21

Phenols and phenolic glycosides

SIMPLE PHENOLIC COMPOUNDS 219
TANNINS 225
COUMARINS AND GLYCOSIDES 233
ANTHRAQUINONES AND GLYCOSIDES 235
NAPHTHOQUINONES AND GLYCOSIDES 250
CHROMONES AND XANTHONES 251
FLAVONE AND RELATED FLAVONOID GLYCOSIDES 252
ANTHOCYANIDINS AND GLYCOSIDES 259
BILBERRY FRUIT 260
STILBENES 260
LIGNANS AND LIGNIN 260

Phenols probably constitute the largest group of plant secondary metabolites. Widespread in Nature, and to be found in most classes of natural compounds having aromatic moieties, they range from simple structures with one aromatic ring to highly complex polymeric substances such as tannins and lignins. Phenols are important constituents of some medicinal plants and in the food industry they are utilized as colouring agents, flavourings, aromatizers and antioxidants. This chapter mainly deals with those phenolic classes of pharmaceutical interest, namely: (1) simple phenolic compounds, (2) tannins, (3) coumarins and their glycosides, (4) anthraquinones and their glycosides, (5) naphthoquinones, (6) flavone and related flavonoid glycosides, (7) anthocyanidins and anthocyanins, (8) lignans and lignin. The biosynthetic origin of some of these compounds involving the shikimic acid pathway is shown in Fig. 21.2. Phenols may also have aromatic rings derived by acetate condensation (Fig. 18.9.).

SIMPLE PHENOLIC COMPOUNDS

Catechol (*o*-dihydroxybenzene) occurs free in kola seeds and in the leaves of *Gaultheria* spp. and its derivatives are the urushiol phenols of the poison oak and poison ivy (q.v.). Derivatives of resorcinol (*m*-dihydroxybenzene) constitute the narcotic principles of cannabis and the glucoside arbutin involves quinol (hydroquinone, *p*-dihydroxybenzene). The taenicidal constituents of male fern, the bitter principles of hops and the lipophilic components of hypericum (q.v.) are phloroglucinol derivatives.

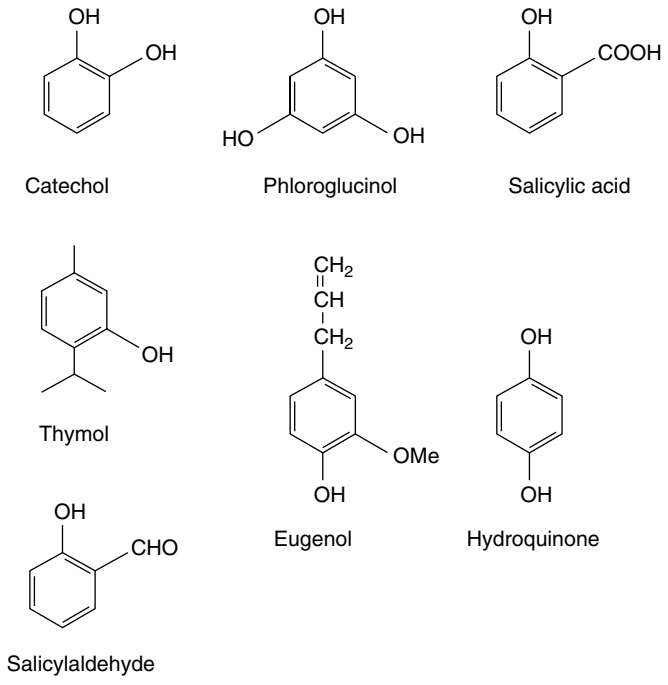

Fig. 21.1
Simple phenolic compounds.

The phenolic compounds in this group often also possess alcoholic, aldehydic and carboxylic acid groups; they include eugenol (a phenolic phenylpropane), vanillin (a phenolic aldehyde) and various phenolic acids, such as salicylic, ferulic and caffeic acids. Glycoside formation is common, and the widely distributed glycoside coniferin and other derivatives of phenolic cinnamic alcohols are precursors of lignin. Some of the best-known simple phenolic glycosides are listed in Table 21.1.

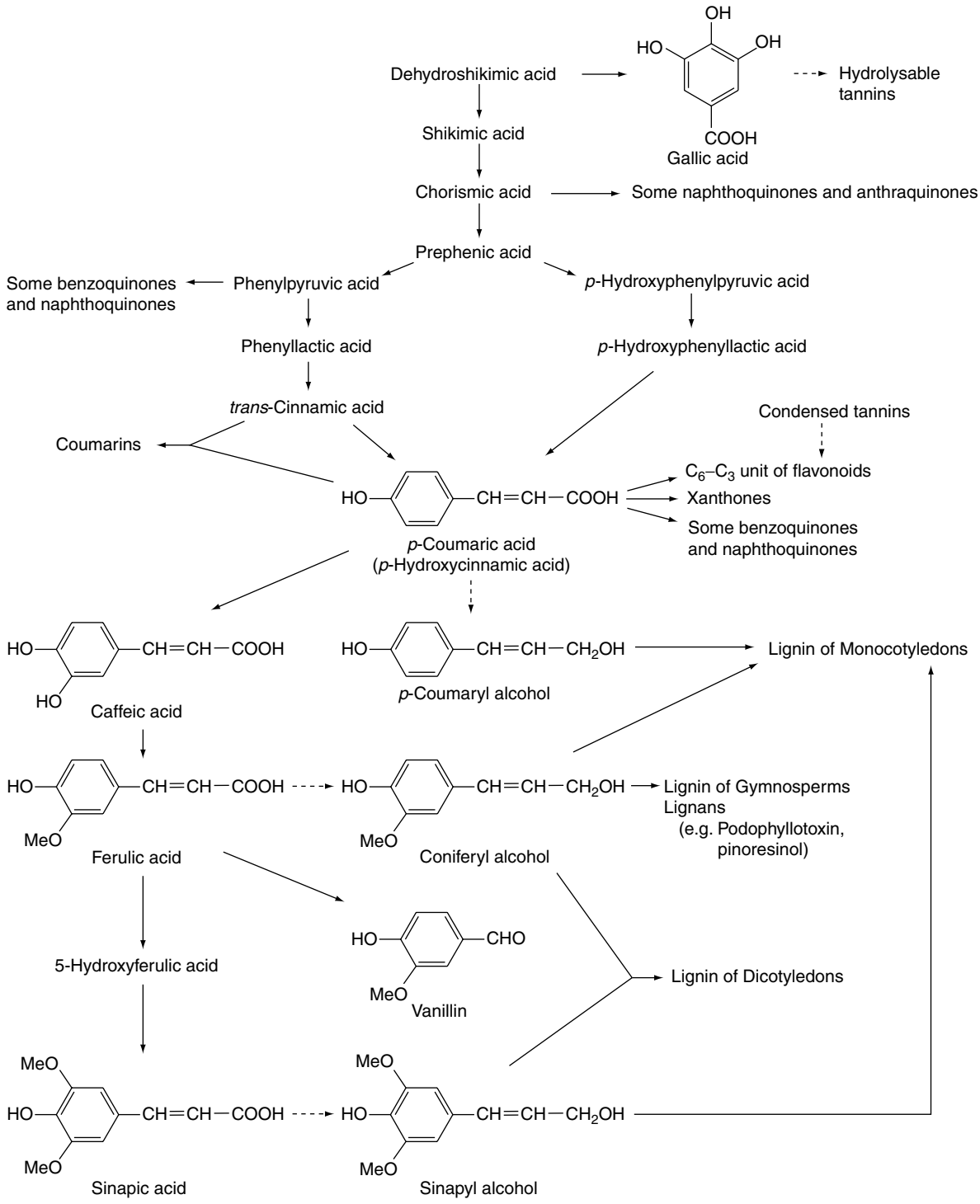

Fig. 21.2
Phenolic compounds originating from shikimic acid (see Fig. 18.8 for details of shikimic acid pathway).

MEADOWSWEET

Meadowsweet *BP*/*EP*, Filipendula *BHP* 1983 consists of the dried flowering tops of *Filipendula ulmaria* (L.) Maxim. [*Spirea ulmaria* L.], family Rosaceae.

This well-known perennial plant is found in wet meadows, marshes, by rivers, etc. throughout most of Europe, temperate Asia and as an escape in the eastern US and Canada. It is up to 120 cm in height with numerous radical longish petioled leaves. Each leaf is composed of up to five pairs of ovate serrated leaflets. Numerous aromatic cream-coloured flowers form irregular cymose panicles, which are particularly dense on the terminal branches of the leafy stems.

The commercial chopped drug occurs as clumps of broken leaflets dark green on the upper surface, paler and tormentose on the lower. Also brown fragmented flowers, unopened flower buds and small, more or less spirally twisted fruits containing brown seeds. Angular,

Table 21.1 Examples of phenolic glycosides.

Name	Examples of sources	Products of hydrolysis
Salicin	*Salix* and *Populus* spp. *Viburnum prunifolium*	Salicyl alcohol, glucose
Populin (benzoyl-salicin)	*Populus tremula*	Salicyl alcohol, benzoic acid, glucose
Arbutin	Ericaceae and Rosaceae	Hydroquinone, glucose
Phloridzin	Rosaceae, including spp. of *Malus*	Phloretin, glucose
Trilobatin	*Malus*, *Spiraea*	Phloretin, glucose
Coniferin	Coniferae	Coniferyl alcohol, glucose
Gaultherin	*Gaultheria*, *Betula* and *Monotropa*	Methyl salicylate, primeverose
Syringin	Particularly in Oleaceae	Methoxyconiferyl alcohol, glucose
Glucovanillin	*Vanilla* spp. and some Gramineae	Vanillin, glucose
Gein	*Geum* spp.	Eugenol, vicianose (glucose + arabinose)
Glucogallin	*Rheum* spp.	Gallic acid, glucose
Hamamelitannin	*Hamamelis virginiana*	Gallic acid (2 mols), hamamelose

greenish-brown longitudinally ridged hollow stems up to 5 mm in diameter constitute a considerable portion of the drug.

Among the complex mixture of structures in the powder the following can be noted: leaves and sepals having lower epidermis with slightly sinuous anticlinal walls, anomocytic stomata and cluster crystals of calcium oxalate up to 40 µm diameter in the mesophyll; papilose epidermis of petals; pollen grains with three pores and a smooth to slightly pitted exine; numerous trichomes, occasionally glandular with a one- to three-celled stalk and multicellular head with brown contents but principally clothing trichomes of various size, often twisted together; vascular tissue of the stem and veins.

Constituents. The *BP*/*EP* requires a minimum concentration of 0.1% for the steam volatile fraction of Meadowsweet; the flowers have recorded higher values. The major component of the oil (up to *ca* 70%) is salicylaldehyde (Fig. 21.1) together with methyl salicylate, benzaldehyde, benzyl alcohol, and smaller amounts of other components such as vanillin. In 1839, Löwingand and Weidmann, working on meadowsweet, were the first to report salicylic acid as a natural product. Other constituents of the drug are the phenolic glycosides gaultherin (Table 21.1) and spiraein (salicyl alcohol + primerose), various flavonoids, e.g. hyperoside (Fig. 21.18), tannins and mucilage.

The pharmacopoeial TLC test for identity indicates the required presence of methyl salicylate and salicylaldehyde in the test sample. The permitted maximum for stems with a diameter greater than 5 mm is 5% and for foreign matter, 3%.

Action and uses. The *BP*/*EP* cites meadowsweet as a diuretic; traditionally it has also been used for its anti-inflammatory, astringent and stomachic properties.

Oil of wintergreen

Natural oil of wintergreen was formerly obtained from the leaves of *Gaultheria procumbens* (Ericaceae), but is now distilled from the bark of *Betula lenta* (Betulaceae). Gaultheria oil of the *Indian Pharmacopoeia* is obtained from the fresh plant of *Gaultheria fragrantissima* and contains not less than 98% of esters calculated as methyl salicylate.

WILLOW BARK

Various species of *Salix* which include *S. purpurea* L., (purple willow) *S. daphnoides* Vill. and *S. fragilis* L. (crack willow) are sources of the official drug (*BP*/*EP*, *BHP*, *ESCOP*, *Complete German Commission E*). There are about 300 species of *Salix* showing much hybridization and unusual forms. They are distributed in all parts of the North Temperate Zone, the Arctic Zone and the South Temperate Zone. Identification can present difficulties. Species range from tall trees to tiny shrubs. The commercial drug is obtained principally from S.E. Europe but also from Britain and other European countries.

The commercial drug occurs as thin, channelled pieces of varying length, about 1.5 cm wide and 1.5 mm thick. It easily fractures longitudinally and, transversely, shows an inner inconspicuous fibrous fracture. The outer surface is brown, grey or greenish, glossy and smooth or dull and rugged; the inner surface is lightish brown and finely longitudinally striated. The powder is characterized by cork cells, parenchymatous cells containing cluster crystals of calcium oxalate and lignified fibre groups with crystal sheaths of calcium oxalate.

Willow bark is a source of salicin (Table 21.1), a phenolic glycoside now seldom used but generally regarded as the natural forerunner of aspirin. The composition of the glycoside mixture is variable in the bark depending on species, age of bark and time of collection. The latter is usually made in spring when the bark is easily removed from the branches. Other phenolic glycosides are salicortin (an ester of salicin), acetylated salicin (fragilin) and salicortin. Salicin is easy to prepare (see 15th edition of this book) and is a suitable compound with which to introduce students to this class of glycoside.

Flavonoids of the bark (to over 4%) include the 5- and 7-glucosides of naringenin, isoquercitrin and chalcone (see Fig. 21.18). Tannins are of the condensed types (q.v.).

The *BP* requires the dried drug to contain a minimum of 1.5% total salicylic acid derivatives, calculated as salicin. Liquid chromatography with spectrophotometric determination at 270 nm is used for the assay.

Willow is employed as an anti-inflammatory in the treatment of rheumatism, arthritis and muscular pains.

Black haw bark

The root bark of *Viburnum prunifolium* (Caprifoliaceae) was formerly official in most pharmacopoeias, but its use for dysmenorrhoea, threatened abortion and asthma has gradually decreased. It contains about 0.2% of salicin, volatile oil and isovaleric acid, tannin and resin.

HOPS

Hops are the dried strobiles of *Humulus lupulus* L. (Cannabinaceae). Only the pistillate plants are cultivated, large quantities being produced in England (particularly Kent), Germany, Belgium, France, Russia and