31

Vitamins and hormones

Both vitamins and hormones constitute a range of many different types of organic molecule which are essential to the proper functioning of the human organism. Their absence or depletion gives rise to deficiency diseases, and, particularly with hormones, an excess can also be harmful. Vitamins are obtained largely from the diet, whereas hormones are manufactured in the body.

VITAMINS

Vitamins, formerly known as 'accessory food factors', are present in many animal and vegetable foods. Their absence from the diet causes deficiency diseases such as scurvy, beri-beri, rickets and night blindness. The value of citrus juices in the treatment of scurvy was realized in the eighteenth century. Systematic feeding experiments began about 1873 and much work on the subject was done by Gowland Hopkins from 1906 to 1912. Fraser and Stanton established that beri-beri was produced in people living mainly on polished rice, who could be cured if 'rice-polishings', the outer part of the grain removed in making polished rice, were added to the diet. In 1911 Funk coined the name 'vitamine' now usually spelt vitamin, for the active fraction of rice-polishings.

The existence of vitamin A was proved in 1915 and other letters were applied to later vitamins discovered. Many vitamins have since been proved to be extremely complex mixtures, and one now speaks, for example, of the vitamin B complex, components of which can be referred to as B_1, B_2, etc., or by their chemical or other names. As the chemical nature of the vitamins has been discovered and vitamin complexes have been resolved into their constituents, there is an increasing tendency in the scientific and medical literature to discard the term 'vitamin' with its associated letter (and number) in favour of the chemical name for the material under consideration (see, for example, the *BP* monographs on Hydroxocobalamin, Riboflavine and Thiamine Hydrochloride). However, in the lay literature the original vitamin terminology persists and pharmacists need to be familiar with this. Some vitamins have as yet no proved role in the treatment of human diseases but others are valuable items of the materia medica. A large number of different pharmacopoeial and proprietary vitamin preparations are available but with a well-balanced diet the normal individual should require no vitamin supplementation (Table 31.1). However, people on a strict vegetarian diet who eat no eggs or dairy produce need a supplement of vitamin B_{12}; and alcoholics need vitamin B_1, which is required for the complete metabolism of ethanol. Other groups, such as narcotic drug users, whose diet is generally inadequate are also prone to vitamin deficiency. Need for vitamins is still great in many underdeveloped countries. Notwithstanding the above, the consumption by the general public of vitamin preparations is enormous and this is one of the larger areas of the pharmaceutical industry. Numerous publications on healthy foods and promotional leaflets ensure that these substances are universally recognized.

It will be noted in Table 31.1 that a number of gaps appear in the naming of the vitamins and this is because some substances once regarded as vitamins (e.g. vitamin F and a number of the B group) are of indefinite character or have been reclassified as essential nutritional factors.

Chemically, vitamins vary from very simple compounds to very complex ones. They belong to no one chemical type. Vitamin A has already been mentioned under 'Diterpene compounds'; vitamin C has affinity with the sugars, being the enolic form of 3-oxo-L-gulofuranolactone; B_{12}, which first became official in 1963, has a very complex molecule. Several forms of vitamin D occur. Vitamin K_1 is 2-methyl-3-phytyl-1,4-naphthoquinone. As might be expected from

Table 31.1 Sources of vitamins.

Vitamin	Alternative names	Distribution
A (A_1, A_2)	Anti-infective or antixerophthalmic vitamin, retinol	Fish livers (cod, halibut, shark, etc.) and other animal fats. Plants contain proto-vitamin A, the vitamin precursors (e.g. α-, β- and γ-carotene) and cryptoxanthine; these are converted to vitamin A in liver
B_1	Aneurine, thiamine	Rice polishings, cereal germ, animal organs, yeast or prepared synthetically
B_2	Riboflavine	Widely distributed in both plants and animals; bacteria, yeasts and other fungi, cereal grains and many fruits
B_3	Niacin, nicotinic acid, nicotinamide, niacinamide, pellagra-preventing or PP vitamin	Milk, eggs, liver, yeast, malted barley, or may be prepared by fermentation
B_5	Pantothenic acid	Yeast, liver, red meat, chicken, milk, mushrooms, beans, bananas, nuts, avocados, potatoes
B_6	Pyridoxine, pyridoxine hydrochloride	Prepared synthetically but present in many foodstuffs, including yeast, liver, red meat, fish, yoghurt, bananas, cabbage, wholegrains
B_9	Folic acid, folacin, vitamin M	Yeast, liver, green plants, wholemeal bread, oranges, nuts
B_{12}	Cyanocobalamin, megaloblastic anaemia vitamin	From livers or from the metabolic products of microorganisms such as *Streptomyces griseus*
C	Ascorbic acid	Fruits, particularly citrus fruits, tomatoes, potatoes, capsicums; raw vegetables; or made synthetically
D_2	Antirachitic vitamin; calciferol, ergocalciferol	Calciferol is produced by irradiation of ergosterol
D_3	Cholecalciferol	Formed by irradiation of cholesterol. It is found in fish-liver oils (e.g. cod, halibut) and in human skin following exposure to sunlight
E	Tocopherols, alpha tocopheryl acetate	Embryos of cereals (wheat and maize germ oils); other vegetable oils (palm, olive, etc.); fresh vegetables, nuts, eggs, butter
H	Biotin (two forms), coenzyme R	Yeast, peanuts, chocolate, carrots, liver, kidney, eggs
K_1	Phytomenadione, coagulation factor, antihaemorrhagic vitamin	From plants (e.g. alfalfa, lucerne, tomatoes, etc.); or by synthesis. Abundant in the human intestine, where it is synthesized by intestinal bacteria
P	Permeability factor (significance now doubtful)	Flavonoids derived especially from *Citrus, Ruta, Sophora* and other genera
Ubiquinone 10	Ubidecanenone; coenzyme Q_{10}. Has been referred to as Vitamin Q_{10}	A coenzyme found in liver; also in other metabolic tissues of plants and animals

these wide variations in structure, vitamins differ from one another in physical properties such as solubility. They have been traditionally classified according to their water-solubility and fat-solubility properties and this division is still useful. In the main, the water-soluble vitamins are non-toxic and can be consumed in large doses without harm; they also remain in the body for a relatively short time. Conversely, the fat-soluble vitamins are more toxic in large doses and are stored in the fatty reserves of organs of the body for long periods of time. The solubilities also determine the type of food products in which the two groups occur, e.g. fatty dairy products as opposed to plant juices.

FAT-SOLUBLE VITAMINS

Vitamin A (A_1; A_2)

Vitamin A is found as such only in the animal kingdom and is particularly abundant in fish-liver oils. The preparation of cod-liver oil is described below. Vitamin A occurs in three or more forms termed vitamers. Vitamin A_1, retinol (see Fig. 31.1), is an alcohol and retinal is its corresponding aldehyde. Vitamin A_2, dehydroretinal, has a second unsaturated bond in the ring system and also occurs as the aldehyde dehydroretinol. The carotenes (see Chapter 24) are C_{40} compounds found in the plant kingdom and are converted to vitamin A in the small intestine and other organs. Although the formulae of the carotenes might suggest that each molecule would give rise to two molecules of vitamin A, the successive oxidations of the molecule in fact give rise to only one molecule of the vitamin. Infants and young children have only a limited capacity to effect this conversion and true carnivores (e.g. cats) and invertebrate animals are unable to utilize carotene in this respect.

Vitamin A is decomposed by exposure to light and may be assayed in fish-liver oils and other preparations by ultraviolet absorption and spectrophotometry.

Vitamin A is essential for the normal functioning of the body epithelia and the retina. Deficiency is indicated by night blindness and by a drying and crusting of the mucous membranes.

Vitamin D

The compounds comprising this group have antirachitic activity and are individually designated D_2–D_6; they are formed by the opening of ring B of a steroidal provitamin. Vitamin D_3 (cholecalciferol, see Fig. 31.1) is the only member to occur naturally in higher animals and is formed photochemically from 7-dehydro-cholesterol by the sun's irradiation of the skin. Vitamin D_2 (calciferol, ergocalciferol) differs from D_3 in having an unsaturated side-chain. D_4, D_5 and D_6 are produced artificially by the irradiation of 22-dihydroergosterol, 7-dehydrositosterol and 2-dehydrostigmasterol respectively. These vitamins are relatively stable and preparations containing them are assayed (*BP/EP*) by liquid chromatography using, as a standard, a preparation of crystalline vitamin D_3.

Vitamin D regulates the calcium and phosphorus balance in the body by direct action on phosphorus metabolism. It promotes calcium

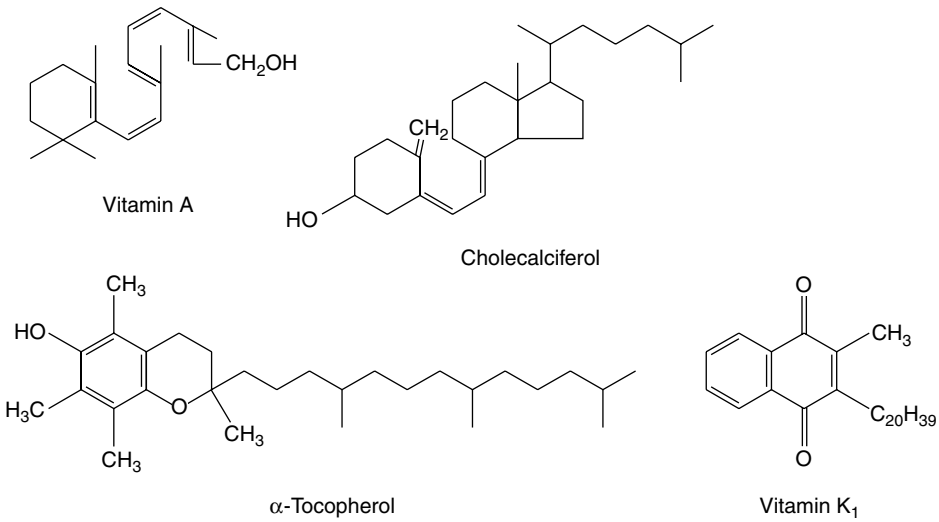


Fig. 31.1
Structures of some fat-soluble vitamins.

absorption and is an essential factor in bone formation (a deficiency causes rickets). Excessive doses of the vitamin should be avoided.

Vitamin E

Contained in this group are a number of tocopherols, prefixed α-, β-, γ-, etc, which are of wide occurrence in plants, being particularly abundant in the germ oil of cereals. For the preparation of vitamin products the cereal embryos are conveniently separated during the manufacture of the appropriate starches; α- (see Fig. 31.1), β- and γ-tocopherols are among those found in the germ of wheat, barley and rye, whereas others are found in soya beans, ground nuts and maize. Oats contains some five different tocopherols. The various tocopherols differ in the methylation patterns of the ring system. Virgin Wheat-germ Oil and Refined Wheat-germ Oil are included in the *BP*/*EP*; also seven monographs based on derivatives of the racemic and RRR-α-tocopherols. These are evaluated by gas chromatography.

Discovered in 1922, vitamin E is a powerful antioxidant and has an important role in the preservation of the well-being of cells, for slowing their ageing effects and in counteracting the harmful aspects of toxins in the blood and lungs. It may assist protection of the cardiovascular system by preventing blood–lipid peroxidation with the subsequent formation of sticky deposits. Traditionally the vitamin has been associated with the improvement of fertility.

A normal diet supplies adequate amounts of the vitamin; deficiency leads to the destruction of red blood cells with resultant anaemia. It may be added to cod-liver oil (q.v.).

Vitamin K (phytomenadione, phylloquinone)

This vitamin occurs in several natural forms. Vitamin K_1 (Fig. 31.1) is found in many plant sources and has a C_{20} side-chain with one unsaturated linkage. K_2, originally prepared from decaying fish, has a polyunsaturated isoprenoid side-chain which is of variable length. These compounds, termed menaquinones (MK), are produced by bacteria and, as an example, MK-8 refers to a menaquinone produced by *Escherichia coli* with 8 isoprene units and 40 carbon atoms in the side chain. (For the biogenesis of these compounds, see R. Bentley and R. Meganathan, *J. Nat. Prod.*, 1983, **46**, 44.) The formation of phylloquinone in green plants has received less attention; chorismic acid (q.v.) and 2-succinylbenzoic acid are probable intermediates. Similar compounds with vitamin K activity have been synthesized.

Vitamin K is a necessary factor in the blood-clotting process; it acts indirectly by activating those substances which are necessary for the conversion of prothrombin to thrombin. In healthy individuals it is possible that the intestinal flora provides an adequate supply of the vitamin. Deficiency symptoms are prolonged bleeding and excessive bruising.

COD-LIVER OIL

Medicinal cod-liver oil is a fixed triglyceride oil prepared from the fresh liver of the cod, *Gadus morhua* L. and other species of *Gadus* (family Gadidae) under conditions which give a palatable oil containing a due proportion of vitamins. To comply with European requirements, two oils (Type A and Type B) are described in the *BP*. Both have identical standards for vitamin contents but the former has a limit test governing secondary oxidation of the oil (see standardization). The Type B oil is the principal commercial product. In Western Europe the principal producers and suppliers of the raw material are now Norway and Iceland with much of the crude oil coming to the UK for subsequent refining and processing. (*Note*: the production of fish-liver oils should not be confused with that of fish-body oils; some tonnage of the latter is produced in the UK but more of the requirement is satisfied by imported material).

History. Cod-liver oil was exported from Norway during the Middle Ages but it appears to have been used solely for non-medical purposes. Its introduction into medicine was largely due to Dr Samuel Kay, a physician at Manchester Infirmary from 1752 to 1784. The original method of preparation was the 'rotting process', in which the livers were allowed to rot in barrels and the oil rising to the surface was skimmed off. The more modern 'steaming process' was introduced about 1850.

Collection and extraction. The following account is based largely on information supplied by Seven Seas Health Care Ltd., leading refiners and processors of cod-liver oil worldwide.

The cod livers, which contain about 50% oil, are removed immediately the fish are boarded and transferred to steamers in which the oil is released from the tissue, or stored in chilled conditions for later processing at a shore station. All this takes place mainly on Norwegian and Icelandic vessels. On arrival in port the oil is stored in land-based tanks prior to bulk shipment to the UK for refining and processing, although some preliminary refining of oils is now conducted at the extraction plants in Norway and Iceland.

Preparation. The principal stages in the preparation of the medicinal oil are (1) refining of the crude oil, (2) drying, (3) winterization, (4) deodorization, (5) standardization for vitamin content.

Refining. Quality and flavour of cod-liver oil are improved by refining under air-free conditions to avoid oxidation; at Marfleet, UK, this is carried out in a continuous, automatic, hermetic refining plant consisting of a battery of mixers linked to centrifuges. The crude oil is rapidly heated to 77°C in a heat exchanger and passed to disc-type mixers, where controlled addition of an aqueous reagent takes place which removes impurities and causes further dissolution of the small amount of liver tissue present. Oil and water phases are separated in a hermetic separator (centrifuge: 7000 r.p.m.) without contact with air. The refined oil is then mixed with water, reheated and the separation process is repeated in a second and third set of centrifuges.

Drying. Drying is effected in a vacuum drying tower which continuously evaporates any small amount of residual water and discharges a clear, bright, highly refined oil. The plant can refine 50–60 tonnes of oil per day.

Winterization. All medicinal oil and veterinary oils are cooled to about 0°C, which causes stearin (triglycerides with a higher saturated fatty acid content) to separate. The solid is removed by cold filtration and a polyunsaturated (enriched) product is left. Photographs illustrating the above processes can be found in the 14th edition of this book.

Deodorization. Final deodorization is achieved by steaming under vacuum which removes about 0.02% of aldehydic and ketonic impurities, and once again protects the oil from oxidation. This process establishes the palatable flavour of the finished oil.

Standardization. The medicinal oil is finally standardized for vitamin content by blending. The *BP*/*EP* oil is required to contain in 1 g, 600 to 2500 Units of vitamin A and 60 to 250 International Units of vitamin D_3. The former is assessed by the HPLC method of the *Pharmacopoeia*, the Unit being equivalent to 0.344 mg of *all-trans*-vitamin A acetate or 0.3 mg of the corresponding alcohol. The determination of the vitamin D content requires two chromatographic procedures—the first for purification of the solution under test and the second for the separation of ergocalciferol and cholecalciferol. Ergocalciferol EPCRS is used as an internal standard and peak heights or areas are measured.

The fatty acid composition of the oil is determined by gas chromatography and limits are given for 15 individual acids classified as saturated, mono-unsaturated and poly-unsaturated fatty acids.

As mentioned above, the *BP*/*EP* includes Type A and Type B oils; both have identical vitamin-content requirements but Type A has, in addition, an anisidine value of $\gtrless 30.0$. The latter represents a limit of aldehydes and ketones produced by secondary oxidation of the oil. For determination, the oil is reacted with anisidine in glacial acetic acid and the yellow–brown colour produced measured at 350 nm (anisidines are methyl ethers of *o*- and *p*-aminophenol).

It is now common practice to add some vitamin E to cod-liver oil (often as dl-α-tocopheryl acetate) to assist in the *in vivo* protection against reduction of the user's vitamin E status, owing to higher intake of polyunsaturates.

Storage. The oil should be kept in well-filled airtight containers, protected from light and in a cool place. The addition of small amounts (0.01%) of certain antioxidants (e.g. dodecyl gallate, octyl gallate) is permitted.

Characters. Medicinal cod-liver oil is a very pale yellow liquid with only a slightly fishy odour and taste. The acid value should not exceed 2.0 but varies with age. The iodine value, as may be inferred from the constituents, is high (150–180). In contrast to halibut-liver oil, the unsaponifiable matter is low (1.5%).

Constituents. The medicinal properties of cod-liver oil are mainly due to vitamin A and vitamins of the D group. The main antirachitic activity appears to be due to D_3 (cholecalciferol). The oil consists of glycerides of unsaturated (about 85%) and saturated (about 15%) acids. In the unsaturated group the acids possess 14, 16, 18, 20 or 22 carbon atoms, and up to 6 ethylenic linkings; in the ω-3 series eicosapentaenoic acid (C20:5) and decosahexaenoic acid (C22:6) are preeminent with smaller amounts of docosapentaenoic acid (C22:5) (see Fatty acids, Chapter 19 for explanation of nomenclature). Evidence is increasing that these polyunsaturated acids are significant for human health. The saturated acids include myristic acid (C14:0), palmitic acid (C16:0) and traces of stearic acid (C18:0).

Uses. Cod-liver oil is still widely used in underdeveloped countries for the prevention and cure of rickets. In Europe and the USA its use has changed somewhat as in addition to its traditional use as a vitamin supplement it now finds application in the relief of rheumatic pains and joint and muscle stiffness. Cod-liver oil has the established activity of reducing blood cholesterol levels and affording protection against cardiovascular disease (see also Chapter 6). It has extensive veterinary use.

Allied drugs. Halibut-liver Oil *BP* is a fixed oil obtained from the livers of the halibut, *Hippoglossus vulgaris* (Pleuronectidae). It is a pale golden-yellow liquid containing relatively large amounts of vitamins A and D, assayed spectrophotometrically. The standard for unsaponifiable matter is not less than 7.0%. It is used for the same purposes as cod-liver oil but in proportionately smaller doses, often in capsule form diluted with a vegetable oil to achieve specific vitamin potencies. Many other fish-liver oils resemble cod-liver oil, and shark-liver oil, Oleum Selachoidei, is included in the *Indian Pharmacopoeia*.

WATER-SOLUBLE VITAMINS

Vitamin B_1 (thiamine, aneurine)

The vitamin B_1 molecule is comprised of a pyrimidine and a thiazole unit connected by a methylene bridge (Fig. 31.2). It is official (*BP*/*EP*) as the hydrochloride and nitrate and is widely available from plant and animal sources (Table 31.1). In plants it is biosynthesized in the leaves and transported to the roots where it acts as a growth factor. Animals accumulate either the pyrophosphate (cocarboxylase) or a protein-magnesium complex.

Vitamin B_1 in food is destroyed by boiling and its preparations should be protected from light. The *BP*/*EP* assay for the hydrochloride and nitrate is by non-aqueous titration.

In the body, carbohydrate metabolism and the normal functioning of the nervous system are dependent on adequate supplies of the vitamin. Severe deficiency causes beri-beri and was classically observed when people whose staple diet was whole ground rice were converted to polished rice. Initially symptoms of deficiency include loss of appetite, muscular atrophy and mental disturbances.

Vitamin B_2 (riboflavine, lactoflavine)

Vitamin B_2 is built up from a ribose and an isoalloxazine residue, the name riboflavin(e) being derived from the sugar component and the intense yellow fluorescence of its aqueous solution. It is of wide occurrence in nature and constitutes a component of the flavin coenzyme systems. Synthesis by microorganisms of the intestinal flora of humans can result in a higher excretion in the faeces of vitamin B_2 than is actually present in the diet. The vitamin is unstable to light and strong alkalis and should be stored in a well-closed container.

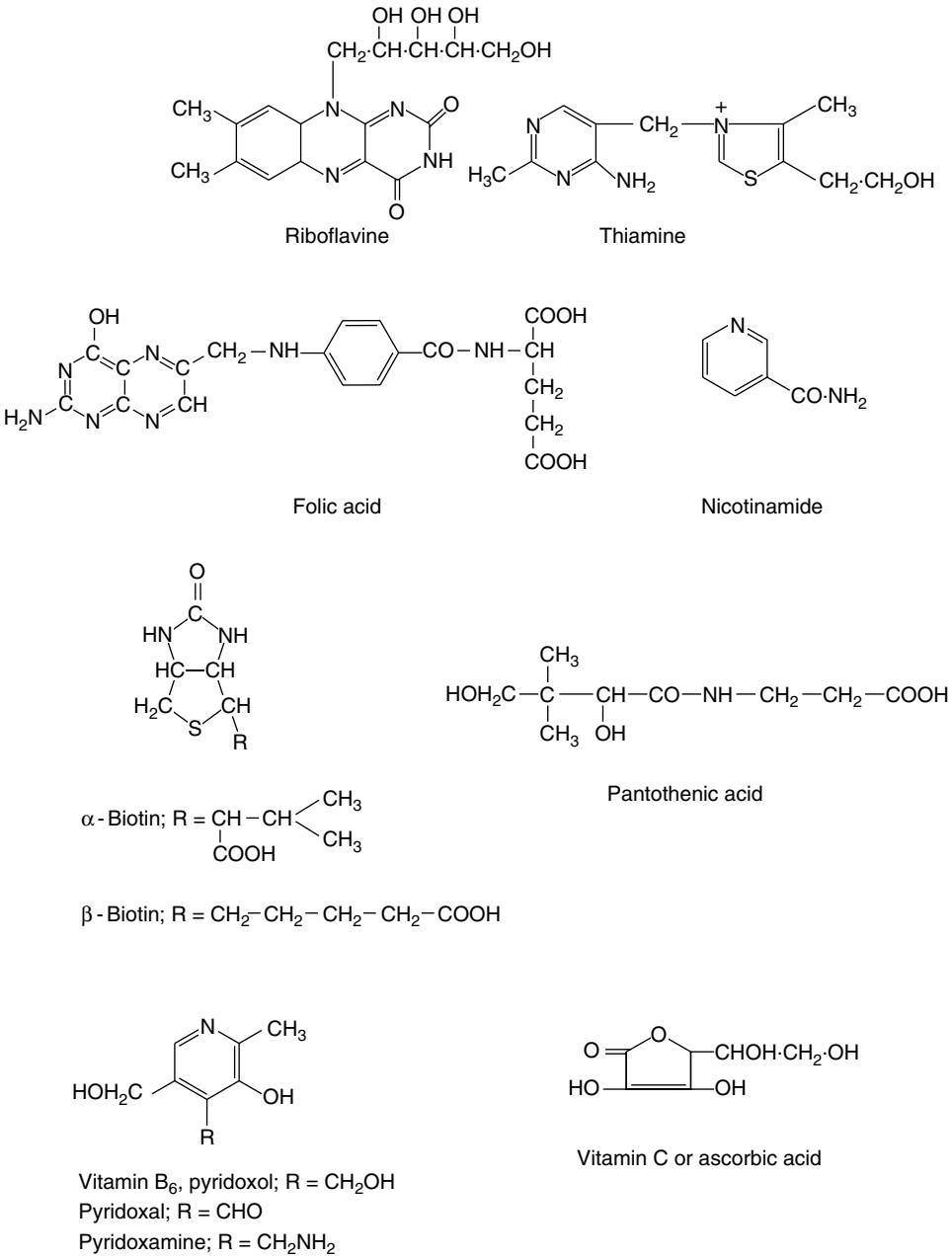


Fig. 31.2
Structures of some water-soluble vitamins.

It is assayed (*BP*/*EP*) by measurement of the absorbance of a solution of the acetate at 444 nm.

Deficiency in humans is rarely encountered; symptoms include a cracking of the corners of the mouth, dermatitis and conjunctivitis.

Pantothenic acid (vitamin B_3 or B_5)

This compound (Fig. 31.2) is a component of coenzyme A (q.v.). Deficiency symptoms are not well-defined and differ appreciably with different species of animal.

Vitamin B_6 (pyridoxine)

Pyridoxol (Fig. 31.2), pyridoxal and pyridoxamine are three forms of the vitamin. The first is found in large quantity in plant sources and the other two in animal tissues. In man, B_6 is synthesized by micro-organisms of the large gut, but how much of this is utilized appears uncertain.

The vitamin participates in an important coenzyme system in protein synthesis and is involved in fat metabolism. It has been tested for various disorders of the body and is indicated by the *BP*/*EP* for the treatment of sideroblastic anaemias. Although not medically proven, many women appear to derive beneficial effects from large doses of the vitamin taken to combat premenstrual tension. Deficiency symptoms, which are rare in humans, resemble those for other B vitamins and include convulsions, polyneuritis and skin disease.

Pyridoxine Hydrochloride of the *BP*/*EP* is assayed by non-aqueous titration; it should be stored protected from light.

Nicotinamide (vitamin B_7, vitamin PP) and nicotinic acid (niacin)

These compounds (Fig. 31.2) are found, principally as the amide, in a variety of foods and are manufactured in the body, with the aid of other B vitamins, from tryptophan. Nicotinamide is a component of a

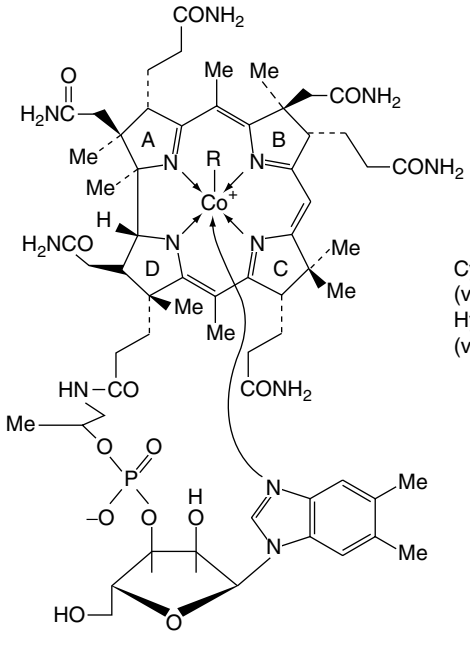
number of coenzymes (Chapter 18) which play an important role in the primary metabolism of the cell.

The classical deficiency disease associated with the vitamin is pellagra but other supplementary factors involving a lack of other B vitamins, an unbalanced diet, and exposure to the sun are also involved. Symptoms of deficiency are skin inflammation, diarrhoea and delirium. Nicotinic acid has a vasodilatory effect.

The vitamin is stable in foodstuffs; nicotinic acid should be protected from light and nicotinamide should be stored in well-closed containers. The *BP*/*EP* assay utilizes non-aqueous titration (nicotinamide) and acid–base titration (nicotinic acid).

Vitamin B_{12} (cyanocobalamin)

This vitamin is not found in plants or yeasts but occurs in meat, in particularly large quantities in livers and kidneys. In the serum it is largely combined with serum globulins. B_{12} is also produced by a number of microorganisms (e.g. species of *Streptomyces* and *Bacillus*) and these are used for the commercial production of the vitamin. The molecule is a porphyrin derivative complexed with cobalt and linked to a nucleotide. As a natural complexed porphyrin derivative it may be compared with chlorophyll (Mg^{2+}) and haemoglobin (Fe^{2+}), which together have been described as 'pigments of life'. The vitamin complex exists in a number of forms designated B_{12} (cyanocobalamin), B_{12a} (hydroxocobalamin), B_{12b} etc., the term cobalamin being restricted to those members having 5,6-dimethylbenzimidazole as the basic portion of the nucleotide. Hydroxocobalamin (B_{12a}) has, in alkaline solution, a hydroxy group instead of the cyanide ion of B_{12}. Cyanocobalamin *BP*/*EP* is assayed by absorbance measurements at 361 nm and hydroxocobalamine, official as the acetate, chloride and sulphate by measurements at 351 nm.



Cyanocobalamin (vitamin B_{12}); R = CN.
Hydroxocobalamin (vitamin B_{12a}); R = OH.

Nearly 40 years after the structure elucidation of vitamin B_{12} by the late Dorothy Hodgkin in 1956, the biosynthetic pathway for this compound was finally established in what Battersby has described as the Everest of biosynthetic problems [for an account (19 refs) see L. R. Milgrom, *Chemistry in Britain*, 1994, **31**, 923].

In the body, vitamin B_{12} is involved with the metabolism of amino acids particularly the methylation of homocysteine to give methionine (see Fig. 18.15) and the breakdown of other amino acids.

Vitamins B_{12} and B_{12a} are used for the treatment of pernicious anaemia; they are best given by injection and replace the former treatment with raw liver and liver extracts. Hydroxocobalamin binds more strongly with the serum proteins than does B_{12} and so has a longer period of action.

Cyanocobalamin (^{57}Co) and (^{58}Co) are radioactive forms of the vitamin used in diagnostic tests for pernicious anaemia; they have radioactive half-lives of 271.7 days and 70.8 days respectively, and are prepared by cultivating suitable microorganisms on a medium containing the radioactive cobaltous ions. Owing to its long radioactive half-life (5.27 years), cyanocobalamin (^{60}Co) should not be used in this test.

Folic acid (folacin, vitamin B_c, vitamin M, factor V)

Folic acid refers to pteroylmonoglutamic acid (Fig. 31.2), as distinct from the tri- and heptaglutamic acids also found in this group of substances. The structure of the original vitamin-like material isolated from spinach leaves in 1941 and named 'folic acid' is not known. In the body, folic acid is necessary for cell division and for the normal production of red blood cells. With normal diets, deficiency is rare, but supplementation may be required during pregnancy and as a result of taking oral contraceptives. Lack of the vitamin produces diarrhoea, loss of weight and megaloblastic anaemia. The last two symptoms resemble those of vitamin B_{12} deficiency and correct diagnosis and avoidance of self-medication is essential.

Vitamin C (ascorbic acid)

Ascorbic acid (Fig. 31.2) is prepared synthetically or by extraction from plant materials such as rose hips, blackcurrants and the juice of citrus fruits (q.v.). One of the richest sources appears to be the fruit of an edible Combretaceous tree, *Terminalia ferdinandiana*, found along the north-west coast of Australia. The edible fruits contain some 2300–3150 mg ascorbic acid per 100 g of edible fruit, a figure two to three times higher than that for rose hips. In the plant ascorbic acid is biosynthesized from D-glucose and a pathway involving fructose, mannose and galactose derivatives has also been proposed (G. L. Wheeler *et al*., *Nature*, 1998, **393**, 365; see also F. A. Loewus, *Phytochemistry*, 1999, **52**, 193).

Vitamin C is essential for the normal functioning of living cells and is involved in many enzymic reactions. It is required for the development of cartilage, teeth and bones, for wound healing and for aiding the absorption of iron from the intestine. Gross deficiency causes scurvy; early signs of a lack of the vitamin in individuals are muscular weakness, tiredness, reduced resistance to infection and easy bruising. Large doses of vitamin C have been tested for the prevention of the common cold, but without significant success.

The pharmacopoeial assay involves titration with 0.05 M iodine solution with starch as indicator.

The reducing and associated antioxidant properties of vitamin C are utilized in the food industry and in the formulation of some pharmaceutical preparations.

Biotin (vitamin H)

Biotin occurs in so-called α- and β-forms, which differ in their side-chain structure (Fig. 31.2). In the body, these substances, in some instances, operate with other water-soluble vitamins and enzymes and are required for digestion and carbohydrate metabolism. Large quantities are produced by the intestinal microorganisms and deficiency conditions such as dermatitis are rare.

The pharmacopoeia illustrates the β form, which is assayed by potentiometric titration with 0.1 M tetrabutylammonium hydroxide. Various possible impurities, largely involving the structure of the side-chain, are listed. Tests include TLC and IR spectrometry.

Ubiquinone (ubidecarenone, coenzyme Q10)

In the mitochondria of plants and animals this coenzyme is involved in electron transport. It may act as a free radical scavenger and function as an antioxidant and membrane stabilizer. For patients with cardiovascular disorders it is regarded as a useful addition to orthodox treatment but a double-blind study involving 46 patients failed to give a positive result; for a brief report see *Pharm. J.*, 1999, **263**, 848. It is sold to the general public as a popular food supplement for protection against heart and gum disease and for maintaining general well-being.

DOG ROSE (ROSE HIPS)

Dog rose consists of the incompletely dried, almost ripe hips, with the achenes removed, of various species of *Rosa* (Rosaceae) including the common dog roses (*R. canina* L.), downy-leaved roses (*R. villosa* L.) and 'alpine rose' (*R. pendulina* L.). The hips should be collected between the period when they just begin to change colour and when they are fully red, and used for the preparation of galenicals as soon as possible.

The hip is an aggregate fruit formed from the apocarpous gynaecium of a single flower. Fruits of different species of *Rosa* naturally vary in size and shape. That of *R. canina* is urn-shaped, almost 2 cm long, bright red and glossy when ripe. As the commercial drug, it occurs as broken fragments of the fleshy, hollow receptacle, strongly wrinkled on the convex surface and bristly on the inner. The upper end of the receptacle bears the scars of the five fallen sepals. A characteristic feature of the powder is the large unicellular trichomes up to 2 mm in length which arise from lignified cells of the inner epidermis.

Rose hips are used for their vitamin content containing 0.1–1.0% ascorbic acid (Vitamin C) (Fig. 31.2) and smaller amounts of vitamin A, aneurine, riboflavine and nicotinic acid. The *BP*/*EP* requires a minimum 0.3% ascorbic acid for the dried drug, which is determined spectrophotometrically.

The syrup, prepared from the fresh fruit, is unstable and loses up to 50% of its ascorbic acid within 6 months.

BLACKCURRANT

The *BP* material requires little description and consists of the fresh ripe fruits of *Ribes nigrum* L. (Grossulariaceae, but often included in the Saxifragaceae) together with their pedicels and rachides. The plants are commonly cultivated in most temperate regions. The fruits contain various acids (e.g. citric and malic), pectin, colouring matter and ascorbic acid. The ascorbic acid content varies from 100 to 300 mg 100 g^{-1}. They are used for the preparation of Black Currant Syrup and in some lozenges. The leaves are used in Europe as a traditional treatment for rheumatic diseases; the active constituents may be prodelphinidin oligomers. Other species of *Ribes*, for example, the gooseberry (*R. grossularia*) and red currant (*R. rubrum*), have also been used in medicine.

Citrus juices

Lemon juice is produced on a large scale in many lemon-growing countries. The fruits yield about 30% of juice, which may be packed at natural strength or after concentration. Large quantities are used for citric acid manufacture. Lemon juice is used for its vitamin C content, but orange juice is richer in this vitamin and is more suited to infant feeding. Decitrated orange and lemon juices are used for making vitamin C concentrates. Vitamin C, or ascorbic acid, may be prepared from other vegetable sources (e.g. the ripe fruits of *Capsicum annuum*) or made synthetically.

Dried yeast

Dried yeast consists of the cells of a suitable strain of *Saccharomyces cerevisiae* (Order Protoascales, Saccharomycetaceae) dried so as to preserve the vitamins present.

Collection and preparation. Yeast is produced by growing the parent cells in a liquid containing sugars and nitrogenous compounds. Distillers' or bakers' compressed yeast is separated from the medium by the use of filter presses and is a by-product in the manufacture of alcoholic liquors. However, yeast may be the sole product of a yeast factory. Compressed yeast contains about 70% of moisture and is converted into dried yeast by heating at a temperature not exceeding 30°C until the moisture content is reduced to below 9%.

Characters. Dried yeast occurs as a pale buff powder. Under the microscope it shows spherical, elliptical or ovate cells up to 8 µm long, some showing budding. They are transparent and have a cell wall enclosing a granular protoplasm in which are one or two glycogen vacuoles. The nucleus exists as a small mass near the centre of the cell and cannot usually be seen without the use of a special staining procedure. Yeast should contain no starchy material.

Constituents. Important constituents of yeast are the vitamins of the B group (aneurine, nicotinic acid, riboflavine, folic acid and B_{12}). It also contains about 46% of protein, 36% of carbohydrates (particularly glycogen), fats, sterols and enzymes (the zymase complex, glycogenase, invertase, maltase and emulsin).

Uses. Yeast is used in the treatment of furunculosis and as a source of the B vitamins. It is a rich source of biologically complete protein and is used in the manufacture of nucleic acid. In addition to the yeast described above, Torula yeast, derived from *Candida utilis* (Cryptococcaceae), is used. It contains about 45% of protein and is rich in vitamins.

In molecular genetics *S. cerevisiae* has been utilized as a suitable organism for the overexpression of active enzymes of other plants and of animals (e.g. hirudin of the medicinal leech).

HORMONES

Some textbooks of pharmacognosy include endocrine organs and hormones; others do not. The pharmacy student usually acquires knowledge of these partly in pharmacology, pharmaceutical chemistry and pharmaceutics. The brief account which follows may form a useful starting point.

Hormones, or 'chemical messengers', are substances secreted by the endocrine or ductless glands of animals. Until recently it was fashionable to deride the therapeutic use of animal products; for example, livers from various animals by the ancient Egyptians and toad-skins by the ancient Chinese. Research has since shown that such materials often contain therapeutically valuable substances. This is especially true of the ductless glands, whose function was a mystery to men such as Galen. An early example of the rational use of endocrine organs was the employment of hog testis by Magnus in the thirteenth century for male impotence. For a long period it was known that abnormalities of the thyroid produced myxoedema and cretinism, and when in 1891 Horsley showed that such patients benefited from the administration by mouth of animal thyroid glands, the modern period of organotherapy started. Suprarenal extracts were introduced about 1894 and two thyroid preparations (a dry powder and a solution) were included in the *BP* 1898. The practice of using the glands or more or less crude preparations of them (organotherapy) has gradually been displaced by

Table 31.2 Distribution of hormones.

Hormones	Nature and occurrence
Gonadotropins	Water-soluble glycoproteins. Pituitary glands of man, horse, sheep and pig
Corticotropins	Polypeptides of pituitary glands
Thyrotropin	Protein combined with carbohydrate. Pituitary gland
Oxytocin and vasopressin	Octapeptides. Pituitary gland
Thyroxin	An iodine-containing compound. Thyroid gland
Adrenalin	(–)-α-3,4-Dihydroxy-phenyl-β-methyl aminoethanol. Suprarenal gland or prepared synthetically
Insulin	Molecule contains two unbranched polypeptide chains linked by two disulphide bridges. Islets of Langerhans of pancreas
Corticosteroids	From adrenal cortex from which over 40 steroids, many having hormonal activity, have been isolated. Examples: cortisone, aldosterone. Many others have been prepared synthetically
Oestrogens	Steroidal female sex hormones. From pregnant mares or human urine, hog ovaries, etc.
Androgens	Steroidal male sex hormones (e.g. testosterone and androsterone). From urine or by partial synthesis

the use of their active principles (hormone therapy). With a knowledge of their chemical structure some hormones can now be best made synthetically. Adrenaline was first used in 1901 and became official in 1914. Thyroxin was isolated in 1915, was synthesized in 1928 and has gradually replaced the use of thyroid glands. In Britain, on grounds of safety and in the light of the more reliable alternatives available, the licensing authority removed all thyroid extract products from the market from October 1982. One of the most notable advances was the discovery of insulin by Banting and Best in 1921, which revolutionized the treatment of diabetes; the hormone became official in the *BP* 1932. In another big step forward, insulin has continued in the forefront of pharmaceutical development in that human insulin is now produced by microorganisms which have been engineered to contain the necessary human genetic material for hormone production. The first sex hormones were isolated from urine in 1931; testosterone became official in 1948 and testosterone implants in 1963. Oral contraception greatly increased the demand for substances of this class (see Chapter 24).

Hormones, like vitamins, are chemically a diverse class (Table 31.2). Some are related to the polypeptides and proteins, while others are steroidal. The preparation and purification of hormones such as insulin from natural sources at first presented difficult technical problems. Chemists also had formidable tasks in determining structures and evolving methods for synthesis.

Phyto-oestrogens are non-steroidal plant substances of flavonoid constitution exhibiting oestrogenic properties. They have recently received considerable press and scientific attention and are described in Chapter 21, p. 252.

32

The plant nutraceuticals

G. B. Lockwood

A number of plant nutraceuticals are common food constituents, and extracts of many others are used as nutraceuticals.

There are a number of definitions of nutraceuticals, but the first and most straightforward is that coined by De Felice, of the Foundation of Innovation in Medicine, who defined a 'nutraceutical' as a 'food, or parts of a food, that provide medical or health benefits, including the prevention and treatment of disease'.

Nutraceuticals are rarely legally classed as medicines, but instances exist in certain countries for particular entities, for example coenzyme Q10 in Japan and melatonin in the UK. This consequent lack of regulation for most nutraceuticals has resulted in a number of poor quality products being available on the market.

There are a number of sources of nutraceuticals, including basic human and mammalian metabolites, dietary components of plant and animal origin, synthetic constituents and plant secondary metabolites; increasingly, they are also produced by microbial fermentation. Arguably the greatest number are derived from plants and are used either as single purified components, such as resveratrol, purified multi-component products, such as pycnogenol, or whole plant foods, such as flaxseed. The most researched nutraceuticals of plant origin are those derived from soy and tea, but large numbers of scientific and medical publications relate to the constituents of grapes and wine, and also the many plants rich in polyphenolic components. Table 32.1 lists plant sources and therapeutic activities of a number of commercially available single-component nutraceuticals, which often occur in a number of plants. Various purified multi-component nutraceuticals are also obtained from specific plants (Table 32.2). Those from grape, soy and tea could realistically be obtained from the diet. Increasingly, a number of foods are being promoted as sources of nutraceuticals specifically for consumers who prefer eating a healthy diet instead of taking supplements; Table 32.3 depicts a wide variety of such products. The last group of nutraceuticals occurs in the plant kingdom either widely, such as coenzyme Q10 and *S*-adenosylmethionine (SAMe), or only in a few specific plants but at insubstantial levels, and are therefore not suitable for realistic incorporation in the diet. These latter nutraceuticals are often produced by chemical or biotechnological synthesis (Table 32.4).

The range of therapeutic applications is wide, encompassing many areas in which conventional pharmaceuticals treat only the symptoms of the disease state. A number of these nutraceuticals have been shown to treat the underlying cause of the illness, e.g. α-linolenic acid. As a consequence of this, many nutraceutical manufacturers and pharmaceutical companies are increasingly investigating the possibility of formulating and marketing plant based nutraceuticals.

Many of the nutraceuticals owe their activities to antioxidant activity (activity is highlighted in Tables 32.1–32.4), but this may not be the full story. It has been claimed that many also have other activities, including enhancement or inhibition of Phase I and II metabolizing enzymes, and modulation of DNA repair.

In addition to the increasing number of clinical trials being published to support the use of plant nutraceuticals, evidence is accumulating regarding synergistic interactions, adverse effects, and quality of commercially available single and multicomponent nutraceuticals.

Carotenoids

A number of plant-derived carotenoids such as lycopene, lutein and zeaxanthin are currently commercially available as single entities and have wide-ranging activities; their structures are shown in Fig. 32.1. Lycopene is present in red fruits and vegetables, particularly tomatoes, and lutein is present in spinach, peas and watercress. Foods that are yellow—maize, orange juice, honeydew melon and orange pepper—are also good sources of lutein.

Table 32.1 Single-component nutraceuticals.

Nutraceutical	Antioxidant	Plant sources	Major application(s)
Lycopene	√	Tomato (*Lycopersicon esculentum*), spinach (*Spinacea oleracea*)	Cardiovascular health and cancer prevention
Lutein	√	Tomato (*Lycopersicon esculentum*), butternut squash (*Cucurbita moschata*)	Cardiovascular and eye health
Zeaxanthin	√	Tomato (*Lycopersicon esculentum*), butternut squash (*Cucurbita moschata*)	Eye health
γ-Linolenic acid	√	Evening primrose (*Oenothera biennis*), borage seed (*Borago officinalis*)	Skin, joint and women's health
Policosanol/octacosanol	√	Sugar cane (*Saccharum officinarum*)	Cardiovascular health
Resveratrol	√	Grapes (*Vitis vinifera*), wine, cranberry juice	Cardiovascular health and cancer prevention
Sterols/stanols	×	Seed oils, e.g. tall oil	Cardiovascular health
Theanine	×	Tea (*Camellia sinensis*)	Cardiovascular health, relaxant and memory enhancement

Table 32.2 Multi-component products.

Nutraceutical	Antioxidant	Source	Typical constituents	Major applications
GSPE	√	Grape	Catechins and derivatives	Cardiovascular health
Pycnogenol	√	Maritime pine (*Pinus pinaster*)	Procyanidins	Cardiovascular and respiratory health
Soy isoflavones	√	Soy (*Glycine max*)	Isoflavones	Cardiovascular, mental, women's health, cancer prevention
Tea catechins	√	Tea (*Camellia sinensis*)	Catechins	Cardiovascular health and cancer prevention

Table 32.3 Dietary sources of nutraceuticals.

Dietary source	Antioxidant	Plant source	Constituent(s)	Major application(s)
Cocoa/chocolate	√	*Theobroma cacao*	Flavonoids	Cardiovascular health
Cranberry	√	*Vaccinium macrocarpon*	Polymers of epicatechin, epigallocatechin and gallic acid	Reduction of urinary tract infections
Flaxseed	√	*Linum usitatissimum*	α-Linolenic acid, lignans	Cancer prevention, cardiovascular and women's health
Olives	√	*Olea europoea*	Oleuropein, hydroxytyrosol, lignans	Cardiovascular health, cancer prevention
Pomegranate	√	*Punica granatum*	Ellagitannins and other polyphenols	Cardiovascular health
Soy	√	*Glycine max*	Isoflavonoids, protein	Cancer prevention, cardiovascular health
Tea	√	*Camellia sinensis*	Catechins, theaflavins	Cardiovascular health, cancer prevention

The recommended daily intake of lycopene is 35 mg, but a number of Western societies consume from 5–25 mg, with processed products accounting for at least 50% of the total intake, therefore supplementation is often advised. A wide range of lycopene levels has been reported in tomatoes (1–15 mg/100 g), and lutein has been found to occur at 0.08 mg/100 g in tomatoes and 2.38 mg/100 g in butter squash. The mixture of lutein and zeaxanthin stereoisomers have also been reported at levels of 40 mg/100 g in kale and 12 mg/100 g in spinach. Zeaxanthin also co-occurs with lutein at 0.28 mg/100 g in butter squash.

Lycopene. Lycopene has antioxidant and free-radical scavenging activity, and serum levels have been shown to be protective against myocardial infarction (MI). Many researchers believe that these mechanisms are most likely to account for its beneficial effects in cancers. Reactive oxygen species (ROS) are the main source of oxidative damage that can generate structural alterations in DNA and decrease DNA repair by damaging essential proteins, and ultimately cause cancer. A number of trials have shown levels of cancer of the oral cavity, pharynx, oesophagus and colorectum, decreased with increasing levels of lycopene intake. An association with lycopene intake is less likely in ovarian and breast cancers.

Epidemiological literature has shown that diets rich in tomatoes are associated with lower lung cancer rates. The presence of lycopene in the human lung following lycopene supplementation has been demonstrated, and it is believed that an increased intake of lycopene might

Table 32.4 Nutraceuticals present in plants but commercially obtained from other sources.

Nutraceutical	Antioxidant	Typical sources	Major application(s)
Co Q10	√	Mitochondria of plants	Cardiovascular health and cancer prevention
Melatonin	√	Banana (*Musa sapientum*), grape (*Vitis vinifera*)	Sleep improvement, jet lag, bone formation and cancer prevention
MSM	×	Capers (*Capparis spinosa*)	Joint health
SAMe	√	Banana (*Musa sapientum*)	Joint and mental health

provide an additional level of protection against oxidative damage. A high intake of tomato products is associated with a 35% lower risk of total prostate cancer, and a 53% lowered risk of advanced prostate cancer. A decline in protective effect of a range of tomato products have been shown to correspond to a decline in plasma lycopene levels.

Overall, preliminary evidence suggests that lycopene intake, and serum lycopene levels are associated with a reduced risk of developing cancer, most notably prostate and lung cancer.

Lutein. Plasma lutein concentration is believed to be inversely related to heart disease, and an inverse relationship has been reported between serum lutein levels and progression of intima-media thickness in carotid arteries.

Lutein and zeaxanthin have been implicated in maintenance of eye health and they selectively accumulate in the retina of mammals, which gives the macula lutea its yellow colour, and makes up a screening pigment known as the macular pigment. This pigment may have both acute and chronic effects on visual performance. Lutein and zeaxanthin are carried in human serum, mainly by high-density lipoproteins (HDL). Lutein and zeaxanthin are both antioxidant and are able to filter blue light. There is evidence that a diet high in carotenoids is associated with a lower risk of age-related macular degeneration (AMD). One case control study found a 43% lower risk of AMD in individuals consuming the highest levels of carotenoids (especially lutein and zeaxanthin) compared with those consuming the least. A strong inverse association was found for consumption of spinach containing high levels.

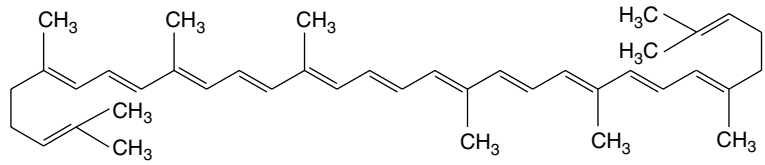
γ-Linolenic acid

γ-Linolenic acid occurs in *Oenothera* spp., notably *O. biennis*, at levels of 7–9 % in the fixed oil. Borage oil yields 25%, but it is not widely found elsewhere in substantial amounts, although it is also present in starflower oil and blackcurrant seed oil. γ-Linolenic acid is not usually purified and the complete oil is used for oral supplementation.

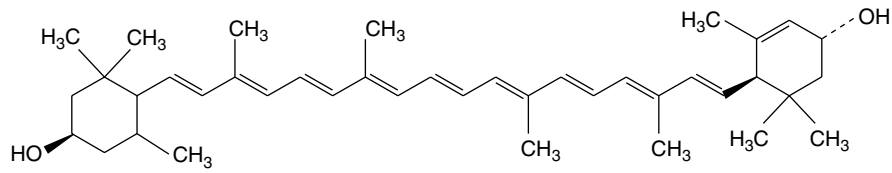
It is an essential intermediate between linoleic acid and dihomogammalinolenic acid (DGLA), and thereafter prostaglandins, thromboxanes and leukotrienes. Disruption of its production by the action of delta-6-desaturase on linoleic acid is thought to be responsible for a number of human disease states. Atopic eczema and premenstrual syndrome are two of the most popular applications. Metabolism of γ-linolenic acid to DGLA in healthy individuals may reduce inflammation via competitive inhibition of leukotrienes and 2-series prostaglandins. Trials using 1.4 or 2.8 g/daily of γ-linolenic acid for up to 12 months have shown progressive improvements in symptoms of rheumatoid arthritis.

Policosanol/octacosanol

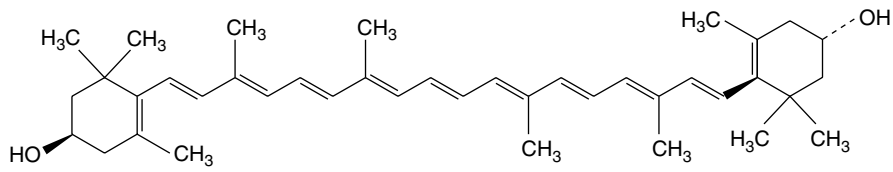
Policosanol is found in sugar cane waste and the leaves of alfalfa and wheat, and is also present in wheat germ. The major component, octacosanol is present at levels of 67% in material obtained from sugar cane waste and wheat germ.



Lycopene



Lutein



Zeaxanthin

Fig. 32.1
Structures of plant-derived carotenoids.

Policosanol was developed in Cuba, and the majority of the reseach (over 60 clinical trials) was carried out there. Most studies confirm effective lipid-lowering effects at doses of 10–20 mg/day. Typical improvements include a lowering of low-density lipoprotein-cholesterol (LDL-C) by 18–26%, total cholesterol by 13–17%, and an increase in HDL-C by 15–28%. Comparison of policosanol (10 mg) with lovastatin (20 mg) showed similar effects on lipid levels, but none of the statin side effects were observed with policosanol. Policosanol is also thought to act by inhibition of cholesterol biosynthesis, but direct inhibition of HMG-CoA reductase as seen with the statins is not the mode of action.

Antiplatelet activity also occurs, at 20% of the dose as with aspirin.

Resveratrol

Resveratrol is found in the leaves, skins and petals of *Vitis vinifera*, and also wines and grape juice, and levels are elevated when the vine is infected with the fungus, *Botrytis cinerea*. Red wines contain increased levels due to extended time in contact with the skins. A number of other stilbene derivatives are also found in grape products. Resveratrol is also present in other plant products, such as peanut butter. Wide-ranging levels of resveratrol have been found in wines from different varieties of grapes and different geographical sources; 0.3–4.7 mg/l (French Barolo, French Chateauneuf). Concommitant levels of catechin, 23–136 mg/l (French Barolo, French Burgundy) and epicatechin, 17–64 mg/l (French Barolo, French Beaujolais) are also present.

Research in animals and humans has demonstrated a range of biological activities, including antioxidant activity, inhibition of platelet aggregation and modulation of hepatic apolipoprotein and lipid synthesis. Red wine is the major dietary source of resveratrol, and it is implicated in risk reduction for a number of cancers, including upper digestive tract, lung and colon cancers. Resveratrol inhibits metabolic activation of carcinogens, induces apoptosis and is anti-inflammatory.

Sterols/stanols

These both exist in all plants, and the major sources are the vegetable oils. Cholesterol absorption ranges from 35 to 70%, but sitosterol and camposterol, which are the major plant sterols, are both poorly absorbed in the intestine (0.4–4%), and the stanols even less so (0.02–0.3%). They are thought to act by inhibition of cholesterol absorption. Plant sterols and stanols are being actively used for reduction in blood cholesterol levels, and the majority of these investigations have involved sterol and stanol enrichment of the subjects' diet, and a positive association has been found for cholesterol reduction. The effects of a plant-sterol-enriched reduced-fat spread have been monitored over 5 weeks, with patients receiving either 1.1 and 2.2 g daily of sterol and a 40% reduced-fat spread. Total cholesterol and LDL-C values were reduced by 5.2% and 6.6%, and 7.6% and 8.1%, respectively, at these two levels of supplementation. A later comparison of trials using a number of sterols and stanols in fortified diets, revealed that effective doses ranged from 1.5 to 3.0 g daily, and total cholesterol reduction was of the order of 10%, while LDL-C reductions were between 8% and 15%. The mode of action was thought to be due to interference with the solubilization of cholesterol in intestinal micelles, consequently reducing cholesterol absorption. However, other mechanisms have also been postulated. Tablets and capsules containing sterols and stanols are commercially available, but there is no evidence that these have the same beneficial effects as sterol- and stanol-enriched spreads.

Theanine

Theanine is a non-protein amino acid present in tea, and other species of the genus *Camellia*. It is the major amino acid in tea, and constitutes 1–2% of the dry weight of tea. Theanine has been shown to possess three potentially useful properties: namely, relaxant, hypotensive activity and memory enhancement.

Oral supplementation with 50–200 mg theanine once weekly, has been reported to increase production of α-brain waves, which causes a state of relaxed alertness. In addition, theanine shows the ability to modulate moods, which is possibly linked to its effects on serotonin, dopamine and other neurotransmitters.

It has been postulated that the reduction in blood pressure may be responsible for mental calming. A reduction in serotonin, and also dopamine, may have an effect on memory and learning ability. It has been reported that doses of theanine up to 2000 mg/kg produced significant reduction in blood pressure in spontaneously hypertensive rats.

Theanine is increasingly being incorporated into a range of convenience foods, as well as pharmaceutical formulations. Confectionary containing 72 mg has been reported to cause relaxation, as indicated by increased generation of α-waves. Whole tea obviously contains both theanine and the catechins (see later), therefore is responsible for a range of activities, often not assigned to specific components.

Long-term social tea drinking appears to have no side effects apart from the effects of the caffeine content, therefore it may be assumed that realistic levels of theanine consumption comparable to those obtained from tea drinking should be safe. The structures of a number of single component nutraceuticals are shown in Fig. 32.2.

GSPE

Grapeseed proanthocyanidin extract (GSPE) constituents are based on either catechin or epicatechin, and monomers, dimers, trimers and other oligomers. The procyanidins are polymers of catechin or epicatechin monomers, composed of 2–12 monomers. Dimeric procyanidins named procyanidin B1 (PCB1), B2, B3 and B4, depending on the configuration of catechin and epicatechin subunits, are present. A number of these catechin derivatives are present as their gallates in addition to the free form. The structures of epicatechin and procyanidin B2 are shown in Fig. 32.3.

Levels of proanthocyanidins have been estimated in a number of wines, Greek red seed extracts have been quantified, PCB1 17 mg/100 g, PCB2 16 mg/100 g, catechin 191 mg/100 g, and epicatechin 100 mg/100 g, and white seed extracts found to contain marginally less. Japanese grape extracts have been found to contain much lower levels.

GSPE is a powerful antioxidant, with higher activity than vitamins C and E, and it is believed that this is responsible for its cardioprotective activity against cardiovascular disease and circulation defects. Most research has shown that GSPE causes a 60–90% reduction in oxidation of LDL-C, and consequently a reduction in atherosclerosis. GSPE is widely used for treatment of vascular disorders such as varicose veins, venous insufficiency and microvascular problems in Europe.

Pycnogenol

Pycnogenol is the registered name of a standardized extract of the bark of the French maritime pine, *Pinus pinaster* Aiton, subspecies Atlantica des Villar, containing mainly phenolic acids and procyanidins. A number of phenolic acids that are derivatives of benzoic acid, vanillic acid or gallic acid, or cinnamic acid derivatives, exist both free and in combination with glucose. The major procyanidin dimers include B1, consisting of catechin and epicatechin, and B3, consisting of two catechin monomers and lower concentrations of the equivalent dimers. Monomeric catechin, free taxifolin and its glucoside, as well

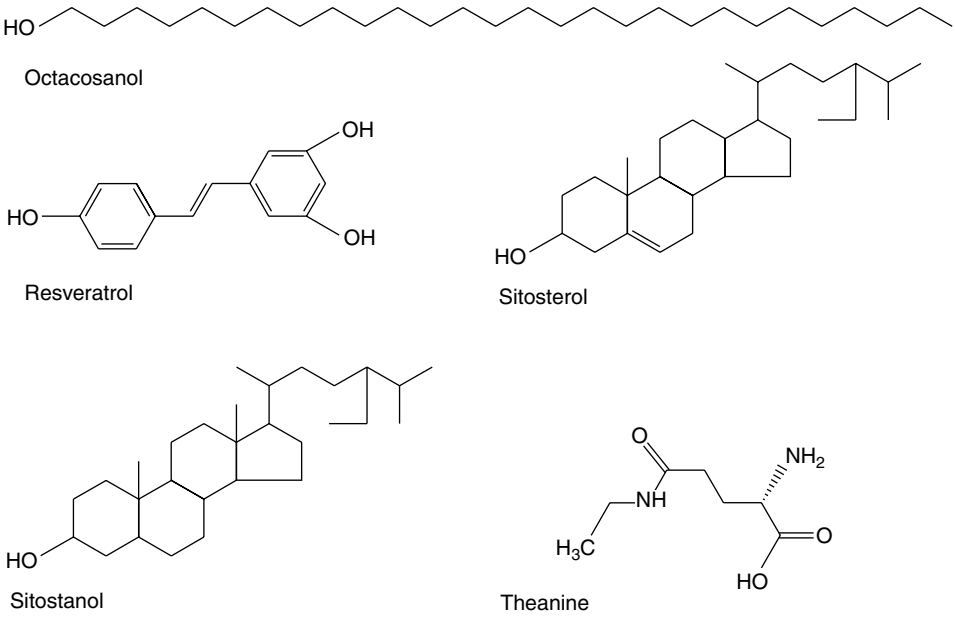


Fig. 32.2
Structures of a number of single-component nutraceuticals.

as vanillin are also present. The structures of procyanidin B3 and B6 are shown in Fig. 32.3.

Historically, pine bark has been used for treating inflammatory diseases, which gives some credence to the use of pycnogenol. A range of cardiovascular effects has also been reported, including vasorelaxant effects, ability to inhibit angiotensin-converting enzyme (ACE) and increase in the microcirculation by increasing capillary resistance.

Pycnogenol, is a highly potent antioxidant with a high affinity for collagen. Larger procyanidins bind to proteins of damaged blood vessels to lower capillary permeability and reduce basement membrane leakage. Pycnogenol increases production of nitric oxide, which may be impaired in certain disease states, such as diabetes, by stimulating endothelial nitric oxide synthetase, and the nitric oxide produced relaxes constricted blood vessels. Pycnogenol reduces leukocyte-mediated degeneration of retinal capillaries, and has also been shown to prevent increased platelet activity without increasing bleeding time.

Adults taking pycnogenol have been reported to have significantly reduced serum leukotrienes. A study conducted in children with mild-to-moderate asthma using the supplement for 3 months showed significantly more improvement in pulmonary functions and asthma symptoms and found that they could reduce their use of prescription medication.

Soy isoflavones

The major soy consumers live in East Asia, and their foods include a wide variety of different forms, some examples being whole soybeans, soy sauce, tofu (soybean curd), tempeh, soymilk, miso (fermented soybean paste) and natto (fermented soybeans).

The major isoflavones present in soybeans in order of concentration are genistein, daidzein, and glycitein, and they occur as β-glycosides. The isoflavone content varies between 0.4 and 2.4 mg/g, depending on growing conditions and crop variety. Processed products contain a much lower isoflavone content due to manufacturing methods, such as alcohol washing of soy concentrates. Genistein occurs in the range of 1–150 mg/100 g in the raw soybean, and is converted to its β-glycoside genistin in biological fluids. Daidzein and its β-glycoside daidzin occur in lower concentrations, at levels of 0.5–91 mg/100 g. Glycitin and its aglycone glycitein, are also present and only found in relatively small amounts.

Daidzein is metabolized by human intestinal flora to give equol in 30–50% of the population. Babies are unable to produce equol, and the ability is developed in susceptible individuals. Equol is powerfully oestrogenic, more so than estradiol, and is therefore probably the major active component in hormone-dependent conditions. Fig. 32.4 shows the structures of the major soy isoflavones and equol.

In 1999, the FDA approved manufacturers of soy foods to state the health claim that 'consumption of at least 25g of soy protein per day may be beneficial to a reduced risk of developing CHD'. It has been claimed that much of the support for this decision was obtained from a meta-analysis published in 1999. The results of this analysis showed that consumption of soy protein instead of animal protein reduced LDL-C levels by 7–24%, depending on initial cholesterol levels. However, it was not clear whether the benefits reported were due to the soy protein or to the constituent isoflavones. A more recent meta-analysis in 2005 reported that soy protein containing isoflavones significantly reduced total cholesterol, LDL-C and triglycerides, while increasing HDL-C. Soy has been reported to improve vascular function and to have beneficial effects in preventing onset and development of atherosclerosis.

Low levels of isoflavones (60–100 mg) taken for up to 12 weeks have been reported to increase memory, pattern recognition and mental flexibility. Improvements in both young males and females, in both short- and long-term memory, and also in mental flexibility, have been reported.

Epidemiological data suggest that consumption of soy isoflavones at typical Chinese or Japanese dietary levels should potentially reduce the risk of developing cancer. Japanese adults are thought to consume around 30–40 mg daily, but the quantity of soy products that need to be consumed to reach these levels of intake varies considerably depending on the dietary form of the soy. The mortality from clinically diagnosed prostate cancer has been shown to be lower in countries with high soy consumption. The death rate of men dying from prostate cancer in Japan is about 25% the level found in the US, and in Japanese men with prostate cancer, many tumours are much

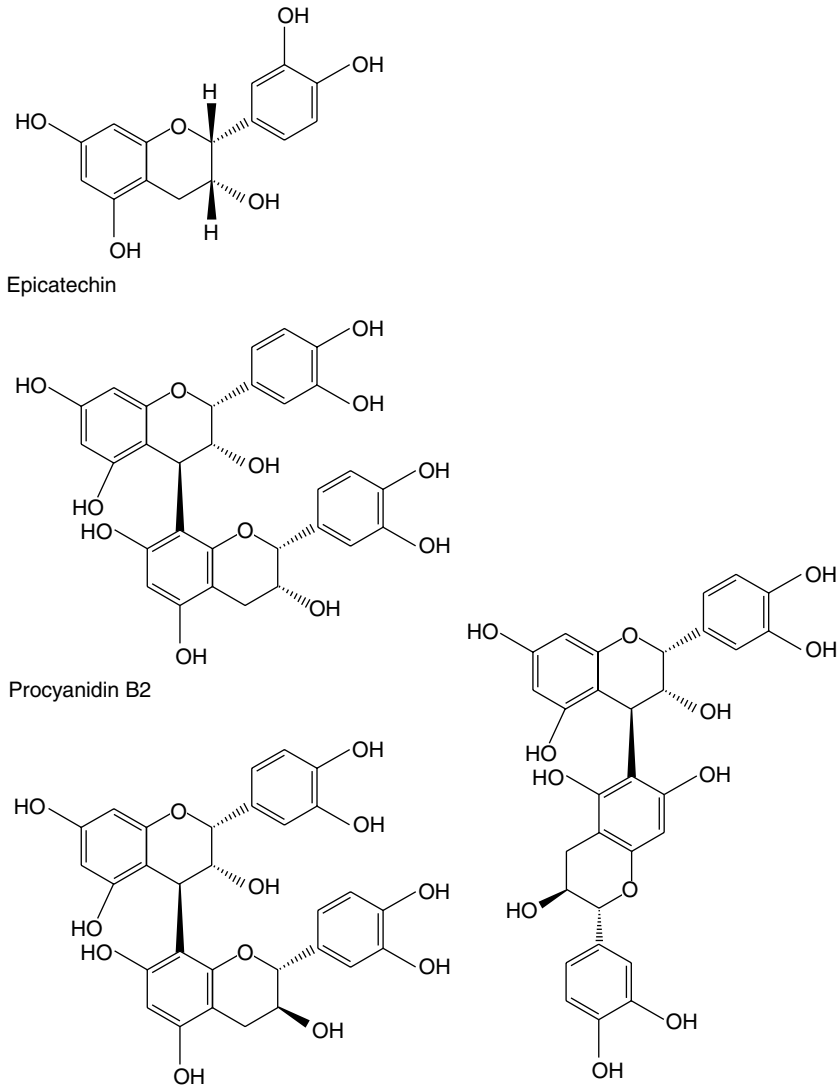


Fig. 32.3
Structures of typical phenolic constituents of GSPE and pycnogenol.

smaller on average. However, Asian emigrants who move to the US and change their dietary habits show a marked increase in the risk of developing prostate or breast cancer, reaching levels comparable to those found in indigenous inhabitants. This is likely to be a result of higher fat and much lower soy isoflavone content of the diet, suggesting that the protective effect found in inhabitants of Asia is diet related. Also, women who had consumed tofu during adolescence were less likely to develop both premenopausal and postmenopoausal breast cancer as adults.

Recent research has identified a further two bioactive constituents, the Bowman–Birk protease inhibitor, and lunasin, a unique 43-amino-acid peptide. Both of these have anticancer activity and may be partially responsible for the beneficial effects of soy consumption.

Soy isoflavones, up to 100 mg per day, may be a safe and effective alternative therapy for many menopausal symptoms. They are thought to be promising as supplements in preventing and treating postmenopausal osteoporosis, due to their oestrogenic activity, and consequently as potential replacements for estrogen deficiency. Most studies with soy isoflavones in osteoporosis have therefore restricted themselves to female subjects during or after the menopause. Epidemiological studies have shown strong evidence that soy isoflavones have a positive effect on bone mineral density (BMD). Far lower rates of osteoporosis and fractures have been observed in oriental women than in their Western counterparts. Over 4.5 years, the level of consumption of soy protein and isoflavones by Chinese women was found to be possibly associated with a reduction in bone fracture, particularly in the early years following menopause. Data from intervention studies are limited, and have shown contradicting results. Clinical trials in postmenopausal and perimenopausal women that have analysed bone mineral content and BMD have demonstrated that isoflavones can significantly increase BMD at the lumbar spine.

Whole soybean contains many constituents, as well as protein and isoflavonoids, so there is the possibility that unknown synergistic effects may be seen.

Studies with isoflavones in humans, suggest that doses ranging from 1 to 16 mg/kg body weight are reasonably safe, although higher doses are being recommended for prevention of bone loss in postmenopausal women. Genistein at high doses, such as 600 mg per day, has been shown *in vitro* to inhibit cell growth and induce apoptosis. In addition, some reproductive disturbances, such as uterotropic effects,

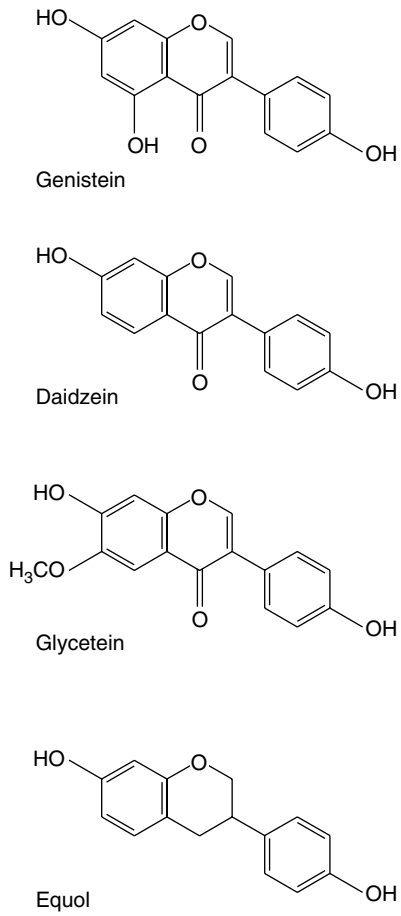


Fig. 32.4
Structures of soy-derived isoflavones.

have been reported in animals fed a diet rich in isoflavones or other phytoestrogens.

Tea catechins

Tea has been discussed previously (see section Alkaloids, Purine alkaloids), and is known to contain caffeine and a number of polyphenols. Black tea accounts for approximately 78% of the total tea consumed world wide, with green tea representing 20% and oolong tea accounting for less than 2%.

The polyphenols include catechins, quercetin, myricetin and kaempferol; these account for 30–42% of the dry weight of tea. Catechins are the main components and the four principal ones found in tea are (−)-epicatechin (EC), (−)-epicatechin gallate (ECG), (−)-epigallocatechin (EGC) and (−)-epigallocatechin gallate (EGCG). EGCG is the most abundant, accounting for 50–80% of the catechins. A typical brewed cup of green tea, approximately 240 ml, can contain up to 200 mg of EGCG. Fig. 32.5 shows the structures of typical tea constituents.

A number of epidemiological surveys have been carried out on the effects of tea consumption, initially with green tea but later with black and oolong teas. The major findings are decreased serum total-cholesterol and triglyceride, with an increase in HDL-C and reduction in the proportion of lipoprotein cholesterol and very-low-density lipoprotein cholesterol (VLDL-C). In particular, black tea consumption has positive effects on endothelial function, atherosclerosis of coronary arteries and hypertension. Subjects consuming 120 ml tea/day for a year have been shown to have a 46% lower risk than non-tea-drinkers.

Tea polyphenols are also thought to have antiplatelet, antithrombotic and anti-inflammatory activity, and thereby reduce the risk of congestive heart disease. Meta-analysis of 17 studies has shown that an increase in tea consumption of three cups/day is associated with an 11% reduction in incidence of myocardial infarction.

EGCG has been claimed to be the most important active constituent, although it is known to have low bioavailability. Studies in human lung cancer cell lines found ECG to be most active in inhibiting growth, followed by EGCG, then EGC, but EC was inactive. Theaflavin-3-3′-digallate appears to have similar activity to that of EGCG and therefore the inhibitory activity of black tea (containing theaflavin-3-3′-digallate) against the development of cancer may be due to the combination of catechins and theaflavins. Tea polyphenols have been proposed to act via a number of different mechanisms to exert their cancer chemopreventive effects.

Studies have shown that EGCG acts specifically on certain cancer cells by mechanisms such as induction of apoptosis, cell-cycle arrest and inhibition of cell growth, but that it does not cause these effects in normal cells. The inhibition of cell growth is thought to be caused by the involvement of tea polyphenols in the activation of genes, via signalling mechanisms.

Laboratory animals with lung cancer treated with black tea had a 19% incidence of tumours, compared with 47% in the control. Apparently contradictory results in Japanese patients have been published. The age of cancer onset in females was increased from 65.7 years, in those who drank less than three cups of green tea a day, to 74.4 years in those consuming over ten cups a day. The age of cancer onset in males was shown to increase from 63.3 years to 68.3 years. The smaller delay in age seen in males was thought to be attributable to the higher number of male smokers. However, the incidence of cancer increased in individuals consuming over ten cups of tea a day, over the age of 80 years. The increase in incidence was higher than in those who drank fewer cups of green tea.

Lung, oral and oesophageal cancers are particularly caused by cigarette smoking. The incidence of lung cancer in males in the US is twice that in Japan, even though the prevalence of smokers in Japan is nearly twice that of the US. This could be due to a number of other factors, including genetic and environmental factors. Green tea is consumed far more in Japan than in the US, a fact that has suggested the possible chemopreventive effects of tea against smoking-induced cancers.

Consumption of ten cups of green tea a day, providing approximately 3000–4000 mg of EGCG, has been shown to produce a chemopreventive effect, and it is possible that there is a dose–response relationship between consumption of tea and cancer prevention.

Cocoa/chocolate

The fresh seed of the cocoa plant, *Theobroma cacao*, contains epicatechol, leucoanthocyanins and anthocyanins, which are decomposed during processing (see Cocoa seed, Alkaloids). Chocolate, which is derived from the fermented seeds, contains 0.8 mg/g of catechin monomers and 4.6 mg/g procyanidins, the latter occurring at levels five to ten times greater than in cranberry juice. The content of catechin and epicatechin represents 10 mg/g. The structure of epicatechin is shown in Fig. 32.5. *In vitro* experiments have shown chocolate to inhibit LDL oxidation. Concentrations used are consistent with plasma epicatechin levels observed following consumption of realistic amounts of dark chocolate. The activity of chocolate in atherosclerosis might be due to its effects on improving endothelial function, which has been demonstrated in both healthy and impaired individuals. This could be caused

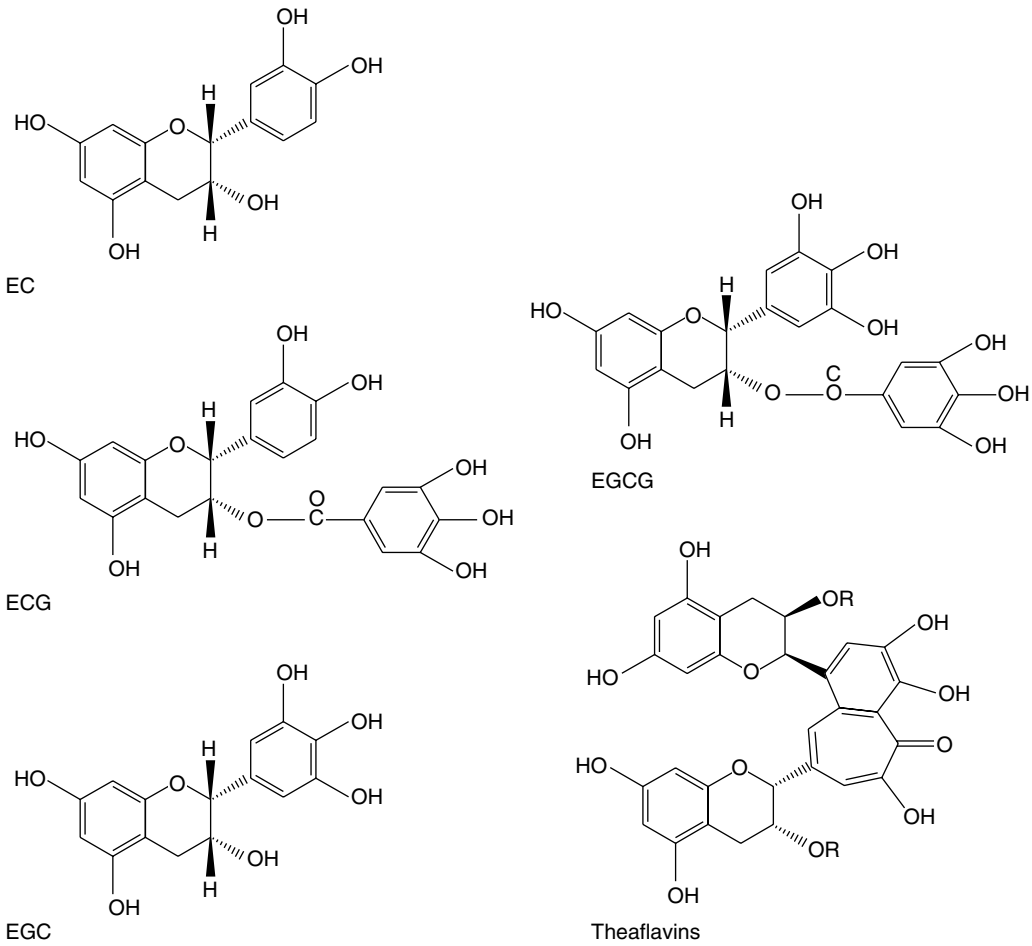


Fig. 32.5
Structures of representative catechins and theaflavins of tea.

by its antioxidant activity, but it is also able to modulate platelet activity, inhibiting platelet activation and reducing platelet function, and hence inflammation.

Cranberry

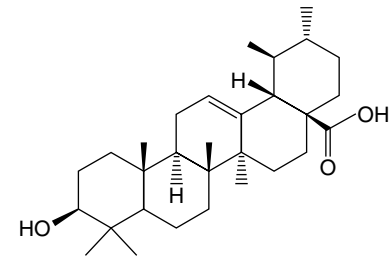
A number of polyphenols have been identified, including ursolic acid, benzoic acid and derivatives, quercitin and hydroxyl flavonol glycosides, such as quercitin glucoside and galactoside. Typical constituents are shown in Fig. 32.6. Cranberry also contains polymeric proanthocyanidins that are thought to be responsible for beneficial health effects, especially those relating to interference with microbial adhesion. Evidence is seen, particularly in the urinary tract, of *Esherichia coli,* and in the gastrointestinal tract of *Helicobacter pylori*. A large body of epidemiological and clinical evidence, and evidence of the mechanism of action of cranberry and its components, exists in the area of urinary tract infections (UTIs). Initial research suggested that the anti-adhesive effect on *E. coli*, with consumption of 300 ml/day of cranberry juice, reduced the risk of UTIs. The action of a large-molecular-weight, non-dialysable polymer of cranberry (NDM) on the pathogenicity of *H. pylori* has only been examined *in vitro,* but it may be possible that it could be inhibited from adhering *in vivo* and prevent the development of stomach ulcers. A number of Gram negative anaerobic bacteria are particularly prone to form dental biofilms. NDM can inhibit the co-aggregation of various oral bacteria in the gingival cavity and produce a 90% inhibitory effect on the enzymes responsible for synthesis of biofilm polysaccharides. Manipulation of the ecology of bacteria in the gingival cavity using cranberry could be an effective approach in controlling periodontal diseases.

Flaxseed

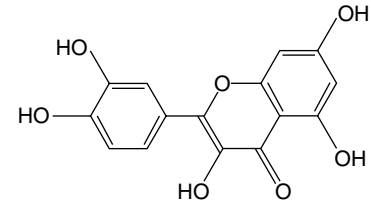
Lignans. Flax contains two major lignans—secoisolariciresinol diglucoside and matairesinol—the major mammalian metabolites of which are enterolactone and enterodiol. Six other lignans have been identified, and these are variably converted to enterolactone and enterodiol, and also to enterofuran. Levels of 370 mg secoisolariciresinol diglucoside per 100 g flax have been reported, but there are other sources, and a low level of 273 μg per 100 g is present in soy. Fig. 32.7 outlines the human metabolism of the major flax lignans.

α-Linoleic acid. There are many sources of α-linoleic acid, flaxseed being the richest, but candlenut, hemp seed, pumpkin seed, canola, walnut and soy contain lesser amounts. Flaxseed oil contains more than 50% α-linoleic acid, which is an essential fatty acid. A high consumption of dietary α-linoleic acid has been shown to result in a reduced prevalence of carotid artery plaques and reduced intima-media thickness of the arteries. However, epidemiological studies have shown that a high intake or blood level of α-linoleic acid can increase the incidence of prostate cancer. Flax lignans have been shown to produce a 73% reduction in the development of hypercholesterolaemic atherosclerosis.

Flaxseed has reported anticancer properties, which are thought to be caused by the lignans, but flaxseed oil (containing α-linoleic acid as the major fatty acid) has also been shown to have activity against metastasis. A significant inverse relationship between the metabolite serum enterolactone level and breast cancer incidence has been reported.



Ursolic acid



Quercitin

Fig. 32.6
Structures of typical cranberry polyphenols.

The lignan metabolites, enterodiol and enterolactone, are thought to be weakly oestrogenic and/or antioestrogenic, and may be of use against hormone-dependent cancers.

In one study into menopausal symptoms, supplementation of women's diets with 40 g/day of flaxseed was shown to produce a decrease in the number of hot flushes, and attenuated menopausal symptoms. A number of studies have confirmed the positive benefits of flax on hot flushes and vaginal dryness, and it is likely that consumption of 40 g or more of flaxseed is required to elicit beneficial effects, whereas 25 g is insufficient.

Olives

The oil extracted from the flesh contains at least 30 phenolic constituents, the major ones being oleuropein, hydroxytyrosol and tyrosol, and these are all powerful antioxidant and radical scavengers. Hydroxytyrosol is a hydrolysis product of oleuopein, and increases in concentration during ripening of the fruit. Both of these have antimicrobial activity. In addition, a hydroxycinnamic derivative, verbascocide, and pinoresinol lignans have been identified. Fig. 32.8 shows a number of major olive phenolics.

There is a large amount of epidemiological data concerning the 'Mediterranean diet', and olive oil in particular. Studies have shown that populations with high olive oil consumption (*c.* 50 g/day) have a low incidence of associated coronary heart disease, and this is thought to be due to the 25 mg of olive phenolics ingested daily. Animal studies have shown oleuropein to lower blood pressure, relieve arrhythmias and prevent internal muscle spasms. Oleuropein and verbascoside have been found to inhibit platelet aggregation. Bactericidal and bacteriostatic activity of oleuropein and its metabolites have been demonstrated against many organisms, and also inhibit growth and enterotoxin B production by *Staphylococcus aureus*. Oleuropein and other olive phenolics have been found to inhibit growth of *E. coli* and other organisms, and verbascoside also has similar activity.

The antioxidant ability of most of these constituents is thought to be responsible for protective activity against a number of cancers, notably breast, prostate and colon cancers, coronary heart disease and the effects of ageing.

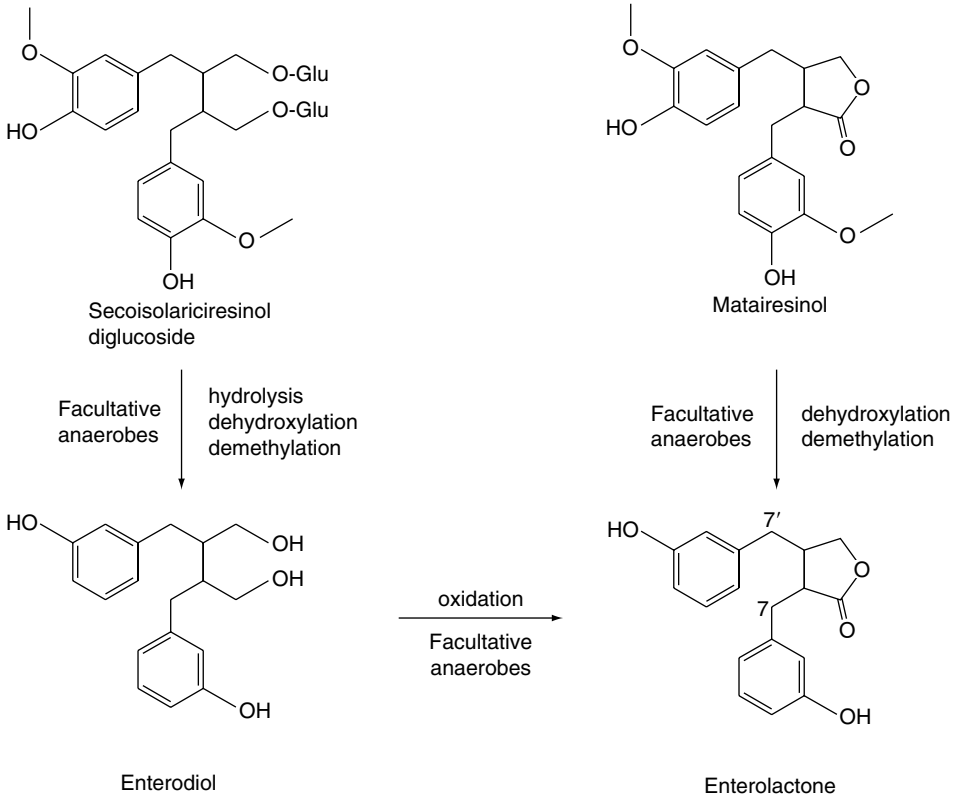


Fig. 32.7
Structures of secoisolariciresinol diglucoside and matairesinol, showing their major human metabolites. Reproduced from Rowland I, Faughnan M, Hoey L, *et al.* Bioavailability of phyto-oestrogens. *Brit J Nutr* 2003; 89: S45–S58, with permission granted by the authors and *British Journal of Nutrition.*

Pomegranate

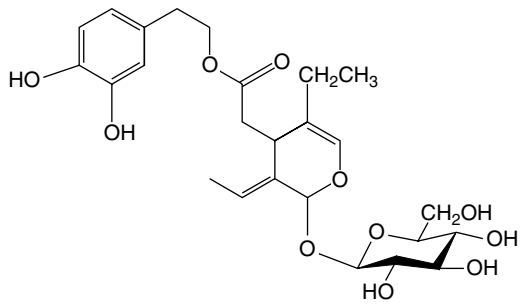
The constituent present in the highest concentration is punicalagin, which is the major fruit ellagitannin. It also contains ellagic acid in free and bound forms, gallotannins and anthocyanins (cyanidin, delphinidin and pelargonidin glycosides), and other flavonoids (quercitin, kaempferol and luteolin glycosides). The structure of ellagic acid is shown in Fig. 32.8. There is great variability in levels of these constituents between the juice and pericarp, and a range of extracts and individual components has been investigated for biological activity. Comparison of activities of these extracts and individual entities with the popular commercially available pomegranate juice can lead to difficulties.

The antibacterial activity of four different extracts from pomegranate fruit rind on a number of organisms have been reported, and the methanolic extract has also been shown to act synergistically with five different antibiotics against isolated strains of methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-sensitive *Staphylococcus aureus* (MSSA) have been reported. The antiviral activity of pomegranate has been investigated, and it was found that a mixture of ferrous salt and pomegranate rind extract reduced the infectivity of the poliovirus, herpes simplex virus type 1 (HSV-1) and human immunodeficiency virus type 1 (HIV-1) in cell culture assays, indicating a possible use in halting the spread of these diseases. A link between the antioxidant activity of juice polyphenols and antiatherogenic effects has been reported, using both humans and mice. This activity was attributed to the antioxidant capacity of the juice to reduce lipid peroxidation in lipoproteins, macrophages and platelets, with tannins being implicated in some of these effects. Evidence indicates a possible therapeutic use of pomegranate juice in realistic daily doses (50 ml/day, and for 240 ml/day in CHD).

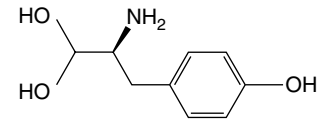
A methanolic extract of pomegranate flower has been investigated for activity in diabetes, and was found to inhibit the increase in plasma glucose in rats loaded with glucose after 6 weeks of treatment.

The effects on a range of cancers have been researched. Pomegranate constituents may interfere with colon cancer cell formation and progression at multiple points. A significant effect of pomegranate fermented juice on breast cancer *in vitro*, has been reported, however, few *in vivo* data are available.

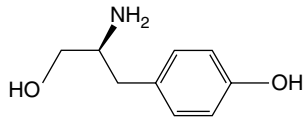
Possibly due to its antioxidant effects, pomegranate is an inhibitor of the markers of skin tumour promotion, along with other markers that could signify further anticancer activities. The constituents responsible for these activities are unknown, pomegranate fractions have shown the potential to prevent UV-B mediated events that could lead to the development of skin cancer. Different pomegranate fractions have shown possible synergistic, interactions against the proliferation and invasiveness of prostate cancer cells. Other areas of possible therapeutic activity include chronic obstructive pulmonary disease, neurological protection, and erectile dysfunction.



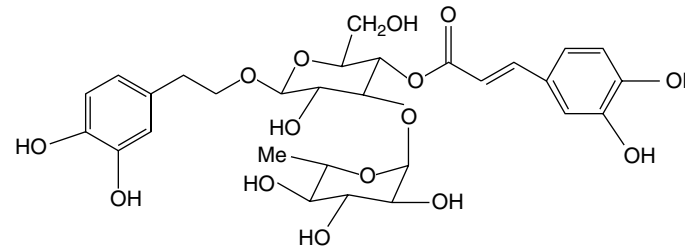
Oleuropein



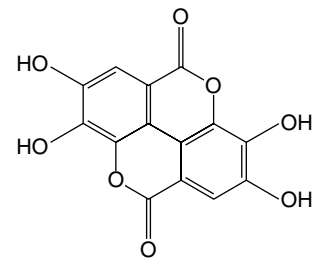
Hydroxy tyrosol



Tyrosol



Verbascocide



Ellagic acid

Fig. 32.8
Structures of typical olive and pomegranate phenolics.

Coenzyme Q10

Coenzyme Q10 occurs widely in vegetables, particularly spinach, and it has been estimated that the average level in human plasma is 1 mg/l in human plasma. It is a powerful antioxidant and free-radical scavenger, and is manufactured and used as a medicine in Japan.

Coenzyme Q10 occurs naturally in the body and is mainly located in the mitochondria of myocardium, liver and kidney cells. It acts as an electron carrier in the mitochondrial synthesis of ATP, has membrane-stabilizing effects and has been used for the treatment of cardiovascular diseases, including heart failure, hypertension, angina and arrhythmias, although the evidence to support its use is contradictory. Significantly reduced levels of myocardium coenzyme Q10, of the order of 50% of normal levels, have been reported in heart failure in animals and humans. Contradictory results have been reported in trials using coenzyme Q10 supplementation in heart failure patients.

Deficiency in coenzyme Q10 has been shown to be significantly higher in cancer patients and asthmatics than in healthy people, and supplementation is thought to have beneficial effects in these disease states.

Melatonin

Endogenous levels of melatonin are a result of production by the pineal gland, normally starting as darkness falls, with maximal production between 2 and 4 a.m. Between 5 and 25 μg/day is secreted by juveniles, but levels decrease with age. In extreme diets, the consumption of plant material containing high levels of melatonin could conceivably alter serum concentrations. Melatonin has been identified in bananas, tomatoes, cucumbers and beetroots, but massive amounts of these foods would have to be eaten to achieve pharmacological doses.

Melatonin has been investigated in many different applications, due to its physiological roles. It controls the circadian rhythms, and has been widely researched as an aid to shift work adaptation, jet lag and for insomnia. The 'melatonin replacement' hypothesis states that age-related decline in melatonin production contributes to insomnia, and that replacement with physiological doses improves sleep. Melatonin has also been found to be a powerful free-radical scavenger and its use as an antioxidant in ageing and related problems has been studied.

Trials of melatonin in jet lag have been studied in great detail, and daily doses of melatonin from 0.5 to 5.0 mg are similarly effective when taken close to the target bedtime at the destination, when traversing five or more time zones. However, doses of 5 mg seemed to be no more effective than lower doses. The benefit is also likely to be greater with more time zones crossed, but less for travel in a westerly direction.

It is apparent that light pollution at night increases the risk of breast cancer; and the risk increases with the length of night shifts; night-shift work, including the work of flight attendants, has been shown to increase breast cancer risk by 48%. The reduced risk of breast cancer in blind women, who cannot perceive light and therefore do not have reduced melatonin levels, suggests possible beneficial activity for melatonin in cancer prevention.

The impact of melatonin on various cancers has been studied both alone and with conventional chemotherapy. Melatonin was found to reduce the death risk at 1 year, with similar effects in different cancers.

A rapid decline in melatonin secretion occurs by old age and supplementation has been suggested to be protective against degenerative conditions including osteoporosis. Bone formation/resorption cycles are also thought to follow a circadian pattern, which might in part be modulated by the cyclical secretion of melatonin.

MSM

Methylsulphonyl methane (MSM) has been found in capers and asparagus, amongst a number of food plants, and is one of the compounds responsible for the pungent urinary odour found in individuals after consumption of asparagus. It exists in human plasma at levels of about 4 mg/person, and 4–11 mg are excreted per 24 hours in the urine.

Only two trials of MSM use in patients with osteoarthritis (OA) have been conducted. One trial used 500 mg three times daily and the other 3 g twice daily, both over 2 weeks. Both resulted in statistically significant reduction in the indices for measurement of severity of OA. How MSM acts in joint disease is not known, but its actions might be due to involvement of its sulphur content in the formation of cartilage matrix.

SAMe

S-Adenosylmethionine (SAMe) is found in every living cell, where it acts as a methyl donor in over 100 reactions catalysed by methyltransferases. It acts as a precursor in the aminopropylation pathway leading to the polyamines, e.g. spermidine.

The majority of clinical applications are in the areas of depressive disorders, OA, fibromalgia and liver dysfunction. The benefits of SAMe in reduction of symptoms of OA were accidentally discovered during clinical trials for its use in depression. SAMe (either 400 mg intravenous or 1200 mg/day orally) has been shown to produce similar benefits to non-steroidal anti-inflammatory drugs (NSAIDs) in reduction of pain and functional limitation. SAMe is metaboloically unstable, and enteric formulations and salt derivatives have been used to prolong the activity.

The structures of a number of nutraceuticals obtained from non-plant sources are outlined in Fig. 32.9.

Synergistic effects

Synergistic interactions between a large number of nutraceuticals and conventional medicines have been the subject of numerous patents, although there is often little published research available. Both soy and tea components are widely quoted in these interactions.

The effects of piperine in enhancing bioavailability of a number of nutraceuticals has been reported.

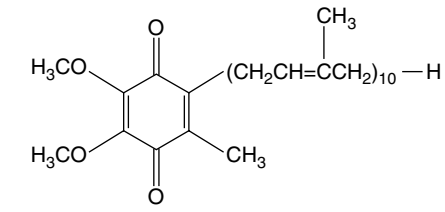
Many combination products are now commercially available, often with no published supporting evidence available.

Adverse effects

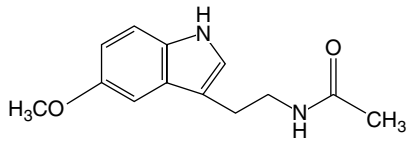
The majority of nutraceuticals appear to be remarkably safe when collating data on their LD_{50}s from a range of animal species. Interactions with prescription medicines have been reported for a number of them, including melatonin with methamphetamine, policosanol with aspirin, warfarin with cimetidine, SAMe with clomipramine, and coenzyme Q10 with warfarin. Prescription medicines have also been reported to depress levels of nutraceuticals; coenzyme Q10 levels have been adversely affected by a number of these, particularly the statins. Overall, a small range of adverse effects are documented, for the majority these are minor gastrointestinal problems, but caution has been advised with soy products.

Quality of commercially available products

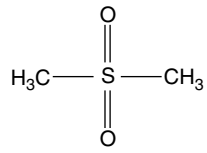
The quality of a number of formulated plant nutraceuticals has been reviewed, but no data are available for resveratrol or pycnogenol products. Poor quality has been reported for a number of these products, based on comparison with levels stated on the labels, and similar great variability in levels of active constituents has been found in flaxseed products, teas, grape products and wines, and soy foods. Similar



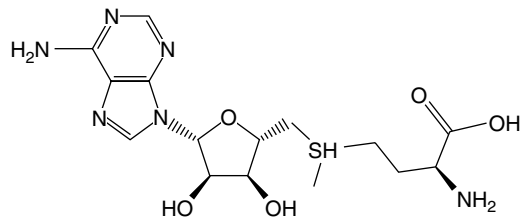
Coenzyme Q10



Melatonin



MSM



SAMe

Fig. 32.9
Structures of nutraceuticals commercially obtained from non-plant sources.

variability will undoubtedly occur in other food sources such as the constituents of cocoa and chocolate, cranberry, olives or pomegranate.

Conclusions

There are a number of clearly defined single component nutraceuticals with both *in vitro* and clinical evidence to substantiate their usage. However, others have limited available evidence.

The situation regarding complex supplements, e.g. tea and soy, makes it exceedingly difficult to effectively quantify the evidence, simply because of their complex nature. This fact often makes it difficult to establish which constituent(s) are demonstrating the effects; there is also the associated problem that it is at present unknown whether synergistic effects or the effects of the food matrix are responsible for the reported effects. Similar problems in identification of the precise origin of any effects can occur with grape products containg both resveratrol and GSPE. GSPE, pycnogenol, tea and chocolate all contain catechins and procyanidins, which are most likely the cause of their activity; these components also occur widely in a number of edible plants.

The majority of plant nutraceuticals are antioxidant and, although we have been aware of their claimed benefits for many years, it is apparent that the picture is not clear. It has been proposed that although humans are continually exposed to reactive oxygen species (ROS), we derive most from the oxygen we breathe. Plants are also exposed to high levels of oxidative stress as they produce oxygen via photosynthesis. It is postulated that they synthesize a range of antioxidants to compensate. However, these particular food sources of antioxidants also produce high levels of ROS in the form of H_2O_2. It has been claimed that this situation stimulates a response from human antioxidant systems, but that excessive levels of antioxidant nutraceuticals do not work because they help generate excessive levels of ROS!

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33

Colouring and flavouring agents

In addition to those materials essential to the pharmacological action of medicaments there is a range of others that are present in formulations for either ethical or technical reasons. Included here are colouring matters, flavourings, stabilizers, emulsifiers, thickeners, preservatives, antioxidants and tablet disintegrants and coatings. In the food industry these are classed as additives and for the EU there is a list of permitted substances that may be used in some of the above categories; each substance is given a number prefaced by the letter E. Under EU rules, for appropriate foods, such additives must be included in the labelling. In the UK consumers can obtain further information from the Food Standards Agency and from commercially produced booklets.

For medicinal purposes these additives, which are often identical to those used in foods, are controlled by the Medicines Act and not all manufacturers' data sheets provide information on the nature of the additives present. Thus, if a patient requires a medicament free of gluten or tartrazine it may be necessary for the pharmacist to make enquiries of the manufacturer. In recent years there has been an increasing demand for materials of natural origin and, particularly regarding colouring agents, the toxic nature of many of the synthetic dyes is becoming widely recognized. A considerable number of the additives used in standard medical practice are covered by the monographs of national pharmacopoeias which give standards for purity etc. Others, not so covered, and used in herbal preparations, may be included in the EU list. In some instances e.g. Raspberry Syrup *BP* 1988 and Cherry Syrup the preparation may have the dual role of colourant and flavouring. Also, as in the case of some flavouring and emulsifying agents, there may be an overlap with medicinal action. Thus oils of clove, and peppermint are used as flavours but the former has antibacterial, and the latter, carminative properties. Similarly, natural gums which are widely used as thickening, emulsifying and suspending agents have, in larger doses, a therapeutic action.

COLOURING AGENTS

The essential subsidiary requirements of a medicinal colourant are non-toxicity and stability. Specific factors to be considered are the effect of pH on colour (many natural pigments are pH indicators), solubility in water and oils, and stability to light, heat and sugars. Table 33.1 lists a range of some of the more important natural colourants used in food and medicinals and Fig. 33.1 shows the chemical structures.

For a report covering the legal aspects appropriate to Europe and Japan, see 'Further reading' (Henry 2000).

RED POPPY PETALS

Red poppy petals of the *BP*/*EP* consist of the dried whole or fragmented petals of *Papaver rhoeas* L. (field poppy, corn poppy) family Papaveraceae. The annual plant is found throughout Europe apart from the far north, N. Africa, temperate Asia and by introduction in N. America, Australia and New Zealand. Once a colourful sight as a weed in cornfields but now, due to the use of selective weed-killers, largely confined in its habit to waste areas and disturbed ground.

When harvested, the petals are a bright scarlet in colour with a dark violet claw and a smooth and shiny upper surface. The dried commercial product is dingy violet, crumpled or broken and often in clumps. Each petal is broadly ovate, about 6 cm long with an entire margin and veins arising from the base and anastomozing just below the margin.

Microscopy of the powder shows sinuously walled epidermal cells, small anomocytic stomata, vascular vibrous tissue, the remains of anthers and pollen grains about 30 μm in diameter with three pores.

The taste is mucilaginous and slightly bitter.

Table 33.1 Natural colourants.

Colourant source	Shade	Solubility	Stability	EU No., etc
Anthocyanins: various sources	Red–violet	Water	Colour pH-dependent	E163
Cochineal: *Dactylopius coccus*	Red	Water	Precipitates below pH 3	E120, *BP*
Beetroot powder (betanin); *Beta vulgaris*	Red	Water	Fair stability in acid; poor in alkali	E162
Carmine powder: *D. coccus*	Purplish-red	Alkali	Precipitates below pH 4	E120, *BPC* (1988)
Paprika oleo-resin (capsanthin, capsorubin): *Capsicum annuum*	Orange-red	Oil	Stable	E160(c)
Gardenia yellow: *Gardenia jasminoides, G. augusta*	Yellow (crocetins)	Water	Stable	
Saffron (crocin): *Crocus sativus*	Yellow–orange	Water		
Carotenes: various sources, e.g. carrot root	Orange	Oil/water	Stable	E160(a)
Annatto (bixin): *Bixa orellana*	Yellow–orange	Oil/water	Good in alkali; precipitates in acid	E160 (b)
Curcumin: *Curcuma longa*	Yellow	Water	Good in acid; poor in alkali	E100
Chlorophyll and complexes	Green, olive-green	Water/oil/acid/ alcohol depending on preparation	Fair in alkali; precipitates in acid	E140, E141

The colour of red poppy petals is due to anthocyanidins, including the gentiobioside of cyanidin (mecocyanin; see Table 21.6). On treatment with acid the drug becomes scarlet, whereas alkalis turn it a greenish-blue. The colour and blotching of the petals is variable and the *BP*/*EP* specifies a colouring capacity of not less than 0.6 when determined by absorbance measurements on an acid ethanolic extract at 525 nm.

Alkaloids with little toxicity (e.g. rhoeadine) and mucilage are also present. For a report on the isolation of two new depsides, (esters composed of two phenolic acids) and other known compounds see M. Hillenbrand *et al.*, *Planta Med.*, 2004, **70,** 380.

Red poppy petals were traditionally employed as an anodyne and expectorant but are now used principally as a colouring for infusions and syrups.

COCHINEAL

Cochineal is the dried female insect *Dactylopius coccus* Costa (*Coccus cacti* Linné) (order Hemiptera), containing eggs and larvae. Cochineal insects are indigenous to Central America. Commercial supplies are derived principally from Peru (85%) amounting in 1998 to 6.99×10^5 kg; other producers are the Canary Islands, Chile, Bolivia and Mexico.

History. Cochineal was used by the Greeks and Romans and was an important dye in 15th century England. It was derived from the swollen females of two scale insects *Kermes vermilio* and *K. ilicis* close relatives of *D. coccus*. These species use as host the kermes oak, *Quercus coccifera*, a native of the Mediterranean coast (for further details see J. Compton, *The Garden*, 1990, **115**, 385).

Culture and life history. Each year eggs from the previous crop, which are protected during the rainy season by shelters placed over the plants, are 'sown' on the cacti (usually species of *Opuntia*) on which it is intended to breed. Both male and female insects emerge. The males are about 1 mm long and possess wings, while the females are about 2 mm long and without wings. After fertilization the females attach themselves to the cacti by means of their probosces, which become embedded in the tissues of the plant; the males then die. The females swell to about twice their former size, owing to the presence of developing larvae, and develop red colouring matter. The larvae mature in about 14 days and escape from the now dead body of the parent. Only a small proportion of the larvae develop into males. For the next fortnight the young females crawl about the plant and the males fly. The sequence of events described above is then repeated. The life cycle thus takes about 6 weeks and three to five generations of the insects may be produced in a season.

Collection and preparation. The insects are brushed from the plants with small brooms and killed, a certain number being left to provide for subsequent crops. The first crop of the season usually contains the most colouring matter. The insects are killed by plunging in boiling water, by stove heat or by exposure to the fumes of burning sulphur or charcoal. If heat is used, the insects change to a purplish-black colour and are known as 'black grain', while the fume-killed purplish-grey ones are known as 'silver grain'. Small immature insects and larvae which can be separated by sieves are sold as 'granilla' or siftings.

Characters. Cochineal insects are 3.5–5.5 mm long and somewhat oval in outline. The convex dorsal surface shows from nine to 11 segments, but there are no constrictions between head, thorax and abdomen. The insect has a pair of seven-jointed antennae and three pairs of very inconspicuous legs. The surface bears tubular glands which secrete wax, the melting of which by heat accounts for the difference in colour between the silver grain and black grain varieties.

Cochineal should be examined microscopically after removing the colouring matter by means of solution of ammonia. Within each insect will be found from 60 to 450 eggs and larvae. For illustrations, see previous editions of this book.

Constituents. Cochineal contains about 10% of carminic acid, (Fig. 33.1), a brilliant purple, water-soluble colouring matter; it is a *C*-glycoside, anthraquinone derivative. The insects also contain about 10% of fat and 2% of wax. Recent research has shown that irradiation, even at the lowest level tested (1 KGy), is effective in eliminating the microbial count and has no significant effect on the stability of the pigment. The *BP* describes a test of absence of salmonellae and

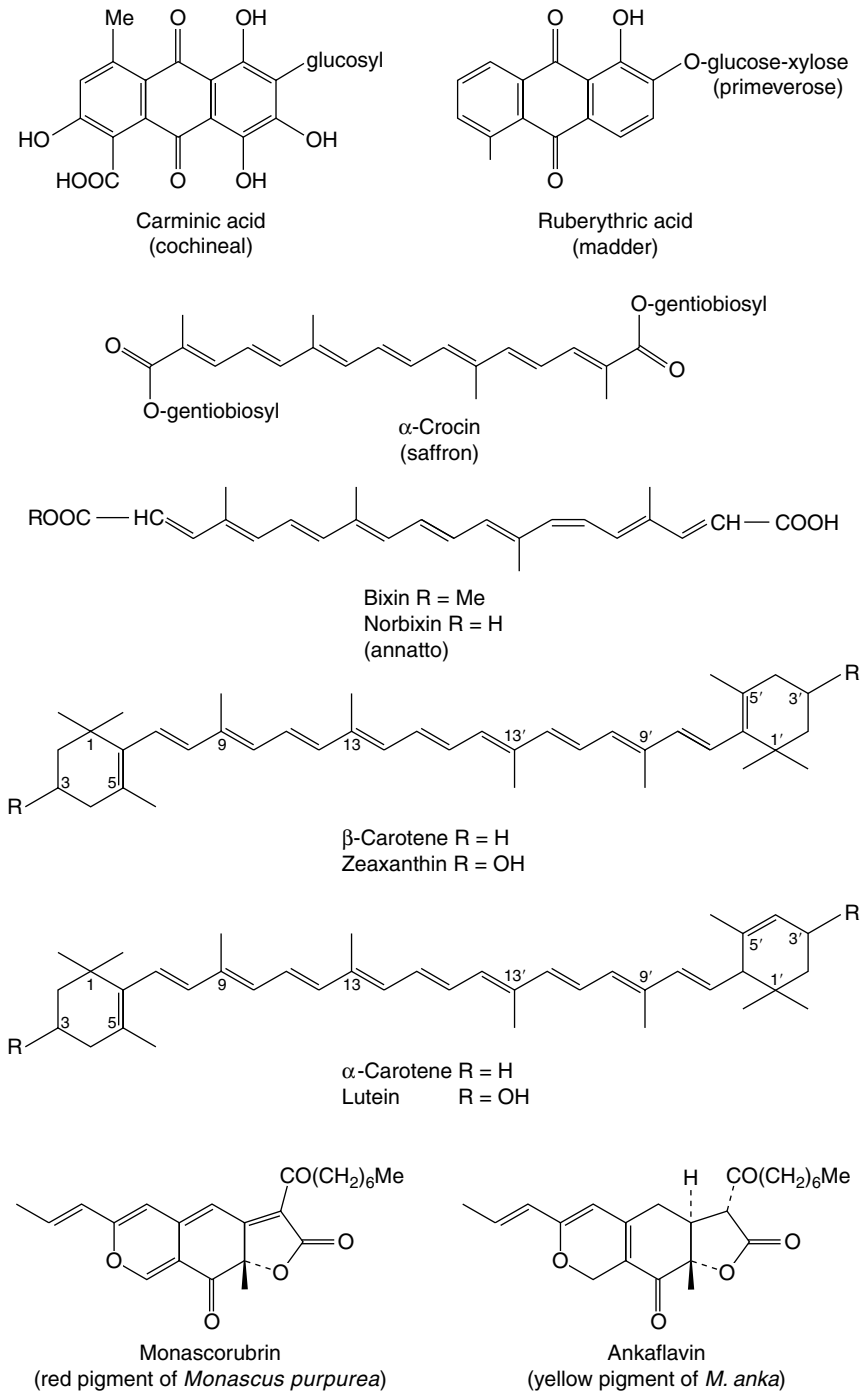


Fig. 33.1
Chemical structures of some natural pigments of pharmaceutical significance (for anthocyanidins see Table 21.6).

Escherichia coli and a colour value test in which the extinction of a diluted extract of pH 8.0 is measured at 530 nm.

Carmine, an aluminium lake, is prepared by precipitation by adding aluminium and calcium ions to an extract of cochineal; it contains about 50% of carminic acid. 'Carmines' are produced which vary enormously in shades and tinting strengths.

Adulteration. The weight of cochineal may be increased by 'dressing' it with inorganic matter, the colour of which is chosen so as to blend with the variety of insect being adulterated. If genuine, no insoluble matter should separate when the insects are placed in water and the ash should not exceed 7%.

Uses. Cochineal and carmine are used as colouring agents for liquids and solids and as indicators. No carcinogenic properties have been demonstrated.

Saffron

Saffron consists of the dried stigmas and tops of the styles of *Crocus sativus* (Iridaceae). The drug is prepared in Spain (70% of world supply); other producers are China, Iran and Kashmir. It is included in the *EP*. Saffron was prized by the ancients and was cultivated in Greece, Asia Minor and Persia. Cultivation of the plant in Spain appears to date from the tenth century and in England from the fourteenth century. In 1728 quite large quantities of English saffron were

being grown, particularly in the area between Saffron Walden and Cambridge.

The corms are planted in July or August in soil carefully prepared during the previous autumn. The first flowering takes place in September or October of the following year, after which each corm replaces itself by one or more daughter corms. After three harvests of flowers, the corms, which have at least doubled in number, are dug up in May or June. The best of these are reserved for planting in fresh ground in July or August. Saffron culture is labour-intensive. Collection is very much family-orientated. The flowers are gathered in the early morning, placed in baskets or hampers and conveyed to the picking house. The picker takes each flower in turn in the left hand and breaks the style just below the stigmas with the nail of the right thumb. The detached stigmas are dried by artificial heat, usually charcoal stoves, over which they are placed in hair sieves. After about 30–45 min the drug is cooled and stored in a dry place. About 90 000–100 000 flowers give 5000 g of fresh stigmas or about 1000 g of the dried drug.

Saffron or hay-saffron, as it is often called, occurs in loose masses consisting of reddish-brown stigmas among which yellowish pieces, the tops of the styles, can usually be seen. It has a sweetish aromatic odour and a bitter taste. When chewed the saliva is coloured orange–yellow. If the soaked drug is examined under a lens or microscope, the stigmas will be found either separate or united in threes to the apex of the yellowish styles. Each stigma is about 25 mm long and has the shape of a slender funnel, the rim of which is dentate or fimbricate.

Saffron contains a number of carotenoid pigments. A hypothetical protocrocin of the fresh plant is decomposed on drying into one molecule of crocin (a coloured glycoside) (Fig. 33.1) and two molecules of picrocrocin (a colourless bitter glycoside). Crocin on hydrolysis yields gentiobiose and crocetin, while picrocrocin yields glucose and safranal. The latter substance is largely responsible for the characteristic odour and together with picrocrocin the taste of saffron. Other related crocins (crocin-2, -3 and -4) have been described. Five new monoterpenoids, crocusatins A–E, have been obtained from the pollen and a further five, crocusatins F–I, reported from the stigmas (C.-Y. Li and T.-S. Wu, *Chem. Pharm. Bull.*, 2002, **50,** 1305; *J. Nat. Prod.*, 2002, **65**, 1452). Crocusatin H and crocins 1 and 3 were shown to have significant tyrinase inhibitory activity. The same authors (*J. Nat. Prod.*, 2004, **67**, 437) have subsequently described further monoterpenoids, crocusatins J–L, a new naturally occurring acid and 31 known compounds from a methanolic extract of the petals of *C. sativa*. The essential oil from the stigmas and petals contains 34 or more components, mainly terpenes, terpene alcohols and esters.

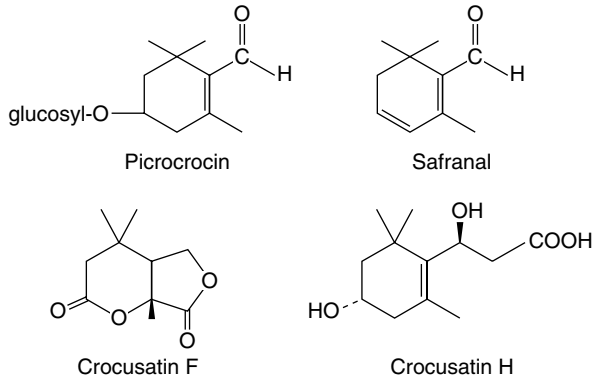


Fig. 33.2
Constituents of saffron (see Fig. 33.1 for formula of crocin).

By the culture of *C. sativus* stigmas on suitable media, stigma-like and style-like tissues which contain crocin, picrocrocin and other pigments have been obtained. Callus cultures at pH 7.0–7.6 with added uridine-diphospho-glucose are able to transform all-*trans*-crocetin into its related glycosides (D. Dufresne *et al*., *Planta Medica*, 1997, **63**, 150). An antioxidant, 3,8-dihydroxy-1-methylanthraquinone-2-carboxylic, claimed to be superior to Vitamin E in its inhibition of oxidation of linoleic acid, has been isolated from callus stem tissue of saffron.

Although orthodox medicine has generally considered saffron to exert no appreciable therapeutic effects, recent work has demonstrated anticancer, antiarthritic, antihypertensive and other activities which probably arise from the powerful antioxidant properties of the constituents.

Saffron is used in Chinese medicine and in the West it is employed to a limited extent as a colouring and flavouring agent. In Cornwall, UK, it is used for making saffron cakes.

Annatto

Annatto seeds are those of *Bixa orellana* (Bixaceae) and are characterized by having on their surface an edible carotenoid pigment.

The plant is a shrub or small tree, native to northern South America and widely cultivated for the seeds or as an ornamental in the West Indies, tropical Asia and Africa; there are white- and pink-flowered varieties which can be propagated by seeds or cuttings. The estimated world annual production of seeds is 4000 tonnes; Ecuador, India, Kenya and Peru are the principal producers. Annatto usage as a colourant dye is lost in antiquity but with the advent of synthetic dyes at the beginning of the twentieth century its use declined dramatically. However, from the late 1950s, corresponding with the quest for safer food additives, its importance in the food industry has again steadily increased. The solubility of the dye in fixed oil, e.g. castor oil, makes it ideally suitable for use in the dairy industry.

Bixin, a C_{24}-apocarotenoid (Fig. 33.1), is the principal component of the dye and it normally constitutes about 2.5% (dry wt) of the seeds although varieties containing higher proportions are being developed in Ecuador. Isolated for the first time in 1875, it was not until 1961 that its structure was fully established; it belongs to a small group of compounds which also includes crocetin (see Saffron) and abscisic acid (q.v.). Removal of the methyl ester group of bixin yields the dicarboxylic acid norbixin (Fig. 33.1) which forms the basis of the water-soluble annatto dyes. Various semi-synthetic derivatives of bixin also find use as food colourants.

Due largely to the work of A. Z. Mercadante and colleagues (*Phytochemistry*, 1999, **52**, 135 and references cited therein) a considerable number of minor pigments of the seeds have now been characterized. These include C_{30} and C_{32} apocarotenoids; C_{19}, C_{22}, C_{24} and C_{25} diapocarotenoids, three of these being the first examples of geranylgeraniol serving as the esterifying alcohol with a carotenoid carboxylic acid; also isolated were a number of known C_{40} carotenes.

The castor-oil extract of the seeds contains, in addition to the pigments, a small amount of essential oil, the principal component of which is the sesquiterpene hydrocarbon ishwarane.

Chromatographic and spectrophotometric methods are available for the quality control of bixin.

Although used chiefly in the food industry, annatto and bixin have been employed in the production of coloured coating materials for tablets, pills, granules and herbal medicine preparations.

Marigold flowers

Tagetes erecta (Compositae), known commonly as the African marigold, is grown commercially in Mexico, Peru and Ecuador for extraction of xanthophyll pigments from the florets. There is an estimated

world area of 7600 ha given over to cultivation; each plant produces on average about 330 mg of xanthophylls. With the exception of flavoxanthin [E161(a)] the xanthophylls have the same carbon skeletons as the carotenes, thus lutein (formerly known as xanthophyll) is 3, 3′-dihydroxy-α-carotene (Fig. 33.1). Lutein finds commercial use as an additive of chicken feed to give colour to egg yolks. The role of lutein in dietary supplements and its pharmacological properties have already been mentioned (Chapter 32).

Note: the common English garden marigold, not to be confused with the above, is *Calendula officinalis*, a well-established herbal remedy.

Red beetroot

Powdered red beetroot, *Beta vulgaris* (Chenopodiaceae), and the isolated red pigment betanin are widely used non-toxic food and pharmaceutical colourants. Betanin is a nitrogen-containing glycoside (Table 33.1) which on hydrolysis gives the aglycone betanidin and glucose. Hairy root cultures of the plant (*Agrobacterium* or *Rhizobium* spp. transformed) release red pigment to the culture medium, which is substantially the same as that contained within the hairy roots and in the original plant cells (M. Taya *et al*., *J. Ferment Bioeng*., 1992, **73**, 31).

Additional to its value as a colourant and food, various medicinal activities have been ascribed to red beetroot, including that of a free-radical scavenger; for a report on its potential hepatoprotective value, see M. Agarwal *et al.*, *Fitoterapia*, 2006, **77,** 91.

Monascus

Monascus purpureus is a mould which, when grown on cooked or autoclaved rice and then the whole dried and pulverized, gives a food colourant that has long been used in Chinese cooking. There is now interest in widening the use of this pigment. Strains of mould have been selected to give various shades and that producing the dark red monascorubrin (Fig. 33.1) is particularly important. Considerable work has been carried out on the production of various pigments from chemical and u.v.-mutant strains of the mould using continuous production methods rather than batch processing. With continuous fermentation it is important that the desired product is released to the medium. New chemically defined media have been described which give an increase in the OD_{500} measurements and a reversal of pigment location from predominantly cell-bound to extracellular. It is envisaged that the red pigment will serve as an edible, non-toxic substitute for expensive cochineal.

For recent work on the isolation of alanine or aspartate derivatives of monascorubrin and rubropunctatin see K. Sato *et al*., *Chem. Pharm. Bull*., 1997, **45**, 227.

Other species of *Monascus* also produce prigments and Korean workers have described strains of *M. anka*, developed by u.v.-mutation and natural selection, which produce enhanced levels of the pigment ankaflavin (Fig. 33.1). From the same species, a new series of pigments (monankarins A-F) having a conjugated pyrano-coumarin skeleton and exhibiting monoamine oxidate inhibitory activity has been isolated (C. F. Hossain *et al*., *Chem. Pharm. Bull*., 1996, **44**, 1535.

Red rose petals

The unexpanded petals of the Provence rose, *Rosa gallica*, were used for preparing the acid infusions of rose of the *BPC* 1949. The drug is mildly astringent and for this reason, and also for the colouring principles, the infusions served as a convenient vehicle for gargles containing alum or tannin. The anthocyanine constituents made the petal extracts unsuitable for prescribing with alkaline salts.

DYESTUFFS

Natural products were at one time of prime importance to the dyeing industry and remain so today in some native societies. Three well-known examples with pharmaceutical links are alkanna, henna and madder. Alkanna and henna contain naphthoquinone derivatives and are described in more detail in Chapter 21. Madder, the root of *Rubia tinctorum* (Rubiaceae) formerly grown in large quantity in the area of Avignon contains anthraquinone derivatives including ruberythric acid (Fig. 33.1). On hydrolysis the latter yields primeverose and alizarin, the pigment responsible for Turkey Red colour. Towards the end of the nineteenth century the use of the natural product was superseded by synthetic material.

For an interesting article on the production of woad, one of the most ancient of dyes known to man, see P. John, 'Further reading,' below.

Further reading

Evans WC 2000 Annatto: a natural choice. Biologist 47(4): 181–184

John P 2006 Indigo reduction in the woad vat: a medieval biotechnology revealed. Biologist 53(1): 31–35

Lauro GL, Francis FJ (eds) 2000 Natural food colorants. Vol 14 of a Basic Symposium Series of the Institute of Food Technologists, Chicago. Marcel Dekker, New York. *This volume includes articles on the following: Carmine, pp 1–9 (J Schul), The betalains, pp 11–30 (JH von Elbe, IL Goldman), Monascus pp 31–85 (RE Mudgett), Paprika pp 97–113 (CL Locey, JA Guzinski), Annatto pp 115–152 (LW Levy, DM Rivadeneira), Lycopene pp 153–192 (ML Nguyen, SJ Schwartz), Turmeric pp 205–226 (R Buescher, L Yang), Chlorophylls pp 227–236 (GAF Hendry), Anthocyanins pp 237–252 (RE Wrolstad), Color measurement pp 273–287 (K Loughrey), Health aspects pp 288–314 (G Mazza), Regulations in Europe and Japan pp 314–327 (BS Henry)*

Negbi M (ed) Hardman R (series ed) 2000 Medicinal and aromatic plants—industrial profiles. Vol. 8. Saffron: *Corcus sativus* L. Harwood Academic, Amsterdam

FLAVOURING AGENTS

Natural flavours are often complex mixtures of compounds such as are found in essential oils and may contain over 100 components, all blending to give a characteristic flavour. Alternatively, a flavouring agent may contain a single compound only, such as vanillin. The design of regulations for flavours for the food industry is obviously a complex task and the EU is currently considering this. Flavours used in medicaments are at present covered by the Medicines Act.

Although food and medicinal flavourings have aspects in common their role in a medicine is different to that in a food. In the former case they are used to disguise an unpleasant taste resulting from the active constituents of the medicine rather than, as in the latter case, to make more attractive an already palatable material. It is questionable whether medicines should be formulated to make them so pleasant to the taste that they are no longer distinguishable as such. Helliwell and Jones discussed this aspect (*Pharm. J*., 1994, **253**, 181) in an article 'How good should a medicine taste?' mentioning conceptual pharmaceuticals in which a postprandial OTC medicine could be formulated as a liqueur so that the particular brand would become associated with a pleasant after-meal experience.

Certain natural flavours traditionally have been formulated as syrups for addition to the active medicament, a practice now somewhat discouraged on dental health grounds. A number have, in addition to flavour, some medicinal properties. The following, for example, are also, together with their oils, carminatives: citrus peels, ginger, peppermint leaf, fennel fruits, dill fruits, coriander fruits, caraway fruits, cardamom, nutmeg and cinnamon. Liquorice extract is used to disguise the taste of nauseous medicines and Wild Cherry Syrup *BPC* 1988, although employed in cough preparations, is primarily used for

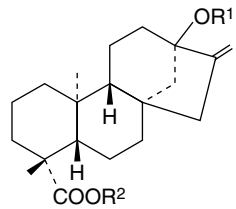
flavouring. Raspberry and blackcurrant syrups have no therapeutic value although the juice of the latter is used for its vitamin C content. Similarly saffron (q.v. above) and oil of rose (used to flavour lozenges) have no medicinal effect.

Sweetening agents

There is a need for alternatives to sucrose as a sweetening agent for medical purposes (e.g. for diabetics) and for diet improvement. Although saccharin is the most widely used substitute two natural products are also noteworthy.

Sorbitol. Sorbitol (D-glucitol), *USP/NF* 1995, is a polyhedric alcohol which was first isolated from mountain ash berries (*Sorbus aucuparia*, Rosaceae) and is now known to occur in other members of the family and widely throughout the plant kingdom. It is prepared synthetically by the catalytic hydrogenation of glucose. Sorbitol solution (Sorbitol Liquid) *BPC* 1988 contains 70% of mainly sorbitol and is used as a sweetening agent and vehicle in elixirs, linctuses and mixtures; it has about half the sweetening power of syrup.

Stevioside. A group of ent-kaurane glycosides, derivatives of steviol, have sweetening properties some three hundred times that of sucrose. Stevioside, the most important, is obtained from *Stevia rebaudiana* (Compositae) a plant native to N.E. Paraguay. Although first isolated in 1931 its structure was not elucidated until 1963 and then some 10 years later it was produced commercially in Japan. New non-glycosidic labdane diterpenoids (sterebins) continued to be isolated (B. D. McGarvey *et al.*, *J. Nat. Prod.*, 2003, **66,** 1395). Now, some 700–1000 tons of plant material are processed annually by Japan, Brazil and other countries. The product is used in the soft drinks and food industries. For a report on the pharmacological and physiological effects of *S. rebaudiana* on animals and humans see M. S. Melis, *J. Ethnopharm*., 1999, **67**, 157.



Steviol $R^1 = R^2 = H$
Stevioside R^1 = Glucose–glucose, R^2 = Glucose

34

Miscellaneous products

There are a few miscellaneous pharmaceutical materials of natural origin which are not included in the preceding chapters; these are considered below.

KIESELGUHR OR DIATOMITE

Large deposits of diatomite are found in Aberdeenshire in the UK, Virginia and California in the USA, Germany and North Africa. The crude product contains about 65–87% of SiO_2, together with organic matter, clay, iron oxide and about 5–15% of water. The silica is mainly amorphous, being present in the siliceous walls of minute, unicellular plants belonging to a number of families of the Bacillariophyceae. A much smaller percentage of silica occurs in the walls of spicules of siliceous sponges and, in a crystalline form, as sand. Depending on the geographical origin of the diatomite, the diatoms may be either freshwater or marine forms.

The material is dried and crushed, ignited to remove organic matter, boiled with dilute hydrochloric acid to remove impurities such as iron, washed with water and dried. It is then sifted or 'air-blown', the finest grades used in face powders being obtained by the latter method.

Characters. Purified kieselguhr is a fine, white or pale-buff odourless powder. For microscopical examination it may be mounted in cresol or olive oil. In the latter medium the amorphous silica of the diatoms becomes almost invisible, while the crystalline particles of sand remain clear. Only small amounts of sand (Fig. 34.1H) should be present.

The diatoms (Fig. 34.1) consist of two halves or *valves* which fit together like a pill-box. The two positions from which they may be studied are known as the valve-view and the girdle-view. The valves show considerable variation in shape, some samples of kieselguhr showing numerous discoid types resembling that of the *Arachnoidiscus* found in agar, while other samples consist largely of pennate forms. A mixture of both types is usually most suitable for filtration. In many diatoms a median cleft is found in the valves, known as the *raphe*. The valves also show dots and lines, which vary in the different species and are due to minute cavities in the wall.

Kieselguhr is insoluble in all acids except hydrofluoric, but is soluble after fusion with alkalis. It is used for the filtration of oils, fats, syrups, etc., and in the form of the Berkefeld filter for sterilization. Highly purified material is used as an inactive support in column, gas and thin-layer chromatography; the powder will hold up to its own weight of water and still retain its powdery consistency. Diatomite is also employed in face powders, pills, polishing powders and soaps, and to absorb nitroglycerin in the manufacture of dynamite; it is a component of the *BP* (*Vet*) pyrethrum dusting powder.

Extant species of diatoms form an important component of plankton and are involved in the food chains of seas and rivers. (For a wide-ranging illustrated introduction to these single-celled plants see *The Diatoms; Biology and Morphology of the Genera* by F. E. Round *et al*. (1990), Cambridge University Press.)

PREPARED CHALK

Chalk is a whitish or greyish rock which is widely distributed in north-western Europe. It consists mainly of the shells of unicellular animals known as the Foraminifera. Chalk as quarried often contains about 97 or 98% of calcium carbonate, the remainder being largely siliceous and therefore insoluble in acids. The impure chalk is finely ground with water and freed from most of the heavier siliceous impurities by elutriation. The coarser product is sold as 'whiting' and the finer elutriated product is allowed to settle and while still pasty is poured into a funnel-shaped trochiscator. The latter is tapped on a porous chalk slab

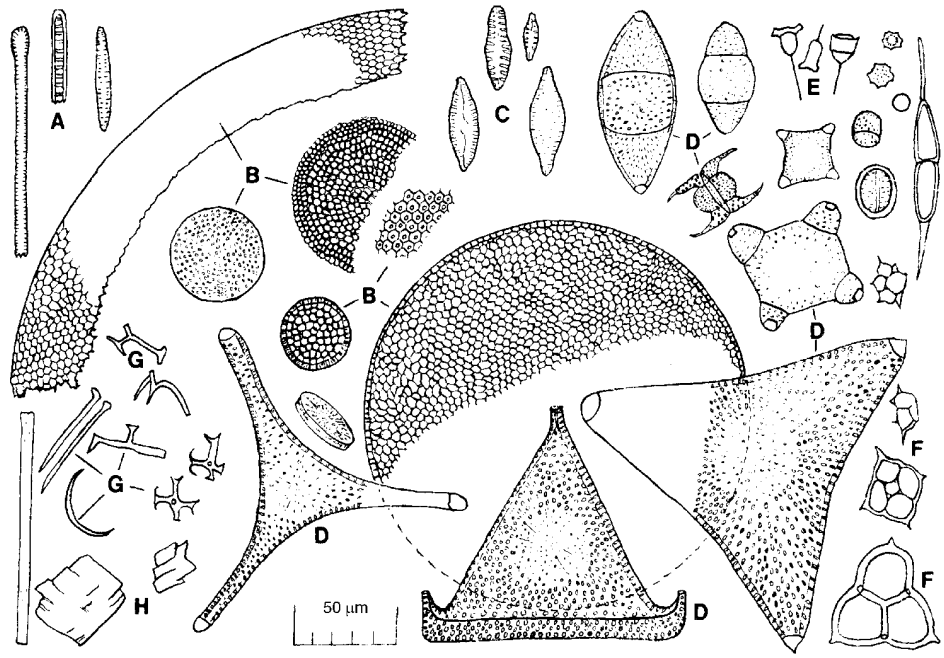


Fig. 34.1
Diatomite (various sources) showing the shells of diatoms and other constituents. A, Diatom skeletons of the Fragilariaceae (e.g. *Synedra, Fragilaria*); B, entire or broken portions of *Coscinodiscus* spp.; C, shells of the Naviculaceae (e.g. *Navicula*); D, various forms belonging to the Biddulphioideae (*Biddulphia, Trinacria*, etc.); E, fragments of *Asterionella* spp.?; F, silicoflagellates; G, sponge spicules; H, sand particles.

and ejects the chalk to form 'cones', which are allowed to dry giving Prepared Chalk *BP*. These cones ('crab's eyes') may be powdered.

Characters. For examination chalk should be mounted in cresol, warmed and examined microscopically (Fig. 34.2). Most of the foraminiferous shells have been broken but a number of whole ones usually remain. The whole shells may be concentrated in a small bulk by removing the broken ones by elutriation and examining the residue. Note the following:

Globigerina. In these the shell is of calcite and is perforated by large canals. Each consists of a few lobular chambers arranged in a plane or helicoid spiral. The size varies from about 35 to 80 µm.

Textularia. In these the shell is composed of grains of sand cemented together by calcareous matter. They are usually conical or cuneiform in shape and are composed of numerous chambers in two alternating parallel series. The size varies from about 50 to 180 µm.

Remains of fossil algae. Small rings or discs about 4–9 µm in diameter, termed coccoliths or morpholites.

Prepared chalk is assayed by acid–alkali back-titration; there are pharmacopoeial limits for heavy metals and arsenic; limits for aluminium, iron, phosphate and matter insoluble in hydrochloride acid are determined gravimetrically.

Precipitated chalk. Precipitated chalk (calcium carbonate *BP/EP* is made by the interaction of a soluble calcium salt and a soluble carbonate. The precipitate varies considerably with the method of preparation. When precipitated at about 0°C, the product is very light and almost entirely amorphous; at about 30°C a denser precipitate of minute rhombohedra is formed, and if boiling solutions are used, the precipitate consists of prismatic rhombohedra with a higher specific gravity than either of the previous forms. The *BP* assay involves a complexometric titration of calcium; there are limits for various metals, etc.

Uses. Chalk is used as an absorbent and antacid.

GELATIN

Gelatin is a mixture of reversible gel-forming proteins derived from certain animal tissues, particularly skin and bones, with hot water. The process converts insoluble collagens into soluble gelatin, the solution of which is then purified and concentrated to a solid form.

The initial stages of the preparation vary with the starting material, bones, for example, being defatted with an organic solvent and sometimes decalcified by treatment with acid. Two types of gelatin are characterized in the *BP/EP*—type A is obtained by partial acid hydrolysis of animal collagen and type B by partial alkaline hydrolysis; mixtures of both types are also permitted.

Characters. Sheet gelatin prepared as above may be cut into strips or made into a granular powder. Gelatin is colourless or pale yellow, is

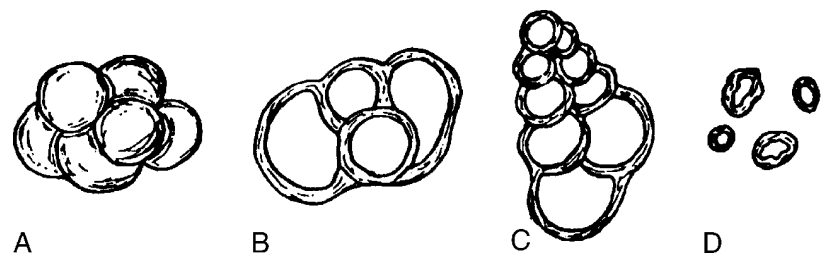


Fig. 34.2
Shells from prepared chalk. Globigerina in (A) water, (B) cresol (×200). C, *Textularia* in cresol (×200). D, coccoliths (×400).

translucent and has little odour or taste. It is insoluble in cold water but absorbs a considerable volume of liquid; it dissolves on heating and a 2% solution forms a jelly on cooling. The gelatinizing power of gelatin is reduced by long boiling. The quality of gelatin is largely judged by its 'jelly strength' or 'Bloom strength' which is determined by a Bloom gelometer. The two types of gelatin (A and B) have isoelectric points in the ranges pH 6.0–9.5 (A) and pH 4.7–5.6 (B). Type B is compatible with anionic substances (e.g. the natural gums), whereas type A is not; for some specific purposes, narrower tolerance limits than above may be required. Note the *BP*/*EP* limit tests and standards.

Constituents. Gelatin consists mainly of the protein glutin and therefore gives the usual tests for proteins. Thus, it evolves ammonia when heated with soda lime (distinction from agar); with mercuric nitrate solution gives a white precipitate that turns brick-red on warming; it gives a precipitate with a solution of trinitrophenol.

Uses. Gelatin is used in the preparation of pastilles, pastes, suppositories, pessaries, capsules, pill-coatings and gelatin sponge. Specially purified and pyrogen-free gelatins are available for intravenous injection, and a grade with high 'Bloom strength' is used for making gelatin capsules and for bacteriological culture media.

Gelatin sponge

Gelatin sponge can be conveniently mentioned here as an absorbable, water-insoluble haemostatic material. It may be prepared by whisking a warm solution of gelatin to a foam of uniform porosity and drying. After cutting into pieces it is sterilized by dry heat. Note the *BP* standards for this material. It is used in a similar manner to oxidized cellulose.

FISH BODY OILS

The oils expressed from the bodies of a number of 'oily' fish of the families cited on p. 43 contain esters of omega-3 fatty acids. As such, they have become important dietary supplements and two such oils are included in the *BP*/*EP*. For an explanation of the structural representation of the various acids, as cited below, see Chapter 19, 'Fatty Acids'.

Fish oil, rich in omega-3-acids. The expressed oil is processed in much the same way as for cod-liver oil (q.v.) and involves winterization and deodorization. The esterifying ω-3 acids, as exemplified in the pharmacopoeia, are: α-linolenic acid (C18:3 n-3), moroctic acid (C18:4 n-3), eicosatetraenoic acid (C20:4 n-3), timnodonic (eicosapentaenoic) acid (C20:5 n-3; EPA), heneicosapentaenoic acid (C21:5 n-3), clupanodonic acid (C22:5 n-3) and cervonic (docosahexaenoic) acid (C22:6 n-3; DHA).

It will be noted that up to six double bonds may be involved in these acids; all are ω-3-acids and the positions of the remaining double bonds occur in sequence, separated by one methylene group (see α-linolenic acid, Table 19.3).

The total omega-3-acids, expressed as triglycerides, should be ≮28.0%; that of EPA ≮13.0% and DHA ≮9.0%. Oligomers, determined by size exclusion chromatography (p. 143), should not exceed 1.5%. The maximum permitted anisidine value (p. 180) is 30.0. An antioxidant may be added to the oil.

Farmed Salmon Oil *BP*/*EP* is obtained from salmon, *Salmo salar*, family Salmonidae, which have been fed in accordance with EU or other applicable regulations. The oil is expressed mechanically at below 100°C either from whole fish or fish from which the fillets have been removed; it is centrifuged and winterized. The pale pink oil contains the important polyunsaturated acids DHA, EPA and moroctic acid (see above); the two former constitute 10.0–28.0% of the oil, expressed as triglycerides. Chromatography is used to identify the acid components and ^{13}C-NMR for their further evaluation. The anisidine value is maximized at 10.0, considerably less than for the Fish Oil described above; similarly with the peroxide value. These figures indicate the extent of secondary oxidation of the oils.

Preparations derived from fish body oils. The following modifications of fish body oils are included in the pharmacopoeia.

Omega-3-marine triglyceride contains a mixture of the glyceryl esters prepared from the purified concentrated acids or from the omega-3-acid ethyl esters. It contains a minimum 60.0% of total omega-3 acids expressed as triglycerides and a minimum 45% of EPA and DHA, also expressed as triglycerides. The maximum permitted peroxide value is 10.0 and that for the anisidine value 30.0.

Omega-3-acid ethyl esters 60 and *omega-3-acid ethyl esters 90* contain higher minimum concentrations of EPA and DHA than the above, as indicated in their names. They are prepared by transesterification of the body oil of 'oily' fishes with subsequent purification, fractionation and molecular distillation.

These preparations are used to treat such conditions as hypertriglyceridaemia, to reduce the risk of CHD, thrombosis and for other disorders, still under evaluation.

SILK

Silk is the prepared fibre from the cocoons of *Bombyx mori*, the mulberry silkworm, and other species of *Bombyx* and of *Antheraea* (order Lepidoptera). It is produced in China, Japan, India, Asia Minor, Italy, France and many other countries. While the silk of *B. mori* forms the greater part of that used, considerable quantities of the so-called wild silks are produced by *Antheraea mylitta* (India), *A. assama* (India), *A. pernyi* (China) and *A. yama-mai* (Japan).

Before the silkworm passes from the caterpillar to the chrysalis or pupal stage, it secretes around itself an oval cocoon about 2–5 cm long, consisting of a continuous thread up to 1200 m long. This thread consists of two silk or *fibroin* fibres cemented together by a layer of silk glue or *sericin*. Strands of semiliquid fibroin, produced by two glands in the insect, flow into a common exit-tube in the head, where they meet the secretion of silk glue produced by another pair of glands. The double fibre with its coating of sericin emerges from a spinneret in the head of the worm, coagulates and hardens on contact with the air and is spun into the cocoon by figure-of-eight movements of the head. If the chrysalis were allowed to mature, the silk would be damaged by the escaping insect. It is therefore killed by heating at 60–80°C for a few hours or by a short exposure to steam. The cocoons are then graded, placed in hot water and beaten to facilitate removal of the outer layer of fibre, which is only of secondary value, and to soften the silk glue.

The double fibre in the cocoon is known as a *bave* and its constituent fibres are known as *brins*. The reeler takes the loose ends of the fibres of 2–15 cocoons and twists and reels them into a single thread. Most raw silk is reeled from about five cocoons and therefore has 10 brins, fibres containing less than six brins being too fine for commercial purposes. Silk is then usually scoured by treatment with hot soap solution to remove the sericin.

Microscopy. Examine some fibres of raw silk mounted in water. The diameter of these is several times that of a single brin; the individual brins may be seen although difficult to count; and flakes of silk glue may be seen on the surface. If a little of this raw silk is now boiled

with soap solution or dilute sodium carbonate solution, the sericin completely dissolves and the constituent brins may be mounted and examined.

The lack of cellular structure and the breadth of the brins are distinguishing characters of mulberry silk. Brins of mulberry silk measure 10–21 μm (mostly about 16 μm), whereas those of wild silks are 30–60 μm. The latter often show well-marked longitudinal striations.

Silk gives the general tests for animal fibres, and the following:

1. Silk is soluble in ammoniacal copper oxide solution. An alkaline solution of copper sulphate and glycerol of a certain strength is used for the separation of silk from wool and cotton.
2. Silk contains little or no sulphur and therefore gives no black precipitate with alkali and lead acetate solution (distinction from wool).
3. Silk rapidly dissolves in concentrated hydrochloric acid (distinction from wool).

Chemical nature. Natural silk is composed of the protein fibroin. Fibroin on hydrolysis gives mainly glycine (44%) and alanine (27%) together with smaller amounts of serine (11%), tyrosine (5%) and other amino acids. The molecule is a chain-like structure, with a repeating unit 0.7 nm long. This repeating unit, as revealed by radiograph analysis, corresponds in length to that of two fully extended amino acid residues.

Surgically, silk is used as a non-absorbable suture and as such must comply with the *BP* requirements for such materials. (For a general article on silk see M. L. Ryder, *Biologist*, 1995, **42**, 52.)

WOOL, ANIMAL WOOL, SHEEP'S WOOL

Wool is prepared from the fleece of the sheep, *Ovis aries* (order Ungulata), by cleansing and washing. The length and quality of the hair varies not only from animal to animal, but also in different parts of the same fleece. In order to get more or less uniform grades, the woolsorter spreads each fleece on a frame covered with wire-netting and separates it into wool of different qualities. At the same time he beats much dust and dirt through the netting and picks out burrs, etc. The wool is washed in tanks of warm, soft, soapy water, being squeezed between rollers as it passes from tank to tank.

The approximate composition of raw wool is as follows: wool fibre, 31%; 'wool sweat' or 'suint', consisting mainly of the potassium salts of fatty acids, 32%; earthy matter removable by washing, 26%; and 'wool grease'.

From the washings of the scouring process 'wool grease' may be separated by mechanical means or by the use of organic solvents. When purified it is known as wool fat or anhydrous lanolin (q.v.). Potassium salts may also be recovered. After washing, the wool is dried, and the fibres are mechanically loosened, carded, and spun into yarn.

Microscopical. The hairs originate in relatively deep pits or hair follicles in the skin and the 'wool grease' is secreted by neighbouring sebaceous glands. If fibres of raw wool are examined under the microscope, they are seen to be covered with irregular masses of grease, the structure of the hair itself being indistinct. If raw wool is to be mounted for microscopical examination, it should be defatted by ether or chloroform, as it will not otherwise wet with water; even with scoured wool, it is advisable to moisten the threads with alcohol before mounting in water, dilute glycerin or solution of picric acid.

Wool hairs are 2–50 cm long and 5–100 μm, usually 13–40 μm, diameter. As the fleeces are removed by shearing, the bases of the hairs are lacking, and tapering ends, known as 'lamb ends' are only found in wool from the first shearing. Three regions of the hair, known as the cuticle, cortex and medulla, are distinguishable.

Cuticle. This consists of imbricated, flattened, more or less translucent epithelial scales. The shape and arrangement of the scales varies in different breeds of sheep, edges being smooth and straight in some and serrated and wavy in others. The number of scales in a 100 μm length is fairly constant, averaging about 9.7–12.1, in different wools. Such counts may be used to distinguish sheep's wool from angora wool, etc.

Cortex. The cortex consists of elongated, fusiform cells coalesced into a horny mass in which scattered pigment cells are sometimes found.

Medulla. The medulla consists of rounded or polyhedral cells containing fatty matter or pigment and is best seen when its cells contain much air or pigment. (For an article on wool describing, among other things, the different fibres found in fleece see M. L. Ryder, *Biologist*, 1994, **41**, 195.)

Tests

1. *Characteristic of animal fibres*. Wool resembles silk in its behaviour with Molisch's test, picric acid, nitric acid and Millon's reagent. It is readily soluble in 5% potash.
2. *Characteristic of wool*.
   (1) Ammoniacal copper oxide solution resembles solution of ammonia in that it causes separation of the scales; it also colours the fibres blue.
   (2) When lead acetate is added to a solution of wool in caustic soda, a black precipitate is formed owing to the high sulphur content (distinction from silk).
   (3) Wool is not appreciably soluble in warm hydrochloric acid (distinction from silk), or in cold concentrated sulphuric acid (distinction from cotton).

Chemical nature of wool. Wool fibres are composed of the protein keratin. They show elasticity, in contrast to the cellulose and silk fibres. X-ray examination of stretched and unstretched fibre shows that the elasticity arises from a reversible intramolecular transformation of the fibre substance. The radiograph of the stretched fibre closely resembles that given by fibres, such as silk, with fully extended polypeptide chains. In this condition each amino acid residue is 0.34 nm long. This unstable form of keratin is known as β-keratin. The stable form, α-keratin is contracted and the structural unit, corresponding to three amino acid residues, is 0.51 nm long. The chemical relationship between these two forms and its importance in conferring elasticity properties on wool fibres is illustrated in former editions of this work.

Leech

The medicinal leech, *Hirudo medicinalis*, is about 6–10 cm long. The sucker at the anterior end has three radiating jaws provided with 'teeth'. Placed in contact with the skin, the animal produces a triradiate cut and can draw about 4–8 ml of blood. The salivary glands secrete hirudin, an acidic polypeptide of molecular weight around 7000; it retards coagulation of blood and allows bleeding to continue after the leech has been removed. Preparations containing hirudin for the treatment of bruises are manufactured commercially. Other enzymes isolated from the leech include hementin, an antithrombin agent, and orgelase, which degrades hyaluronic acid.

Some 12 000 kg of leeches are used annually in Europe and are exported from France, Italy, Portugal and Central Europe. The animal,

classed as a threatened species, is officially protected in some countries including Britain. Future supplies of leech products may need to be met by commercial farms (one currently operates in S. Wales) and by genetically engineered organisms. The cloning and expression of a recombinant gene for hirudin in yeast and bacteria has been reported (1988).

Although used less than formerly, leeches are often the least painful way to reduce inflammation. They have also staged a medical revival by their use in skin grafting for the removal of coagulated blood from beneath the new skin. Unfortunately, the leech is host to *Aeromanas hydrophila*, an organism on which it depends to digest the blood consumed. This is a potential source of infection of wounds and, according to a report in the *British Medical Journal* (11 April 1987), three types of infection, including diarrhoea, have been reported in patients receiving leech treatment. However, the problem can be eliminated by the use of suitable antibiotics.

(For a general review article (20 refs) on the medicinal leech see J. M. Elliot and P. A. Tullett, *Biologist*, 1992, **39**, 153.)

SHELLAC (LAC)

Shellac (lac) is a resinous substance prepared from a secretion that encrusts the bodies of a scale insect *Karria lacca* (*Lucifer lacca*), order Hemiptera. Lac is produced in India, Thailand and to a lesser extent in China (5% of world production). In India the chief plants are members of the Leguminosae (*Acacia* spp., *Butea frondosa*), Euphorbiaceae (*Aleurites laccifera*), Moraceae (*Ficus* spp.), Dipterocarpaceae (*Cajanus indivus, Shorea talura*), Rhamnaceae (*Ziziphus jujuba*) and Sapindaceae (*Schleichera trijuga*). In China the host trees are mainly species of *Ficus* and *Dalbergia* (Leguminosae) (C. Saint-Pierre and O. Binrong, *Econ. Bot*., 1994, **48**, 21). The insects resemble cochineal insects in structure and life history.

Lac is found most abundantly on the smaller branches and twigs. These are broken off and constitute *stick lac*. Usually, however, the lac is not exported in this form but is scraped from the twigs by means of curved knives. The lac is usually ground in India and the colouring matter extracted with water or dilute soda solution. The solution evaporated to dryness constitutes *lac dye*, and the exhausted lac when dried *seed lac*. From the latter the four types of shellac recognized in the EP/BP are prepared (Table 34.1). Other commercial grades are also utilized. *Button lac* is the molten lac poured into circular moulds and stamped with the maker's name. Flake shellac having a brownish-yellow colour is known in commerce as orange shellac and the darker, reddish-brown varieties are known as ruby or garnet shellac. A number of varieties, required to conform to a table for acid value, loss on drying and wax content, are including in the *USP/NF* 1995. Lac contains about 6% of wax, 6.5% of red water-soluble colouring matter, laccaic acid, 70–85% of resin and a few insect remains, vegetable debris, etc. The resin, composed of two parts, a hard and a soft fraction, is formed from hydroxy fatty acids and sesquiterpenes. An example of the former is aleuritic acid (9,10,16-trihydroxypalmitic acid) and of the latter, a cedrene-type sesquiterpene acid; a water-insoluble yellow pigment is erythrolaccin, a tetrahydroxy-4-methylanthraquinone. The *BP*/*EP* includes tests for colophony (TLC), arsenic, heavy metals, etc. Shellac is classified as a pharmaceutical aid and is also used in varnishes, polishes, sealing wax, etc.

Isinglass

Russian isinglass or ichthyocolla consists of the dried prepared swimming bladder of the sturgeon, *Acipenser huso*. The fish are caught in South Russian rivers and in the Black and Caspian seas. Isinglass consists chiefly of collagen and resembles gelatin in its properties. Brazilian isinglass is a similar product but derived from fish of different genera.

Ambergris

This very expensive substance used in perfumery is a pathological product found in the intestines of sperm whales or cast by them into the sea. It occurs in streaky grey or brown waxy masses which, exceptionally, may weigh up to 45 kg. It is associated with the beaks of squids on which the whales feed. Ambergris contains about 25% of ambrein. It has a fragrant musk-like odour but its main value lies in the fact that it has a subtle effect on fine perfumes and gives them great tenacity or persistence of odour.

Musk

Musk is the dried secretion from the preputial follicles of the musk deer, *Moschus moschiferus*. This small deer is found in China and

Table 34.1 Pharmacopoeial types of shellac.

Type	Preparation	Characters
Wax-containing shellac	From molten seedlac by filtration through bags or by hot solvent extraction. When sufficiently cool the product is stretched into a large sheet and then broken into flakes	Flakes, brownish-orange or yellow. Almost insoluble in water and partly soluble in ether. With alcohol it gives an opalescent solution
Bleached shellac	Seedlac is dissolved in hot soda solution, bleached with hypochlorite or chlorine and precipitated by acid. It is 'pulled' under water into sticks and dried	A cream to brownish-yellow powder. An opalescent solution is given with alcohol
Dewaxed shellac	From seedlac or wax-containing shellac by treatment with a suitable solvent and removal of the wax by filtration	Flakes as wax-containing shellac. With alcohol it gives a clear solution
Bleached dewaxed shellac	Seedlac or wax-containing shellac is treated with hot soda solution and bleached with hypochlorite; the insoluble wax is removed by filtration, the product precipitated from solution with dilute acid, and dried	Appearance as bleached shellac. With alcohol it gives a clear solution

the Himalayas. The musk-containing sacs are known as 'pods'. They are about 5–7 cm diameter, weigh up to 30 g and contain about half their weight of musk. When distilled, musk yields about 1.4% of dark brown volatile oil, the chief odorous constituent of which is muskone. This is a cyclic ketone having a closed chain of 15 carbon atoms. Other constituents of musk are steroidal hormones, muscopyridine and other alkaloids and peptides. A synthetic compound, which differs from muskone only in the absence of a methyl group, is cyclopentadecanone. Most other synthetic musk substitutes have little chemical similarity to the natural product. Musk acts as a fixative and is an important ingredient of many high-class perfumes.

Civet

This product, which resembles musk, is obtained from the perineal follicles of African or Indian civet cats, *Viverra* spp. It contains civetone, a cyclic ketone closely related to muskone but having a closed chain of 17 carbon atoms.

Royal jelly/Queen bee jelly

This hive product of Chinese origin consists of the milky fluid produced by the salivary glands of worker bees and used as essential nourishment for the development of the queen bee larvae. It contains a mixture of amino acids, vitamins (including most of the vitamin B complex and vitamin C), lipids, fatty acids, carbohydrates and minerals. The fresh material is unstable and requires refrigeration. It may also be freeze-dried but more satisfactory preparations are stated to be capsules containing royal jelly stabilized by the addition of honey. Royal jelly is an expensive dietary supplement recommended in health magazines for counteracting the effects of ageing and for the treatment of myalgic encephalomyelitis, depression, dermatitis and other conditions. Its value, which has yet to be clinically proved, may arise from the biologically favourable relative proportions of the many constituents rather than from their quantity.

PART

6 Plants in complementary and traditional systems of medicine

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Introduction

The previous chapters have been concerned mainly with those plant drugs that are associated with allopathic medicine, but there are other systems of great significance which also employ plants in the treatment of disease. A number of these, including herbal medicine, homoeopathy, aromatherapy and Bach remedies, are widely practised in the West and are discussed below. A consensus of other alternative systems of medicine which do not involve plants may be obtained from the many publications now available. An indication of the changing conventional attitude towards alternative (complementary) medicine was the establishment in 1987 of a Centre of Complementary Health Studies at the University of Exeter, UK and a Chair in the discipline in 1993. This was the first of its kind in this country and was followed by the introduction of degree courses involving complementary medicine at other universities.

Concerning patients, despite the advances made in orthodox medicine there has been an increasing interest in the complementary systems, particularly by those who have not benefited from previous treatment, by those who have apprehensions concerning the toxicity and safety of modern drugs, and by those who benefit from the holistic approach (rarely achievable in a 5–10 min consultation with a GP). The availability of such treatments under the British NHS, provided referral is made by the patient's general practitioner, has given added status to these treatments and some, such as aromatherapy, are now provided as a hospital service.

In addition to the above there are the traditional systems of medicine widely practised outside Europe. Of these the Asian (Ayurvedic and Unani) and Chinese are two of the most significant, each having a long recorded history. Often disciplines have interacted; thus, traditional Tibetan medicine has been receptive to Ayurvedic, Chinese and Arabian influences and the Japanese is an offshoot of the Chinese (see Chapter 37). In large Asian immigrant populations such as there are in Britain, the Asian and Western types of medicine may have to coexist, sometimes with unforeseeable results.

About 80% of the world's population relies on herbal medicines, and governments of Third World countries, unable to sustain a complete coverage with Western-type drugs, have encouraged the rational development of traditional treatments. At present the World Health Organization is taking an official interest in such developments in order to facilitate its aim of making health care available for all. UNIDO also supports the industrial utilization of medicinal plants which are a source of export earnings for the producers.

Modern research establishments now exist in many countries, e.g. India, Pakistan, Saudi Arabia, China, Japan, South America, etc. and their work is largely devoted to assessing the value of thousands of ethnic remedies along lines acceptable to current medical thinking. Thus the pharmacological effectiveness of many herbal treatments has been vindicated, but unfortunately the side-effects produced are often untenable by modern standards. In some successful instances the drugs have been adopted outside their countries of origin. Another feature is that those plants which have been selected for medicinal use over thousands of years constitute the most obvious choice for examination in the current search for new therapeutically effective drugs.

Except for the well-documented Asian and Chinese drugs it is often a difficult problem to investigate traditional remedies, and researchers in the field need to be skilled in the language, customs, prejudices, etc. of the people and practitioners with whom they are dealing. As religious practices and rituals are often associated with the healing treatment, a multidisciplinary approach is necessary. Abebe (*J. Ethnopharm*., 1992, **36**, 93) pointed out that researchers all too often report on the alleged therapeutic indications of traditional medicines without recording those adverse effects of which the traditional healers are well aware.

Selection, at this stage, of the crucial botanicals for study is of fundamental importance to the ultimate success of the subsequent lengthy scientific investigation.

For a consideration of the interdisciplinary methods used to record and collect ethnopharmacological field data see F. J. Lipp, *J. Ethnopharm*., 1989, **25**, 139.

Notices of the numerous symposia and conferences on medicinal plants world-wide are published in the *Newsletter of the International Council for Medicinal and Aromatic Plants* and some journals.

The *Journal of Ethnopharmacology, Fitoterapia*, and *Pharmaceutical Biology* (formerly *International Journal of Pharmacognosy*) have proved particularly valuable for the publication of interdisciplinary research and reviews devoted to indigenous drugs. Many of the reviews cover relatively small regional areas; the following selection of books involve wider geographical regions:

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35

Herbal medicine in Britain and Europe: regulation and practice

S. Y. Mills

REGULATORY BACKGROUND

The supply of herbs as healthcare products in Europe is more tightly regulated than other commodities. It is also notoriously complex, covering over-the-counter sales through various outlets, as well provision of 'phytomedicines' by health professionals (i.e. doctors and pharmacists in most of Europe and herbal practitioners in the UK and Ireland). The vague and less regulated 'borderline' area within which many natural products have been supplied direct to the consumer is becoming much more constrained and is intended to disappear altogether after 2010. Essentially, in the case of the direct sale of herbs, there are two regulatory options: food supplements or medicinal products.

Herbal products used for therapeutic purposes are classified as medicines by default under European law. If the UK Medicines and Healthcare products Regulatory Agency (MHRA) determines that a herbal product is a medicinal product then it is a criminal offence to supply it without a licence or registration (or transitional protection until 2011 for products on the market before 2004). In addition, the scope for selling herbs as foods is increasingly limited by 'novel foods' legislation and also by the European Food Standards Agency (see below).

There have been exemptions from requirements of formal licensing in European law for herbal medicinal products provided by professionals. However, this legislation did not envisage exemptions for non-registered practitioners. Herbalists exist in appreciable numbers only in the UK, where, by contrast, there is relatively little interest in herbal medicine by orthodox registered health professionals. There have been exemptions provided in UK law for the provision of herbal remedies on a one-to-one basis but this is not secure in a European framework and the legal status of herbal practitioners is thus undefined. However, with government support, herbal practitioners in the UK are moving towards statutory registration by 2010.

Since the early twentieth century, legislation relating to foods and to medicines has diverged, with natural products gradually falling out of the medicine stream from the 1930s. By the time of the thalidomide tragedy in the early 1960s, and the ensuing new raft of drug laws throughout much of the developed world, natural medicines were largely discounted as a significant force in healthcare. In Europe, the pivotal harmonizing measure, to which all member states of the European Union have subsumed their individual legislations, was passed in 1965. EC Directive 65/65/EEC (now supplanted by Directive 2001/83/EEC) defined medicinal products as any substance or combination of substances:

- presented for treating or preventing disease in human beings or animals;
- which may be administered with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions in human beings or animals.

These definitions are sweeping. They clearly include any natural materials used for therapeutic ends. In Europe, if one claims for any product an active effect on the human body, one needs by law to have a medicines licence for that product. This means convincing the medicines regulators that any therapeutic effect is warranted, generally by producing controlled clinical trial evidence. It also means that such products have to meet pharmaceutical standards of quality and safety. This default status as medicines is clearly distinct from that applying in the USA, where natural products are in the first instance considered as foods.

In Germany, France and the United Kingdom especially, a large number of herbal medicinal products have obtained marketing authorizations, according to laws within each member state but within the

terms of this European legislation. Nevertheless, the governments of Germany, France, the Netherlands and the UK provided exemptions in their own national legislatures to protect herbal medicines from some of the requirements imposed upon synthetic drug manufacturers. These exemptions were highlighted in a report to the European Commission in 1999 and have led to moves for greater harmonization of herbal regulations within new applications of the pivotal 65/65/EEC Directive. The first amendment was enacted quickly and allowed products with 'established use' as medicines to establish their efficacy by reference to this use.

More significantly, and only for 'herbal products with traditional use' registration as a medicine (rather than full licensing) is now possible (Directive 2004/24/EC—an amendment to Directive 2001/83/EC). This will excuse the manufacturer from providing evidence of efficacy, although not from assuring standards of pharmaceutical quality and on-going safety monitoring. Registrations will thus require significant investment by manufacturers and importers. At the time of writing there are concerns that this will be too difficult for many. This option is only available for herbal products where there is evidence of at least 15 years of traditional use somewhere in the European Union, plus at least 15 years elsewhere (i.e. a total of 30 years).

It used to be legal, without a licence, to sell in the UK a simple herbal medicinal product—without claims or brand name (under 'Section 12.2' of the 1968 Medicines Act); this no longer applies. The new traditional use Directive was published on 30 April 2004. Any product that was legally on the UK market under '12:2' on that date has 'transitional protection' and is not required to comply with the Directive until 30 April 2011. After that date, it must have either a traditional herbal registration or a marketing authorization (full licence) or it can no longer be placed on the market. This transitional protection does not apply to any products placed on the UK market at any time after 30 April 2004.

Alone among major industrial countries, the UK has maintained a common law basis to its legal system, in which historical practice provides the default precedent in a court of law. In the delivery of medical care this has meant that there have been very many fewer restrictions than in other developed countries. The statutory rights of doctors, pharmacists and other health professionals have not been monopolies: the common law right of every subject to pursue the health care he or she wishes is still formally protected. Thus unlicensed health professionals and health-food shopkeepers are legally able to provide any service not formally proscribed by Acts of Parliament.

The main statutory control on the supply of medicines is the 1968 Medicines Act. All herbal remedies included on a 'General Sale List' could be freely supplied and under the provisions of section 12.2 for:

2) … the sale, supply, manufacture or assembly of any herbal remedy where the process to which the plant or plants are subjected in producing the remedy consists only of drying, crushing or comminuting, and the remedy is, or is to be, sold or supplied
   a) under a designation which only specifies the plant or plants and the process and does not apply any other name to the remedy, and
   b) without any written recommendation (whether by means of a labelled container or package or a leaflet or in any other way) as to use the remedy.

Although 12.2 has fallen, the General Sale List (GSL) still is referred to as a directory of herbal remedies. Over 300 herbal substances are named for internal use (Schedule 3[A]). Some 30 are listed for external use (Schedule 3[B]). Where maximum doses (MD) or maximum daily doses (MDD) are listed for GSL products it is implied that any dose in excess of that figure cannot be marketed over the counter (OTC) and the medicine becomes prescription only. Herbal remedies on the various schedules are listed in Table 35.1.

Under the terms of the second stage of the Medicines Act (1971) 'Licences of Right' were provided to established medicines already on the market, subject to review before 1990. Around 2000 herbal products obtained these medicines licences. However, the review process was very demanding, with manufacturers having in effect to become modern pharmaceutical companies, ensuring conventional standards of quality medicine production. After 1990, around 600 were successfully reviewed, and now have full medicine licences. However, only a proportion of these are still available on the market and their future in relation to the enactment of the Traditional Use Directive remains uncertain.

INDUSTRY STANDARDS

The British Herbal Medicine Association (BHMA) has, since its founding in 1964, engaged the legislature in productive discussions about the controls of herbal medicines. Its most prominent achievement has been the production of the *British Herbal Pharmacopoeia*, first in 1983 and then, through substantial revisions, to the latest, with 169 monographs published in 1996. The *Pharmacopoeia* has been widely used by regulators in the UK and elsewhere around the world as an effective practical quality standard where official monographs do not exist. The herbal monographs covered in the final 1996 edition are listed in Table 35.2.

The BHMA is also the UK member of a European network of national herbal or phytotherapy associations called the European Scientific Cooperative on Phytotherapy (ESCOP). Since its formation in 1989, ESCOP has been involved in producing harmonized therapeutic monographs for 'plant drugs' as formal submissions to the European medicines regulators. A total of 80 such monographs have been published, listed in Table 35.3. More details of this work can be obtained at the ESCOP website (http://www.escop.com).

THE HERBAL PRACTITIONER

There is another group supplying herbal medicinal products who have clearly been affected by the UK exemptions from European law. Under 12.1 of the 1968 Act no licence is required for:

1) … the sale, supply, manufacture or assembly of any herbal remedy in the course of business where
   a) the remedy is manufactured or assembled on premises of which the person carrying on the business is the occupier and which he is able to close so as to exclude the public, and
   b) the person carrying on the business sells or supplies the remedy for administration to a particular person after being requested by or on behalf of that person and in that person's presence to use his own judgement as to the treatment required.

This exemption for one-to-one supply reflected the fact that herbal medicine in the UK has often been provided by practitioners. As a common folk system, it was first recognized by an Act of Parliament in the reign of Henry VIII in 1533, and its practitioners were in this protected from the hostile intentions of the new physicians and surgeons. With the Industrial Revolution, herbal medicine became an urban phenomenon and the National Association (later Institute) of Medical Herbalists was established in 1864. The NIMH is the oldest professional association of medical herbalists in the developed world. Its members have lately been provided by 4-year BSc programmes at several universities. The NIMH has a full professional constitution, codes of ethics and disciplinary

Table 35.1 General sale list.

Abietis Oil
Absinthium
Acacia Powder
Aesculus
Agar
Agrimony
Almond Oil
Aloes – MD: 100 mg
Aloin – MD: 20 mg
American Cranesbill Root
American Liverwort
Ammoniacum
Angelica Oil
Angelica Root
Anise
Anise Oil
Arbutus, Trailing
Asafoetida
Asarabacca
Ash
Australian Sandalwood Oil
Avocado Oil
Balm of Gilead Buds
Balmony
Baptisia
Barberry Bark
Bayberry
Bearberry
Bearsfoot
Beech
Benzoin
Bethroot
Birch, European
Birthwort
Bistort
Blackberry Leaf
Blackberry Root Bark
Black Catechu
Black Haw
Black Root
Blackthorn
Blood Root
Blue Flag
Boldo
Boneset
Broom
Buchu
Buckbean
Buckthorn
Bugle
Bugleweed
Burdock
Burnet Saxifrage
Butterbur
Butternut
Calamint
Calamus
Calumba
Canella
Capsicum
Capsicum Oleoresin – MD 1.2 mg; MDD 1.8 mg; External 2.5% max
Caraway
Cardamom
Cascara
Cascarilla
Cassia Oil
Castor Oil
Catechu
Catmint
Caulophyllum
Celery Oil
Celery Seed
Centaury
Centella
Ceratonia
Cetraria
Chamomile
Chamomile, German
Chestnut
Chickweed
Chiretta
Cimicifuga
Cinchona – MD 50 mg
Cinnamon Bark
Citrus Bioflavonoids
Clivers
Clove
Cochlearia
Cocillana
Coltsfoot
Comfrey
Condurango
Coriander
Cornflower
Cornsilk
Corydalis
Cotton root
Couchgrass
Cowslip
Crampbark
Cubeb
Cudweed
Cynara
Cypripedium
Damiana
Dandelion
Dill
Dogwood
Echinacea
Elder
Elder, Dwarf
Elecampane
Elm
Equisetum
Eriodictyon
Eryngo
Eucalyptus
Euonymus
Eupatorium
Euphorbia
Eyebright
Fennel
Fenugreek
Feverfew
Figs
Figwort
Fir cones
Fluellin
Frangula
Fringetree
Frostweed
Fucus
Fumitory
Galangal
Gamboge
Garlic Oil
Gentian
Germander
Ginger
Ginseng
Golden Rod
Golden Seal
Greater Burnet
Grindelia
Ground Ivy
Guaiacum
Harts Tongue
Hay Flower
Heartsease
Heather Flowers
Hemlock Spruce – External 10% max
Holly
Holy Thistle
Honeysuckle Flowers
Horehound
Hydrangea
Hyssop
Ipecacuanha
Irish Moss
Ispaghula
Jamaica Dogwood
Jambul
Jujube Berries
Juniper
Kava
Kino
Kola
Krameria
Lactuca
Lady's Mantle
Laminaria
Larch Bark
Lavender
Lemon Grass Oil
Lemon Oil
Leptandrin
Lime Flowers
Lime Leaf
Linseed
Liquorice
Lobelia – MD 65 mg
Lovage
Lucerne
Lungwort
Lupulin
Lupulus
Maidenhair
Marigold Flowers
Marshmallow
Masterwort
Maté
Meadow Grass
Meadowsweet
Melissa
Motherwort
Mountain Flax
Mousear
Mugwort
Muira Puama
Mullein
Myrrh
Neroli Oil
Nettle
Nutmeg
Oak
Ononis
Orange Oil
Origanum
Papaya Leaves
Pareira Root
Parsley Piert
Parsley Root
Passiflora
Peach Leaves
Pellitory-of-the-wall
Pennyroyal
Peony
Peppermint
Periwinkle
Pichi
Pilewort
Pimento Oil
Pimpernel
Pinus Sylvestris
Pipsissiwa
Plantain
Pleurisy Root
Poke Root
Pollen
Poplar
Potentilla
Prickly Ash
Prune
Psyllium
Pulsatilla
Quaking Aspen
Quassia
Queen's Delight
Quillaia
Raspberry Leaves
Red Poppy Petals
Red Sanderswood
Rhubarb Rhizome
Rose Fruit
Rosemary
Rue
Rutin
Safflower
Sage Oil
St John's Wort
Salep
Salicaria

(Continued)

Table 35.1 General sale list. (Cont'd)

Sandalwood Oil
Sandarac
Sanguinaria
Sanicle
Saponaria
Sarsaparilla Root
Sassafras
Saw Palmetto
Senega
Senna Fruit
Senna Leaf
Serpentary
Shepherd's Purse
Skullcap
Skunk Cabbage Root
Slippery Elm – Powdered Bark
Soya (Protein)
Spearmint
Speedwell
Spigelia
Squaw Vine
Squill, White
Star Anise
Sterculia – Gum
Stone Root
Storax
Strawberry Leaf
Sumach
Sumbul
Sundew
Sunflower
Sweet Birch Oil
Tag Alder
Tansy
Thyme
Tolu Balsam
Tragacanth
Unicorn Root, False
Unicorn Root, True
Valerian
Verbena
Violet
White Pond Lily
Wild Carrot
Wild Cherry
Wild Oats
Wild Rose
Wild Thyme
Willow, Black
Willow, White
Wintergreen Leaves
Wood Betony
Wood Sage
Yarrow
Yellow Dock

General sale (external use only)

Arnica
Bay Oil
Bergamot Oil
Birch Tar Oil
Cade Oil
Cajaput Oil
Camphor Oil
Cedar Wood Oil
Coconut Oil
Colophony
Copaiba
Gall
Geranium Oil
Hamamelis
Jaborandi
Linseed Oil
Lycopodium
Meleleuca Oil
Mustard Oil
Neatsfoot Oil
Olibanum
Orris
Palm Kernel Oil
Peru Balsam
Pine Oil
Pyrethrum
Rape Oil
Sassafras Oil

Schedule Part I

Areca
Canadian Hemp
Catha edulis
Chenopodium ambroisioides
Cocculus indicus
Crotalaria spp.
Croton Oil and Seed
Curcubita maxima
Digitalis Leaf
Duboisia spp.
Elaterium
Embelia
Ergot, prepared
Erysium
Holarrhena
Ignatius Bean
Kamala
Kousso
Male Fern
Mistletoe Berry
Nux Vomica
Podophyllum spp.
Poison Ivy
Pomegranate Bark
Poppy Capsule
Rauwolfia spp.
Sabadilla
Santonica
Savin
Scopolia
Slippery Elm Bark (whole)
Stavesacre Seeds
Strophanthus spp.
Veratrum, Green
Veratrum, White
Yohimbe

Schedule Part III Remedies for internal use

False Hellebore	*Adonis vernalis* (100 mg tds)
Quebracho	*Aspidosperma quebracho-blanco* (50 mg tds)
Deadly Nightshade	*Atropa belladonna* (herb:50 mg; root: 30 mg tds)
Greater Celandine	*Chelidonium majus* (2 g tds)
Cinchona Bark	*Cinchona* spp. (250 mg tds)
Meadow Saffron	*Colchicum autumnale* (100 mg tds)
Lily-of-the-valley	*Convallaria majalis* (150 mg tds)
Jimson Weed	*Datura stramonium* (50 mg tds)
Ma-huang	*Ephedra sinica* (600 mg tds)
Yellow Jasmine Root	*Gelsemium sempervirens* (25 mg tds)
Henbane	*Hyoscyamus niger* (100 mg tds)
Lobelia	*Lobelia inflata* (200 mg tds)

Remedies for external use

Aconite	*Aconitum* spp.
Hemlock	*Conium maculatum*
Jaborandi	*Pilocarpus microphyllus*
Poison Oak	*Rhus toxicodendron*
Ragwort	*Senecio jacobaea*

Table 35.2 Monographs in the *British Herbal Pharmacopoeia* 1996.

Monograph name	Botanical name	Action
Agnus Castus	*Vitex agnus-castus* L.	Hormonal modulator
Agrimony	*Agrimonia* spp.	Astringent
Aloes, Barbados	*Aloe barbadensis* Miller.	Stimulant laxative
Aloes, Cape	*Aloe ferox* Miller.	Stimulant laxative
Ammoniacum	*Dorema ammoniacum*	Expectorant
Angelica Root	*Angelica archangelica* L.	Aromatic bitter, spasmolytic
Aniseed	*Pimpinella anisum* L.	Expectorant; carminative
Arnica Flower	*Arnica montana* L.	Topical healing
Artichoke	*Cynara scolymus* L.	Hepatic
Asafoetida	*Ferula assa-foetida* and other *F.* spp.	Spasmolytic
Ascophyllum	*Ascophyllum nodosum* Le Jol.	Thyroactive
Balm Leaf	*Melissa officinalis* L.	Sedative; topical antiviral
Balm of Gilead Bud	*Populus nigra* and other *P.* spp.	Expectorant
Barberry Bark	*Berberis vulgaris* L.	Cholagogue
Bayberry Bark	*Myrica cerifera* L.	Astringent
Bearberry Leaf	*Arctostaphylos uva-ursi* Spreng	Urinary antiseptic
Belladonna Herb	*Atropa belladonna* L.	Antispasmodic
Birch Leaf	*Betula pendula* and other *B.* spp.	Diuretic; antirheumatic
Black Cohosh	*Cimicifuga racemosa* Nutt	Anti-inflammatory
Black Haw Bark	*Viburnum prunifolium* L.	Spasmolytic
Black Horehound	*Ballota nigra* L.	Antiemetic
Bladderwrack	*Fucus vesiculosis* L.	Thyroactive
Blue Flag	*Iris versicolor, I. caroliniana* Watson	Laxative
Bogbean	*Menyanthes trifoliata* L.	Bitter
Boldo	*Peumus boldus* Molina	Cholagogue
Broom Top	*Cytisus scoparius* Link.	Antiarrhythmic, diuretic
Buchu	*Barosma betulina* Bartl. et Wendl.	Urinary antiseptic
Burdock Leaf	*Arctium lappa* L. *A. minus* Bernh.	Dermatological agent
Burdock Root	*Arctium lappa* L. *A. minus* Bernh.	Dermatological agent
Calamus	*Acorus calamus* vars	Carminative
Calumba Root	*Jateorhiza palmata* Miers.	Appetite stimulant
Caraway	*Carum carvi* L.	Carminative
Cardamom Fruit	*Elettaria cardamomum* Maton.	Carminative
Cascara	*Rhamnus purshianus* DC.	Stimulant laxative
Cassia Bark	*Cinnamomum cassia* Blume.	Carminative
Catechu	*Uncaria gambier* (Hunter) Roxb.	Astringent
Cayenne Pepper	*Capsicum frutescens* L.	Rubefacient, vasostimulant
Celery Seed	*Apium graveolens* L.	Diuretic
Centaury	*Centaurium erythraea* Rafn.	Bitter
Cinchona Bark	*Cinchona pubescens* Vahl.	Bitter
Cinnamon	*Cinnamomum zeylanicum* Nees.	Carminative
Clivers	*Galium aparine* L.	Diuretic
Clove	*Syzygium aromaticum* L.	Carminative, topical analgesic
Cocillana	*Guarea rusbyi*	Expectorant
Cola	*Cola nitida, C. acuminata*	Central nervous stimulant
Comfrey Root	*Symphytum officinale* L.	Vulnerary
Coriander	*Coriandrum sativum* L.	Carminative, stimulant
Corn Silk	*Zea mays* L.	Diuretic; urinary demulcent
Couch Grass Rhizome	*Agropyron repens* P. Beauv.	Diuretic
Cranesbill Root	*Geranium maculatum* L.	Astringent
Damiana	*Turnera diffusa* and possibly other spp.	Thymoleptic
Dandelion Leaf	*Taraxacum officinale* Webber.	Diuretic; choleretic
Dandelion Root	*Taraxacum officinale* Webber.	Hepatic
Devil's Claw	*Harpagophytum procumbens* DC.	Antirheumatic
Echinacea Root	*Echinacea angustifolia* DC.	Immunostimulant
Elder Flower	*Sambucus nigra* L.	Diaphoretic
Elecampane	*Inula helenium* L.	Expectorant
Eleutherococcus	*Eleutherococcus senticosus* Maxim.	Adaptogen; tonic
Equisetum	*Equisetum arvense* L.	Diuretic; astringent
Eucalyptus Leaf	*Eucalyptus globulus* Labill.	Antiseptic
Euonymus Bark	*Euonymus atropurpureus* Jacq.	Laxative

(Continued)

Table 35.2 Monographs in the *British Herbal Pharmacopoeia* 1996. (Cont'd)

Monograph name	Botanical	Action
Fennel, Bitter	*Foeniculum vulgare* Miller.	Carminative
Fennel, Sweet	*Foeniculum vulgare* Miller.	Carminative
Fenugreek Seed	*Trigonella foenum-graecum* L.	Demulcent, hypoglycaemic
Feverfew	*Tanacetum parthenium* Schultz Bip.	Migraine prophylactic
Frangula Bark	*Rhamnus frangula* L.	Stimulant laxative
Fumitory	*Fumaria officinalis* L.	Choleretic
Galangal	*Alpinia officinarum* Hance.	Carminative
Garlic	*Allium sativum* L.	Hypolipidaemic; antimicrobial
Gentian	*Gentiana lutea* L.	Bitter
Ginger	*Zingiber officinale* Roscoe.	Carminative; antiemetic
Ginkgo Leaf	*Ginkgo biloba* L.	Vasoactive; platelet aggregation inhibitor
Ginseng	*Panax ginseng* C.A. Meyer.	Adaptogen; tonic
Goldenrod	*Solidago virgaurea* L.	Diuretic; anticatarrhal, diaphoretic
Goldenseal Root	*Hydrastis canadensis* L.	Anti-inflammatory
Grindelia	*Grindelia robusta* Nutt.	Expectorant
Ground Ivy	*Glechoma hederacea* L.	Expectorant
Guaiacum Resin	*Guaiacum officinale* L. *G. Sanctum* L.	Anti-inflammatory
Hamamelis Bark	*Hamamelis virginiana* L.	Astringent
Hamamelis Leaf	*Hamamelis virginiana* L.	Astringent
Hawthorn Berry	*Crataegus monogyna* Jacq.	Cardiotonic
Hawthorn Flowering Top	*Crataegus monogyna* Jacq.	Cardiotonic
Heartsease	*Viola tricolor* L.	Expectorant; dermatological agent
Helonias	*Chamaelirium luteum* A. Gray.	Uterine tonic
Holy Thistle	*Cnicus benedictus* L.	Bitter
Hops	*Humulus lupulus* L.	Sedative; bitter
Horse-chestnut Seed	*Aesculus hippocastanum* L.	Venoactive
Hydrangea	*Hydrangea arborescens* L.	Diuretic
Hyoscyamus Leaf	*Hyoscyamus niger* L.	Antispasmodic
Hyssop	*Hyssopus officinalis* L.	Expectorant
Iceland Moss	*Cetraria islandica* L.	Demulcent
Ipecacuanha	*Cephaelis ipecacuanha, C. acuminata*	Expectorant; emetic
Irish Moss	*Chondrus crispus* Stackh.	Demulcent
Ispaghula Husk	*Plantago ovata* Forssk.	Bulk-forming laxative
Ispaghula Seed	*Plantago ovata* Forssk.	Bulk-forming laxative
Jamaica Dogwood	*Piscidia piscipula* Sarg.	Analgesic
Java Tea	*Orthosiphon aristatus*, (Blume) Miq.	Diuretic
Juniper Berry	*Juniperus communis* L.	Diuretic
Kava-Kava	*Piper methysticum* G. Forst.	Anxiolytic
Lady's Mantle	*Alchemilla xanthochlora*, Rothm. *A. vulgaris* L. S. l.	Astringent
Lily of the Valley Leaf	*Convallaria majalis* L.	Cardioactive
Lime Flower	*Tilia cordata* Mill. and other spp.	Antispasmodic; diaphoretic
Linseed	*Linum usitatissimum* L.	Bulk-forming laxative; demulcent
Liquorice Root	*Glycyrrhiza glabra* L.	Respiratory stimulant
Lobelia	*Lobelia inflata* L.	Respiratory stimulant
Lovage Root	*Levisticum officinale* Koch.	Carminative; mild diuretic
Lucerne	*Medicago sativa* L.	Tonic
Marigold	*Calendula officinalis* L.	Anti-inflammatory, vulnerary
Marshmallow Leaf	*Althaea officinalis* L.	Demulcent
Marshmallow Root	*Althaea officinalis* L.	Demulcent
Maté	*Ilex paraguariensis* A. St.-Hil.	Stimulant
Matricaria Flower	*Matricaria recutita* L.	Anti-inflammatory; antispasmodic
Meadowsweet	*Filipendula ulmaria* Maxim.	Anti-inflammatory
Melilot	*Melilotis officinalis* Pall.	Venotonic, vulnerary
Milk Thistle Fruit	*Silybum marianum* (L.) Gaertn.	Hepatoprotective
Mistletoe Herb	*Viscum album* L.	Hypotensive
Motherwort	*Leonurus cardiaca* L.	Antispasmodic
Mugwort	*Artemisia vulgaris* L.	Emmenogogue
Mullein Leaf	*Verbascum densiflorum* Bertol.	Expectorant
Myrrh	*Commiphora molmol* Engler and other spp. of *C.*	Antiseptic
Nettle Herb	*Urtica dioica* L.	Diuretic
Nettle Root	*Urtica dioica* L.	Prostatic

(Continued)

Table 35.2 Monographs in the *British Herbal Pharmacopoeia* 1996. (Cont'd)

Monograph	Botanical name	Action
Oak Bark	*Quercus robur* L. and other *Q.* spp.	Astringent
Parsley Herb	*Petroselinum crispum*	Diuretic
Parsley Root	*Petroselinum crispum*	Carminative, diuretic
Passiflora	*Passiflora incarnata* L.	Sedative
Peppermint Leaf	*Mentha piperata* L.	Carminative
Pilewort Herb	*Ficaria ranunculoides* Moench.	Astringent
Poke Root	*Phytolacca americana* L.	Anti-inflamatory
Prickly Ash Bark	*Zanthoxylum clava-herculis* L.	Circulatory stimulant
Psyllium Seed	*Plantago afra* L. *P. indica* L.	Bulk-forming laxative
Pulsatilla	*Pulsatilla vulgaris* Miller, *P. pratensis* (L.) Miller	Sedative
Pumpkin Seed	*Cucurbita pepo* L.	Prostatic
Quassia	*Picrasma excelsa*	Appetite stimulant
Queen's Delight	*Stillingia sylvatica* L.	Expectorant
Raspberry Leaf	*Rubus idaeus* L.	Partus praeparator
Red Clover Flower	*Trifolium pratense* L.	Anti-inflammatory
Rhatany Root	*Krameria triandra* Ruiz and Pavon.	Astringent
Rhubarb	*Rheum palmatum* L., *R. officinale* Baillon, hybrids	Laxative
Roman Chamomile Flower	*Chamaemelum nobile* All.	Antispasmodic
Rosemary Leaf	*Rosmarinus officinalis* L.	Carminative, spasmolytic
Sage Leaf	*Salvia officinalis* L.	Antiseptic, astringent
Sarsaparilla	*Smilax* spp.	Anti-inflammatory
Saw Palmetto Fruit	*Serenoa repens*	Prostatic
Senega Root	*Polygala senega* L. and related spp.	Expectorant
Senna Fruit, Alexandrian	*Cassia senna* L.	Stimulant laxative
Senna Fruit, Tinnevelly	*Cassia angustifolia* Vahl.	Stimulant laxative
Senna Leaf	*Cassia senna, C. angustifolia*	Stimulant laxative
Shepherd's Purse	*Capsella bursa-pastoris* Medik.	Antihaemorrhagic
Skullcap	*Scutellaria lateriflora* L.	Mild sedative
Slippery Elm Bark	*Ulmnus rubra* Muhl.	Demulcent
Squill	*Drimia maritima* Stearn.	Expectorant
Squill, Indian	*Drimia indica* J.P. Jessop.	Expectorant
St John's Wort	*Hypericum perforatum* L.	Antidepressant
Stramonium Leaf	*Datura stramonium* L.	Antispasmodic
Thyme	*Thymus vulgaris, T. zygis*	Expectorant
Valerian Root	*Valeriana officinalis* L.	Sedative
Vervain	*Verbena officinalis* L.	Tonic
Violet Leaf	*Viola odorata* L.	Expectorant
White Deadnettle	*Lamium album* L.	Astringent
White Horehound	*Marrubium vulgare* L.	Expectorant
Wild Carrot	*Daucus carota* L.	Diuretic
Wild Cherry Bark	*Prunus serotina* Ehrh.	Antitussive
Wild Lettuce	*Lactuca virosa* L.	Sedative
Wild Thyme	*Thymus serpyllum* L.	Expectorant
Wild Yam	*Dioscorea villosa* L.	Spasmolytic, anti-inflammatory
Willow Bark	*Salix alba* L. and other spp.	Anti-inflammatory
Wormwood	*Artemesia absinthium* L.	Bitter
Yarrow	*Achillea millefolium* L.	Diaphoretic

procedures and mandatory professional indemnity cover for its members. Professional members carry the letters MNIMH or FNIMH after their name. A more recent professional association dedicated to a raised professional profile of herbal medicine in the healthcare community in the UK and Europe is the College of Practitioners of Phytotherapy (CPP). Its members carry the letters MCPP or FCPP and often overlap with membership of the NIMH.

There are a number of other practitioner groups in the Western herbal tradition: The Association of Master Herbalists, the International Register of Consultant Herbalists and the Unified Register of Herbal Practitioners. There is also a major practitioner group practising the herbal medicine of China (the Register of Chinese Herbal Medicine) of Tibet (the British Association of Traditional Tibetan Medicine) and three groups practising Ayurvedic medicine from India (the Ayurvedic Medical Association, the Ayurvedic Practitioners Association and the Maharishi Ayurveda Practitioners Assocation).

As the limits of 12.1 exemptions within Europe became more obvious, and herbal practitioner associations faced an uncertain future, the European Herbal and Practitioners Association (now the European Herbal and Traditional Medicine Practitioners Association; EHTPA: http://www.ehpa.eu) was founded in 1993 to represent their interests. The EHTPA has published an agreed core curriculum and developed an accreditation board for educational standards; it has amended its constitution to reflect the standards pertaining for statutory organizations, and constituent organizations of the EHTPA have moved to harmonize with it.

Table 35.3 ESCOP monographs in the medicinal uses of plant drugs.

Monograph name	Common name	Botanical name	Therapeutic indications
Absinthii herba	Wormwood	*Artemesia absinthium* L.	Anorexia, dyspepsia
Agni casti fructus	Agnus castus	*Vitex agnus-castus* L.	Premenstrual syndrome
Allii sativi bulbus	Garlic bulb	*Allium sativum* L.	Prophylaxis of atherosclerosis
Aloe capensis	Cape aloes	*Aloe ferox* Miller.	Short-term use in occasional constipation
Althaeae radix	Marshmallow root	*Althaea officinalis* L.	Dry cough
Anisi fructus	Aniseed	*Pimpinella anisum* L.	Dyspeptic complaints
Arnicae flos	Arnica flower	*Arnica montana*, other *A.* spp.	Treatment of bruises, sprains and inflammation
Betulae folium	Birch leaf	*Betula pendula*, other *B.* spp.	Irrigation of the urinary tract
Boldo folium	Boldo	*Peumus boldus* Mol.	Minor hepatobiliary dysfunction
Calendulae flos	Calendula flower	*Calendula officinalis* L.	Inflammations of the skin and mucosa
Carvi fructus	Caraway	*Carum carvi* L.	Internal use: spasmodic gastrointestinal complaints External use: flatulent colic of infants
Centaurii herba	Centaury	*Centaurium erythraea* Rafn.	Dyspeptic complaints
Chelidonii herba	Greater celandine	*Chelidonium majus* L.	Mild to moderate spasms of upper gastrointestinal tract; minor gallbladder disorders
Cimicifugae rhizoma	Black cohosh	*Cimicifuga racemosa* (L.) Nutt	Climacteric symptoms
Cinnamomi cortex	Cinnamon	*Cinnamomum zeylanicum* Nees	Dyspeptic complaints
Crataegi folium cum flore	Hawthorn leaf and flower	*Crataegus monogyna* Jacq. Lindm.	Declining cardiac performance
Curcumae longae rhizoma	Turmeric	*Curcuma longa* L.	Mild digestive disturbances and minor biliary dysfunction
Cynarae folium	Artichoke leaf	*Cynara scolymus* L.	Digestive complaints and hepatobiliary disturbances
Echinaceae pallidae radix	Pale coneflower root	*Echinacea pallida* Nutt.	Adjuvant therapy and prophylaxis of recurrent infections of the upper respiratory tract
Echinaceae purpureae herba	Purple coneflower herb	*Echinacea purpurea* Moench.	Adjuvant therapy and prophylaxis of recurrent infections of the upper respiratory tract and also of the urogenital tract
Echinaceae purpureae radix	Purple coneflower root	*Echinacea purpurea* Moench.	Adjuvant therapy and prophylaxis of recurrent infections of the upper respiratory tract
Eleutherococci radix	Eleutherococcus	*Eleutherococcus senticosus* (Rupr. et Maxim) Maxim	Decreased mental and physical capacities
Eucalypti aetheroleum	Eucalyptus oil	*Eucalyptus globulus* and other *E.* spp.	Symptomatic relief of catarrh of the upper respiratory tract
Filipendulae ulmariae herba	Meadowsweet	*Filipendula ulmaria* (L) Maxim	As supportive therapy for the common cold
Foeniculi fructus	Fennel	*Foeniculum vulgare* Miller.	Dyspeptic complaints
Frangulae cortex	Frangula bark	*Rhamnus frangula* L.	Short-term treatment of occasional constipation
Gentianae radix	Gentian root	*Gentiana lutea* L.	Anorexia
Ginkgo folium	Ginkgo leaf	*Ginkgo biloba* L.	Symptomatic treatment of mild to moderate dementia syndromes
Ginseng radix	Ginseng	*Panax ginseng* C.A. Meyer	Decreased mental and physical capacities
Hamamelidis aqua	Hamamelis water	*Hamamelis virginiana* L.	Minor inflammatory conditions of skin and mucosa (topical)
Hamamelidis cortex	Hamamelis bark	*Hamamelis virginiana* L.	Inflammation of the mucous membranes of the oral cavity; short-term symptomatic treatment of diarrhoea
Hamamelidis folium	Hamamelis leaf	*Hamamelis virginiana* L.	Varicose veins and haemorrhoids
Harpagophyti radix	Devil's claw	*Harpagophytum procumbens* DC.	Painful arthrosis
Hederae helicis folium	Ivy leaf	*Hedera helix* L.	Cough, especially associated with hypersecretion of viscid mucus
Hippocastani semen	Horse-chestnut seed	*Aesculus hippocastanum* L.	Chronic venous insufficiency
Hyperici herba	St John's wort	*Hypericum perforatum* L.	Mild to moderate depressive states

(Continued)

Table 35.3 ESCOP monographs in the medicinal uses of plant drugs. (Cont'd)

Monograph name	Common name	Botanical name	Therapeutic indications
Juniperi fructus	Juniper berries	*Juniperus communis* L.	Renal elimination
Lichen islandicus	Iceland moss	*Cetraria islandica* Ach.	Dry cough
Liquiritiae radix	Liquorice root	*Glycyrrhiza glabra* L.	Adjuvant therapy of gastric and duodenal ulcers and gastritis; coughs and bronchial catarrh
Lini semen	Linseed	*Linum usitatissimum*	Constipation
Lupuli flos	Hop strobiles	*Humulus lupulus* L.	Tenseness, restlessness and difficulty in falling asleep
Matricariae flos	Matricaria flower	*Matricaria recutita* L.	Internal use: symptomatic treatment of gastrointestinal complaints External use: minor inflammation and irritations of skin and mucosa
Meliloti herba	Melilotus	*Melilotus officinalis* Desr.	Symptomatic treatment of problems related to varicose veins
Melissae folium	Melissa leaf	*Melissa officinalis* L.	Internal: tenseness, restlessness and irritability External: herpes labialis
Menthae piperitae aetheroleum	Peppermint oil	*Mentha* × *piperata* L.	Internal use: symptomatic treatment of digestive disorders External use: relief of coughs and colds
Menthae piperitae folium	Peppermint leaf	*Mentha* × *piperata* L.	Symptomatic treatment of digestive disorders
Myrrha	Myrrh	*Commiphora molmol* and other *C.* spp.	Topical treatment of gingivitis, stomatitis minor skin inflammations, wounds and abrasions
Myrtilli fructus	Bilberry fruit	*Vaccinium myrtillus* L.	Symptomatic treatment of problems related to varicose veins; topical mild inflammations of mucous membranes of mouth and throat
Ononidis radix	Restharrow root	*Ononis spinosa* L.	Irrigation of the urinary tract
Orthosiphonis folium	Java tea	*Orthosiphon aristatus* and other *O.* spp	Irrigation of the urinary tract
Passiflorae herba	Passiflora	*Passiflora incarnata* L.	Tenseness, restlessness and irritability
Piperis methystici rhizoma	Kava-kava	*Piper methysticum* G. Forst	Anxiety, tension and restlessness
Plantaginis lanceolatae folium/herba	Ribwort plantain Leaf/herb	*Plantago lanceolata* L.	Catarrh of the respiratory tract; temporary mild inflammations of the oral and pharyngeal mucosa
Plantaginis ovatae semen	Ispaghula	*Plantago ovata* Forskal.	Habitual constipation
Plantaginis ovatae testa	Ispaghula husk	*Plantago ovata* Forskal.	Relief of constipation
Polygalae radix	Senega root	*Polygala senega* L.	Productive cough
Primulae radix	Primula root	*Primula veris* L.	Productive cough
Psyllii semen	Psyllium seed	*Plantago afra* spp.	Constipation
Rhamni purshiani cortex	Cascara	*Rhamnus purshianus* D.C.	Occasional constipation
Rhei radix	Rhubarb root	*Rheum palmatum* and other *R.* spp.	Short-term use of occasional constipation
Ribis nigri folium	Blackcurrant leaf	*Ribes nigrum* L.	Adjuvant in the treatment of rheumatic conditions
Rosmarini folium cum flore	Rosemary	*Rosmarinus officinalis* L.	Internal use: hepatic and biliary function External use: adjuvant in rheumatic conditions and peripheral circulatory disorders
Rusci rhizoma	Butcher's broom	*Ruscus aculeatus* L.	Supportive therapy for symptoms of chronic venous insufficiency and haemorrhoids
Salicis cortex	Willow bark	*Salix purpurea* and other *S.* spp.	Feverish conditions
Salviae folium	Sage leaf	*Salvia officinalis* L.	Inflammations and infections of the mouth and throat
Sennae folium	Senna leaf	*Cassia senna* and other *C.* spp.	Short-term use for occasional constipation
Sennae fructus acutifoliae	Alexandrian senna pods	*Cassia senna* L.	Short-term use for occasional constipation

(Continued)

Table 35.3 ESCOP monographs in the medicinal uses of plant drugs. (Cont'd)

Monograph name	Common name	Botanical name	Therapeutic indications
Sennae fructus angustifoliae	Tinnevelly senna pods	*Cassia angustifolia* Vahl.	Short-term use for occasional constipation
Serenoae repentis fructus (Sabal fructus)	Saw palmetto fruit	*Serenoa repens* (Bartram) Small	Symptomatic treatment of micturition disorders in mild to moderate benign prostatic hyperplasia
Solidaginis virgaureae herba	Goldenrod	*Solidago virgaurea* L.	Irrigation of the urinary tract
Tanaceti parthenii herba/folium	Feverfew	*Tanacetum parthenium* Sch. Bip.	Prophylaxis of migraine
Taraxaci folium	Dandelion leaf	*Taraxacum officinale* Weber sensu latiore	Adjunct to treatments where enhanced urinary output is desirable
Taraxaci radix	Dandelion root	*Taraxacum officinale* Weber sensu latiore	Restoration of hepatic and biliary function, dyspepsia, loss of appetite
Thymi herba	Thyme	*Thymus vulgaris* and other *T.* spp.	Catarrh of the upper respiratory tract
Trigonellae foenugraeci semen	Fenugreek	*Trigonella foenum-graecum* L.	Adjuvant therapy in diabetes mellitus and adjuvant to diet in mild to moderate hypercholesterolaemia
Urticae folium/herba	Nettle leaf and herb	*Urtica dioica* and other *U.* spp.	Adjuvant treatment of rheumatic conditions
Urticae radix	Nettle root	*Urtica dioica* and other *U.* spp.	Symptomatic treatment of micturition disorders
Uvae ursi folium	Bearberry leaf	*Arctostaphylos uva- ursi* Spreng.	Uncomplicated infections of the lower urinary tract
Valerianae radix	Valerian root	*Valeriana officinalis* L.	Tenseness, restlessness and irritability
Zingiberis rhizoma	Ginger	*Zingiber officinale* L.	Prophylaxis of the nausea and vomiting of motion sickness

In 2000, the House of Lords Select Committee on Science and Technology published its report on Complementary and Alternative medicine and called for the statutory regulation of herbal practice and acupuncture. In its response, the government agreed that this should happen. There is the precedent for such a move in the statutory registration of osteopaths and chiropracters in 1994 and 1996, respectively, although the new regulated profession is most likely to come within the existing Health Professions Council rather than under its own Act of Parliament. Such registration gives the profession the ability to protect its title and thus more effectively control the standard of practice in that discipline (entry into the profession is formally controlled, and a practitioner can be struck off the statutory register and cannot then practice under the title). In the case of the herbal practitioner, there is the additional hope that statutory registration will take over in providing regulatory cover from the increasingly untenable 'section 12.1'. Currently, however, 12.1 does not distinguish between herbal practitioners and anyone else supplying treatment on a one-to-one basis (homoeopaths, naturopaths, aromatherapists, and shop assistants have all become used to supplying herbal products under this cover). It remains unclear how the new statutory regulation will cover these activities.

There are a few doctors practising herbal medicine, usually as members of the NIMH or CPP, but not nearly as many as there are medical phytotherapists in other EU countries.

HERBAL PRACTICE IN THE UK

Unlike the situation pertaining to the use of Chinese herbs (see Chapter 37) and the Ayurvedic traditions of the Indian subcontinent (see Chapter 36), there is no obvious organized therapeutic framework to distinguish Western herbal prescription from that of modern conventional medicine. There are certainly older traditions of practice that certain modern practitioners defer to. In Europe, the historical tradition since Roman times has followed Galenic practices, which are based on making assessments of disturbances of body fluids (or humours), including in particular their temperaments (degrees of heat, cold, dryness and damp) and providing counteracting influences in the herbal materia medica (strictly speaking, this is literally a form of 'allopathic' medicine). Galenic medicine is all but extinct in Europe except as the foundation for classical Islamic medicine. The latter underpins the practice of much ethnic medicine, especially among the Pakinstani and Bangladeshi communities in the UK, but these traditions have not engaged with the legislative initiatives outlined above. Islamic medicine probably informed the practice of Tibetan medicine historically, but this has developed its own blend of Chinese and Indian influences in addition.

Galenic ideas influenced the nineteenth century articulation of European herbalism in North America by Samuel Thomson and his successors, who, ironically, repatriated their ideas, and materia medica, to Britain soon after. The NIMH adopted Thomsonian medicine and its more articulated development, physiomedicalism, soon after its foundation. Right up to the 1980s the NIMH characterized itself as a 'body of physiomedical practitioners' and provided some training in this system that combined some Galenic principles with early insights into the role of the autonomic nervous system. However, these ideas had never been fully developed after the early decades of the twentieth century and they withered as an active tradition.

The prevailing current tradition is to apply herbal medicines empirically to a physiological assessment of the body's needs. The language is most often that of modern Western medicine but the emphasis is different, looking at the underlying disturbances in function, rather than solely at the pathology or symptoms. Herbal remedies are understood by the practitioner as helping the body to do particular things rather than, as in the popular books or media,

reducing symptoms. Recent attempts are beginning to better understand this distinction and how it might adapt herbal pharmacology and therapeutics, how medicines of the herbal variety might be suited to supporting self-recuperation that underpins all healing (and as seen in the formidable phenomenon known as the 'placebo effect'). Such modern ruminations will take some years to come to articulation. In the meantime, herbal practice in the UK will be largely pragmatic, imbued by whatever other traditions and practices the individual practitioner finds most helpful.

For the patient, the herbal consultation is usually the start of a remedial path, the timing of which will depend almost entirely on the length of time the illness has been present (the more established the condition, the longer it will take to repair) and could for some conditions be very brief. Typically, a herbal practitioner will take an hour or more at a first visit, with shorter visits thereafter, and much more emphasis than other health professionals on the patient taking a medicine at home. Medicines will often be tinctures or fluid extracts blended into individual mixtures at the end of each consultation in the practitioner's dispensary. Such liquids will most often be provided in bulk by specialist suppliers. It is also likely that solid forms, such as fixed tablets and capsules, will be prescribed as adjuncts; topical creams, ointments and other applications are applied as necessary. Costs often compare favourably with conventional prescription charges, reflecting even today the origins of much herbal medicine among the working class from the time of the Industrial Revolution.

Other current herbal traditions have adapted Chinese and Ayurvedic principles; a few practitioners have applied techniques such as iris diagnosis and other new usually uncharted techniques.

In Europe, there is almost nothing that distinguishes herbal from orthodox medicine. Herbs are simply seen as gentler versions of synthetic medicines, applied by physicians often at the same time and dispensed by pharmacists from the same counters.