person eliminate or resist these influences. It was more an interaction with the body's functions than, as in the modern case, with pathologies (that are usually the end-result of dysfunctions).

The underlying principles of Chinese medicine often appear to the Western observer to be wrapped in vague or mystical notions. However, such prejudices arise from the nineteenth-century Western view of the world as clockwork mechanisms. As modern science begins to appreciate the complexities of living systems, it has rediscovered principles that may be consistent with the oriental insights.

The *yin* and *yang* concepts are obvious examples where speculative entities are seen to substitute for empirical data. This disquiet may be diminished, however, if they are instead seen as means of classifying the experience of constant change. The *yang* is the active aspect of any phenomenon, the dispersive, centrifugal, transforming and expansive. Such descriptors are similar to those ascribed to chaotic tendencies in complex dynamic systems. The *yin* is the substantive or nourishing aspect of any phenomenon, the condensing, centripetal, sustaining and preserving. The tendencies to ordered behaviour in dynamic systems have similar qualities.

In the language of complex dynamic systems, life is seen to exist at the edge of chaos, maintaining maximum adaptibility and creativity by balancing static orderliness and turbulent chaos, and avoiding extremes of either. The essential endeavour of the Chinese physician is to restore the balance of the body, the *yin* nourishment and *yang* activity. Obviously this is done in terms of clinical symptoms rather than as an abstract philosophical construct.

The *yin–yang* polarities are imbued with shifting temporal and spatial relationships. At any position or in any event there will always be a blend of the active and the substantial, a blend that is always shifting in time and when viewed from different perspectives. To take a simple example: in the West, a table is an object, fixed and substantial. In the Chinese view that structure is merely in a transitory substantial, *yin*, phase: it also forms a relationship with the people who use it and has an influence on the room in which it stands. Moreover, these active, *yang*, aspects of its existence determine when its *yin* aspect changed from being a tree, and when it changes again to a heap of ash or a children's playhouse! Thus, each table becomes a different entity to each individual human being and at each moment in time, its active aspect always reflecting the position of its substantial and vice versa: it becomes an experience.

Similarly, any symptom of ill health might either be the mark of excessive activity (*yang*) in a system or alternatively relative stasis or congestion (*yin*). In the first case, treatment would concentrate on encouraging the nutritive, assimilative and/or calming influences in the body, mind or spirit; in the second there would need to be a degree of stimulation or mobilization. The art of diagnosis was to distinguish between the two radically different scenarios; the art of medicine to develop appropriate strategies for the particular system defect.

Other polarities would be taken into account (heat versus cold, internal origins versus external, deficient constitutions versus the highly charged, and so on) along with a good number of other qualitative markers of the interior climate. One early view, for example, was that chronic diseases arose when external pathogenic influences drove deeper and deeper into the body. Treatment therefore required that the pathogenic influence was best intercepted at the surface, that is, at its most acute (even alarming, often febrile) stage, to prevent the development of more intractable 'embedded' pathologies. Treatment strategies would be quite different at each stage of penetration.

Another Chinese fundamental is the concept of an underlying energy in all phenomena, as a motive force and determining principle. They did not measure *qi* as calorific or electrical energy. Instead, *qi* is appreciated and judged by ordinary experience, and indeed for this reason is clearly felt as tangible. *Qi* is thus an energetic construct implicit in, and defined by, its outcomes, i.e. by events. It is therefore manifest in all movement and is itself in movement, constantly transforming itself into relatively *yang* and *yin* aspects.

In physiological terms, *qi* was often subdivided into fluids of different densities, some visible and some not. One of the substantial or *yin* aspects of *qi*, for example, is blood or *xue.* Although this was obviously the same fluid as understood anywhere else it also had other qualities. *Xue* can be appreciated as incorporating both what the West knows as blood and the subjective effect of that fluid, warming, pulsing and nourishing. It can also be seen as a deeper, slower, more profound or tangible response to change than other *qi*, a response that is, by definition, also slower to reverse. For example, it may be manifested as long-term physiological responses or the organic change that leads to observable pathologies. Incidentally, in this context herbal medicines were seen to be more effective in moving *xue* (the more substantial shifts in body function) than acupuncture.

The Chinese view of organ function is also quite distinct, derived from induced insights of clinical presentations and the meridianal connections applied in acupuncture. Thus, *gan*, the liver, has the function of distributing energies around the body, governing muscle and sinew activity and eyesight, and is particularly disturbed by emotional distress, particularly anger and frustration. The spleen, *pi*, is responsible for assimilative functions, notably digestion, and for maintaining the integrity of the tissues and circulation, but also includes emotional assimilation as manifested in empathy, maternalism and nurturing. (These notions of concentric repetition of patterns, so that activity at a physical level is manifested also at psychological, emotional, spiritual or even social levels now resonates with one of the mathematical principles of complex system analysis, the fractal, where a pattern is repeated through infinite levels of scale.)

The Chinese herbs were classified according to their perceived ability to affect any of these manifestations of the living body. These classifications are used in Table 37.1, which lists some of the most widely used Chinese herbs in the West. Herbs were also characterized pharmacologically in terms of their taste: bitter, sweet, acrid, salty and sour, this being seen to denote particular properties. Some of the conclusions drawn about such properties can now be supported with modern knowledge of the action of the archetypal plant constituents involved (Mills and Bone, 'Further reading').

It is useful to compare modern and Chinese medical approaches. Faced, for example, with excessive bowel activity, modern physicians would apply diagnostic techniques to eliminate observable pathologies like diverticulitis, dysentery or ulceration, and then lump anything less tangible as 'irritable bowel', with an implicit psychological cause. The traditional Chinese physician would assess the nature of the symptoms, their chronicity, severity and other qualities and correspondences, and might then conclude that the problem was the result of either sluggish digestive metabolism, unwholesome diet, suppressed anger, emotional disruption of assimilative functions, one or more various forms of debility, cold in the stomach or in the bowel, imbalance of heat and cold in the body, damp heat (e.g. hepatic disease), or digestive imbalances. The presence of blood or mucus in the stool, deep persisting pain or wider debility would immediately signify a deep-seated (*xue*', *yin*) disturbance requiring particularly nurturing treatment (see Porkert, 1983, 'Further reading'). The treatments adopted in each case would be completely different.

Another result of the longevity of Chinese herbal medicine, however, is its reliance on accumulated traditional practices rather than on innovation. Thus, well-established and revered formulae of medicines are more widely used than individual herbs. The mixtures are thought to benefit from interactions between the ingredients that extend the breadth of activities, improve tolerability or potentiate one or more particular effects. These claims have been almost impossible to substantiate in any controlled study. Nevertheless, it is also doubtful whether formulations developed to deal with the diseases of medieval China have the same application to the health priorities of the developed West. Although there is undoubtedly a great deal of favourable human experience of the standard formulations, without controlled clinical scrutiny and the application of clear quality standards for all the many ingredients, it is impossible to verify their value in the modern context.

The adherence to classic texts and precedent rather than assertive enquiry is an essential feature of Chinese medicine, and indeed traditional medicine as a whole. Much that is handed down from Chinese medical history is dogma: there is little sign of a tradition of radical reappraisal, of 'individual seekers after truth'. But this is true of all early traditions. In their struggle for survival, early humans prospered in relation to the fitness of their behaviour to their circumstances. They learned from their elders (who had by definition so prospered) and were justly cautious about reckless questioning.

Table 37.1 Chinese herbs widely used in the West classified by traditional therapeutic activity.

Botanical name	Part used	Action	Constituents
Warming remedies releasing exterior conditions			
Ephedra sinica Stapf	Herb	Diaphoretic, antiasthmatic, diuretic	Ephedrine and related alkaloids
Perilla frutescens L.	Leaves, stem	Diaphoretic, digestive stimulant	Essential oils (including limonene, apinene), perillaidehyde
Angelica dahurica Bentham & Hooker	Root	Diaphoretic, antiseptic, analgesic	Furanocoumarins, angelic acids
Ligusticum sinense Oliver	Root	Diaphoretic, antirheumatic	Essential oil, cnidilide
Zingiber officinale Roscoe	Rhizome	Diaphoretic, antiemetic, expectorant	Zingiberene, shogaol, gingerol, zingiberone, zingiberol
Cooling remedies releasing exterior conditions			
Mentha arvensis L.	Herb	Febrifuge	Essential oil (menthol, menthone, etc.)
Pueraria pseudohirsuta Tang & Weng	Root	Diaphoretic, analgesic, febrifuge, vasodilator	Isoflavones (including daidzein), puerarin
Bupleurum falcatum L.	Root, herb	Febrifuge, digestive tonic, relaxant	Saponins (including saikosaponin, daikogenin)
Cimicifuga foetida L.	Rhizome	Diaphoretic, detoxifier	Triterpenoid (including dahurinol), cimicifugoside, cimicifugin, visnagin
Purgatives			
Rheum palmatum L.	Root	Laxative, choleretic, detoxifier	Anthraquinones (including rhein, emodin)
Cooling remedies			
Anemarrhena asphodeloides Bunge	Rhizome	Febrifuge, anti-inflammatory, antiasthmatic	Steroidal saponins (including timosaponin, sarsapogenin)
Gardenia jasminoides Ellis	Fruit	Febrifuge, sedative, detoxifier, choleretic	Iridoid glycosides (including gardenin, genipin, gardenoside, crocetin)
Trichosanthes kirilowii Maximowicz	Root	Anti-inflammatory, detoxifier, increasing mucosal secretions	Saponins
Camellia sinensis Kuntze	Leaves	Anti-inflammatory, choleretic	Xanthines
Remedies cooling *gan* (liver function)			
Cassia tora L.	Seeds	Laxative, sedative, ophthalmic remedy	Anthraquinones (including emodin, chrysophanol, rhein), mucilage
Remedies cooling *xue* (blood)			
Paeonia suffruticosa Andrews	Bark	Antipyrexic, vasostimulant, antitoxaemic	Paeonolide, paeonoside, paeonoflorin, tannins
Cooling and drying remedies			
Scuteliaria baicalensis Georgi	Root	Bitter digestive, choleretic, detoxifier, haemostatic	Flavonoid glycosides (including balcalein, baicalin, woogonin)
Coptis chinensis Franchet	Rhizome	Bitter digestive, choleretic, sedative	Alkaloids (including herberine, columbamine, coptisine, palmatine)
Phellodendron amurensei Ruprecht	Bark	Bitter digestive, choleretic, detoxifier, febrifuge, tonic	Alkaloids (including berberine, palmatine, phellodendrine), triterpenoids, sterols
Sophora flavescens Aiton	Root	Bitter digestive, choleretic, diuretic, antipruritic	Alkaloids (including matrine, sophoranol), flavonoids
Gentiana scabra Bunge	Root	Bitter digestive, choleretic, urinary antiseptic, anxiolytic	Gentianine, gentiopicrin, gentisin
Cooling and disinfecting remedies			
Lonicera japonica Thunberg	Flowers	Antipyretic, detoxifier	Luteolin, tannin
Forsythia suspensa Vahl	Fruit	Anti-infective, antipyretic, urinary antiseptic, anti-inflammatory	Saponins, flavonoids
Taraxacum mongolicum Handel-Mazetti	Whole plant	Anti-infective, antipyretic, choleretic	Bitter principles, taraxasterol
Aromatic remedies transforming damp			
Agastache rugosa Fischer & Meyer	Herb	Digestive stimulant, antiemetic	Essential oil (including anethole, methyichavicol, limonene, pinene)
Atracyloides lancea Thunberg	Rhizome	Digestive stimulant, antirheumatic	Essential oil (including atractylol, atractylone, atractylin)
Magnolia officinalisi Rehder & Wilson	Bark	Digestive stimulant, expectorant	Magnolol, essential oil (including eudesmol) alkaloids (including magnocurarine, magnoflorine)
Amomum cardomomum L.	Fruit	Antiemetic, digestive stimulant, expectorant	Essential oil (including camphor, borneol)
Inula britannica L.	Root	Expectorant, antinausea	Essential oil (including camphor, alantol, alantoic acid), bitter principles (including lactones), triterpenes

Diuretic remedies			
Poria cocos Wolff	Fungus sclerotium	Diuretic, sedative	Triterpenes, polysaccharides
Alisma plantago aquatica L.	Rhizome	Diuretic	Alisol, triterpenes, resin
Artemisia capillaris Thunberg	Herb	Diuretic, choleretic	Essential oil (including pinene, capillene), esculetin, scoparone
Coix lachryma jobi L.	Seed	Diuretic, antidiarrhoeal, antirheumatic	Coixol, starches
Remedies expelling wind and damp			
Chaenomeles sinensis (Thouin) Koehne	Fruit	Spasmolytic, anticramping, diuretic	Saponins, flavonoids, tannins
Acanthopanax gracilistylus W.W. Smith	Root bark	Antirheumatic, diuretic	Salicylates
Remedies warming the interior			
Cinnamomum cassia Blume	Bark	Diaphoretic, circulatory stimulant	Essential oil (including cinnamic aldehyde), resin
Eugenia caryophyllata Thunberg	Flowers	Antiemetic, digestive stimulant, circulatory stimulant	Essential oil (including eugenol, caryophylene)
Sedative remedies			
Biota orientalis (L.) Enlicher	Seeds	Sedative, aperient	Essential oil, fatty oil
Sedative remedies calming *gan* (liver function)			
Gastrodia elata Blume	Rhizome	Spasmolytic, sedative, antirheumatic	Vanillyl alcohol, vanillin
Uncaria rynchophyllai (Miguel) Jackson	Stems with hooks	Spasmolytic, antipyretic	Alkaloids (including rhynchophylline, hirsutine)
Remedies regulating *qi*			
Citrus tangerina Hort & Tanaka	Peel	Carminative, expectorant	Essential oil (including limonene, linalool), carotene
Lindera strychnifolium Villars	Root	Carminative, reducing urinary irritation, antidysmenorrhoeic	Essential oil (including borneol, linderane, linderalactone)
Remedies moving *xue* (blood)			
Ligusticum wallachii Franchet	Rhizome	Circulatory stimulant, analgesic, menstrual regulator	Essential oil (including cnidium lactone)
Carthamus tinctorius L.	Flowers	Circulatory stimulant, analgesic, menstrual regulator	Carthamin
Achyranthes bidentata Blume	Root	Circulatory stimulant, tonic	Saponins, insect-moulting hormone (ecdysterone, inokosterone)
Prunus persica (L.) Batsch.	Seed	Circulatory stimulant, aperient, antitussive	Cyanogenic glycosides (including amygdalin)
Remedies transforming phlegm and stopping coughs			
Platycodon grandiflorum (Jacqain) de Candolle	Root	Expectorant, antiseptic	Saponins, sterols
Cooling remedies transforming hot phlegm			
Peucedanum praeruptorum Dunn	Root	Expectorant, antiasthmatic	Coumarins
Antitussives			
Eriobotryajaponica Lindley	Flowers	Expectorant, antitussive, antiemetic	Essential oil, cyanogenic glycosides (including amygdalin)
Remedies tonifying *qi*			
Panax ginseng C. A. Meyer	Root	Tonic, sedative	Saponins (including ginsenosides), panax acid, glycosides (including panaxin, panaquilin, ginsenin) sterols
Astragalus membranaceus (Fischer) Bunge	Root	Tonic, immune stimulant, diuretic	Sterols, betaine, astragalin
Atractyloides macrocephala Koidzumi	Rhizome	Tonic, digestive stimulant, diuretic	Atractylone
Zizyphus jujuba Muller	Seed	Tonic, sedative, digestive stimulant	Triterpenes
Glycyrrhiza uralensis Fischer	Root	Tonic, spasmolytic, expectorant, pharmaceutical moderator	Saponins (including glycynrhizin), flavonoids (including liquiritin)

(Continued)

Table 37.1 Chinese herbs widely used in the West classified by traditional therapeutic activity. (Cont'd)

Botanical name	Part used	Action	Constituents
Remedies tonifylng *yang*			
Trigonella foenum-graecum L.	Seed	Tonic, spasmolytic, warming	Alkaloids (including trigonelline), steroidal saponins (including diosgenin), mucilage
Eucommia ulmoides Oliver	Bark	Tonic	Resin, gutta-percha
Remedies tonifying *xue*			
Rehmannia glutinosia (Gaertner) Liboschitz	Prepared root, rhizome	Tonic	Iridoid glycosides (including catalpol), rehmannin, mannitol, sterols
Angelica sinensis (Oliver) Diels	Root	Tonic, menstrual regulator, aperient	Essential oil (including carvacrol, safrol), furanocoumarins
Paeonia lactiflora Pallas	Root	Tonic, analgesic, spasmolytic	Paeoniflorin, paeonol
Remedies tonifying *yin*			
Lycium chinense Miller	Bark	Tonic, antiasthmatic, antitubercular	Solanaceous alkaloids, betaine, physaline, carotene
Asparagus cochinensis (Loureiro) Merrill	Root	Tonic, expectorant, aperient	Asparagin, mucilage, sterols
Ophiopogon japonicus (Thunherg) Ker-Gawler	Root	Tonic, sedative, antitussive	Saponins, mucilage
Codonopsis pilosula Franch	Root	Tonic	Saponin, alkaloids, mucilage

Such survival imperatives, however, no longer apply in the a modern Western context. It is now necessary for the potential of Chinese herbal remedies to be assessed more rigorously and with reference to the undoubted benefits of modern Western medical techniques. It is otherwise too easy to characterize the new Western interest in Chinese herbal medicine as a romantic retreat.

CHINESE HERBAL MEDICINE IN WESTERN PRACTICE

The use of Chinese herbs has continued in traditional manner by physicians and pharmacists serving Chinese communities around the world. In many major Western cities, the Chinatown districts support many herb shops and practices, with remedies imported diectly from Asia and practitioners trained by the old system of apprenticeship. Much of this activity has remained closed to Westerners, although this has changed in recent years as the remedies have become better known and demand for treatment has increased. In recent years, there has been a proliferation of Chinese herb shops in towns and shopping precincts across the UK. Concerns have been raised about their promotional and labelling activities, given the current state of the law in the UK, and nor have these businesses been involved in steps to statutorily register herbal practitioners (*see* Herbal Medicine in Britain and Europe: regulation and practice). The traditional separation between Chinese and western cultures within western countries is in this case challenging the legislature.

Chinese herbal medicine is also among the most rapidly growing in popularity of the complementary therapies in the English-speaking Western world. It is particularly applied as a second tier of treatment by Western acupuncturists who, having started with the most accessible Chinese therapy, discover how closely herbs and acupuncture are integrated into clinical practice in China itself. Thus, many of the colleges of acupuncture in the USA and UK have introduced courses in herbalism. At least some of these new courses are rather brief, despite the fact that their graduates face different legislative and professional responsibilities as prescribers of pharmacologically active medicines.

The leading professional group of practitioners of Chinese herbal medicine in the UK is the Register of Traditional Chinese Medicine, which has around 400 members. It provides a 2-year course covering around 300 herbs and 150 classical formulae, a course often taken up by Western acupuncturists, the majority of whom will have received several years of training in that discipline in one of the main acupuncture colleges in the UK. Further postgraduate seminars are available on an occasional basis. Very few Western physicians have been persuaded to prescribe Chinese herbs.

Consultations with practitioners of Chinese herbal medicine average around an hour in the first instance. Treatment will often be combined with acupuncture and advice on diet and exercises (these often based on the Chinese *Qi Gong* routine). The average cost of a prescription is between £5–8 in a consultation that might cost £40–50 (in 2008). Herbs are traditionally provided as mixtures of individual dried plant parts that patients have to cook or steep themselves at home. This is an involved process in which taste and smell contribute fully to the experience of taking the medicine. For those who are ill-suited to this labour, there is a wide range of patented preparations in coated pill, tablet and recently tincture or capsule form. The diagnostic and therapeutic principles applied are of the 'Eight Principle' approach based on classifications derived from the eight polarities alluded to above: *yin–yang,* 'cold–hot', 'internal–external', 'full–empty'), which has also been applied as the basis of the TCM acupuncture treatment most widely used in the West.

STATE RECOGNITION: EVIDENCE OF EFFICACY

There is a considerable and growing literature of clinical and other experimental evidence published from China with, however, very much less from Western countries. Much of the evidence cited from China has been of uncontrolled studies, although this is now improving, and the regulatory agencies in North America, Australasia and Europe will not accept Chinese data in support of applications for licensing as medicines. The attitude of such agencies is generally sceptical of the case for such remedies, although there is also widespread acceptance of their pharmacological potential in pharmaceutical development.

In part, the view of the medical establishment is affected by a general unease about the lack of pharmaceutical precision in all herbal remedies. Regulators in the West have been persuaded (reluctantly) that remedies that have been traditionally used among the population have a continuing place in healthcare. What they resist is the prospect of recognizing the claims of 'new' herbal remedies from abroad. In almost all Western countries, therefore, Chinese herbalism is practised without endorsement or recognition from the state. The one notable exception is the state of California, which registers OMDs (Doctors of Oriental Medicine) as practitioners who can legally prescribe herbal remedies, and conducts State examinations with a standard syllabus of around 300 herbs.

Conventionally conducted clinical trials in the West are relatively rare and have not been sufficient to change this climate of scepticism. The case for such a radical challenge to conventional pharmacology is unlikely to be swung without consistent clinical trial evidence showing significant effect over and above the effect of placebo. Unfortunately, for many of the less clinically severe conditions for which Chinese herbalism is now applied in the West, the placebo effect is likely to be considerable. This means that studies have to be larger and particularly well-conducted, and adds another to the many difficulties (like lack of patentability, low retums on investment and the scepticism of ethics committees and potential collaborating physicians) faced in providing such evidence.

Questions of efficacy also raise issues of safety in the conventional view. A substance with pharmacological effect has, by definition, the possibility of a toxicological effect. The claim of proponents of herbal medicine is that in plant remedies the pharmacological effect is a balanced complex of interactions: in those that have stood the test of time this complex has demonstrated a lack of risk, possibly by the synergism of low-level constituents or by the buffering of one constituent with another. There is little evidence of at least acute adverse effects in clinical experience. However, the pharmacotoxicological case is still circumstantial.

Chinese remedies that establish clinical efficacy in clinical trials will suffer the default implication that they will manifest concordant risks until they demonstrate otherwise. Even those who report with enthusiasm the results of a controlled clinical study of the use of a mixture of Chinese herbs in the treatment of persistent atopic eczema of children (M. P. Sheehan *et al., Lancet,* 1992, **340**: 13–17) advised that such herbs should only be prescribed with 6-monthly monitoring of liver and kidney function, and not supplied to women of child-bearing age without contraception and to those with histories of jaundice or alcohol misuse. It is important to note that there has been no follow-up to these important studies, not least because it proved impractical to generate a licensable medicine out of the formalation.

QUALITY OF CHINESE HERBS IN WESTERN MARKETS

All herbal remedies suffer the complications of being crude natural products grown or collected from a wide range of sources. The consumer is protected only by sound industrial practices informed by effective pharmacognostic disciplines. With the rapid increase in demand of Chinese herbs in the West there is undoubtedly greater temptation for suppliers to test the market with whatever they can sell. The faking of Chinese pharmaceuticals in some Asian countries is now suspected to be widespread. There have been serious incidents where adulteration has led to adverse effects, notably in a case in Belgium where adulteration with an *Aristolochia* species (especially *Aristolochia fang-chi*) for *Stephania tetranda* (mandarin name *hang fang ji*) was implicated in an outbreak of kidney failure among patients at a slimming clinic. Over 30 patients sustained terminal kidney failure and a number have since developed kidney cancer. Although the prospect of interaction with the concurrent prescription of diuretics is high, aristolochic acid in *Aristolochia* is known to be moderately nephrotoxic. Unfortunately, this form of substitution has been found to be common and ongoing, and regulators in the UK, Europe and North America have banned not only *Aristolochia* but a number of other remedies, such as *Stephania tetandra* and species of *Clematis* and *Akebia* (either of which may be sold as *mu tong*), as well as some formulae containing the above, because the risk of substitution could not reasonably be ruled out.

The whole incident has cast a serious cloud in the minds of Western regulators over the reliability of herbal medicines imported from China and Asia, and it is likely that there will be other developments. For the practitioner or user of Chinese herbs, problems are most likely in those buying from unfamiliar or small suppliers, especially those providing 'patented' formulations. Fortunately, there are a number of responsible importers in the West, some of whom use Chinese pharmacognostic expertise through their production process, and who favour dealing with State pharmaceutical houses on mainland China where quality regulation is applied. The *Chinese Pharmacopoeia* (Guangdong Science and Technology Fress, Guangzhou) provides quality standards for most of the herbal products available in the West. The best samples of Chinese herbs are among the highest-quality products available on the market. It behoves a potential user to ensure that they seek out such sources.

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Plants in African traditional medicine—some perspectives

A. Sofowora

In 1991, the World Health Organization (WHO) redefined traditional medicine (TM) as comprising 'therapeutic practices that have been in existence, often for hundreds of years, before the development and spread of modern scientific medicine and are still in use today. These practices vary widely, in keeping with the social and cultural heritage of different countries'. The practice of TM in Africa, even today, contains considerable mysticism and secrecy. Therefore, the WHO's original definition of TM, coined in the African region in 1976, and which took cognisance of the importance of 'the concept of nature which includes the material world, the sociological environment whether living or dead and the metaphysical forces of the universe' is still valid in Africa.

TRADITIONAL MEDICINE PRACTITIONERS AND THEIR TECHNIQUES

The practitioners of TM in Africa include herbalists, herb sellers, traditional birth attendants, bone setters, diviners, faith healers, traditional surgeons, spiritualists and others. The training of these practitioners is still by an apprenticeship of about 7 years minimum. The content of such training is not standardized. The techniques used in African TM derive from the basic understanding of the aetiology of disease, as conceived by traditional medical practitioners (TMPs), who believe that diseases arise not only from physical ailments and psychological causes (as in Western medicine) but also from astral influences, spiritual causes (due to evil thoughts and machination by enemies), esoteric causes (i.e. originating from the soul or caused by deeds of an individual before reincarnation). Because TMPs in Africa place so much emphasis on supernatural forces, they are consulted not only for sickness but also when misfortunes occur in the family or to an individual, as many such evil omens are ascribed in Africa to supernatural forces. TMPs observe their patients for symptoms and signs but do not perform any pathological examination because they lack training in such techniques. Diagnosis of the disease is made through anamnesis—observation of the patient for signs and symptoms, including visual examination, clinical examination, biological examinations (such as tasting of urine for the presence of sugar in the case of diabetics, or allowing the patient to urinate on the ground and watching for infestation by ants, smelling of sores for putrefaction etc.), divination, which can be by throwing of seeds (Sofowora, 2008) or bones, use of mind-changing plant drugs, use of astronomical signs and analysis of dreams. Although many of these methods can be utilized by TMPs, specializations do occur. The practitioners also refer patients to one another in appropriate cases.

Treatment types in African traditional medicine

African TM provides holistic treatment. The type of treatment varies and is sometimes indicative of the specialization of the practitioner.

Medicaments intended for internal and external application involve the use of vegetable organs (leaves, barks, roots, etc.), latex, resin, etc. Whole or parts of animals (snail, bone, etc.) and mineral substances (alum, kaolin, etc.) are also used. Although the medicine prescribed may contain only a single active item, it is often a multi-component mixture, some of the components of which act as preservatives, flavours or colouring agents. The multi-component preparation also contains ingredients for all the ailments (or symptoms) that need to be removed to restore the patient's balance. In this way, African TM differs from Western medicine, where a patient can receive a prescription of various tablets, capsules, mixtures along with other dosage forms to eradicate a reported case of illness. The medicaments used in African TM can be administered in the form of a liquid (decoctions, oily mixtures, etc.), solid (powders, ointments), semi-solid (balsams, etc.) or gas (steam

inhalation, incense, etc.). The only route of drug administration that is absent in TM in Africa is the intravenous (i.v.) route. The other routes are employed though in rather crude forms.

Other types of treatment used in African TM include therapeutic fasting and dieting, hydrotherapy, treatment of burns, dry heat therapy, blood letting (cupping or venesection), bone setting, spinal manipulation, massage, psychotherapy, faith healing (spiritual healing), therapeutic occultism and also obstetric and gynaecological practice.

Surgical operations carried out in African TM include male and female circumcision, tribal marks, whitlow operation, cutting of the umbilical cord, piercing ear-lobes, uvulectomy, tooth abstraction, trephination (or trepanation) and abdominal surgery. Common complications from the various surgical operations include tetanus, meningitis and septicaemia. No anaesthesia or X-ray diagnosis is used for these operative procedures. After each of the operations, the patient is treated with herbs to heal the wound.

Preventive medicine in African TM takes the form of simple hygiene in some cases, or the performance of regular sacrifices against the wrath of those gods, which, it is believed, leads to periodic epidemic diseases like smallpox and plague. However, health education is helping to modify these beliefs. Armlets, medicated rings, waist leather bands or special necklaces or charms are often worn as a preventive measure or talisman. Some charms are also used to prevent car crashes or to ward off evil spells from witchcraft; the efficacy of such preventive care has yet to be proven. Again, education by road safety corps personnel helps to dispel beliefs in charms for preventing road accidents.

Although there are minor differences all over Africa in TM practice, there is considerable similarity because of the closeness of the cultures of the African peoples, especially between neighbouring countries as the geographical barriers are artificial. For example, the sale of herbs is usually in the markets where food items (vegetables, etc.) can be purchased. This is so all over Africa, although a section of a big market may be set aside for herb sellers' stalls.

In divination, bone throwing is done in southern Africa but seed throwing is done in Western and Central Africa. Seven seeds are used in Central Africa, whereas seed throwing of sixteen or eight seeds is used in Western Africa. The divination process involves, in all cases, the interpretation of the arrangement of the elements (seeds or bones) after being thrown on the ground by the TMP in order to predict or divine on a particular complaint or situation for the patient. These practices continue despite education, and diviners are consulted both by the educated elite as well as by the illiterate.

Ethnopharmacological themes, as illustrated by sub-Saharan art objects and utensils, have been discussed in an illustrated article by De Smet (1998).

Scientific evidence supporting some practices and remedies in African traditional medicine

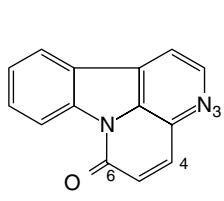
Attempts have been made by scientists to justify or rationalize, on a scientific basis, many aspects of the practice of the African TMP. Some of these practices are inexplicable, whereas others, like the use of many of the herbs, can be rationalized.

Plants of *Ageratum conyzoides* L. collected at night are used to treat children who cry too often for no known cause, especially at night. Night collection of this herb is particularly indicated when the frequent crying is suspected to be due to the influence of witchcraft, or to persistent disturbance from the spirits of the child's playmates (dead or alive), thus requiring the use of the 'occult' power of the herb. The following procedure is followed: A suitable location of *A. conyzoides* is found during the day. Very late at night, the collector approaches the plant and chews nine or seven seeds (for male or female, respectively) of melegueta pepper (*Aframomum melegueta* K. Schum.). The chewed grains are spat on the plant while the appropriate incantations are recited. The plant is then plucked and warmed over a fire at home before the juice is expressed. Palm oil (expressed from the mesocarp of *Elais guineinsis* family, Palmaceae) is added to the pressed juice and the mixture used to rub the whole body of the patient. *Ageratum conyzoides* is commonly used in TM for dressing wounds and ulcers, for scabies and as an eyewash. It is used as a styptic in East Africa (Kokwaro, 1993). These common uses result from its antimicrobial properties, which have been demonstrated scientifically but the special effect (occult power) it is claimed to possess when collected at night cannot easily be rationalized on a scientific basis, especially when there is no precise diagnosis of the disease. There are, however, other practices in African TM that are justifiable scientifically. Some examples are given below.

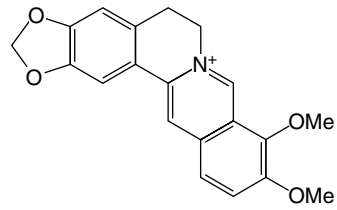
In many African homes, teeth are cleaned in the morning by chewing the root or slim stem of certain plants until they acquire brush-like ends. The fibrous end is then used to brush the teeth thoroughly. These chewing sticks impart varying taste sensations: a tingling, peppery taste and numbness is provided by *Zanthoxylum zanthoxyloides* Waterman (*Fagara zanthoxyloides* Lam.) root, a strong bitter taste and frothing by *Masularia acuminata* (G. Don.) Bullock ex Hoyle stem, and an initial bitterness becoming sweet later by *Vernonia amygdalina* Del. root. The root of *Terminalia glaucescens* Planch. produces a discoloration of the mouth. The most popular chewing sticks are those with a good flavour and texture, and a recognized effect on the teeth and supporting tissues. Freshly cut specimens are always desirable because they are more easily chewed into a brush. Some of them, however, possess such tough fibres that they penetrate the gums during use, thus causing some discomfort (Sofowora, 2008).

Buffered extracts of the common chewing sticks show antimicrobial activity against oral microbial flora but to varying degrees (Sote and Wilson, 1995; Taiwo *et al.*, 1999; Almas, 2002; Ndukwe *et al.*, 2005). Some African chewing sticks are also reported to contain fluoride ions, silicon, tannic acid, sodium bicarbonate and other natural plaque-inhibiting substances that can reduce bacterial colonization and plaque formation. The antimicrobial activity of the most effective (*Z. zanthoxyloides*) was shown to be due to berberine, chelerythrine and canthine-6-one (Fig. 38.1), which are most active at pH 7.5 (or during tooth decay) and simple benzoic acid derivatives, which are most active around pH 5 (or after an acid drink like lime juice). These data indicate that the chewing sticks, in addition to providing mechanical stimulation of the gums and removing food particles from the teeth crevices, also destroy oral microbes. Some African chewing sticks have been reported to contain fluoride ions, although their fluoride content was considered insufficient to produce a significant increase in the fluoride content of the dental enamel. Plant parts used as chewing sticks also have been shown to contain not only fluoride but also silicon, tannic acid, sodium bicarbonate and other natural plaque-inhibiting substances that could reduce bacterial colonization and plaque formation (Ogunmodede, 1991; Sote and Wilson, 1995; Taiwo *et al.*, 1999; Almas, 2002; Ndukwe *et al.*, 2005).

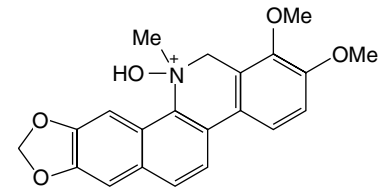
Other practices used in African TM, such as collecting certain plants only at certain seasons, using cold extraction instead of hot for some herbs, using young instead of old leaves of certain plants, using fallen dead leaves of certain plants rather than fresh ones, etc. have been rationalized as being due to seasonal, diurnal or age variations in active constituents of plants or the thermolability of the active ingredients of certain plants.



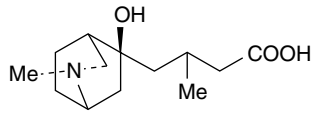
Canthine-6-one



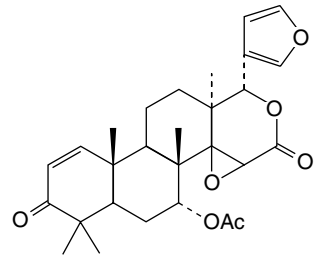
Berberine



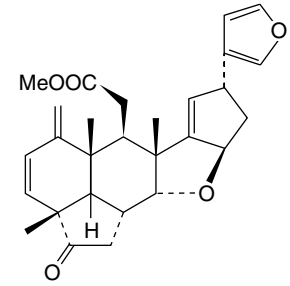
Chelerythrine



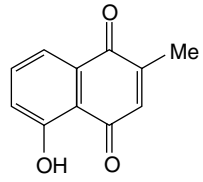
Dioscoretine



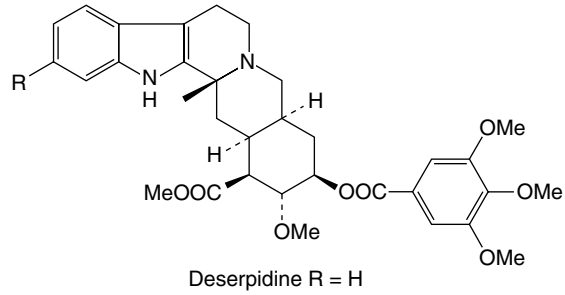
Gedunin



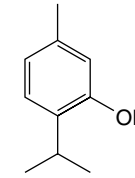
Nimbolide



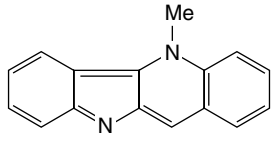
Plumbagin



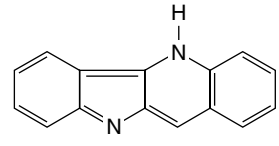
Deserpidine R = H
Reserpine R = OMe



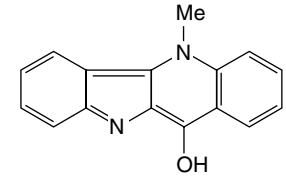
Thymol



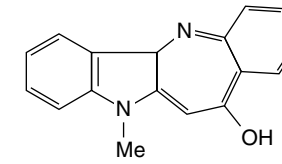
Cryptolepine



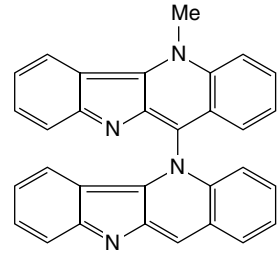
Quindoline



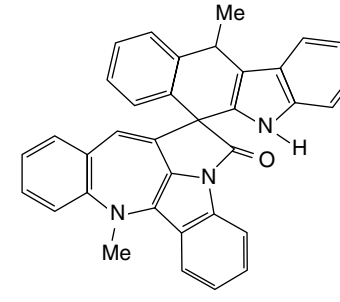
Hydroxycryptolepine



Cryptoheptine



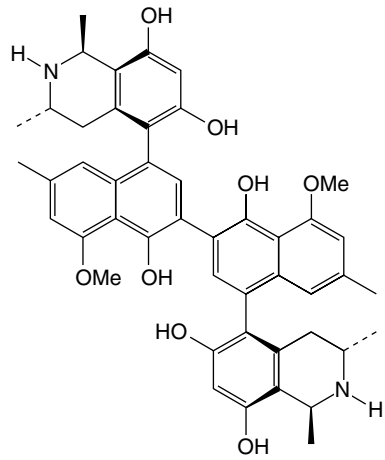
Cryptoquindoline



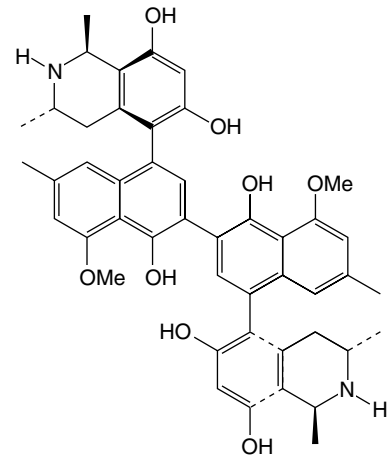
Cryptospirolepine

Fig. 38.1
Some chemical structures associated with African medicinal plants (see text).

(Continued)



Michellamine A



Michellamine B

Fig. 38.1—Cont'd

The following are the summarized results from a few examples of the investigations carried out to prove the efficacy claimed for medicinal plants used in African TM.

Dioscorea dumetorum (Kunth) Pax tubers are used in African TM, in carefully regulated doses, for the management of diabetes mellitus (Iwu, 1993). Crude extracts of the tuber were shown to possess a hypoglycaemic effect in normal rats and rabbits and were checked for hypoglycaemia produced by alloxan. From the active aqueous fraction, dioscoretine (Fig. 38.1) was characterized as the hypoglycaemic agent by using bioassay-guided fractionation of the extract. Of the solvent fractions tested for toxicity, the aqueous fraction used in TM was the least toxic LD_{50} = 1400 mg kg^{-1}. Further work has been recommended by the researchers before dioscoretine or the extract of the tuber can be exploited commercially as careful control of the dosage was found necessary even by TMPs.

Polygala nyikensis is used by the highlanders of Malawi and bordering countries to treat various skin problems of fungal origin. The root of the plant was recently shown to exert its antifungal activity owing to the presence of xanthones (Marston *et al.*, 1993).

Azadirachta indica leaves and stem bark are used in treating malaria and have been shown to be effective *in vitro* and *in vivo*. Rochanankij *et al.* (1985) associated the antimalarial activity with nimbolide while Khalid and Duddeck (1989), using a bioassay-directed purification procedure, named another limonoid, gedunin (Fig. 38.1), as the active principle. The possibility that the extract of neem acts by causing a redox perturbation by imposing substantial oxidant stress during malarial infection has been postulated. The antiplasmodial and larvicidal activity of neem has been confirmed by others (Dhar *et al.*, 1998; Isah *et al.*, 2003; Nathan *et al.*, 2005; Udeinya *et al.*, 2006; Okumu *et al.*, 2007; Soh and Benoit-Vical, 2007).

The published scientific proof for the efficacy of other African plants was reviewed by Sofowora (1993) while the efficacy of others can be readily deduced from their active constituents. For example, the use of *Rauwolfia vomitoria* roots (containing reserpine) in treating some mentally ill patients; *Plumbago zeylanica* root (containing the naphthoquinone, plumbagin) for treating various fungal skin diseases; *Ocimum gratissimum* leaves (containing essential oils rich in thymol) for treating diarrhoea are all clearly justifiable (Sofowora, 2008). Other plants whose active constituents have not been characterized have also been demonstrated experimentally in the laboratory to be efficacious. Examples of these include remedies used in treating skin diseases and the use of *Combretum mucronatum* and *Mitragyna stipulosa* as anthelminthics (Sofowora, 2008).

Theories on the origin of herbal medicine in Africa

Although it is not known exactly when the humans first practised herbalism in Africa, a number of theories have been advanced by scholars and TMPs alike to explain the acquisition of this knowledge by early Africans. One such theory states that early man in Africa deliberately selected specific plant materials for the treatment of his ailments as man had the ability to rationalize rather than to rely on instinct as do lower animals. The choice was certainly not based on the knowledge of the plant constituents. Some anthropologists state that early man lived in fear, and that, to allay this, he indulged in mystical and religious rituals. Thus, it could well be that the initial selection of plant materials for medicinal purposes was influenced by religious thoughts and collections were accompanied by magical rituals. Some plants are still used in the rituals of traditional religion in many parts of Africa today.

It has been proposed that the knowledge of medicinal plants in Africa was gained by accident, although this theory has been refuted by a number of African TMPs, who claim that information on such plants was communicated to their ancestors in various ways. However, early Africans could have gained some specific knowledge by watching the effects produced by various plants when eaten by domestic animals. Even today, some herbalists try out remedies, in the presence of their patients, on domestic animals, especially when testing for toxicity, and on themselves or their relations. Such tests prove to the patient that the preparation is harmless and sometimes also confirm that the dosage prescribed is also justifiable. Such information on African medicinal and toxic plants has been passed on orally from generation to generation and even today there are many herbal cures in Africa that have not been written down (Sofowora, 2008).

According to some TMPs another possibility is that knowledge of traditional cures came from wizards and witches. It is believed that some witches, whether living or dead, attend village markets in strange forms—as goats, sheep or birds. If their presence in this disguise is detected by someone very shrewd or gifted, such as a TMP, the practitioner is promised some useful herbal cures in return for not exposing the witch in disguise. The same reward would be offered if a real-life witch was caught in the process of performing an evil act.

Hunters, especially in African countries, have been reported as the original custodians of some effective traditional herbal recipes. Such knowledge could have been acquired when, for example, a hunter shot an elephant. If the elephant ran away, chewed leaves from a specific plant and did not die, it is believed the hunter noted the plant as a possible antidote for wounds or for relieving pain. Similar observations were made in villages where, for example, a domestic animal chewed

the leaf of a specific plant when that animal was ill and recovered later or when another animal accidentally chewed a leaf and died (Sofowora, 2008). Similar observations by scientists have confirmed that chimpanzees use medicinal plants in Africa for self-medication (Huffman and Wrangham, 1993).

TMPs also claim that, when in a trance, it is possible to be taught the properties of herbs by the spirit of an ancestor who practised herbalism. Spirits are said sometimes to assume various forms, e.g. an alligator, or a human being with one leg and one arm using a walking stick. If one encounters such a creature very late at night it can be a useful source of original information of herbal cures. In whatever manner the early Africans gained their knowledge of the curative powers of herbs, one must assume that they were able, thereafter, to recognize the plant, as the detailed flora available today describing medicinal plants were then non-existent.

RESEARCH INTO AFRICAN MEDICINAL PLANTS

Information on the use of medicinal plants has been obtained from herbalists, herb sellers and indigenous people in Africa over many years (Baba *et al*., 1992). Under the umbrella of Agence de Coopération Culturelle et Technique (ACCT) in Paris, ethnobotanical surveys with international teams had been carried out by 1988 in the following African countries: Central African Republic, Rwanda, Mali, Niger, Federal Islamic Republic of Comoros, Mauritius, Seychelles, Gabon, Dominica, Tunisia, Madagascar, Togo, Congo and Benin Republic. The African Union's Scientific Technical and Research Commission (AU/STRC) carried out similar surveys in Western Nigeria, Uganda, Cameroon, Ghana, Swaziland and Mozambique as at 2004 (Adjanohoun *et al.*, 1989, 1993, 1996; Mshana *et al.,* 2000; Adeniji *et al.*, 2001, 2004). All these ethnobotanical surveys have been published. Other ethnobotanical surveys on the region have also been published (Samuelsson *et al*., 1991).

As early as 1968, it was decided at a conference organized in Dakar by the AU/STRC that the efficacy of herbs used by TMPs should be tested, particularly in the following areas: anticancer, antimalarial, antihelminthic, antimicrobial, antihypertensive, cardiac activity, antisickling and antiviral. The following is a summary of the research to date, as indicated by publications on African medicinal plants collated by NAPRALERT database for natural products. Only 36% of all publications dealt with bioassay-guided isolation of plant constituents along with their pharmacological and toxicological testing. The remainder dealt with purely phytochemical research (including quantitative analysis). Biological screening work resulted in publications on antimicrobial activity (16%), molluscicidal (11%), antimalarial (7%), toxicity testing (7%) and antitumour related (4%), while other minor biological testing amounted to 55% of the total publications relating to bioassay-guided research on African medicinal plants to 1993 (Sofowora, 1993, 2008). In molluscicidal testing, three plants came out as having potential commercial exploitation, namely *Phytolacca dodecandra, Swartzia madagascariensis* and *Tetrapleura tetraptera*. The field trials on these and toxicity studies against non-target organisms have been carried out successfully in ponds where the intermediate host snail of schistosomiasis is prevalent (Hostettmann, 1991).

Cryptolepis sanguinolenta, which is used for treating urinary infections in TM, has been shown to be strongly antimicrobial. Cryptolepine was identified as the active alkaloid. The extract of this root has been formulated for therapeutic use by the Centre for Research into Plant Medicine in Ghana. A new alkaloid, named cryptospirolepine (Fig. 38.1), was characterized from this root by Tackie *et al*. (1993) whereas hydroxycryptolepine, cryptoheptine and cryptoquindoline (three new alkaloids) were reported from a specimen of the same root collected in Guinea Bisau by Houghton *et al.* (1993). Paulo *et al.* (1993) have examined the alkaloids characterized by Houghton *et al.* (1993) from this root for antibiotic activity. All the alkaloids showed activity but to varying degrees against the test organisms used. According to Cimanga *et al.* (1996, 1997), this plant showed potent antibacterial, anticomplementary and moderate antiviral activities, but no antifungal effect. The results obtained by Paulo *et al.* (1994a, 1994b) after testing the root extracts and its alkaloids against diarrhoeal and other bacteria suggested that the roots could be a therapeutic alternative for bacterial etiologic diarrhoea in West Africa. See Sofowora (2008) for more research on *Cryptolepis sanguinolenta*.

Garcinia kola seeds are chewed for protection against liver disease and were shown to contain biflavonoids (Iwu, 1993; Tarashima *et al*., 2002). The biflavonoids and the crude extracts of the seed have been shown to be effective in protecting against liver damage (Farombi *et al.*, 2004, 2005; Odunola *et al.*, 2005; Adaramoye and Adeyemi, 2006a) and they ameliorate di-*n*-butylphthalate-induced testicular damage in rats (Farombi *et al.*, 2007). The mechanisms involved in the hepatoprotection were explained by Farombi in 2000. 'Kolaviron' has been patented for commercial exploitation and the methods for its isolation and quantification have been enunciated. Other activities reported for 'Kolaviron' and the extract of *Garcinia kola* include: Attenuation of indomethacin- and HCl/ethanol-induced oxidative gastric mucosa damage in rats, and hypoglycaemic and hypolipidaemic effects (Adaramoye and Adeyemi, 2006b), whereas toxicological investigations include on erythrocytes (Esomonu *et al.*, 2005), alteration of oestrous cycle in rats (Akpantah *et al.*, 2005) as well as the brine shrimp lethality and mutagenicity tests (Sowemimo *et al.*, 2007). The amino acid composition of the seeds has been reported by Adeyeye *et al.* (2007).

Thaumatococcus danielli produces a red fruit, the aril of the seed of which contains the polypeptide thaumatin. Thaumatin is almost 5000 times as sweet as sucrose on molar basis. It is a low-calorie, high-intensity sweetener suitable for sweetening pharmaceuticals for diabetics. The plant grows readily in the moist areas of Africa and the early researches on its development were carried out jointly by researchers in Ife (Nigeria) and Tate and Lyle Ltd in UK. It is used in soft drinks in Japan (Sofowora, 2008). Thaumatin I and Thaumatin II have been cloned and synthesized through recombinant DNA. The cloning experiments showed that the N- and C-terminal regions of both of the thaumatin molecules do not play any important role in eliciting the sweet taste of thaumatin (Masuda *et al.*, 2004; Zemanek and Wassermann, 2005; Ide *et al*., 2007).

Cassia podocarpa, which is used as a laxative in TM, has been shown to contain anthraquinone derivatives similar to those found in official senna of the *British Pharmacopoeia*. The leaves and pods were also compared for their biological efficacy with official senna and shown to be just as effective on a weight basis. *C. podocarpa* was also shown to be less toxic than official senna. This leaf has been formulated into tablets and recommended as a substitute for official senna in Africa through the work of African researchers (Abo and Adeyemi, 2002; Akomolafe *et al.,* 2004). Danafco (Ghana) Ltd. produces standardized tea bags of this leaf on a commercial scale. Similar work on *C. italica* has led to the development of laxatives based on this plant, now commercially available in Mali and other African countries.

Euphorbia hirta is used traditionally in treating diarrhoea and dysentery in African TM. Although it contains phorbol derivatives this plant has been shown to be effective *in vitro* and *in vivo* against *Entamoeba*, which causes amoebic dysentry. The plant has been formulated into mixtures and a preparation of the whole plant is also available commercially in Mali for use against amoebic dysentery (Keita, 1994; see also Sofowora, 2008).

Zanthoxylum zanthoxyloides (Lam.) Waterm. The 'antisickling' property of the root of *Z. zanthoxyloides* was discovered when it was observed that the aqueous extract preserved the red colour of blood in blood-agar plates during a screen for its antimicrobial activity. The extract was later shown to revert sickled HbAS, HbSS and crenated HbAA red blood cells to normal *in vitro*. The activity was also demonstrated in the root of other *Zanthoxylum* species, and *Z. gilletti* was found to be just as active as *Z. zanthoxyloides*. This, and previous observations, led to postulation of a membrane-based activity earlier reported for the extracts. Activity-directed fractionation of the aqueous extract located the ether fraction as the active fraction. GC-MS analysis of the ether fraction indicated the presence of phenolic and fatty acids. These acids are 2-hydroxymethylbenzoic acid, *p*-hydroxybenzoic acid, vanillic acid, *m*-hydroxybenzoic acid, 2-hydroxy-3-phenylpropionic acid, traces of stearic acid, linoleic and palmitic acids. Further analysis of the fraction confirmed the presence of these acids and identified additional ones: *p*-coumaric, caffeic and ferulic acids. Xanthoxylol [2-dimethylallyl-4-(3-hydroxypropyl)phenol] was also isolated from the root. *p*-Hydroxybenzoic acid, 2-hydroxymethylbenzoic acid, vanillic acid, 2,2-dimethyl-2H-1-benzopyran-6-butyric acid (DBA; which is a chemical modification of xanthoxylol) and two uncharacterized non-acidic isomers of butyric acid isolated from the root have all been shown to possess antisickling activity. DBA also causes a slight increase in the pO_2 of the HbSS. Although the extract from the root (*Z. zanthoxyloides*) and DBA have been reported as generally non-toxic to (whole) animals and intracellular enzymes of the red blood cell, such as glucose-6-phosphate and 6-phosphogluconate dehydrogenases, the extract was observed to revert sickled cells to round rather than discoid shapes in some experiments. DBA, however, has been shown to increase the activity of Ca^{2+}-activated Mg^{2+}-dependent ATPase in both normal HbAA and sickle HbSS cell membranes, suggesting an antisickling activity based on Ca^{2+} mobilization in the HbSS red cell membrane for the root extractives. Other synthetic benzoic acid derivatives known to possess antisickling activities are *p*-methoxybenzoic acid, 3,4-dihydroxybenzoic acid, 3,4-dimethylbenzoic acid and *p*-fluorobenzoic acid. Relating the observed antisickling activity to physicochemical parameters of substituted benzoic acids showed that increased lipophilicity enhances sickle-cell reversal activity and that electron-donating substituents play an important role in antisickling activity. Although the attempted preliminary clinical trial on sickle cell anaemia (SCA) patients was plagued with a high default rate, the results obtained appear to indicate significant diminution of painful episodes in treated individuals (Adesanya and Sofowora, 1994). A product developed from the extract of 'Fagara' is being marketed under the name DREPANOSTAT® in Togo and Benin Republics. In Burkina Faso and surrounding countries the herbal product FACA® which is a mixture of 'Fagara' and *Calotropis procera* is marketed for SCA (Sofowora 2008). The use of a leaf extract of *Terminalia catappa* as having antisickling potential has been supported by recent research involving human blood samples (Mgbemene and Ohiri, 1999). Research on other plants used in the management of SCA have been discussed by Adesanya and Sofowora (2008).

The development of bioassay techniques (Hostettmann, 1991) for antiviral activity in plants and the importance of finding a cure for HIV/AIDS has brought some African medicinal plants into prominence. About 120 plants have been reported to show antiviral activity (many of these grow in Africa, e.g. *Diospyros, Spondias, Terminalia* spp.), whereas others are reported to have immunomodulating properties, such as *Aloe* and *Zingiber* spp. etc. A new plant species, *Ancistrocladus korupensis* (Ancistrocladaceae), was discovered in Cameroon and found to contain new alkaloids: michellamines A and B, which have a wide spectrum of antiviral activity, including anti-HIV cytopathic activity. Efforts were made to develop michellamine B for use in HIV/AIDS treatment. It was characterized by collaborative effort of some Cameroon scientists and the National Cancer Institute in the USA. The plant is rare. Efforts are in progress to germinate the seeds in its natural habitat at Korup National Park, in glass houses and through tissue culture in collaboration with J. B. Johnson Biotech Laboratories (Manfredi *et al.*, 1991; Jato *et al.*, 1993). Readers should consult the review by Elujoba (2008) on plants used for the management of HIV/AIDS in Africa.

Nwosu (1999) has reported on 30 plants from 21 families which are used traditionally for the treatment of mental disorders in southern Nigeria.

In a review of over 240 higher plants that are used in Africa as arrow poisons, Neuwinger (1996) cites many as having medicinal properties.

TRADE IN MEDICINAL PLANTS IN AFRICA

The amount of trade in the area of medicinal plants in some African countries is well documented (see Table 38.1). It is known, for example,

Table 38.1 African medicinal plants exported for their active ingredients.

Species	Part used	Ingredient	Source area
Allanblackia floribunda	Fruit	Fat	Côte d'Ivoire
Ancistrocladus abbreviatus	Plant	Michelamine A and B(Alk) (Fig. 38.1)	Cameroon, Ghana
Corynanthe pachyceras	Bark	Yohimbine, corynanthine, corynanthidine	Ghana
Dennetia tripetala	Fruit	Essential oil	Ghana
Griffonia simplicifolia	Seed	BS11 lectin	Ghana, Côte d'Ivoire, Cameroon
Harpagophytum procumbens	Root	Glucoiridoids	Namibia
H. zeyheri	Root	Glucoiridoids	Namibia
Hunteria eburnea	Bark	Eburine, etc.	Ghana
Jateorhiza palmata	Root	Palmatine, jateorhizine, colombamine	Tanzania
Pausinystalia yohimbe	Bark	Yohimbine	Cameroon
Pentadesma butryacea	Fruit	Fat	Côte d'Ivoire
Physostigma venenosum	Fruit	Physostigmine (eserine)	Ghana, Côte d'Ivoire
Prunus africana	Bark	Sterols, triterpenes, n-decosanol	Cameroon, Kenya, Madagascar
Rauwolfia vomitoria	Root	Reserpine (Fig. 38.1), yohimbine, etc.	Zaire, Rwanda, Mozambique
Strophanthus spp.	Fruit	Ouabain	West Africa
Voacanga africana	Seed	Voacamine	Côte d'Ivoire, Cameroon, Ghana
V. thouarsii	Seed	Voacamnie	Cameroon

After Cunningham (1993a & b)

that the government of Cameroon is the major source for the world market of *Prunus africana* bark, where it has been harvested since 1972. Over a 6-year period (1986–1991), 11 537 metric tons of the bark (reaching an average of 700 tons) were processed by Plantecam Medicam, a French-owned company based in south-west Cameroon. *P. africana* bark represents 86% of the medicinal plants exported by this company between 1985 and 1991 (Cunningham and Mbenkum, 1993). The bark is used in treating prostate gland hypertrophy and benign prostate hyperplasia (Shenouda *et al.*, 2007; Dedhia *et al.*, 2008). Another major plant material exported by Cameroon is the seed of *Voacanga africana* (Apocynaceae), which is used for the production of the alkaloid tabersonine, used as a CNS depressant in geriatric patients. Cameroon exported US$40 million worth of *V. africana* in 1993 alone. Cameroon also exports *Tabernanthe iboga* and *Myrianthus arboreus*, but in small quantities (Cunningham and Mbenkum, 1993).

Capsules containing the extract of *P. africana* bark are marketed in Europe, where the market value of this trade is estimated at US$150 million per year. In addition to Cameroon, Kenya (1923 tons per year), Uganda (193 tons per year), Zaire (300 tons per year) and Madagascar (78–800 tons per year) export this bark to various pharmaceutical companies in Europe, mainly to Madaus in Germany and Spain, Laboratoires Debat in France, Prosynthèse in France, Inverni Della Beffa and Indena Spa in Italy (Cunningham and Mbenkum, 1993).

Three plants out of the 24 000 indigenous species of the Republic of South Africa have been developed as export products. These are Rooibos tea (*Asplathusa linearis*), Marula (*Sclerocarya birrea*) and *Aloe ferox*. About 500 million South African Rands per annum are spent on traditional remedies in the Republic of South Africa.

Namibia exports 200 tons of *Harpagophytum procumbens* and *H. zeyheri* tubers annually to Germany (80.4%), France (12.8%), Italy (1.9%), USA (1.5%), Belgium (1%) and South Africa (1.2%) (Cunningham *et al.*, 1992).

In Madagascar, the export sale of *Catharanthus roseus* and other plants represents a major export earner.

The roots of *Swartzia madagascariensis* and *Entada africana* are traded 500–800 kilometres from Burkina Faso and Mali to Abidjan in Côte d'Ivoire. Similarly, most of the common chewing sticks are sold across the borders of neighbouring countries in West Africa; 75–80 tons of *Griffonia simplicifolia* seeds are exported each year to Germany from Ghana; commercial gatherers in Côte d'Ivoire chop down *Griffonia simplicifolia* vines and *Voacanga africana* and *Voacanga thouarsii* trees in order to obtain the fruits for export (Cunningham, 1993a, 1993b). Large quantities of various medicinal plants are also exported to France by SETEXFARM in Senegal. These plants are collected from the wild and there is currently no evidence of any replanting. The harvesting of such large quantities of medicinal plants from the wild will eventually result in serious social or environmental consequences. To ensure the sustainable use of the medicinal plant resources of Africa, uncontrolled exportation of plants collected from the wild should give way to large-scale cultivation of the desired plants. Table 38.2 shows African medicinal plants whose demand exceeds supply.

Office National de Développement des Forêts (ONADEF) in Cameroon has applied its experience of indigenous (e.g. *Terminalia superba*) and exotic timber to species with medicinal values. Three species cultivated for bark production (*Prunus africana* and two exotic *Cinchona* species) and *Voacanga africana* cultivated for its seed have been propagated on a large scale. The foresight of ONADEF in implementing medicinal tree cultivation in plantations and through enrichment planting is exceptional in Africa and is encouraging (Cunningham and Mbenkum, 1993).

Table 38.2 African medicinal plants whose demand exceeds supply.

Species	Families
Alepidea amatymbica	Apiaceae
Asclepias cucullata	Asclepiadaceae
Begonia homonymma	Begoniaceae
Bowiea volubilis	Liliaceae
Cassia abbreviata	Fabaceae
Cassia sp.	(unidentified species known as muwawani)
Dianthus zeyheri	Illecebraceae
Garcinia afzellii	Clusiaceae*
Garcinia mannii	Clusiaceae*
Howorthia limifolia	Liliaceae
Monanthotaxis capea	Annonaceae
Pimpinella caffra	Apiaceae
Plectranthus grallatus	Lamiaceae
Siphonochilus aethiopicus	Zingiberaceae
Warburgia salutaris	Canellaceae*

*Trees/shrubs with agroforestry potential
Compiled from Cunningham (1993a, b)

Conservation of medicinal plants in Africa

More than 200 000 out of about 300 000 plants species identified in the whole of our planet are in the tropical countries of Africa and elsewhere. Among the potential uses of these African plants, those involving traditional medicines and pharmacopoeial drugs are foremost; 80% of the population of Africa living in rural areas relies on TM.

Approximately 1.8 million km^2 of the world's tropical rain forest (totalling roughly 9 million km^2) are in Africa, the rest being in America, Asia and few patches in the Indian Ocean and Pacific Islands. One-fifth of the total 120 000 (including 30 000 undescribed species) seed plants present in the tropical moist forest has been estimated to be present in Africa (Farnsworth and Soejarto, 1991). All over the world, and especially in Africa, factors that cause forest depletion include direct human pressure as well as indirect factors: commercial logging in the forest, fuel wood consumption, cattle ranching (where either excessive grazing causes depletion or selective grazing by cattle results in prolific growth of poisonous species), forest farming and forest fires. Environmental factors such as desert encroachment, pollution, acid rain, the greenhouse effect and erosion are other factors causing loss of forests.

The collection of medicinal plants by herbalists and herb sellers (herb traders) for local use and export also has had a noticeable depletion effect on this important forest resource in Africa, where collectors now have to travel farther afield to obtain the herbs to be used in their practice, as few of these are cultivated. According to Cunningham (1993a, 1993b), indigenous forests cover only 0.3% of South Africa but are a source of over 130 commercially exploited traditional plants; over 400 indigenous species and 70 exotic species are commercially sold to Zulu people as herbal medicines. These indigenous species are causing concern because of the depletion of wild stocks when demand exceeds supply. Scarce, slow-growing forest species are particularly vulnerable to this over-exploitation.

Mauritius and Rodriguez have two of the most threatened flora in the world. Over 150 species of plants on these African islands are threatened with extinction, out of which at least 30 species are known from less than 10 collections (Owadally *et al.*, 1991). According to Kokwaro (1991), high- and medium-potential land in Kenya constitutes about 17% of the country and supports 90%

of the population, which is mostly rural. The plant communities in such areas are usually the most threatened by over-utilization. The depletion rates of the forest resources, which include medicinal plants, are very high. For example, Kakamega, North and South Mandi forests, which occur in high-potential areas, are being cleared at the rate of 245, 295 and 490 ha per year, respectively (Kokwaro, 1991).

The sustainable management of the forest resources and the medicinal plants in them is important, so that while the benefits to present generations are satisfied the potential to meet the needs and aspirations of future generations is not jeopardized. Conservation activities involving medicinal plant gardens maintained by herbalists, herbaria and various arboreta are scattered all over Africa. Some countries have also started special programmes to conserve the genetic resources of their medicinal plants. Although there is a need to utilize all the conventional methods of conservation (*in situ* and *ex situ* conservation, gene banks, biotechnology, etc.), the education of rural dwellers, particularly the herbalists and the herb sellers, in conservation awareness is important for an effective approach to the sustainable utilization of the medicinal plant resources in Africa. One group of TMPs in South Africa collaborates with the conservation of Traditional Healing Practices and Plants Project (CTHPPP) at Bulwer, in South Africa, for the conservation of medicinal plants. The project successfully cultivated more than 30 indigenous plant species. This young ethnobotanical reserve is currently being used to train TMPs in the Bulwer area in the identification of medicinal plants. This kind of approach, rather than merely relying on legislation, is to be encouraged. Attempts to stop the exploitation of *Prunus africana* in Cameroon by banning merely led to a rise in its exportation through illegal channels from 700 tons per year to over 1000 tons per year (Mbenkum and Thomas, 1993). Since 1995, *P. africana* has been included in CITES Appendix II as an endangered species. In 2000, Plantecam, the largest bark exporter in Africa, closed its extraction factory in Cameroon, due to complex ecological, social and economic factors. Wild collection is no longer sustainable (and probably never was) where harvest seriously affects morbidity and mortality rates of harvested populations (Stewart, 2003). Alternatives to wild collection to meet future market demand—including conservation practices, enrichment plantings, small- and large-scale production and protection of genetic resources—have been proposed by Stewart (2003). *P. africana* is at the beginning of a transition from an exclusively wild-collected species to that of a cultivated medicinal tree.

THE AFRICAN PHARMACOPOEIA

Reports of the uncontrolled dosage of herbal remedies used by TMPs necessitated a research programme to carry out quantitative pharmacognostical analysis on some common African medicinal plants. Data accumulated from such research were used to compile the first *African Pharmacopoeia* (*AP*) published by AU/STRC (1985, 1986). The *AP* specifies quality control standards to be met by the plants when used in commerce and in manufacturing pharmaceutical preparations. Volume 1 of the *AP* contains monographs on 100 medicinal plants, whereas volume 2 describes the methods to be used in their quality control. Some of the old reliable methods of plant analysis are still retained (along with the most modern techniques) as alternatives in this volume as many African countries cannot afford the sophisticated spectroscopic instruments used in quality control today. The *AP* is available in English, French and Arabic. Some African countries have produced their own national herbal pharmacopoeiae, e.g. Ghana and Nigeria.

CONCLUSION

With the development of simpler, inexpensive bench-top bioassays (Hostettmann, 1991), it is expected that in future many hitherto untested natural products isolated from African plants will be put through a variety of biological tests.

The current awareness of HIV/AIDS in Africa and the development of screening programmes for anti-HIV activity in plants will herald the screening of more African plants claimed by TMPs to be used in treating HIV/AIDS-related symptoms. This is of increasing importance because, in addition to being a sexually transmitted disease, HIV/AIDS is also contracted through blood transfusion when adequate care is not taken to use only HIV-free blood. Some patients with diseases like sickle-cell anaemia who require blood transfusion because of lack of an available cure (this disease kills 120 000 or more children annually in Africa) need to be considered especially in HIV/AIDS and primary health care programmes. More attention should also be given to the possibility of cures, from plant sources, for HIV/AIDS. However, it will be necessary to determine what indications in the treatment or diagnostic mode of the TMP should be looked for in identifying candidate plants for HIV/AIDS cure (see Elujoba, 2008).

Tissue and suspension cultures of some African medicinal plants have also been developed in various laboratories, but mainly outside Africa, for the future biotechnological production of the secondary plant metabolites of these plants for drugs needed world-wide. Examples include *Catharanthus roseus, Ammi majus* and *A. visnaga*, and *Tribulus terrestris* (see also *Thaumatococcus danielli*, above). This trend will probably be intensified to prepare for the future demand for drugs in relation to conservation efforts.

While national *materia medica* of herbs are being compiled, it is expected that efforts will continue to eliminate toxic plants from the recipes of the TMPs, and to encourage the use of the harmless ones, which will be made available on a large scale in standardized dosage forms not only for home use but also for export.

Many countries in Africa (for example, Rwanda, Egypt, Mali) now cultivate medicinal plants on a large scale for local processing into galenicals, teas, various dosage forms and other standardized preparations for use in health care. It is expected that activity in this direction will increase in Africa with assistance from UNIDO as more can be derived economically by making simple extracts of medicinal plants rather than exporting them as raw materials. Drug production from medicinal plants in Africa should be further intensified in African countries through public/private/partnership (PPP) arrangements, so that Africa can contribute more to the global trade in medicinal plant products.

The formation of networks of laboratories to bring African countries together for collaborative research and development work on natural products generally and medicinal plants in particular is expected to increase. The creation of the Natural Products of East and Central Africa (NAPRECA) network by UNESCO has given a boost to inter-African collaborative research efforts on medicinal plants in that subregion of Africa. This led to the creation of the West African network, also with UNESCO support. The International Organization for Chemistry in Development (IOCD) has encouraged the creation of a Network of Analytical and Bioassay Services in Africa (NABSA), with headquarters in Addis Ababa University, Ethiopia. This network was created to encourage the bioassay of natural products from phytochemical research by pooling existing analytical facilities in African laboratories. All these efforts are expected to boost output in research and development work in this field. With institutional strengthening of African laboratories taking place, it is hoped that more and more of

the collaborative research with developed countries can take place in Africa where labour is relatively cheap.

The old methods and practices of traditional medicine in Africa are being transformed with the awareness of the TMPs for the need for more precise dosage in the use of their herbal remedies. Retraining programmes are going on in several countries, with a view to improving the competence of the TMPs and the quality of health care that they deliver on a continent where 80% of the people have only TM available to them. Research has provided evidence for the rationalization of some of the practices of the TMPs and the efficacy of some of the herbs they use while new natural products with potential for drug development for management of diseases rampant world-wide are emerging from African plants. It is hoped that increased inter-African and international collaborative research and sustainable use of biodiversity resources in Africa will help to develop new drugs from the rich untapped forests of Africa for the betterment of mankind.

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PART

7 Non-medicinal toxic plants and pesticides

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39

Hallucinogenic, allergenic, teratogenic and other toxic plants

The plants included in this chapter are toxic species which, although finding little use in modern medicine, are, because of the pharmacological effects which they produce, of considerable interest to pharmacognosists.

HALLUCINOGENS

Most cultures of man, from earliest times, have had recourse to some form of narcotic, often hallucinogenic, drug. These hallucinogens, often derived from plants, have frequently been used within a religious context. In recent years peyote, Indian hemp and lysergic acid derivatives have received much attention, but there are many other similar drugs used by local populations whose existence and use are still being investigated by ethnobotanists. In this respect, Professor R. E. Schultes (1915–2001) made extensive studies of such plants in South America and has emphasized the great need for recording the wealth of knowledge possessed by native tribes on narcotic plants before the activities of these peoples are overcome by 'civilization'.

With the exception of cannabis, the principal known hallucinogenic plants contain alkaloids related to the neurophysiological transmitters noradrenaline and 5-hydroxytryptamine (serotonin).

FUNGI

Some of the poisonous fungi when taken orally produce hallucinations; these include toadstools of the genera *Amanita, Psilocybe* and *Conocybe*.

The Amanitas. A number of *Amanita* species, in addition to promoting hallucinogenic effects, are extremely toxic. The appearance of the serious symptoms is considerably delayed (particularly with amatoxins, formula Fig. 39.1) after ingestion, by which time effective treatment becomes difficult. Three classes of toxins are recognized in the genus—tryptamines (e.g. bufotenine), cyclic peptides (phallotoxins and amatoxins) and isoxazole alkaloids (e.g. ibotenic acid, formula Fig. 39.1). The three classes of compound appear to be restricted to certain specific sections of the genus.

The fly agaric. The fly agaric (*Amanita muscaria*) is readily distinguished by its red or orange cap, often covered with white flecks. It contains a mixture of isoxazole alkaloids ibotenic acid and muscimol. Polysaccharides and a carboxymethylated derivative of the fungus have been shown to possess antitumour activity (T. Kiho *et al*., *Biol. Pharm. Bull*., 1994, **17**, 1460). The pigments (betalains) of the fungus, also found in the Caryophyllales, are formed from tyrosine and the rapid development of pigment formation in *A. muscaria* has given an ideal system for isolating the enzymes involved (L. A. Mueller *et al*., *Phytochemistry*, 1996, **42**, 1511; 1997, **44**, 567).

The pharmacological effects appear within an hour or so of ingestion, with an initial period of excitation followed by muscular twitches, a slowed pulse rate, impaired breathing, delirium and coma; however, ingestion of the fungus is rarely fatal. The mushroom has a traditional use as an inebriant in regions of Siberia; one hypothesis suggests it to be the *soma* of the Rig Veda. The panther cap, *A. pantherina*, contains similar principles including pantherine (5-aminomethyl-3-hydroxyisoxazole), a flycidal alkaloid. A branched (1→3)-β-D-glucose isolated from an alkaline extract of the fungus exhibited significant activity in mice.

Hallucinogenic Mexican mushrooms. A number of small toadstools—particularly species of *Psilocybe* (*P. mexicana*), *Conocybe*

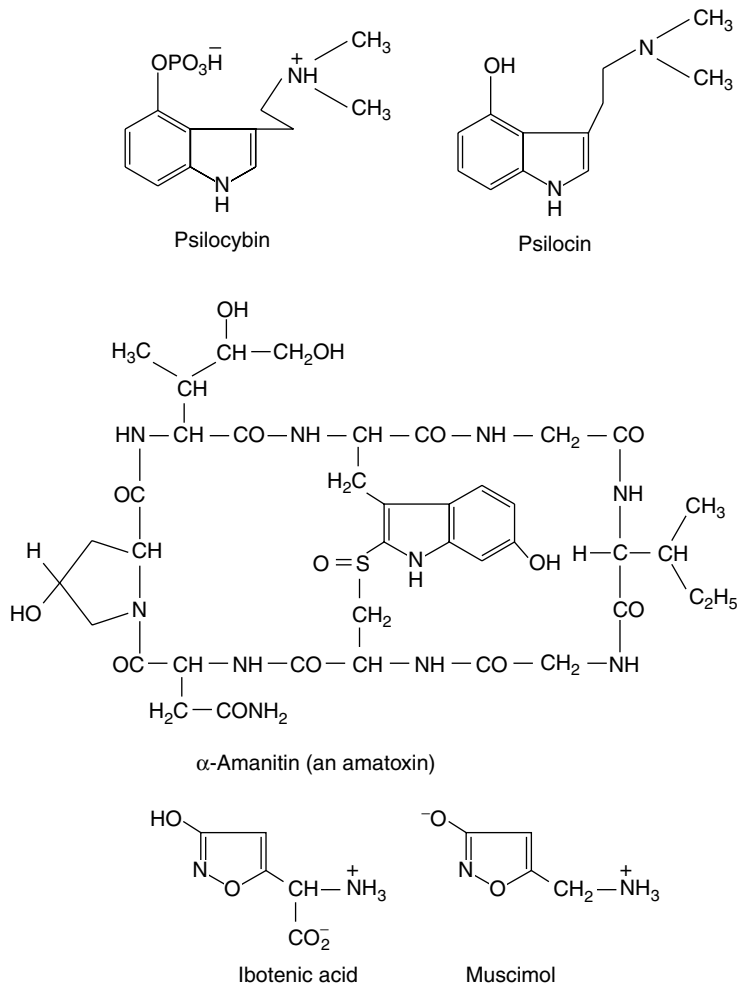

Fig. 39.1
Toxic and hallucinogenic constituents of fungi.

(*C. cyanopus*) and *Stropharia*—constitute the Mexican hallucinogenic mushrooms (*teonanacatl*, 'flesh of the gods', much revered by the Aztecs). The onset of symptoms after ingestion of the fungi is rapid, and includes inability to concentrate and the occurrence of hallucinations. The active constituents are the tryptamine derivatives psilocybin and psilocin, compounds related to serotonin. These compounds are also found in similar toadstools (e.g. *Psilocybe* and *Paneolus, Copelandia, Gymnopilus, Inocybe, Panneolina, Pluteus* and *Stropharia* spp.) which are found in temperate regions. In Britain the 'liberty cap', *Psilocybe semilanceata*, a small toadstool common on lawns and parkland, and in Australia *P. subaeruginosa* both contain psilocybin. What is claimed to be the highest proportion of psilocin contained in any mushroom (3.3%, dry weight) was reported in *Psilocybe cubensis*; for a review of the mushroom alkaloids (567 refs), see R. Autkowiak *et al*., *Alkaloids*, 1991, **40**, 189); for the concise large-scale synthesis of psilocin and psilocybin, see O. Shirota *et al*., *J. Nat. Prod*., 2003, **66**, 885.

Puffballs. Species of *Lycoperda* contain constituents which produce auditory hallucinations and a state of half-sleep about half an hour after consumption. The effects are distinct from those caused by the mushrooms. Puffballs are used by the Mixtecs of Southern Oaxaca in Mexico.

LYSERGIC ACID DERIVATIVES

The hallucinogenic properties of lysergic acid, and, in particular, the diethylamide derivative (LSD), are well-known. This acid forms the non-peptide portion of a number of ergot alkaloids (q.v.) and can also be produced by suitable cultivation of the fungus in liquid culture. It was with some surprise that lysergic acid was also found as a component of some convolvulaceous seeds (species of *Ipomoea, Rivea* and *Argyreia*), and as far as is known at present they constitute the only higher plants containing ergot-type alkaloids.

Morning Glory seeds. In the sixteenth century the Spaniards in Mexico reported the use of sacred hallucinogenic seeds known as 'ololiuqui'. The climbing plant from which they were obtained was subsequently identified as *Rivea corymbosa*. Closely related in constituents and action are the seeds of *Ipomoea tricolor* (*I. violacea*) and those of various species of *Argyreia*. The name 'Morning Glory' is applied to *Ipomoea tricolor* but also to a number of other species (e.g. to *I. purpurea* and to the Japanese Morning Glory, *I. hederacea*). The trade names of species of *Ipomoea* are endlessly mixed. The seeds of the above-mentioned *Ipomoea hederacea* have long been used in the East as a purgative and were formerly official in the *British Pharmacopoeia* under the name 'kaladana' or 'pharbitis seeds'.

PEYOTE

Certain cacti are of pharmaceutical and pharmacological interest, as they contain protoalkaloids, some of which have marked hallucinogenic properties. One of these is the cactus *Lophophora williamsii* which has long been used by Mexican Indians. It is known as peyotl, anhalonium or mescal buttons. The latter name is derived from the cactus stems, which are cut into slices about 20–50 mm in diameter. An interesting report (H. R. El-Seedi *et al*., *J. Ethnopharm*., 2005, **101**, 238) sheds more light on its possible use by native N. Americans some 5700 years ago: two specimens from the Witte Museum in San Antonio were radiocarbon-dated to 3780–3600 BCE and, on analysis (TLC and GC-MS), gave alkaloids (2%) in which mescaline was identified, making these the oldest examples of a plant drug to yield a major bioactive compound. The chief active constituent is the alkaloid mescaline. The chemistry dates back to 1888, in which year Lewin isolated anhalonine, a crystalline tetrahydroisoquinoline alkaloid. By 1973 some 56 alkaloids had been characterized from the cactus and these could be classified as (1) mono-, di- and trioxygenated phenethylamines and their amides; (2) tetrahydroisoquinoline alkaloids and their amides; (3) phenethylamine conjugates with Kreb's cycle acids; (4) pyrrole derivates. Examples of these groups are given in Fig. 39.2. The alkaloids can arise in the plant from dopamine, and grafting experiments involving *Trichocereus pachanoi* ('San Pedro') (a mescaline-producing species) and *T. spachianus* (no mescaline) have indicated that biosynthesis of the hallucinogen is confined to the aerial parts.

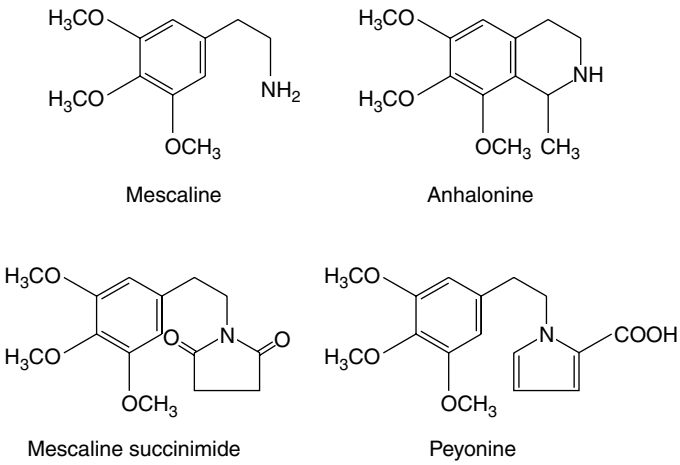

Fig. 39.2
Representative alkaloids of peyote.

INDIAN HEMP

The Indian hemp plant was originally considered as a distinct species but came to be regarded as a variety of *Cannabis sativa*, the common European hemp, which thus exhibited a variety of ecotypes giving rise to differing cannabinoid mixtures. Subsequently (in 1974), a case was presented by American taxonomists for the recognition of three distinct species. *C. sativa, C. indica* and *C. ruderalis*. Other botanists have proposed sub-species of *C. sativa*.

The plant is found wild in India, Bangladesh and Pakistan. The drug consists of the dried flowering and fruiting tops of the pistillate plants from which no resin has been removed. Limited cultivation is permitted in some countries. The drug has been produced in East Africa, South Africa, Tripoli, Asia Minor and USA. Large confiscations of illicit cannabis and its preparations continue to be made in most countries. In temperate climates large quantities of hemp are grown for the stem fibre and for the seeds, which yield 30–35% of a drying oil.

History. Hemp has been cultivated for its seeds and fibres from a very remote period, but the narcotic properties are usually not marked in plants grown in temperate regions, and even in India an active drug can only be grown in certain districts. The drug is mentioned in early Hindu and Chinese works on medicine, and its use slowly spread through Persia to the Arabs. It was used by the Mohammedan sect known as the Hashishin or Assassins, who came into contact with the Crusaders in the eleventh and twelfth centuries. The drug attracted the attention of Europeans at the time of Napoleon's Egyptian expedition.

Hemp products

Three main type of narcotic product are produced.

1. The Indian hemp or *ganja* of the *Indian Pharmacopoeia* (1955) is required to contain 'not more than 10% of its fruits, large foliage leaves and stems over 3 mm'. This is the *flat-* or *Bombay-ganja*, which was formerly official in many pharmacopoeias. Round- or *Bengal-ganja* is prepared by rolling the wilted tops between the hands.
2. *Bhang* (Hindustani) or *Hashish* (Arabic) consists of the larger leaves and twigs of both male and female plants. It is used in India for smoking, either with or without tobacco and drugs such as opium or datura, or is taken in the form of an electuary made by digestion with melted butter.
3. *Charas* or *churrus* is the crude resin. This is obtained by rubbing the tops between the hands, beating them on cloths or carpets, or by natives who wear leather aprons walking among the growing plants. The resin is scraped off and forms an ingredient of numerous smoking mixtures. Like *bhang*, it is also used with butter.

In America and Europe the product used by addicts is known as *marihuana*, in north Africa as *kief*, in South Africa as *dagga*, and in Arabia and Egypt as *hashish*.

Production of ganja. This is legally only produced by a few licensed growers in Bengal, Mysore and Madras. The seed is sown in rows about 1.3 m apart and male plants are eliminated as soon as they can be recognized. The resinous tops, largely of unfertilized female plants, are cut about 5 months after sowing and pressed into cakes. The yield is about 120 kg per acre.

Macroscopical characters. The flat- or Bombay-ganja occurs in agglutinated flattened masses of a dull green or greenish-brown colour. The resin is no longer sticky but hard and brittle; the odour, which is very marked in the fresh drug, is faint. The drug has a slightly bitter taste. Here and there ovoid hemp seeds may be picked out. Before further examination the drug should be soaked in successive quantities of alcohol to remove the resin and then softened in water.

The lower digitate leaves of the plant are seldom found in the drug. The thin, longitudinally furrowed stems bear simple or lobed, stipulate bracts. These subtend the bracteoles, enclosing the pistillate flowers. The bracts are stipulate and the lamina may be simple or three-lobed. The bracteole enclosing each flower is simple. The perigone enveloping the lower part of the ovary and the two reddish-brown stigmas can be seen with a lens.

Microscopical characters. The resin is secreted by numerous glandular hairs, 130–250 μm long (see Figs 39.3; 42.5). The head is usually eight-celled and the pedicel multiseriate or unicellular. To differentiate these from similar trichomes (e.g. those of the Labiatae) specific

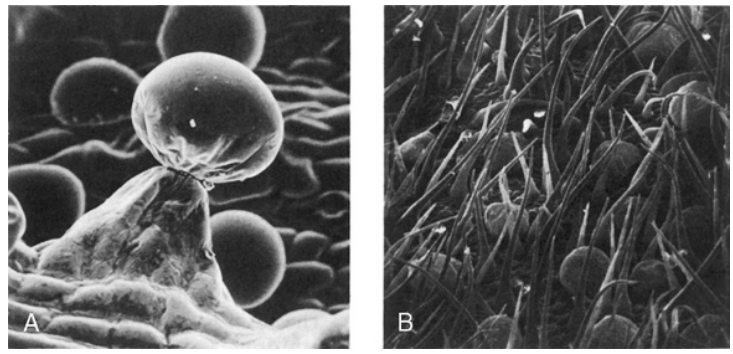

Fig. 39.3
A, typical stalked glandular trichome from bracteole ×270. B, sessile glandular trichomes and covering trichomes, ×130. (J. W. Fairbairn.)

stains can be used. These include Fast Blue Salt B and, as described by Corrigan and Lynch in 1978, a reagent consisting of vanillin in ethanolic sulphuric acid which stains the cannabis glands a deep reddish-purple. It is possible to analyse individual trichomes by GLC by which means it has been shown that the glands represent a dynamic system in the cannabinoid synthetic activity of the plant. In addition, sessile glands (Fig. 39.3), abundant conical, curved, unicellular hairs, are also found, many having cystoliths of calcium carbonate in their enlarged bases (see Figs 39.3; 42.3); however, these cystolith hairs are not confined solely to the genus *Cannabis*. Cluster crystals of calcium oxalate are abundant, particularly in the bracteoles.

Constituents. The narcotic resin is a brown, amorphous semisolid; soluble in alcohol, ether and carbon disulphide. It contains over 60 compounds (cannabinoids) all composed of an aromatic portion (C_{11} or C_{12}), theoretically derivable from six acetate units, and an isoprenoid component (C_{10}). They appear to form a natural group of C_{21} terpenophenolics of unique occurrence. Some principal components are cannabinol, tetrahydrocannabinol (THC), cannabidiol (CBD), cannabidiol-carboxylic acid, cannabigerol and cannabichromene (Fig. 39.4). Cannabinodiol is the aromatic analogue of cannabidiol. Cannabigerol precedes Δ^9-THC in the biosynthetic pathway and is incorporated, by the plant, into the latter and other neutral cannabinoids. The identification

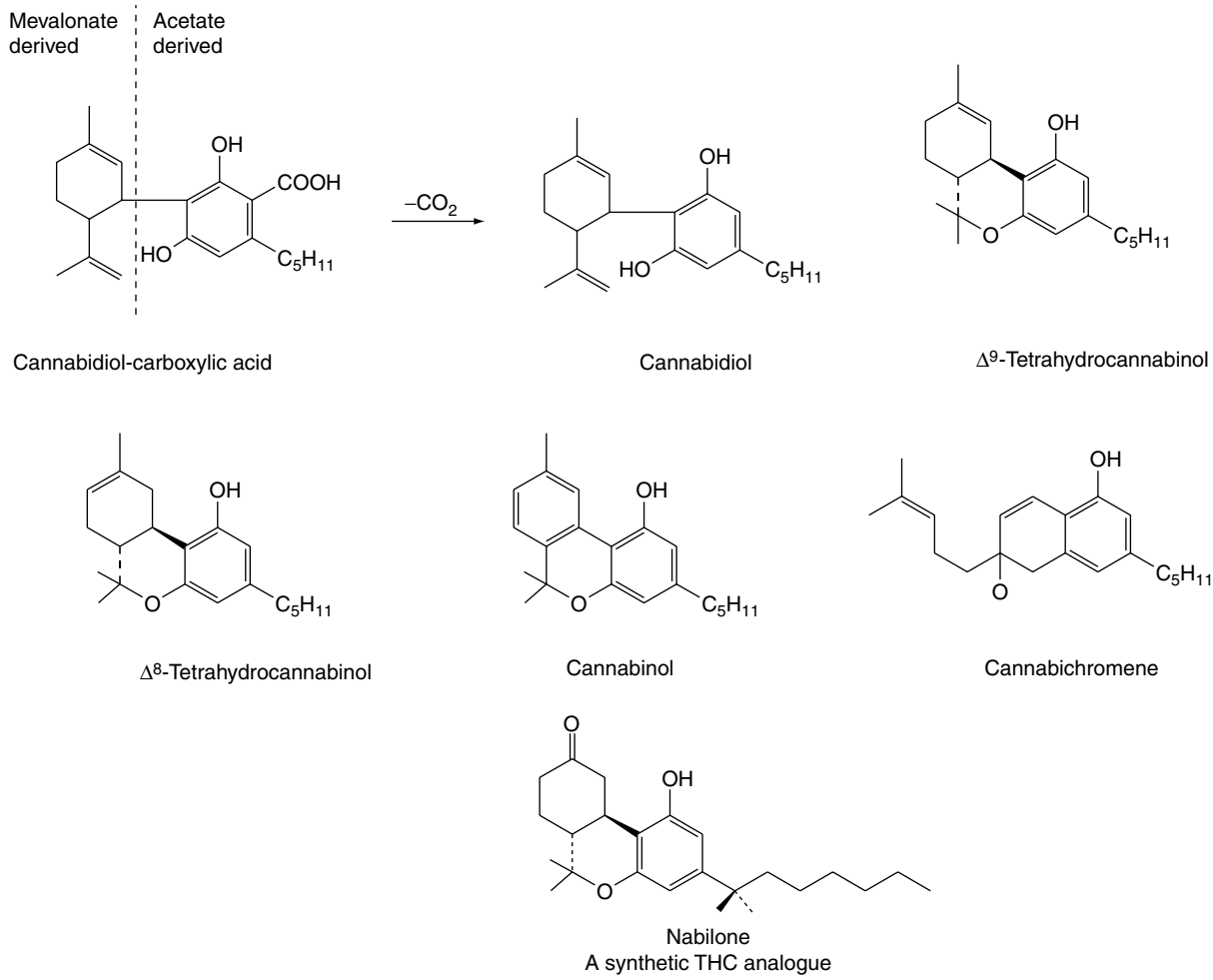

Fig. 39.4
Principal cannabinoids of *Cannabis sativa* and synthetic analogue.

of phloroglucinol β-D-glucoside in the shoot laticifer exudate of *C. sativa*, and phloroglucinol as a prominent component, and the only phenol, in the glandular trichomes suggests that it may have an important role in the *in vivo* enzymatically regulated biosynthesis of the cannabinoids (C. T. Hammond and P. G. Mahlberg, *Phytochemistry*, 1994, **37**, 755).

Cannabipinol, isolated in 1967, contains a bicyclic monoterpene moiety in addition to the acetate-derived portion. Cannabidivarin, described in 1969, is a cannabidiol homologue with a 5-propyl-resorcinol moiety. In view of the importance of the detection of Indian hemp, a number of gas and thin-layer chromatographic techniques coupled with mass spectrometry have been developed for the separation of these substances.

Δ^9-THC is the principal psychoactive constituent; Δ^8-THC is almost as active but is only present in the plant in small amounts; cannabinol is less potent; although lacking psychotropic properties cannabidiol has anticonvulsant and possible analgesic effects. Cannabichromene may enhance THC activity and has antifungal, antimicrobial and anti-inflammatory activity; for enzyme studies related to its formation see S. Morimoto *et al*., *Phytochemistry*, 1998, **49**, 1525.

The plant also contains a small quantity of laevorotatory volatile oil (about 30 components) containing terpenes and a sesquiterpene (cannibene); the bases choline, trigonelline, spermidine and an alkaloid cannabisativine; flavonoid *O*-glycosides of both vitexin and orientin; and calcium carbonate. It yields about 15% of ash and 10–18% of alcoholic extract.

Resin production. The study of resin production in cannabis continues to attract considerable attention. In practice, two varieties of *Cannabis sativa* are recognized: one produces fibre and the other resin. However, there is still no unanimity of opinion on the generic status of resin production, a situation which makes difficult a realistic legal definition of the narcotic drug. Cannabinoid production does not appear to be directly dependent on the presence of chlorophyll, and both green shoots and completely white shoots (as from a sport) will continue synthesis in the dark. Some evidence indicates that the plant's ability to produce resin is governed mainly by the environment; thus, progeny of seeds of European fibre-producing plants when grown in Egypt reverted to resin-producing plants in a matter of a few years and, conversely, seeds from resin-producing plants of the Middle East failed to produce abundant narcotic resin when grown in temperate Europe. These observations have been supported by work at the phytotron near Paris, which suggests that cannabis has, from its early growth stages, the chemical capacity to become either fibrous or resinous, depending on the climate. Nevertheless, it is possible to raise resin-containing plants in temperate regions and plants raised in the UK from overseas seed-stock (Morocco, Sri Lanka, Zambia) for a number of generations broadly retained the cannabinoid content typical of the source countries but tetrahydro-cannabinolic acid (THCA) consistently predominated over THC, the ratio THCA/THC being 17 compared with 2 in plants from the original areas (J. E. Pitts *et al*., *J. Pharm. Pharmacol*., 1992, **44**, 947).

Apart from ability to produce resin *per se*, it appears certain that resin-producing plants do exist as chemical races. The principal chemotypes recognized are those involving a preponderance of Δ^9-THC, CBD or cannabigerol together with others having various ratios of THC/CBD. There may also be a variation in resin content between male and female plants; again, this may be an inherited feature or may be differing climatic responses of the male and female. A study of wild-growing plants of cannabis collected in northern India at different altitudes and locations showed that these, too, showed great variations in the proportions of cannabinoids present. Possibly, a complete range of genetic types covering the transition from the fibrous form to the various resin types will emerge, with climatic factors also influencing the chemical products of any one type.

All the above factors obviously contribute to the very variable narcotic action of different samples of the drug.

Cannabis evaluation. The many factors above which determine the cannabinoid composition mean that care must be taken in ascertaining the chemical phenotype of a plant. The general view that cannabis preparations can be evaluated on their Δ^9-THC content neglects other active components, and in attempts to classify cannabis on the basis of its narcotic/fibre content a number of systems, some very complex, have been devised. A relatively simple relationship introduced by Waller is based on the combined Δ^9-THC and cannabinol (CBN) in relation to cannabidiol (CBD).

The phenotype is expressed as

$$= \frac{\Delta^9\text{-}THC + CBN}{CBD}$$

A sample with a value greater than 1 = a drug type of cannabis; a sample with a value less than 1 = a fibre type.

High potency grades of marihuana (>20% Δ^9-THC dry wt.) are reportedly available on the illicit drug market and from one such sample S. A. Ahmed *et al*. have characterized eleven new cannabinoid esters (*J. Nat. Prod.*, 2008, **71**, 536).

Uses. Medicinal properties of cannabis were recognized some 5000 years ago. In the mid-nineteenth century it was used in Europe as a hypnotic, anticonvulsant, analgesic, antianxiety and antitussive agent and was still official in the *BPC* 1949, together with the extract and tincture. Over many years it fell into disuse in human and veterinary medicine, and because of its narcotic properties importation into many countries became illegal. Promising results on the use of Δ^9-THC (dronabinol) for the relief of nausea and vomiting caused by cancer chemotherapy led to its use in the USA as an antiemetic. It is also employed to stimulate the appetite of AIDS patients. It can be prescribed in the UK under licence on a named-patient basis. Sativex is a relatively new Canadian product containing a mixture of THC and CBD. It is a spray not licensed for production in the UK but can be prescribed under Home Office licence for specific patients. Nabilone (Fig. 39.4), a synthetic cannabinoid antiemetic, is described in the *British National Formulary*; it is recommended to be administered in a hospital setting under close observation.

Cannabis also appears to have value in the relief of the symptoms of multiple sclerosis and other neurological disorders. The debate on its clinical usefulness continues. Subject to Medicines Control Agency approval, Phase II trials by GW Pharmaceuticals involving MS sufferers and patients with other neurological disorders were proposed (Report, *Pharm. J.*, 1999, **263**, 811).

Addiction has been common in many parts of Asia for more than 1000 years but only in recent years has the problem become world-wide.

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OTHER HIGHER PLANTS

Apocynaceae. Iboga root (*Tabernanthe iboga*), an African narcotic, contains alkaloids of the indole group. The alkaloid ibogaine has received attention as a possible antiaddictive drug (P. Popik and P. Skolnick, *The Alkaloids*, 1999, **52**, 197).

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Compositae. *Calea zacatechichi*; in Mexico taken first as an infusion and then smoked.

Labiatae. *Salvia divinorum*: the leaves have long been used in Mazatec shamanistic divination ceremonies in the region of Oaxaca, Mexico. R. G. Wasson, working in the 1950s and 1960s, reported and identified this unusual intoxicant plant, which he believed to represent the sacred Aztec narcotic called pipilzintzintli. He stated that the hallucinogenic effects were similar to, but shorter and less striking than, those of the Mexican narcotic mushrooms (q.v.). Later, the ethnobotanist Daniel Siebert described the hallucinogenic effects of a minute amount of the active constituent, salvinorin A, as 'awesome and frightening'.

The active constituents comprise a considerable number of neoclerodane diterpenes, including salvinorins A–I, salvinicins A and B and others. Salvinorin A is a κ-opioid selective agonist and salvinicin A is a partial κ-opioid agonist; salvinicin B is the first known neoclerodane μ-opioid antagonist (T. A. Munro and M. A. Rizzacasa, *J. Nat. Prod.*, 2003, **66**, 703; A. K. Bigham *et al.*, *J. Nat. Prod.*, **66**, 1242; O. Shirota *et al.*, *J. Nat. Prod.*, 2006, **69**, 1782).

The use of *S. divinorum* ('magic mint', 'Sally D') as an hallucinogen has now spread globally and its possession in Australia, Italy, Sweden and four American States is illegal. For a current overview, see G. Vince, *New Scientist*, 2006, Sept. 30, 44; and for a review update on the pharmacology and analytical methodology of the plant and salvinorin, A. O. Grundmann *et al.*, *Planta Medica*, 2007, **73**, 1039.

Leguminosae. The beans of *Anadenanthera peregrina* are used in northern South America for the preparation of snuff. A root decoction of *Mimosa hostilis* is used in east Brazil. Both contain tryptamines. *M. ophthalmocentra* root is used similarly and contains *N,N*-dimethyltryptamine, *N*-methyltryptamine and hordenine (L. M. Batista *et al.*, *Pharm. Biol.*, 1999, **37**, 50).

Malpighiaceae. A number of *Banisteriopsis* species, e.g. *B. caapi*, a forest liana, are used as a snuff or beverage in the Amazon basin. Such species are reportedly psychoactive and contain tryptamine derivatives and the simple β-carboline alkaloids harmine, harmaline and tetrahydroharmine (Fig. 39.5).

Ayahuasca (hoasca) is an Amazonian ritual decoction made by boiling together a mixture of *B. caapi* and *Psychotria viridis* (Rubiaceae) the latter containing the psychedelic compound *N,N*-dimethyltryptamine (DMT) (Fig. 39.5). Modern research involving human volunteers has demonstrated the subtlety of this shamanistic preparation in which DMT consumed orally exerts its full effect by the build-up of 5-hydroxytryptamine made possible by the monoamine oxidase inhibitory properties of the *Banisteriopsis* alkaloids. It would appear that the combination of these two drugs produces a pharmacological response equivalent to that observed in acute psychotic unmedicated patients. For details of the above research see A. B. Pomilio *et al.*, *J. Ethnopharmacology*, 1999, **65**, 29; J. C. Callaway *et al.*, *ibid.*, 1999, **65**, 243.

Ayahuasca is banned in the USA but in 2006 the Supreme Court unanimously ruled that a small religious sect could continue to import and utilize a hallucinogenic tea central to its ritual ceremonies (see report by C. Cavaliere and M. Blumenthal, *HerbalGram*, 2006, **17**, 62).

Myristicaceae. Nutmeg has received attention as a psychotropic agent and this action may possibly arise from the myristicin and elemicin components; the formal relationship of these compounds to the amphetamines (some of which exert hallucinogenic effects) is of interest. Dimeric phenylpropanoids are also found in the seeds.

Virola spp. are also of the family Myristicaceae. They yield a blood-red, bark resin which is used by Indian tribes of the Amazon region for the preparation of hallucinogenic snuffs. They contain various tryptamines. *Virola sebifera*, used in Venezuela, contains the well-known psychotomimetic *N,N*-dimethyltryptamine (DMT) and also 5-hydroxy-DMT, 5-methoxy-DMT and 2-methyl-1,2,3,4-tetrahydro-β-carboline. *V. multinerva* also contains diarylpropanoids similar to those found in nutmeg.

Besides nutmeg, other essential oils that contain elemicin are those of parsley (*Petroselinum sativum*) and elemi-tree (*Canarium commune*) (M. DeVincenzi *et al.*, *Fitoterapia*, 2004, **75**, 615).

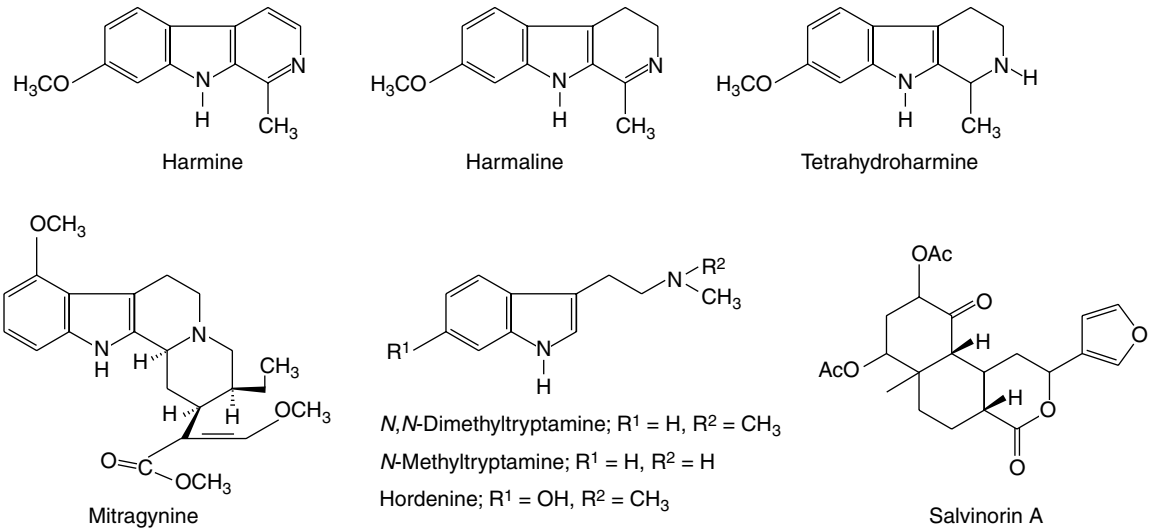
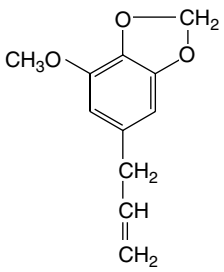
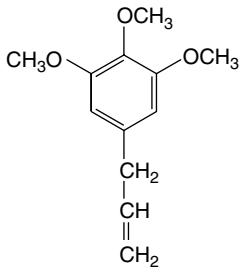


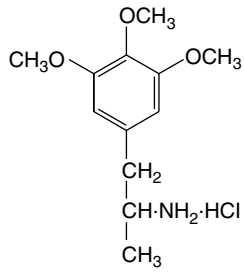
Fig. 39.5
Constituents of various hallucinogenic plants (see text).



Myristicin



Elemicin



Amphetamine corresponding to elemicin

Rubiaceae. *Mitragyna speciosa* leaves (q.v.) contain the alkaloid mitragynine, which binds to the same opioid receptor in the brain as morphine, codeine and diamorphine. The leaves (kraton) are widely available in the US, where it is used for its energizing and euphoric effects. It is an illegal substance in some S.E. Asian countries and in Australia. For a survey, see G. Vince under *Salvia divinorum* above.

Solanaceae. A number of genera containing tropane alkaloids feature in native rituals.

Zygophyllaceae. *Peganum harmala* produces a range of harmine alkaloids and the seeds are recognized in India for their psychoactive properties.

African hallucinogens. For ethnopharmacological notes on genera including *Alchornea*, *Monadenium*, *Mostuea* and *Voacanga* see P. A. G. M. De Smet, *J. Ethnopharm.*, 1996, **50**, 141.

The so-called Iboga alkaloids, which possess a catharanthine-type structure, are found in a number of African plants and are used locally as a stimulant. Apparently, a global medical subculture has arisen in which the alkaloid ibogaine is used principally to alleviate the symptoms of opioid withdrawal (K. R. Alper *et al.*, *J. Ethnopharm.*, 2008, **115**(1), 9–24).

Further reading

Dobkin de Rios M 1996 Hallucinogens. Cross-cultural perspectives. Waveland Press Inc., IL, USA

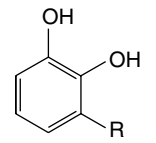
NATURAL ALLERGENS

A large number of plant and animal materials give rise to allergic reactions in certain individuals. The allergenic material is transmitted by direct skin contact, by airborne pollens, smoke and dried plant particles, and on the coats of domestic animals. Once a person has been sensitized to a particular allergen, subsequent exposure to the materials produces an antigen–antibody reaction which results in the liberation of histamine or histamine-like compounds which in turn cause the allergic symptoms. Allergies are commonly manifested as hay fever, asthma and dermatitis. Desensitization is often possible once the specific cause has been established, and a considerable number of allergenic extracts are now available for diagnostic and prophylactic treatments. As fatal anaphylactic reactions are possible, desensitization using allergenic extracts should be carried out only in situations where full cardiorespiratory resuscitation facilities are available. The following allergens are well-known.

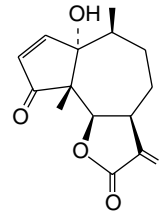
Pollens. Responsible for seasonal hay fever, which may progress to chronic asthma. Pollen counts of the atmosphere are regularly recorded and published. Grass pollens form the highest proportion of the total count and may constitute 62% of the total count during June and July. In London, for these months, daily counts of 200 m^{-3} are not uncommon. Pollen counts of 50, and as low as 10, will produce discomfort in susceptible individuals. Common grasses involved include timothy (*Phleum pratensis*), cocksfoot (*Dactylis glomerata*) and perennial rye (*Lolium perenne*). The pollen of nettle (*Urtica dioica*) is second in importance to the grasses in this connection in the UK. It occurs in the air throughout the summer, reaching a peak in late June to July. Other relevant pollens are those of the plantain (*Plantago* spp.) and mugwort (*Artemesia vulgaris*). In the USA pollens of the ragweeds (*Ambrosia* spp.) are important. Tree pollens are contained in the atmosphere in the spring; they are not as common as allergens as those of grasses, the ones of most clinical importance being from the birch and plane trees.

Spores. A number of common moulds produce spores which cause rhinitis and asthma in sensitive individuals. They are often responsible for those conditions which extend beyond the normal pollen season and up to the beginning of frosts. Moulds flourish in damp conditions where organic decay is progressing, and peak sporulation occurs during hot, dry conditions when the atmosphere may become heavily contaminated. In the UK the spores of *Cladosporium herbarum* and *Sporobolomyces roseus* cause the most trouble. Exposure to lycopodium spores (q.v.) has caused allergic reactions varying from dermatitis to severe asthma attacks. There are also reports of spores causing adhesions on serous surfaces and foreign-body granulomas in soft tissues. This could have implications for the use of lycopodium powder as a dusting powder for non-lubricated condoms.

***Rhus* (Toxicodendron) spp.** *Rhus radicans* (poison ivy), *R. toxicodendron* (poison oak), *R. diversiloba* (Pacific poison oak) and *R. vernix* (poison sumach, poison elder) (Anacardiaceae) contain contactant allergens which produce severe dermatitis associated with watery blisters which burst and quickly spread across the skin. The allergens are contained in the plant sap and are easily transmitted (on clothing, hands, animal fur and even as the result of bush fires). These compounds are known as urushiols and belong to a class of alkenyl polyphenols found in the Anacardiaceae. They constitute an interesting chemotaxonomic group and are an example of the use of a starter other than acetyl-CoA in fatty-acid synthesis by which C_2 units derived from malonate are added to an unsaturated fatty acid; subsequent cyclization forms, as one example, the urushiols. With the exception of the cultivated sumach, which does not appear to be troublesome, these plants are not found in Britain, but they constitute a consider-



Urushiol phenols
For poison ivy:
R = C_{15} aliphatic side-chain
For poison oak:
R = C_{17} aliphatic side chain
R may possess 0, 1, 2 or 3 double bonds



Parthenin

able hazard in the USA, where poison ivy, in particular, is particularly widespread as a woody vine. Lacquer, used in the sixteenth and seventeenth centuries for producing an oriental-type finish on furniture, was derived from *R. vernicifera*, and its use constituted an industrial hazard for the craftsmen. Similar compounds to the above have been isolated from the fruit pulp of *Ginkgo biloba* and from the glandular trichomes of annual *Phacelia* spp. (Hydrophyllaceae) of the Californian Mojave desert. The dermatitic action of these compounds is consistent with oxidation of the allergen to a quinone which then binds covalently to a protein nucleophile giving an antigenic complex.

Sesquiterpene lactones. These compounds (see Chapter 24), obtained from members of the Compositae, Lauraceae and Magnoliaceae and from the liverwort *Frullania* (Jubulaceae), are a major class of substances causing allergic contact dermatitis in man. The presence of an α-methylene group, exocyclic to the γ-lactone, appears to be the principal immunochemical requisite for activity. The compounds are illustrated, from the many, by the pseudoguaianolide parthenin, obtained from the plant *Parthenium hysterophorus*, an aggressive weed causing public health problems in parts of India. Some individuals are sensitive to feverfew and others to chrysanthemums. Two other plant species which can give rise to allergic reactions are the common rue (*Ruta graveolens*) and the indoor ornamental 'dumb cane' (*Dieffenbachia seguine*, Araceae). In the latter instance it would appear that the irritant substances are introduced into the body tissues by abrasion, through punctures caused by acicular crystals of calcium oxalate contained in idioblasts.

Miscellaneous. Hair, feathers and house dust can all act as allergenic material; house dust often includes mites. Numerous other materials, not of natural origin (e.g. detergents, dyes, cosmetics), may also act as contact allergens.

TERATOGENS OF HIGHER PLANTS

Teratogenic substances, when ingested by the mother, can cause abnormalities in the developing fetus; thalidomide represents the tragic example of a synthetic drug having such undetected properties at the time of its use. Such substances undoubtedly occur also in plants, but no species has been shown as having been responsible for malformations in humans. That the possibility exists is demonstrated by the teratogenic effects of certain plants when incorporated into animal fodder.

Teratogens usually, but not invariably, act during a short, relatively early period of the gestation cycle, so that when the abnormalities become apparent in the offspring the causative plant may have disappeared from the fodder source. The range of plant constituents known to have teratogenic effects, albeit often demonstrated using only laboratory animals and large doses not normally experienced by humans, includes 14 different groups of alkaloids, coumarins, lignans, macrolides, nitriles, terpenoids, toxic amino acids and unidentified compounds of many plants. As with the hallucinogens, the majority of teratogens contain nitrogen; for some examples see Table 39.1.

OTHER TOXIC PLANTS

In addition to those plants mentioned in this chapter and those of medicinal significance considered in Chapters 19–26, there remain many others with poisonous properties. Such plants are generally of local importance, and it is desirable that the pharmacist should have some knowledge of those found in his own locality, be familiar with those characters by which the plant can be identified and be aware of the antidotes required for the treatment of poisoning.

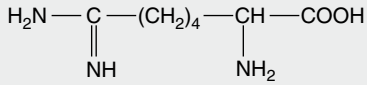
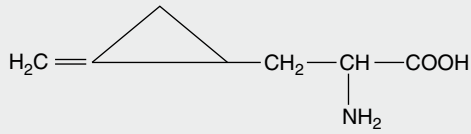
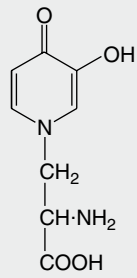
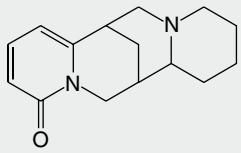
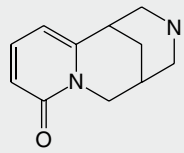
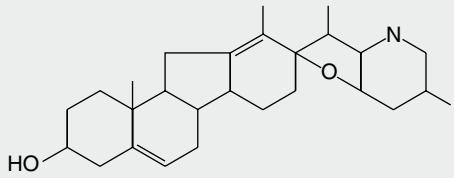
Cases of poisoning of humans by higher plants are most likely to occur with children and to involve those plants that produce attractive berries (e.g. belladonna, cotoneaster), seeds (e.g. laburnum) eaten for green peas, and those which may be introduced into the mouth for other reasons (e.g. the hollow stems of hemlock used as pea-shooters). Mistaken identity occasionally leads to fatalities and this is particularly so in the case of members of the Umbelliferae. Cases include a fatality in Maine, USA from consumption of *Cicuta maculata* (spotted cowbane) in mistake for ginseng. The poisonous principle present in *Cicuta* spp. is a C_{17}-polyunsaturated alcohol named cicutoxin. Some eleven such polyacetylenes have been isolated from *C. virosa* (water-hemlock) and using a model neurone, U. Wittstock *et al*. have suggested that the toxic property of cicutoxin could be due to a prolonged neuronal action potential (*Planta Medica*, 1997, **63**, 120). In Holland, four people were poisoned by *Oenanthe crocata* (hemlock water dropwort) consumed in mistake for celery (these people probably survived because the roots were boiled before eating). This plant its widespread in marshy and damp woodland areas of Europe; its roots have an odour and taste resembling parsnips or celery and the poisonous principle is oenanthetoxin, isomeric with cicutoxin.

The poisoning of livestock by plants is relatively common, particularly in extensive grazing areas where there is no attempt to control weeds. Poisonous plants may be consumed by animals because the plants happen to be growing among the fodder or were collected and dried with hay. In the latter case some unstable poisonous constituents may disappear with drying and storage. In poor seasons animals may forage and consume plants which they would not normally eat. During the dry summer of 1976 numerous cows died near Crediton, UK after eating *O. crocata*.

Some widespread poisonous plants owe their properties to the presence of hepatotoxic pyrrolizidine alkaloids (see Fig. 26.10). These include the *Senecio* spp. (ragworts) and members of the tribe Eupatorieae of the Compositae. Several commonly used herbs containing small quantities of these alkaloids include comfrey, Russian comfrey, coltsfoot and petasites. Human fatalities have been reported in relation to the herbal use of *Senecio longibobus* in the USA. In the UK, a voluntary agreement by herbal medicine suppliers not to supply senecio products is now being followed with proposed legislation by the Medicines and Healthcare products Regulatory Agency to implement a ban (*Pharm. J.*, 2007, **278**, 448).

Another group of compounds which has been shown to promote liver cancer in rats is that containing safrole and other alkenylbenzene derivatives. Although these are weak carcinogens and concentrations in products for human consumption never approach the toxic levels observed in laboratory tests, the desirability of their use has been questioned. Oils in which they occur include sassafras, Brazilian sassafras, star-anise, nutmeg, cinnamon, camphor (natural), calamus, tarragon, basil and ylang-ylang. M. De Vincenzi *et al*. have consid-

Table 39.1 Teratogens of higher plants.

Plant source	Constituents	Notes
Senecio spp. (Compositae)	Pyrrolizidine alkaloids: lasiocarpine, retrorsine	Possible teratogenic effects in rats and *in utero* deaths of calves
Indigofera spicata (Leguminosae)	 Indospicine	Cleft palate and embryo lethality in rats. Possible malformations in domestic livestock. Indospicine teratogenesis
Nicotiana spp. (Solanaceae), *Lobelia* spp. (Campanulaceae)	Pyridine alkaloids	Probably responsible for some skeletal deformations in pigs but effect not positively attributable to alkaloids
Blighia sapida (Akee) fruits and seeds (Sapindaceae)	 Hypoglycin A	Hypoglycin A is known to be hypoglycaemic in humans and teratogenic in rats; it is twice as toxic as its peptide derivative hypoglycin B
Leucaena leucocephala; Mimosa spp. (Leguminosae)	 Mimosine	Large quantities toxic to livestock. Teratogenic effects demonstrated in pigs and rats
Locoplants e.g. *Astragalus lentiginosus* (Leguminosae)	Unknown	Contains osteolathyrogens (substances ingested by young through mother's milk), and teratogens characterized by causing excessive flexure of carpal joints or contracted tendons
Lupins e.g. *Lupinus sericeus* (Leguminosae)	Quinolizidine alkaloids, e.g. cytisine, anagyrine  Anagyrine  Cytlsine	Teratogenic effect results in crooked calf disease
Conium maculatum (Umbelliferae)	Coniine	Alkaloid teratogenic, shown to produce crooked calf disease
Veratrum californicum (Liliaceae)	Many steroidal alkaloids  Cyclopamine	Teratogenic effect causes cyclopian and related cephalic malformations in lambs. The three active alkaloids have a fused furanopiperidine ring E/F arrangement as in cyclopamine

ered the specific occurrence of methyleugenol as a component of aromatic plants (*Fitoterapia*, 2000, **71**, 216).

Other carcinogens or cocarcinogens discussed elsewhere are the betel quid and tigliane and daphnane derivatives and related diterpenes.

The fruits of *Blighia sapida* have been mentioned elsewhere in connection with teratogenesis (Table 39.1) and hypoglycaemia (Chapter 29). The unripe fruits present an exceptional hazard for young children in the areas in which the trees grow. In 1998 an epidemic of fatal encephalopathy involved 29 preschool children in Burkina Faso, W. Africa (H. A. Meda *et al.*, *Lancet*, 1999, **353**, 536) and a similar explanation was suggested for an epidemic involving more than 100 children in the Ivory Coast in 1984 and for poisonings in Jamaica. The

unripe fruits contain the highest hypoglycin A content but nevertheless the ripe fruits also need to be par-boiled before consumption. As in all cases of poisoning, rapid identification of the poison is essential if the most effective treatment is to be given. Often, the material available for identification is scant and rarely sufficient to enable identification by means of standard methods based on a flora; this reinforces a need for knowledge of the local poisonous plants and the characters of their various morphological parts.

Fungi have a geographically universal potential as toxic agents, and the significance of their active constituents, mycotoxins, is only now coming to be fully appreciated. Well-established are the poisonous principles of various Basidiomycetes which may be confused with the edible mushroom and toadstools. Also, the infection of rye with the ergot fungus resulting in the disease St Anthony's Fire, which, although now rare, still occasionally occurs in rye-eating countries. The polyketide patulin is produced by species of *Penicillium* and is often present in mouldy apples; it was originally studied for its antibiotic properties but proved also to be a potent carcinogen.

The more widespread danger of mycotoxins became apparent in World War II, when the consumption of mouldy grain in Russia led to thousands of fatalities. The mycotoxins produced by various *Aspergillus* spp. (e.g. *A. flavus*, *A. parasiticus*) are termed aflatoxins, all having a coumarin nucleus fused to a bifuran unit and possessing in addition a pentenone ring (B series) or a six-membered lactone (G series). Examples are given in Fig. 39.6.

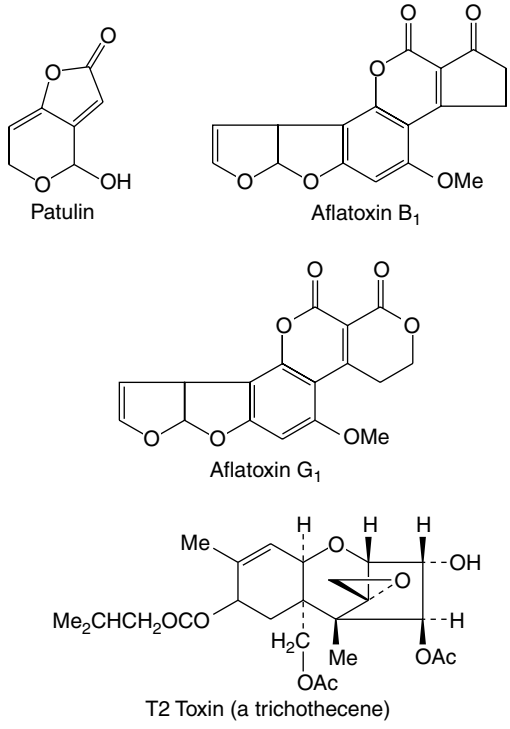


Fig. 39.6
Structures of some mycotoxins.

The above moulds are particularly likely to occur in oil-seed meals and in cereals; they have been circumstantially implicated in the deaths of children in a number of countries. Animal tests have shown the aflatoxins to be potentially harmful in a number of respects—as potent toxins, as carcinogens, as teratogens and as mutagens. In Britain these compounds came to prominence in 1959 when great numbers of turkeys and chickens in East Anglia rapidly succumbed to their toxicity after being fed contaminated groundnut meal imported from S. America. The recognition of the serious health hazards to humans and animals of aflatoxins in foods has led to the legal imposition in the UK of a limit of 10 μg kg^{-1} aflatoxin B_1 in nuts and nut products for human consumption, and an EU guideline for a limit of 20 μg kg^{-1} aflatoxin B_1 for animal feedstuffs. Methods of assay for these compounds have been developed in recent years and include HPLC and TLC (slow and cumbersome) and various RIA and EIA techniques.

Another condition arising from consumption of overwintered mouldy cereals, and reported to occur principally in Russia, is alimentary toxic aleukia; other manifestations include weight loss, skin inflammation and death. The responsible organisms (largely *Fusarium* and *Trichothecium* spp.) produce active constituents termed trichothecenes of which about 172 had been reported by 1981 (see J. F. Grove, *Nat. Prod. Rep*., 1993, **10**, 429). These compounds are tricyclic sesquiterpenes and the majority are exemplified by the structure of T2 toxin (Fig. 39.6). However, some 67 compounds are macrocyclic in structure and it is interesting that they also occur in two toxic Brazilian species of *Baccharis* (Compositae), a finding which was originally incorrectly attributed to fungal infection (B. B. Jarvis *et al.*, *J. Nat. Prod.*, 1988, **51**, 736; *Phytochemistry*, 1991, **30**, 789). Matossian of the University of Maryland considers that *F. tricinctum* was the probable fungal food contaminant causing 'putrid malignant fever', a great child-killer of the early eighteenth century. These compounds also achieved notoriety as alleged agents of chemical warfare ('yellow rain').

Crude drugs, unless sterilized, are often grossly contaminated with mould spores, and if such drugs are to be consumed as such (as distinct from use for the isolation of active constituents), then it is important that they are free of dangerous mycotoxins. A Polish survey of 246 crude drug samples found only two (salvia leaves and tormentilla rhizome) which contained *Aspergillus* spp. producing aflatoxin B_1. Nevertheless, it is a situation that requires monitoring.

Further reading

Frohn D, Pfander HJ, Alford I (translator) 2005 Poisonous plants: a handbook for doctors, pharmacists, toxicologists, biologists and veterinarians, 2nd edn. Timber Press, Portland, OR. *An appendix includes information concerning N. American plants*

Harborne J B, Baxter H, Moss G P (eds) 1996 Dictionary of plant toxins. John Wiley, Chichester, UK. *A number of books on poisonous plants, now mostly out of print but useful if accessible, are given in the 14th edition of this book, p. 532*

40

Pesticides of natural origin

Pesticides may be classified according to the type of organism against which they are effective, namely, fungicides, herbicides, insecticides, molluscicides, nematocides, rodenticides. The origin of the use of natural products in these respects is lost in antiquity (see Further Reading) and a large number of such materials, of local use, still remain to be chemically investigated and evaluated. Although the majority of pesticides used in modern agriculture are synthetic, plant products still contribute to the insecticides and rodenticides. Phytochemicals can also serve as lead compounds from which others, exhibiting, for example, a greater toxicity towards the pest, a wide spectrum of activity such as the inclusion of mites, a lowered mammalian toxicity and a decrease in photodecomposition, can be developed.

ACARICIDES

Mites and ticks are small arachnids of the order Acarina (Acari). Specific mites infest crude drugs and food (Chapter 13) and the house-dust mite, *Dermatophagoides pteronyssinus*, is well known for its possible association with asthma. Ticks are the largest members of the order and economically the most important. They are all blood-sucking parasites responsible for microbial infections, e.g the spirochaete infection causing Lyme disease, and protozoal diseases in animals.

The control of mites by plant products has centred largely on essential oils. In a report (*Pharm. J*., 1998, **261**, 406) on the laboratory testing of three oils by I. Burgess and colleagues, tea tree oil was the most effective, giving 100% immobilization of house-dust mites at 30 min, and 100% mortality at 2 h; for the same exposure times lavender oil gave figures of 87% and 87% and lemon oil 63% and 80% respectively. Australian workers have demonstrated that for laundering purposes several essential oils are effective acaricides when emulsified in low concentrations of the laboratory detergent Tween and that a simple washing procedure with eucalyptus oil, without the use of very hot water, controlled house-dust mites and their allergens in clothing and bedding (E. R. Tovey and L. G. McDonald, *J. Allergy Clin. Immunol*., 1997, **100**, 464).

For Third World countries where synthetic acaricides are relatively expensive the exploitation of suitable local plants is important. The essential oils of some members of the Capparidaceae have been shown to be effective antitick agents and the situation is outlined by W. Lwande *et al*. (*Phytochemistry*, 1999, **50**, 40) in their studies on the tick-repellent properties of the essential oil of *Gynandropsis gynandron*. This East African annual species has been proposed as an antitick pasture plant as it disrupts the free-living stages of *Rhipicephalus appendiculatus*, the vector of the pathogen causing East Coast fever in animals. Twenty-eight compounds were identified in the essential oil, carvacrol, phytol and linalool being the major constituents, although greatest repellency towards the tick was shown by a number of minor constituents. Methyl isothiocyanate was also identified in the oil (2.1%) and could contribute towards the activity. It may be noted here that *G. gynandron* is also employed in traditional medicine for a number of conditions and its essential oil is used as a repellant for head-lice.

INSECTICIDES

PYRETHRUM FLOWER

Pyrethrum flowers (Insect flowers, Dalmatian insect flowers) are the dried flower-heads of *Chrysanthemum cinerariifolium* (Trev.) Vis. [*Tanacetum cinerariifolium* (Trev.) Sch. Bip., *Pyrethrum cinerariifolium* Trev.] (Compositae). The plant is perennial, about 1 m high, and

indigenous to the Balkans. Principal cultivated sources are Kenya, Tasmania, Tanzania and Rwanda. Smaller amounts are grown in Japan, Eastern Europe, Brazil and India.

History. The insecticidal properties of Persian or Caucasian insect flowers (*Chrysanthemum coccineum* Willd. and *C. marshallii* Aschers) have long been known in their country of origin, but the use of the Yugoslavian species dates from the middle of the last century. Persian insect flowers are now rarely seen in British commerce, and Kenya, the largest exporter, produces flowers of the Dalmatian type, the original Dalmatian seed being introduced by Gilbert Walker in 1928.

Collection. Conditions for pyrethrum cultivation are particularly favourable in Kenya; the producing areas have an altitude of 1900–2700 m and an annual rainfall of 76–180 cm. The altitude is important, giving a low night temperature (5–15°C), which stimulates maximum bud production. Collection takes place for about 9 months of the year. As about 90% of the insecticidal activity of the plant is present in the flowers, only these are collected. Before drying they are not toxic to insects. In Kenya all the flowers are delivered to the Pyrethrum Marketing Board at Nakuru. Here all samples are analysed and the growers paid on the pyrethrin content of their deliveries. The thousands of African smallholders are organized on cooperative lines and all the profits of the Board are returned to the growers. At the factory of the Board some of the flowers are baled for export but the majority are made either into powder or into standardized liquid extract. Current developments may be followed in the biannual journal *Pyrethrum Post*.

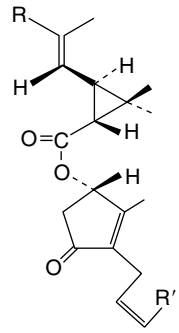
Characters. The closed flower-heads are about 6–9 mm in diameter and the open ones about 9–12 mm in diameter. They bear a short peduncle which is striated longitudinally. The involucre consists of two or three rows of yellowish or greenish-yellow, lanceolate, hairy bracts. The receptable is nearly flat and devoid of palae. It bears numerous, yellow tubular florets and a single row of cream or straw-coloured ligulate florets. The ligulate corollas are 10–20 mm in length and have about 17 veins and three rounded teeth, the central one very small (distinction from ox-eye daisies, *C. leucanthemum*, in which the ligulate corollas have seven veins and three teeth, the centre one being the largest). The achenes are five-ribbed (achenes of Persian flowers usually 10-ribbed). The flowers have a slightly aromatic odour and a bitter, acrid taste.

Characters of powders. The species used as insecticides are *C. cinerariifolium, C. coccineum* and *C. marshallii*, the powders from which show the following elements: parenchyma often containing aggregate crystals, T-shaped hairs, numerous spherical pollen grains, sclerenchymatous cells (particularly from Persian flowers), tracheids and epidermal cells having a striated, papillose cuticle. Kenya flowers are guaranteed to contain not less than 1.3% of pyrethrin; Japanese usually contain 0.9–1.0% and Dalmatian about 0.7–0.8%.

Constituents. Pyrethrum owes its insecticidal properties to esters which are reportedly produced by a number of different cell types (oil glands, resin ducts and mesophyll cells). Pyrethrin I, jasmolin I and cinerin I are esters of chrysanthemic acid (chrysanthemum monocarboxylic acid), while pyrethrin II, jasmolin II and cinerin II are esters of pyrethric acid (monomethyl ester of chrysanthemum dicarboxylic acid). The alcohol component of the pyrethrins is the keto-alcohol pyrethrolone and of the cinerins the keto-alcohol cinerolone. Pyrethrum flowers also contain sesquiterpene lactones and the triterpenoid pyrethrol. The biosynthesis of pyrethrin I in seedlings of *C. cinerariifolium* has been studied using [1-^{13}C]-D-glucose as a precursor; the acid portion of the molecule is derived from D-glucose and the alcohol moiety possibly from linoleic acid (K. Matsuda *et al*., *Phytochemistry*, 2005, **66**, 1529).

Pyrethrum Extract of the *BP* (*Vet*.) contains 24.5–25.5% of pyrethrins; it may be prepared extemporaneously from the flower-heads and is used for the preparation of the *BP* (*Vet.*) dusting powder and spray. The dusting powder (pyrethrum extract, diatomite, talc) has a pyrethrin content of 0.36–0.44%, of which not less than half consists of pyrethrin I. It is assayed by titrimetry for both pyrethrin I and II. Extracts containing 50% more active material compared with commercial extracts can be obtained by extraction of the plant material with liquified carbon dioxide (100 bar). The extract is usually diluted on farms with kerosene to a pyrethrin strength of about 0.2%. For work on *Pyrethrum* hybrids, see Chapter 14.

The popularity of pyrethrum derived from its rapid knock-down action (largely due to pyrethrin II), lethality to insects (pyrethrin I) and low mammalian toxicity. However, synthetic analogues of natural pyrethrins with higher insecticidal activity (over 1000 times that of pyrethrin I), more photostability and a similar low toxicity have virtually displaced pyrethrin from the market, particularly in the area of domestic insecticidal sprays. There continues, however, to be a market for natural pyrethrins in special areas such as food processing plants and insecticidal spraying of edible fruits and vegetables shortly before harvest.



	R	R^1
Pyrethrin I	CH_3	$CH{=}CH_2$
Jasmolin I	CH_3	$CH_2{-}CH_3$
Cinerin I	CH_3	CH_3
Pyrethrin II	$COOCH_3$	$CH{=}CH_2$
Jasmolin II	$COOCH_3$	$CH_2{-}CH_3$
Cinerin I	$COOCH_3$	CH_3

Uses. Insect flowers are a contact poison for insects. They are largely used in the form of powder, but sprays in which the active principles are dissolved in kerosene or other organic solvent are more efficient. For recent developments, see above.

Derris and lonchocarpus

The roots of many species of *Derris* and *Lonchocarpus* (Leguminosae) have insecticidal properties which are usually, but not invariably, due to the presence of rotenone. The former *British Veterinary Codex* included monographs on 'Derris', the dried rhizome and roots of *Derris elliptica, D. malaccensis* and possibly other species, and on 'Lonchocarpus', the dried roots of *Lonchocarpus utilis, L. urucu* and possibly other species. Other genera of the same family with rotenoid-producing species are *Millettia, Neorautanenia* and *Tephrosia*.

Derris is indigenous to Malaya and is cultivated there and in Burma, Thailand and tropical Africa. Lonchocarpus is indigenous to Peru and Brazil and it is the usual source of material on the UK and USA markets, frequently being sold as a black resinous extract containing about 30% of isolatable rotenone and about 20% of the structurally related deguelin.

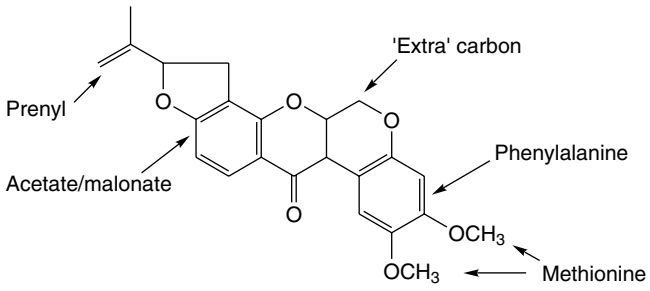
Characters. Derris roots are up to 2 m long and 1 cm or more diameter. They are sometimes attached to short pieces of rhizome. The outer surface is greyish-brown to reddish-brown and bears fine longitudinal furrows and, in the larger pieces, elongated lenticles. The drug is flexible and breaks with a fibrous fracture. It has a slight aromatic odour; and when chewed, gradually produces a feeling of numbness in the tongue and throat. Prolonged grinding of the drug is necessary

on account of its fibrous nature, and special precautions are necessary, owing to the objectionable properties of the dust. A transverse section shows a thin brown bark and a cream to pale-brown wood which in the larger pieces show three or four concentric rings.

Lonchocarpus usually occurs in pieces 4–30 cm long and 1.5–2.5 cm in diameter. The outer surface is brownish-grey, with wrinkles and scars and, in the larger pieces, transverse lenticles.

Constituents. Derris and lonchocarpus contain about 3–10% of rotenone, a colourless crystalline substance which is insoluble in water but soluble in many organic solvents. However, rotenone is not the only constituent with insecticidal properties, and the evaluation of the drug depends both on rotenone content and on the amount of chloroform extractive it contains.

Rotenone is an isoflavone derivative and is biosynthesized from acetate, mevalonate and phenylalanine with an extra carbon arising from a C-1 pool. Its toxicity to mammals limits its usefulness.



Rotenone (a rotenoid)

The roots also contain deguelin which is similar to rotenone but possesses a *gem*-dimethylpyran moiety. Flavonoids and stilbenes with the same moiety are minor components.

Rotenoid derivatives, having a larvicidal property, have been isolated from *Derris trifoliata*; activity is due mainly to rotenone (A. Yenesew *et al*., *Phytochemistry*, 2006, **67**, 988).

Nicotinoids

As early as 1763 nicotine, in the form of a tea prepared from tobacco, was recommended for the destruction of aphids.

The genus *Nicotiana* (Solanaceae) comprises about 100 species. Tobacco for smoking, chewing and snuffing is prepared by a curing process, largely of the cultivated Virginian tobacco, *N. tabacum*, and the Turkish tobacco, *N. rustica*. Tobacco is believed to be a native of tropical America, and was cultivated and used by the native inhabitants before the discovery of the American continent by Europeans. *N. tabacum* is of hybrid origin, and various 'synthetic tobaccos', somewhat resembling it, have been raised by crossing and breeding wild, possibly ancestral, species. Nicotine (structure and biogenetic origin, Fig. 26.2) is the characteristic alkaloid of the genus and is prepared commercially from waste material of the tobacco industry; it has long been used as an effective insecticide but is gradually being replaced by safer products. Other species (e.g. *N. glutinosa*) produce nornicotine by demethylation of nicotine in the leaves, whereas some (e.g. *N. glauca*) contain, in addition to the nicotine alkaloids, the homologous anabasine (structure and biogenetic origin, Fig. 26.11). Nornicotine and anabasine are also insecticidal. An interesting report (J. E. Huesing and D. Jones, *Phytochemistry*, 1987, **26**, 1381) indicated that extracts of species of *Nicotiana*, section Repandae, caused high levels of mortality in *Manduca sexta*, the tobacco hornworm, a tobacco-associated insect which is not susceptible to the toxic effects of nicotine. The insecticidal component is an *N*-acylnornicotine which is found only in this section of the genus and is absent from the other 65 spp.

The nicotinoids are also found in some other members of the Solanaceae (spp. of *Duboisia, Anthocercis, Cyphanthera* and *Crenidium*), a few *Erythroxylum* spp., *Asclepias syriaca* and *Anabasis aphylla*.

Cevadilla seed. Cevadilla or sabadilla consists of the seeds of *Schoenocaulon officinale* (Liliaceae), a plant found from Mexico to Venezuela. The seeds are dark brown to black, sharply pointed and about 6 mm long. They contain about 2–4% of mixed alkaloids known as 'veratrine'. The chief alkaloids, cevadine and veratridine, are closely related to the ester alkaloids of veratrum (q.v.). The powdered seeds and preparations of 'veratrine' are used as a dust or spray to control thrips and various true bugs which attack vegetables.

Ryania. The roots and stems of *Ryania speciosa* (Flacourtiaceae), a plant native to South America, contain 0.16%–0.2% of alkaloids having insecticidal properties. Ryanodine, the principal alkaloid, is a complex ester involving 1-pyrrole-carboxylic acid. The plant is used in the control of various lepidopterous larvae which attack fruits, and particularly the European corn borer.

Miscellaneous

A number of other plants containing insecticidal compounds with scope for synthetic improvement include *Mammea* spp., Guttiferae (coumarins); Ebenaceous spp., containing the naphthoquinone plumbagin (q.v.) and *Phryma leptostachya*, Verbenaceae (a highly active lignan, haedoxan A). *Melia azedarach* (Meliaceae), native to N.W. India, has been long recognized for its insecticidal properties and is still the subject of considerable research. Three diacylated meliacarpin derivatives with strong insecticidal activity against the larvae of *Spodoptera littoralis* have been isolated from the leaves (F. I. Bohnenstengel *et al*., *Phytochemistry*, 1999, **50**, 977); two insecticidal tetranortriterpenoids have potential for further development (B. S. Siddiqui *et al*., *Phytochemistry*, 2000, **53**, 371) and positive antifeedant properties have been demonstrated with extracts of unripe fruits and green or senescent leaves against mature adults of the elm leaf beetle, *Xanthogaleruca luteola* (M. Defagó *et al*., *Fitoterapia*, 2006, **77**, 500).

RODENTICIDES

Red squill. Red squill and white squill (see 'Cardioactive Drugs', Chapter 23) are both varieties of *Urginea maritima* (Liliaceae). The red squill may be distinguished in either the whole or powdered state by the reddish-brown outer scales and the white to deep purple inner ones. In addition to other cardioactive glycosides, the bulb of the red squill also contains the glucosides scilliroside and scillirubroside. Strains selected for high scilliroside content have been developed from plants introduced to southern California in 1946. Unlike other mammals, rodents do not regurgitate the squill bulb, and death follows convulsions and respiratory failure.

Strychnine. The occurrence of strychnine in *Strychnos* species (Loganiaceae) has already been discussed. This alkaloid has been used traditionally for the extermination of moles, but its toxicity to other animals and its painful poisonous action do not make it a poison of choice.

MOLLUSCICIDES

Pharmaceutical interest in molluscicides is concerned primarily with the control of schistosomiasis (bilharzia), a parasitic disease of humans

in which certain freshwater snails act as intermediate hosts for the blood flukes, *Schistosoma haemotobium, S. mansoni* and *S. japonicum*. The disease, which causes intestinal and bladder damage, is prevalent in S. America, Africa and the Far East and is increasing as a result of the construction of dams and irrigation systems which provide enlarged breeding areas for snails. Eggs are eliminated in the faeces or urine of infected humans and, in water, hatch as miracidia which enter the host snails (*Biomphalaria pfeiffer* (S. America), *B. glabrata, Bulinus globosus*, etc.) where numerous cercaria are produced. The cercaria emerge into the water and infect humans by passing through the skin into the bloodstream. Synthetic drugs are available to combat the infection but for the general control of the disease the eradication of the intermediate stages of the life-cycle of the fluke is necessary together with improved sanitary arrangements. In 1998 it was estimated that there were over 20 million severely diseased individuals in the tropics and some ten times that number infected to some degree.

During the last two decades it has been shown that a wide range of phytochemicals exhibit molluscicidal activity. Prominent families in this connection are the Leguminosae, Araliaceae, Compositae and Liliaceae. However, before a plant, shown to possess molluscicidal activity in laboratory tests, can be utilized on a large scale a number of other, fairly obvious, criteria need to be satisfied. Thus, the plant material must be available in sufficient quantity and, if necessary, capable of easy propagation in the region where required; the active constituents should be water-soluble and easily extractable from the plant source; the molluscicidal activity should be high and the toxicity towards other organisms, including humans, low. Few plants as yet examined appear to have satisfied all of these requirements.

The berries of the Ethiopian plant *Phytolacca dodecandra* (Phytolaccaceae) have proved effective in clearing stretches of waterways of snails, but cultivation in areas outside of the natural habitat has produced disappointingly low yields of fruits. The most active components of this plant are triterpenoid saponins composed of oleanolic acid (Fig. 23.10) with a branched sugar side-chain at C-3; they are liberated by the enzymatic cleavage of the ester-bound saccharide chains of non-molluscicidal bidesmodic saponins (S. T. Thiilborg *et al*., *Phytochemistry*, 1993, **32**, 1167). A plant the pods of which contain similar saponins is *Swartzia madagascariensis* (Leguminosae), a tree widespread throughout Africa; it has local medicinal, insecticidal and piscicidal uses. The leaves of the S. America species *S. simplex* have a similar activity to those of the African plant and glycosides of oleanolic acid, gypsogenin (Fig. 23.10) and gypsogenic acid have been isolated as active constituents. Saponins are also present in *Tetrapleura tetraptera* (Leguminosae), a promising Nigerian molluscicide. A number of these plants containing effective saponins are also well established piscicides.

Spirostanol saponins, as found in *Balanites aegyptica* (Zygophyllaceae), are potent molluscicides. This plant contains balanitin-1, -2 and -3; balanitin-1, for example, possesses a yamogenin aglycone (q.v.) with a branched glucose and rhamnose side-chain. In the same family, saponins from the pericarps of *Guaiacum officinale* have molluscicidal activity. In an evaluation of plant molluscicides against the freshwater snail *Lymnaea luteola*, the vector of animal schistosomiasis in India, *Sapindus trifoliatus* (Sapindaceae) was the most effective of the species tested (D. Sukumaran *et al*., *Pharm. Biol*., 2002, **40**, 450). The aqueous extracts of three other Indian-grown plants (*Thevetia peruviana, Alstonia scholaris* and *Euphorbia pulcherrina*) have also been shown to possess considerable molluscicidal activity (A. Singh and S. K. Singh, *Fitoterapia*, 2005, **76**, 747).

Tannins constitute the active principles of some Leguminosae e.g. *Acacia* spp., and napthoquinones of the juglone and plumbagin type (p. 251) constitute those of the Malawi Ebenaceous species *Diospyros usambarensis*. The disadvantage of the latter source, investigated by Hostettman *et al*., is that the naphthoquinones are at their highest concentration in the root-bark.

Other phytochemical groups of compounds having recognized molluscicidal activity are isobutylamides of the Asteraceae, Rutaceae and Piperaceae, steroidal glycoalkaloids (*Solanum mammosum*), anthraquinones (*Morinda lucida*, Rubiaceae) and flavonoids of various families. Two N.E. Brazilian species of *Solanum* (*S. jabrense* and *S. stipulaceum*) have shown promising activity (T. M. S. Silva *et al*., *Fitoterapia*, 2006, **77**, 449).

Some of the most active substances known are the unsaturated anacardic acids of cashew nut shells (*Anacardium occidentale*), but unfortunately field trials carried out in Mozambique showed the treated water to give rise to dermatitis.

Continued progress in this area is to be expected; other plants tested and shown to possess molluscicidal activity include *Ambrosia maritima, Ammi majus, Azolla pinnata, Calendula micrantha officinalis, Croton campestris, Cucumis prophetarum, Euphorbia splendens, Millettia thonningii* and *Rhynchosia minimum*.

Further reading

Casida JE, Quistad GB (eds) 1995 Pyrethrum flowers, production, chemistry, toxicology and uses. Oxford University Press, New York

Dales MJ 1996 A review of plant materials used for controlling insect pests of stored products. Bulletin 65, Natural Resources Institute, Chatham, UK

Regnault-Roger C, Philogène BJR 2008 Past and current prospects for the use of botanicals and plant allelochemicals in integrated pest management. Pharmaceutical Biology 46(1–2): 41–52. *A review with 90 references*

PART 8

Morphological and microscopical examination of drugs

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Introduction

In standard works such as the *European Pharmacopoeia*, the *British Pharmacopoeia*, the *British Herbal Pharmacopoeia* and similar publications of other countries one will find detailed morphological and anatomical descriptions of those plant drugs that are included as monographs. Microscopical characteristics of the powdered drugs are also given. Such descriptions form the basis for the identification of drugs and from this the detection of adulterated and poor quality material.

Of recent significance concerning the above is the introduction of EU directives governing the quality control of licensed herbal medicinal products. These regulations require manufacturers of such medicinals to have available personnel with the particular expertise to carry out identification tests and to recognize adulterants, the presence of fungal growth, infestation and non-uniformity within a delivery of crude drugs, etc.

To understand, and to make practical use of, the pharmacopoeial and other descriptions requires a knowledge of the botanical terminology used and an acquired skill in recognizing the structures cited for both the whole and powdered plant. It is also necessary to appreciate the function of, and to select the most appropriate, mounting reagents for the microscopical examination of drugs. Formerly, a student's practical training in pharmacognosy was largely devoted to developing such skills but now, particularly in the UK, USA and Australia these studies have been reduced to a minimum with greatest emphasis being placed on the theoretical aspects, and practical applications, of the more recent developments of the subject. Nevertheless as readers will have perceived from Part 5 of this book, such morphological and anatomical studies still form a very necessary core of the subject and are a prerequisite to the use, for medicinal purposes, of any plant consignment.

For the UK, further explanation of the EU regulatory requirements is given in 'Rules and Guidance for Pharmaceutical Manufacturers and Distributors 2007, Annex 7—Manufacture of Herbal Medicinal Products' compiled by the Inspection and Standards Division of the Medicines and Healthcare products Regulatory Agency, published by the Pharmaceutical Press.