Chapter 3
Forest Products with Health-Promoting and Medicinal Properties

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Abstract Forests are a rich renewable source of health-promoting and medicinal products. Not only the trees but also berries, nuts and mushrooms in forests contain a multitude of natural bioactive compounds which can be used in health-promoting products and medicines. In addition to the main structural components that trees contain, namely cellulose, hemicelluloses and lignin, thousands of bioactive compounds have been identified. Forest products have always had a key role in traditional medicine which continues to be of great importance, especially in developing countries. In the industrialized countries, the pharmaceutical industry is again increasingly looking at

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plant-derived natural drugs. Plant-derived compounds help to build a bridge between the traditional medical drugs in developing countries and the modern pharmaceuticals in the developed countries. Plant-derived bioactive compounds serve especially as preventive agents helping to maintain health.

3.1 Introduction

This chapter looks at the health-promoting effects of forest products from both a historical and scientific perspective. The use of medicinal plants – ethnomedicine – is a tradition common to all civilizations and according to WHO (Gurib – Fakin 2006), over 80% of the world's population rely on plant-derived medication for their health-care needs. At the same time, Western scientific research has begun to show the value of many traditional approaches, so that pharmaceutical companies in the Western world have revived their interest in plant-derived drugs and traditional knowledge of health care. Forests, the most diverse of all habitats, can be seen as natural pharmacies and over the past 2 decades, there has been a gradual return to the study of medicinal plants. As a consequence, the national and global markets for a wide range of forest products are growing rapidly. According to the World Bank (2004) the international trade in medicinal plants is worth $60 billion per year and is increasing at a rate of 7% per year.

Today, tree-derived bioactive compounds are produced in Europe in large amounts and marketed world-wide as ingredients in dietary supplements and health foods. We describe three products of this kind: xylitol, sitosterol and sitostanol. We also consider the development of products from knots and bark, including HMR lignan.

Plants produce a great variety of chemicals with important biological and ecological roles, including substances that protect plants themselves. Most of these chemicals can be classified as secondary natural plant products or secondary metabolites, i.e. any natural chemical product of plants not normally involved in primary metabolic processes, such as photosynthesis and cell respiration. The largest group of secondary plant products is terpenoids, among which many are used in food and beverages, and some are used in folk medicine and in pharmaceuticals, such as the anticancer drug Taxol and the antimalarial drug artemisinin. In this chapter we discuss the health benefits of volatile and non-volatile terpenoids in some *Cupressaceae* species, showing their traditional use for treating body ailments and diseases in both humans and animals. Uses include disinfectants, parasiticides, antiseptics, stimulants and painkillers.

3.2 Historical Perspectives for Medicinal Plants and Their Current State in Europe

3.2.1 Medicinal Plants in the History of Mankind

As old as man, the use of medicinal plants to cure diseases is rooted in tradition, empiricism and symbolic meaning. Whilst the number of plant species that have been used for medicinal purposes can only be estimated, Lange (2004) suggests that at least every fourth flowering plant of the approximate total of 422,000 flowering plant species (Scotland and Worthley 2003) has been used in ethnobotany somewhere in the world.

Several authors have estimated the number of plant species used for medicinal purposes. WHO has listed 21,000 medicinal species (Groombridge 1992), Farnsworth and Soejarto (1991) estimate that about 70,000 species are used in folk medicine. According to Schippmann et al. (2002), the number of higher plant species used for medicinal purposes worldwide is more than 50,000. This equates to approximately 17% of the world's vascular flora and constitutes the biggest spectrum of biodiversity used by people for a specific purpose (Hamilton et al. 2006).

India, China, the United States, Indonesia, Malaysia and Thailand (Schippmann et al. 2002) are the main countries where plants are used for medicinal purposes. A few plant families, including *Apocynaceae, Araliaceae, Apiaceae, Asclepeiadaceae, Canellaceae, Guttiferae* and *Menispermaceae* have higher proportions of medicinal plants than others. In developing countries, medicinal plants and forest products have always been a resource for primary health care, as part of first-line and basic health services not only to people living in remote areas, where it might be the only available health remedy, but to also to poor people.

Even where modern medicine is available, the interest in medicinal plants has increased rapidly in recent years, and it is still the case that in developing countries most people rely on herbal compounds rather than pharmaceutical drugs. WHO expects their use to be increased further, not only because of population growth, but also because of the increasing importance being attached to traditional health care in public health policy. In the industrialized countries, the use of medicinal plants was progressively abandoned in the twentieth century. This is perhaps due to the development of modern pharmacology and the achievements of medicinal products in fighting diseases, but it can also be seen a post-enlightenment phenomenon where traditional approaches were disregarded in the new scientific doctrine of medicine.

However, since the 1970s the Western world is also looking more to plant-derived drugs in its search for novel pharmaceuticals. In part, this seems to stem from the increasing costs of discovering new drugs, a reducing success rate for traditional drug development (Mintzberg 2006) and problems with synthetic drugs that have not always met their expectations. Thus, the past 2 decades have seen a gradual return to the study of phytochemicals used in herbal medicine. Fabricant and Farnsworth (2001) studied 122 compounds, obtained from only 94 plant species that are used globally as drugs. They showed that 80% of these have had an ethno-medical use that was identical or related to the current use of the active elements of the plant. They reported that when evaluating plants for bioactive compounds an ethno-medical approach based on traditional knowledge has been more successful than the random collection of plants. Nevertheless, they reported that random testing was the model increasingly adopted.

This interest extends beyond drug companies to include governments, research institutions and the wider public. Governments are considering policies about the appropriate use of plant-derived products. They are also concerned about the legal and ethical questions involved in patenting traditional medicines or drugs developed from them (Mintzberg 2006). The search for new pharmaceuticals is not restricted to drug companies. There are many researchers looking for active principles able to cure modern diseases or decrease the side effects often connected to medicinal products. The role of traditional knowledge is being re-appraised, with some researchers arguing that experience built over many centuries can provide a substantial basis for safe and effective use of medicinal plants.

3.2.2 State of Plant-Derived Products in Europe

Global and domestic markets for medicinal plants and their derivatives are growing rapidly. It has been estimated that internationally the trade in medicinal plants is worth $60 billion per year (World Bank 2004) increasing at a rate of 7% a year (Koul and Wahab 2004). The international trade in medicinal and aromatic plants (MAP) probably involves between 2,500 and 3,000 species worldwide (Shippmann et al. 2006). The 12 countries that were most active in the trade of pharmaceutical plants, during 1991–2000, imported a total of 326,300 t with a value of $97.8 million and exported 344,400 t with a value of $8.74 million (UNCTAD COMTRADE database). In that period, Europe imported annually around 127,000 t of medicinal plants while the annual European export average amounts to 75,900 t. The principal European export countries are Bulgaria, Albania, Poland and Hungary (Lange 1998, 2001, 2002). Within the European Union, the cultivation of medicinal and aromatic plants occupies an area of about 70,000 ha (Verlet and Leclercq 1997), though 90% of the European native species used in medicine are harvested in the wild (Lange 1998). Of the 3,000 or so species known to be traded internationally, only about 900 are cultivated commercially (Mulliken and Inskipp 2006). We can see that 70–80% of the medicinal plants traded in the world's most important markets for medicinal plants are collected in the wild (WWF/TRAFFIC Germany 2002). In Europe, the products derived from medicinal plants are used both for therapeutic and dietary purposes, and they are currently regulated in three categories: (1) Food supplements, according to Directive 2002/46/EC; (2) Traditional herbal medicinal products, according to Directive 2004/24/EC; (3) Medicinal products, that should be prescribed by medical doctors and sold in pharmacies (Directive 2001/83/EC; Directive 2003/94/EC, Directive 2004/27/EC).

The distribution of sales of over-the-counter herbal medicines, amounting overall to just under $5 billion (at manufacturers' prices to wholesalers), is shown in Table 3.1.

A further $132 million in sales was divided among Portugal, Hungary, Ireland, Slovakia, Finland, and Norway. The spending per capita was $25.00 in Germany, $18.80 in France, $9.50 in Italy, $6.50 in Poland, $3.60 in the United Kingdom, $4.10 in Spain, $12.30 in Belgium, $13.00 in Switzerland, $10.90 in Austria, $5.00 in the Netherlands, and $7.40 in the Czech Republic (De Smet 2005).

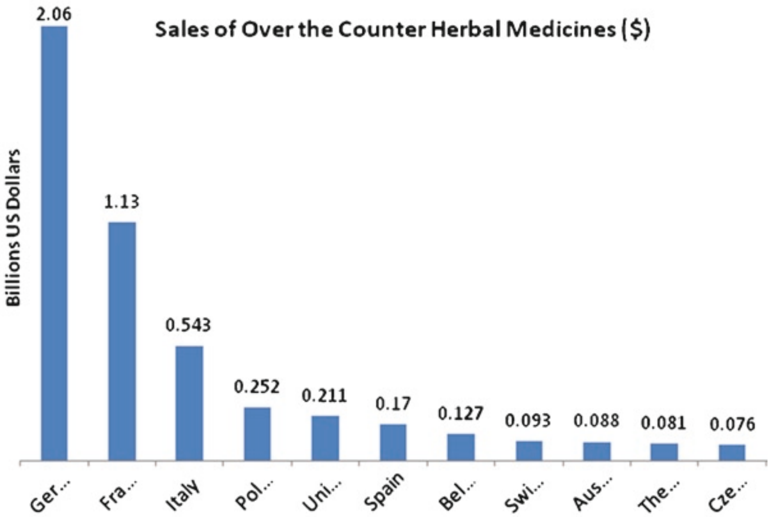


Table 3.1 Sales of OTC herbal medicines in Europe (De Smet 2005)

3.2.3 Potential Role of Medicinal Plants in Human Health and Critical Topics

Medicinal plants and forest products are already important sources for pharmaceutical manufacturing. As many as 50% of prescription drugs are based on a molecule that occurs naturally in a plant, with some 25% of prescription drugs derived directly or modeled on molecules from flowering plants (Foster and Johnson 2006). Plants and trees contain a large number of bioactive compounds such as polyphenols, flavonoids, phytoestrogens, terpenoids, phytosterols, fatty acids and vitamins which are known to exert beneficial health effects. Their use for the prevention and treatment of diseases ranges from traditional and popular medicines to the use of botanical extracts following the methodology of mainstream medicine. They embrace, among the other, therapeutic categories such as anticonceptives, steroids and muscle relaxants for anesthesia and abdominal surgery, quinine and artemisinin against malaria, digitalis derivatives for heart failure, and the anticancer drugs vinblastin/vincristin, etoposide and taxol. So far, scientific research has documented significant pharmacological activities of several medicinal plants that are used in association with medicinal products, and form the basis for a safe use of these products.

Collecting raw materials from natural habitats, however, can be damaging and potentially cause not only the extinction of rare species but also affect local economies on which communities depend. The number of endangered plant species is still unclear. In 1997, the World Conservation Union's (IUCN) Red List of Plants included some 34,000 threatened species out of 60,000 evaluated. Since then, the IUCN Red Listing criteria have changed, and around 11,000 species have been evaluated with the new system. Of those evaluated, some 8,000 species were found to be under threat. Both of these assessments indicate that well over half of all plants evaluated are at risk (Walter and Gillet 1998), implying that they should not be collected for medicinal purposes. WHO (2003) has compiled the Guidelines on Good Agricultural and Collection Practices (GACP) for medicinal plants.

Medicinal plants protected by national and international laws may be collected only with the appropriate permission. The provisions of the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES) constrains the trade in particularly endangered species.

Intellectual property rights for compounds derived from plants, and the traditional knowledge associated with them, is a contested topic. The debate centers on the protection provided under international and national patent laws and whether this can deliver equitable sharing of the benefits arising from the exploitation of traditional resources. Does bio-prospecting in forests disenfranchise traditional knowledge? What must be done if indigenous peoples are to benefit from the use of their resources? What say do indigenous people have in the decision-making process that deals with the use of their resources? Mintzberg (2006) is one of many authors who ask further questions about the ethics of restricting access to life-saving drugs through the use of patents and other intellectual property rights.

3.3 Evaluation of Forest Products

3.3.1 Introduction

Because of the limited supplies of some plant material from the wild and exhaustion of natural sources there is a need to cultivate analogues, both to conserve medicinal plants and to ensure adequate supply. Plants and trees contain a large number of bioactive compounds that can contribute to health (Kris-Etherton et al. 2002; Holmbom et al. 2007; Moutsatsou 2007). There are many variables, including climate, soil, the degree of ripeness, plant genetics and cultivation conditions that strongly influence the characteristics of the plants and the composition of chemical extractives (Ross and Kasum 2002). In many cases efforts to cultivate the same subspecies in other geographical areas have failed. The chemical content and relative concentration of compounds may vary even in the same species depending on their floral origin (Oddo et al. 2004; Terrab et al. 2004; Ruoff et al. 2006).

3.3.2 Extraction and Chemical Analysis

The main aim of this section is to describe the procedures typically used to isolate and analyze plant-derived bioactive compounds. Prospecting for plant-based pharmaceuticals can be done using high-throughput screening protocols on selected or

Table 3.2 Typical procedure for extraction, analysis and biotesting of forest and other plant products

Procedure	Aims – results
(a) Sampling	Well defined samples
(b) Extraction	Extracts of different polarity
(c) Fractionation and Purification	Compound groups or individual compounds
(d) Chemical Analysis	Identity and concentrations of compounds
(e) Biotesting (Clinical tests, In vitro, In vivo)	Bioactivity of extracts, compound groups and individual compounds

random samples, computational and molecular modeling and ethno-botanical studies. Whatever method is used to select a plant for analysis, the next step is to test for biological activity and potential health effects. The analytical procedure involves three basic steps: extraction from the sample, fractionation and purification and chemical analysis (Table 3.2). The extraction procedure is the first critical step since different solvents extract compounds with different chemical characteristics. The goal is to obtain a sample extract that has a high concentration of the components of interest, but is free from interfering substances.

Chemical analysis aims at distinguishing between already known compounds (dereplication) and new molecules in plant extracts. Techniques such as liquid chromatography/mass spectrometry (LC/MS), liquid chromatography/mass spectrometry/mass spectrometry (LC/MS/MS) and liquid chromatography/nuclear magnetic resonance (LC/NMR) are applied to plant extracts to identify new bioactive compounds or to quantify already known constituents. Mid-Infrared-Spectrometry (FT-MIR) and Near-Infrared Spectrometry (FT-NIR) are also valuable tools for confirming the botanical and geographical origin of plant-derived products (Ruoff et al. 2006). Further methods used to analyze bioactive compounds in plants are chromatographic methods including, thin-layer chromatography (TLC), gas chromatography (GC), high-pressure liquid chromatography (HPLC) and capillary electrophoresis (CE) (Wolfender et al. 2003). Gas chromatography/mass spectrometry is a very powerful tool for the simultaneous identification and quantification of individual compounds.

3.3.3 Biomedical Evaluation

Bioactive compounds found in tree and plant extracts include polyphenols (including flavonoids, phenolic acids, tannins, lignans and stilbenes), carotenoids (lycopene), sterols (sitosterol), polysaccharides, beta-glucans, and various terpenoids (Kris-Etherton et al. 2002; Holmbom et al. 2007). Numerous studies have shown that these phytochemicals can be biologically active with properties such as anticancer activity, antiatherogenic and antioxidant potential, neuroprotection effects, and bone-favoring effects (Kris-Etherton et al. 2002; Moutsatsou 2007).

To assess the biological activity of plant extracts and plant-derived compounds an array of in vitro test systems is used. There are high-throughput screening tests which set priorities for further assessment. A combination of several in vitro test systems is required in order to predict the effects in vivo. However, in vitro assays do not include metabolites of compounds and aspects of the absorption of compounds so they may give false negative or false positive results. Only in vivo studies are able to predict the action of a substance in the organism, since under these in vivo conditions the substance is exposed to both absorption processes and multiple metabolic transformations.

3.3.4 In Vitro Test Systems

To assess the estrogenic or anti-estrogenic potential of phytochemicals (an activity usually shown by certain polyphenols) several in vitro test systems are typically used: (1) a radiometric competitive receptor-binding assay, (2) reporter gene assays, (3) assays that measure the expression of endogenous estrogen receptor (ER) target genes (end point assays), and (4) a proliferation assay using an established cell line that is known to respond to estrogens (Diel et al. 1999; Gutendorf and Westendorf 2001; Mueller 2002).

Assessment of the anti-carcinogenic potential of phytochemicals usually includes: (1) a proliferation assay or a cell viability assay (MTT assay), and (2) investigation of apoptosis by using flow-cytometry techniques, measuring apoptotic or anti-apoptotic proteins and DNA fragmentation products (Kassi et al. 2007). Since cancer is a multi-factorial disease that requires modulation of multiple pathways and multiple targets, one may also assess the potential of phytochemicals on various other processes. This includes suppression of growth factor expression or signaling, inflammatory molecules and signaling (NF-kB, JNK and AP-1 signaling pathways), cell-cycle molecules (cylin-D1) as well as down-regulation of angiogenesis.

Atheromatosis is also a complex disease characterized by alterations in numerous cellular processes, among which the oxidative stress and inflammation play a key role. Thus, the anti-inflammatory and anti-atherogenic potential of phytochemicals may be assessed in cells of cardiovascular system (endothelial cells, smooth muscle cells) by determining inflammatory protein molecules such as adhesion molecules, cytokines, metalloproteinases and related signaling (NFkB, AP-1 signaling, Papoutsi et al. 2007a).

The effects of phytochemicals on bone health may be assessed by using the appropriate cells (osteoblasts, osteoclasts, monocytes) and tests such as mineralization of osteoblasts, measurement of proliferation or apoptosis of osteoclasts and osteoblasts, determination of cytokines, osteoprotegerin (OPG), osteocalcin and other bone parameters (Kassi et al. 2004; Papoutsi et al. 2007b).

3.3.5 In Vivo Test Systems

Various in vivo assays (animal models) are used to characterize the biological potency of phytochemicals and their mechanisms of action. The animals used are usually rats, mice or rabbits. In the tests the phytochemical is given orally or subcutaneously. Among the common animal models are several tumor models, which are mainly used to assess the potential chemopreventive properties of phytochemicals. There are several approaches, such as spontaneous carcinogenesis, chemical carcinogen-induced tumor models and tumor models by xenotransplantation of tumor cells. Spontaneous carcinogenesis may be applied for prostate and endometrial carcinogenesis. Chemical carcinogen-induced tumor models involve the exposure of rats to DMBA or NMU for the development of mammary carcinomas. Finally, some tumor cell lines, if xenotransplanted to immune-deficient nude mice or rats, grow tumors at the ectopic site and eventually metastasize through blood or lymphogenic pathways. This model is used for breast, prostate and endometrial tumors (Diel et al. 2002). Furthermore, there are more specific animal models to evaluate the estrogenic effects of phytochemicals. These animal models usually use immature, hypophysectomized or ovariectomized rats, mice or rabbits. In this case, the uterotrophic assay is combined with the analysis of estrogen-sensitive endpoints (such as morphological, histological, biochemical and molecular endpoints) in the uterus and other estrogen-sensitive target tissues, such as the vagina, the mammary gland, the liver, the bone, the cardiovascular system and the brain (Diel et al. 2002). The uterotrophic assay assesses the ability of phytoestrogens to stimulate uterine growth. However, this assay may not be very suitable for assessing estrogenicity, since there are compounds, like raloxifene, that exert tissue-specific estrogen-like activity, without effects in the uterus (Jefferson et al. 2002). The possible beneficial effects of phytoestrogens in osteoporosis, atherosclerosis and neurodegeneration are examined by using the ovariectomized adult rat model of osteoporosis, the rabbit model of high-cholesterol induced atheromatosis and several animal models of brain injury, respectively (Kalu 1991; Jee and Yao 2001; Picazo et al. 2003). In conclusion, the use of a suitable panel of different in vitro test systems combined with a final assessment in animal models will predict the real biological potential of phytochemicals.

3.4 Health-Promoting Effects of Honey and Walnuts

3.4.1 Introduction

Honey plays an important role in nutrition throughout Europe, with beekeeping deeply rooted in every European culture. Many European countries produce honey; Greece, Italy, Spain, France and Portugal being the main honey-producing countries.

Walnut trees are also important in Europe because of their fruits and decorative, valuable timber.

3.4.2 Honey

This natural product has been used for thousands of years in Greece. According to the philosopher Plato's concepts of health diet, a moderate and thus healthy diet consists of cereals, legumes, fruits, milk, honey and fish. Athenaeus, the Greek philosopher and author of 'The deipnosophists', reported that the Greek philosopher Democritus (500 BC) used honey in his daily diet for longevity and fertility. Democritus, along with Hippocrates and Dioscorides, considered honey as an important agent for strengthening the body and maintaining good health (Skiadas and Lascaratos 2001).

In Europe, more than 100 botanical species can give unifloral honeys (Oddo et al. 2004). Depending on flora and geographical origin, European honey is derived either from plant flowers, such as Danish honey or from conifers such as pine and fir trees. The conifer-derived honeys are marketed in central Europe as 'forest' honey. The quality of honey is judged by its botanical or floral origin and chemical composition. The floral source of a honey has been identified traditionally by the analysis of bee pollens present in the honey, while modern approaches rely on accurate chemical analysis of flavonoids and other phenolic compounds (Ruoff et al. 2006; Gómez-Caravaca et al. 2006).

Honey contains hundreds of substances and is considered as a traditional medicine. Among its important constituents are flavonoids, phenolic acids, certain enzymes, ascorbic acid, carotenoid substances, amino acids and proteins. The phenolic content and the antioxidant activity of honey vary greatly depending on the floral source and external factors such as the season and environment (Gheldof et al. 2002; Gómez-Caravaca et al. 2006). The total phenolic content of honeys derived from various flora sources ranges from 46 to 400 mg/kg honey (Gheldof et al. 2002). The high flavonoids content endows honey with antioxidant properties and an array of other biological properties, including antibacterial, antitumor, anti-inflammatory, anti-allergic, antithrombotic and vasodilatory actions (Ceyhan and Ugur 2001; Schramm et al. 2003; Swellam et al. 2003). Honey has shown wound-healing properties and also metabolic effects in diabetes (Katsilambros et al. 1988; Molan 2006).

3.4.3 Walnut

Walnut trees *Juglans regia* are important in Europe because of their fruits and decorative, valuable timber. They grow well on fertile, deep and well-drained soils in temperate climates. The main areas of its distribution in Europe are in flat regions in Germany, France, Italy and the eastern part of Austria. Walnut (*Juglans ssp.*) has a potential for use in agroforestry since it produces high-value products (e.g. good quality timber and nuts).

The naturalized European walnut tree is traditionally cultivated for fruit production, but it is also highly valued for its wood (Fady et al. 2003). Walnut (*Juglans regia*) is rich in substances such as ellagic acid, a known polyphenol, α-tocopherol (vitamin E), fiber, essential fatty acids, flavonoids and phenolic acids (Jurd 1956; Fukuda et al. 2003; Maguire et al. 2004; Colaric et al. 2005, Li et al. 2006).

The high content of polyunsaturated fatty acids (linoleic and linolenic acid) in walnuts has been suggested to reduce the risk of heart disease by decreasing total and low-density lipoprotein (LDL) cholesterol and increasing high-density lipoprotein (HDL) cholesterol. This favorable lipid profile of nuts has previously been proposed as the mechanism of walnuts' apparent anti-atherogenic effect in humans (Zambon et al. 2000; Almario et al. 2001). The cardiovascular protective effect of a walnut diet has also been related to its antioxidant effects as well as to modulation of endothelial functions (Anderson et al. 2001; Ros et al. 2004; Tsuda and Nishio 2004). The inflammatory process plays an important role in the pathogenesis of atherosclerosis through the interaction of the endothelium with the immune cells. The adhesion molecules, the vascular cell adhesion molecule (VCAM-1) and the intracellular cell adhesion molecule (ICAM-1) activated by inflammatory cytokines, such as tumor necrosis factor-α (TNF-α), participate in the initiation of this interaction. Recent data support that the methanol extract of walnut inhibits the inflammatory process in endothelial cells and that it also has favorable effects on bone cells (Papoutsi et al. 2007a, b). In conclusion, honey and walnuts are important, health-promoting forest products. A diet enriched with honey and walnuts may be beneficial for the prevention of many degenerative diseases.

3.5 Medicinal Properties of Pine Resin and Chios Mastic Gum

3.5.1 Pine Resin

Among the conifers in the northern hemisphere, the family *Pinaceae* is second only to the *Cupressaceae* in the extent of its range. Comprising about nine genera and 225 species it includes the economically important cedars, firs, hemlocks, larches, pines and spruces. Its members extend from deserts to rain forests and from the sea level to the mountain tree line (Scagel et al. 1965). The pine genus is the largest in the family, with around 120 species in two sub-genera.

The great success of pine trees rests partly on defense systems that have allowed them to withstand inter-specific competition and to deter pathogens, particularly saprophytic fungi but also other microbes, and attacks from herbivores, insects and other animals. Their principal defense mechanism is the production of resin (termed also oleoresin or pitch), which is a viscous, odoriferous secretion that appears at wound and infection sites (Philips and Croteau 1999). Pine resin is a complex mixture of terpenoids, consisting of roughly equal parts of volatile turpentine (monoterpenes, C_{10}, and sesquiterpenes, C_{15}, including oxygenated types) and rosin (diterpenes, (C_{20}) resin acids) (Croteau and Johnson 1985; Jonnessen and Stern 1978).

Pine resins have been used in traditional medicine since ancient times. Today, they are still used as the basic component of various medicinal preparations, often in ointments containing pine resin and beeswax. However, the pharmaceutical and medicinal properties of pine resin have not yet received extensive attention from the research community.

Simbirtsev et al. (2002a) reported that medical trials on animals have shown that **pine resin (PR)** and **pine resin ointments (PRO)** can be highly effective in the treatment of wounds and burns during phase I of the wound process, in cell regeneration at the wound surface and formation of early granulation tissue. They undertook in vitro studies of the antibacterial activities of PR and PRO on wounds and burns on standard test strains (gram-positive *St. aureus* and gram-negative E. coli and *Ps. aueroginosa*), and the effects of PRO on reparative processes studies in vivo on animals (Simbirtsev et al. 2002a). PR was characterized by pronounced bactericidal effects, while PRO had no effect on microorganism growth, which was perhaps caused by beeswax ester macromolecules that inhibited its diffusion. Their results showed that during the early stage of the inflammatory process, PRO modulated non-specific and inhibited specific immune response, normalized hemodynamics in the inflammation focus, activated regenerative processes in tissue, and was effective against anaerobes and bacilli. The same group of scientists also studied the immune-toxic properties of PRO during therapy of burns, wounds in phase I of the wound process, and of purulent and inflammatory diseases of the skin and subcutaneous fat testing, as well as the possible irritating and allergic effects of PRO (Simbirtsev et al. 2002b). The results of this study show that long-term treatment with PRO in clinical doses has no effect on non-specific immunity, but modulates specific immunity. The preparation of PRO inhibits humoral, but stimulates cell immunity. Neither local irritation nor allergic reactions were observed after long-term epicutaneous application of PRO. In particular, in the therapy of burns PRO stimulates non-specific immune response, normalizes hemodymanics in damaged regions, and stimulates proliferation of epithelial cells (Khmel'nitskii et al. 2002).

Inflammatory cells are mobilized over the first hours after burning or wound infection. In vitro experiments show that preparations containing PR activate phagocytosis and hold much promise for the therapy of burns, wounds, purulent and inflammatory diseases (Simbirtsev et al. 2002c). The same experiments show that PR and PRO contain various bioactive substances producing opposite and dose-dependent effects on phagocytosis (Simbirtsev et al. 2002d).

Rosin, formerly called **colophony** or **Greek pitch** (*Pix græca*), is the major product obtained from pine resin. It is a brittle, transparent, glassy solid produced by heating fresh liquid resin to vaporize the volatile liquid terpene components. Rosin and rosin derivatives have been pharmaceutically evaluated as microencapsulating materials and as anhydrous binding agents in tablets (Fulzele et al. 2002, 2007; Pathak and Dorle 1990; Sahu et al. 1999; Satturwar et al. 2004; Lee et al. 2005). Rosin biomaterias have excellent biocompatibility and degradation features, and film-forming ability (Fulzele et al. 2003). They show potential as components in film-based drug delivery systems and dosage technology (Satturwar et al. 2005; Fulzele et al. 2007).

3.5.2 Chios Mastic Gum

Pistacia lentiscus var. Chia of the *Anacardiaceae* family is grown almost exclusively in the southern part of Chios island, a Greek island in the Aegean. Chios mastic gum (CMG) is a white, semitransparent, natural resin that is obtained as a trunk exudate from mastic trees. Mastic gum and essential oils from *P. lenticus* are natural antimicrobial agents that have found extensive uses in Mediterranean and Middle Eastern countries since ancient times, both as a dietary supplement and as herbal remedy. Kolliaros (1997) suggests that they were used in Greek medicine in classical times by physicians such as Hippocrates, Dioscorides and Galenos, who mentioned their properties and recommended their use for various gastrointestinal disorders like gastralgia, dyspepsia and peptic ulcer. Nowadays, mastic gum is used in surgery for the production of special stitches that are absorbed by the human body. In dentistry it acts as an oral antiseptic and tightens the gums (Topitsoglou-Themeli et al. 1984), and for that reason it is used in toothpastes and chewing gums (Stauffer 2002). Mastic is used in Mediterranean cuisine as a seasoning, such as in biscuits and ice cream, or as a sweet additive in drinks. The essential oil is used in perfumery and in the cosmetic industry (Doukas 2003).

The biological activity of Chios mastic gum can be attributed to a variety of compounds. It mainly consists of triterpenes of the oleanane, euphane and lupane type (Andrikopoulos et al. 2003; Assimopoulou and Papageorgiou 2005). Koutsoudaki et al. (2005) reported that the major constituents of mastic oil and gum were α-pinene, β-myrcene, β-pinene, limonene and β-caryophyllene.

Medical trials have shown that mastic gum may have cyto-protective or anti-acid effects for the gastrointestinal system, such as relief of ulcers (administration of 1 g of CMG daily relieved the pain and healed the stomach and duodenal ulceration in the majority of the patients within 2 weeks (Al-Habbal et al. 1984) and reduction of the intensity of gastric mucosal damage caused by antiulcer drugs and aspirin, with little or no side effects. It has been reported that mastic gum possesses considerable in vitro antibacterial and antifungal activity (Magiatis et al. 1999; Tassou and Nychas 1995), for which verbenone, alpha-terpineol, and linalool seem to be responsible (Koutsoudaki et al. 2005). It has been specifically reported to be effective against *Helicobacter pylori* and peptic ulcer in vitro (Huwez et al. 1998; Bona et al. 2001; Marone et al. 2001). However, in a more recent in vivo study against of *H. pylori* infection, the activity of CMG was compared with antibiotic eradication schemes, and after a 7-day treatment no eradication of the bacterium from the stomachs of mice receiving mastic was observed (Loughlin et al. 2003). The same experiment was repeated in humans, where *H. pylori* positive patients were treated with mastic capsules for 7 days, and all remained *H. pylori* positive after the administration (Bebb et al. 2003). We have to take into consideration that the crude resin that was used in all previous studies contained a high percentage (30%) of an insoluble and sticky polymer (poly-β-myrcene) (Van den Berg et al. 1998) that obviously hinders its oral administration and reduces the bioavailability of the contained active compounds. To bypass this problem in subsequent studies, researchers used a total mastic extract without polymer.

Pistacia lentiscus has also been traditionally regarded as an anti-cancer agent, especially against tumors of the breast, liver, stomach, spleen, and uterus. These beliefs accord with recent studies demonstrating that CMG induces apoptosis (Balan et al. 2005) and possesses antiproliferative activity in human colon cancer cells (HCT116) in vitro (Balan et al. 2006). Furthermore, CMG has already been associated with cardiovascular protection. It inhibits human LDL oxidation in vitro (Andrikopoulos et al. 2003) and due to the triterpenes that are major constituents both of the neutral and the acid fraction, it acts on peripheral blood mononuclear cells to elicit an antioxidant and anti-atherogenic effect (Dedoussis et al. 2004). Although CMG's antioxidant effect is widely known, whether it can directly inhibit atherogenesis has not been clarified.

3.6 Edible Wild Forest Mushrooms as a Source of Health-Promoting Compounds

3.6.1 Introduction

Mushrooms comprise a large and yet mostly untapped source of new pharmaceutical products. Whilst the medicinal use of mushrooms has a very long tradition in Asian countries, their use in the Western hemisphere has been slightly increasing only since the last decades (Lakhanpal and Rana 2005; Lindequist et al. 2005).

Several reviews have been written lately on the medicinal properties of mushrooms, which give an overview of the pharmacological potential of many fungi. The most investigated mushrooms for medicinal value are cultivated species such as *Ganoderma lucidum* (Reishi), *Lentinus edodes* (Shiitake), *Grifola frondosa* (Maitake), *Agaricus blazei* (Hime-matsutake), *Cordyceps militaris* (Caterpillar fungus), *Pleurotus ostreatus* (Oyster mushroom) and *Hericium erinaceous* (Lion's mane) (e.g. Lakhanpal and Rana 2005). For a comprehensive review of this subject concerning cultivated fungi, the reader is referred to the works of Wasser and Weis (1999), Borchers et al. (1999), Wasser (2002), Lakhanpal and Rana (2005), Lindequist et al. (2005), and Zaidman et al. (2005).

Edible wild mushroom species have not been studied as extensively as those in cultivation although interest in wild mushrooms has been raised recently partly due to the abundance of wild mushroom harvests. The nutritional value of these mushrooms has been recognized for a long time, since they are high in protein and low in fat. Mushrooms also contain significant quantities of vitamins, such as thiamine, riboflavin, ascorbic acid, and vitamin D_2, as well as minerals (Mattila et al. 2000). As much as 10–50% of dried matter from mushrooms can be dietary fibers belonging to β-glucans, chitin, and heteropolysaccharides (Wasser and Weis 1999). Mushrooms are a good source of trace elements, such as copper, zinc, selenium, iron, and molybdenum. Especially selenium has emerged with the most anticancer effect among a number of micronutrients tested in animal experiments and clinical trials (Zaidman et al. 2005).

In this section, we focus on antimicrobial and anti-tumor properties of edible wild forest mushrooms commonly used, especially in northern European countries.

3.6.2 Antimicrobial Activity

Mushrooms need antibacterial and antifungal compounds to survive in their natural environment (Zak 1964; Kope and Fortin 1989). Extracellular antibiotics produced by ectomycorrhizal fungi have been suggested to be one form of protection for roots against infection of phytopathogenic fungi (Zak 1964). Antimicrobial compounds that could also be of benefit for humans have been isolated from many species (Lindequist et al. 2005). Macro-fungi have been found to have wide antimicrobial properties, tending to inhibit the growth of bacteria, fungi, protozoa and cancerous cells in mammals.

In the study of Dulger et al. (2002) methanol extracts from several *Lactarius* species (*L. deterrimus, L. sanguifluus, L. semisanguifluus, L. piperatus, L. deliciosus, L. salmonicolor*) revealed antimicrobial activity against some Gram (+) and Gram (−) bacteria, but showed no antagonistic effect against yeasts. A general characteristic of the genus *Lactarius*, is that the fruit bodies contain a latex which can be observed if they are cut or broken. The creation of sesquiterpenes in the injured fruit-bodies appears to be enzymatic and in the pungent *Lactarius* species clearly contribute to the fungus's defense system (Bergendorff and Sterner 1988; Clericuzio et al. 2002). *L. deliciosus* and *L. deterrimus*, which are not pungent species, also contain fatty acid esters of a single sesquiterpene, and these esters are transformed to sesquiterpene aldehydes and alcohols as a response to injury (Bergendorff and Sterner 1988). However, the sesquiterpenes of *L. deliciosus* and *L. deterrimus* have a quaiane skeleton, which is not formed the same way as in the pungent species. The class of protoilludane sesquiterpenes occurs rather widely in higher fungi in addition to *Lactarius* species (Clericuzio et al. 2002).

Ethyl acetate, chloroform and ethanol extracts of *Cantharellus ciparius* Fr. (*Cantharellaceae*) (Photo 3.1) were tested for antimicrobial activity by the disc diffusion method by Dulger et al. (2004). In that study, C. *ciparius* revealed antimicrobial activity against some Gram (+) and Gram (−) bacteria, yeasts, filamentous fungi and actinomycetes. All the extracts showed more antifungal than antibacterial activities.

Peptaibols are a family of peptides characterized by a short chain lengths (≤20 residues), C-terminal alcohol residues and high levels of non-standard amino acids, principally α-aminoisobutyric acid, isovaleric acid and the imino acid hydroxyproline (Whitmore and Wallace 2004). Peptaibols originate from fungal organisms, some of which exhibit antibiotic activity against phytopathogenic fungi and Gram-positive bacteria (Lee et al. 1999). The antibiotic functions of peptaibols arise from

Photo 3.1 *Cantharellus ciparius* Fr. (*Cantharellaceae*) extracts display antimicrobial activity against some bacteria, yeasts and fungi (Photo: Tytti Sarjala) (*See Color Plates*)

their membrane insertion and pore-forming abilities (Whitmore and Wallace 2004). A new peptaibol, boletusin, was isolated and sequenced by Lee et al. (1999) from an extract of fresh, fruiting bodies of *Boletus* spp. Boletusine was composed of 19 residue amino acids and it showed antimicrobial activity against several Gram-positive bacteria (Lee et al. 1999).

3.6.3 Anti-Tumor Activity

Over the past 2–3 decades, scientific and medical studies in Japan, China, Korea and the United States have increasingly demonstrated the potent and unique properties of mushroom-extracted compounds for the prevention and treatment of cancer (Zaidman et al. 2005). There are about 650 species of higher Basidiomycetes that have been found to possess antitumor activity (Wasser 2002).

High-molecular-weight polysaccharides or polysaccharide-protein complexes from mushrooms appear to enhance innate and cell-mediated immune responses, and exhibit antitumor activities in animals and humans (Zaidman et al. 2005). Although immunomodulators (agents that activate or suppress the body's immune system) isolated from many mushroom species have shown anticancer action in animals (Wasser and Weis 1999), only a few have been taken to the next step, that is, objective clinical assessment for anticancer potential in humans. Polysaccharides with antitumor action vary greatly in their chemical composition and configuration, as well as their physical properties, which have been summarized by Wasser (2002). Structural features such as β-(1→3) linkages in the main chain of the glucan and additional β-(1→6) branch points are needed for antitumor action

(Wasser 2002). All main taxonomic mushroom groups have been investigated for biologically active polysaccharides, and most of them possess such substances. According to Wasser (2002), quite commonly used fungal species in Europe for example in the following genus (number of species studied in parenthesis) *Boletus* (11), *Leccinum* (2), *Suillus* (5), *Cantharellus* (5), *Tricholoma* (1), *Rozites* (1), *Lactarius* (18), and *Russula* (23) have been reported to have antitumor or immunostimulating activity.

Tricholoma matsutake is quite common in Northern Europe and Asia and is recognized as a high-quality and expensive culinary mushroom in Japan. A novel α-glucan-protein complex with immunomodulatory activities has been isolated and characterized from the mycelium of *Tricholoma matsutake* by Hoshi et al. (2005). The immunomodulatory activity of a biological response modifier derived from the mycelia of the *Tricholoma matsutake* was proved by Ishihara et al. (2002) by demonstrating inhibition of stress-induced decrease in Natural Killer Cell activity in mice. Antitumor polysaccharides have been isolated also from other *Tricholoma* species (Mizuno et al. 1996).

Polyhydroxysteroids, which have been found to possess cytotoxic activity on hepatome cell line, were found by Lanzotti and Iorizzi (2000) in *Tuber borchii*, a valued culinary species in Europe.

It is interesting that a common constituent of fungal membranes, ergosterol, has been reported by Takaku et al. (2001) to have antitumor activity which may be due to direct inhibition of angiogenesis (a physiological process involving the growth of new blood vessels from pre-existing vessels).

Most of the studies on the efficacy of medicinal mushrooms that are available to the public are based on animal studies (usually in mice) or cultured cells. In these cases, the bioactivity of the mushroom extracts cannot always be correlated to their activity when ingested by humans – either orally or by injection. In future, more clinical assessment to investigate the immunomodulators would be needed to utilize the medicinal properties of fungi.

3.7 Nutritional and Medicinal Properties of Forest Berries

Berries, both cultivated and from the wild, are part of the traditional diet in many European countries. In Scandinavia the importance of berries is thought to be partly explained by the fact that they are generally low-growing and accessible. The geographical distribution of different wild berry species varies. For example, black currant species (*Ribes nigrum L.*) are found in Europe in Central Europe, Scandinavia and the British islands. Red and white currant species (*Ribes rubrum*) are found in alpine areas of West and Central Europe and in Northern Europe. Arctic bramble species (*Rubus arcticus*) are generally found between the 60th and 70th degrees of latitude and cloudberry (*Rubus chamaemorus L.*) is found extensively in Europe only in Norway, Sweden and Finland. Lingonberry (*Vaccinium vitis-idaea*), often called cowberry or mountain cranberry is widely found in

Europe whilst blueberry/bilberry (*Vaccinum myrtillus*), is common in northern Europe, as well as on mountains of southern Europe and is absent only from southern Italy and the Iberian Peninsula.

Gathering berries is a social activity and is part of the traditional culture of rural life, especially in Scandinavian countries where, since the thirteenth century people have had the so-called 'everyman's right' to go into the forests and pick berries and mushrooms. Berries are a natural source of antioxidant vitamins (C and E), fiber (mostly insoluble; cellulose and minor quantities of soluble; pectin), beneficial fatty acids with a high portion of unsaturated fatty acids such as omega-3 and omega-6, no cholesterol and low sodium (Na) but high potassium (K) content. These affect human health in different ways. Insoluble fiber has an effect on gut health and prevents constipation. Soluble fiber lowers blood cholesterol and sugar levels. Low Na and high K contents have an effect on blood pressure. There is seasonal variation in the composition of berries, influenced by the weather conditions during the growth period and environmental stress on the plants. There is also a difference in the abundance of these health-promoting compounds between different genotypes of the same berry species.

In addition to being good sources of essential nutrients, berries contain phenolic compounds such as flavonoids, phenolic acids, procyanidins, lignans, stilbenes and polymeric tannins. Flavonols (see Fig. 3.1 for a chemical structure) in food are found to be an interesting subject since they owe several biological functions positive for human health. Among these can be mentioned antioxidative effects, binding of free radicals, inhibition of saturation of fat, inhibition of inflammation and allergy, inhibition of raise of blood pressure and antimicrobial activity (Puupponen-Pimiä et al. 2001). Lingonberry, blueberry, and bilberry, which are members of the *Vaccinium* (*Ericaceae*) family, are particularly known for their flavonoid content (flavonols, anthocyanins and proanthocyanidins) (see Fig. 3.2 for a chemical structure). These have anti-cancer characteristics and anti-carcinogenic activity. The full effect is still under investigation (Bomser et al. 1996). The highest concentration of flavonols is found in cranberry, lingonberry (cowberry), black currant and bog whortleberry (50–200 mg/kg fresh berries). The main group of flavonoids present in berries is the anthocyanins, which are dark in color and found in great concentrations in blueberry/bilberry and black currant (2,000–5,000 mg/kg fresh berries).

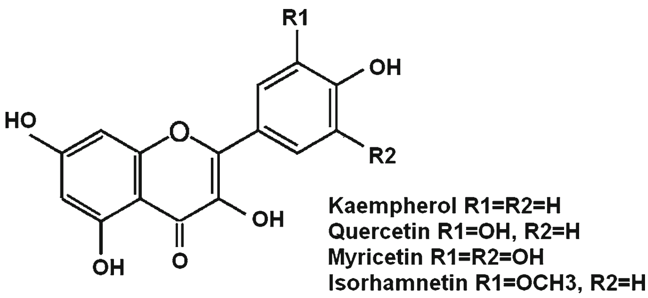


Fig. 3.1 Chemical structures of flavonols

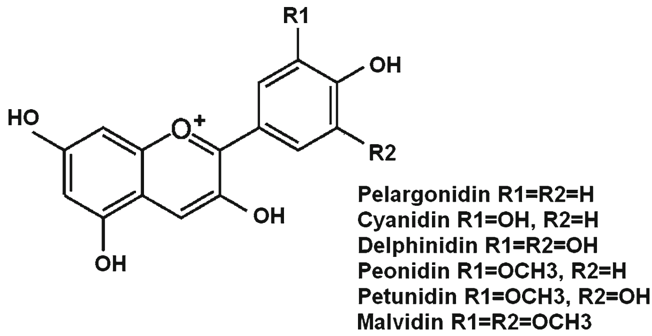


Fig. 3.2 Chemical structure of anthocyanidins

The most abundant flavonoids are kaempferol, quercetin and myricetin and among the phenolic acids p-coumaric acid, coffeic acid, ferulic acid, p-hydroxybenzoic acid, gallic acid and ellagic acid are the most common. In *Vaccinium* species (lingonberry, cranberry and bilberry/blueberry) and *Ribes* species (red currant, black currant) the most abundant flavonoid is quercetin. The most abundant phenolic compounds found in cranberry and lingonberry are hydroxycinnamon acid and flavonols which is also very abundant in red and black currant. Ellagic acid is the most abundant phenolic compound in cloudberry and red bramberry (Häkkinen et al. 1999). In red berries the major flavonol group present is the anthocyanins. A recent clinical study stated that the consumption of moderate amounts of berries resulted in favorable changes in platelet function, HDL cholesterol, and blood pressure (Erlund et al. 2008).

The antimicrobial activity of bilberry/blueberry, bramberry, lingonberry, black currant, cloudberry, cranberry and sea buckthorn was tested against gram-negative and gram-positive probiotics and other intestinal bacteria including some pathogenic species (*Salmonella enterica* and *E. coli*). In general berry extracts inhibited the growth of gram-negative bacteria, but not the growth of gram-positive ones. Extracts from cloudberry and bramberry (Puupponen-Pimiä et al. 2005a) seemed to be the especially effective against *Salmonella.*

Phenolic compounds present in berries have a varying effect in inhibition of the growth of pathogenic bacteria. The best inhibition effect has been found with cloudberry and bramberry. Ellagitannin compounds effectively inhibited the growth of *Staphylococcus* bacteria (Puupponen-Pimiä et al. 2005b).

Plant extracts containing phenolic compounds have strong antioxidant properties. The total amount of phenolics in berries is relatively high (12.4–50.8 mg/g GAE, gallic acid equivalent) (Kähkönen et al. 1999).

Storage of the berries in normal room temperature (RT) causes a loss of phenolics, but low-temperature storage only slightly reduces the amount of phenolics in the berries and does not seem to affect the antimicrobial activity. For some berries storage in a freezer increased the antimicrobial effect (Puupponen-Pimiä et al. 2005a).

Processing crushed blueberry/bilberry and cloudberry samples with enzymes increased the total phenolic content in the juice and also the antimicrobial activity against bacteria of *Salmonella* and *Staphylococcus* species (Puupponen-Pimiä et al. 2005b). Enzymatic treatment liberates the phenolic compounds bound to the cell walls and the treatment might also change their structure. Clinical studies have shown that urinary tract infections can be reduced by drinking cranberry-lingonberry juice (Kontiokari et al. 2001, 2003). One clinical study on cranberry juice's influence on risk factors for kidney stone formation concluded that cranberry juice has anti-lithogenic properties that warrant its consideration as part of a therapeutic protocol in managing calcium oxalate kidney stone formation (McHarg et al. 2003).

Cranberry has been shown to affect the balance and level of cholesterol. Wilson et al. (1998) found that cranberry extract inhibits low density lipoprotein oxidation. The cranberry juice had a polyphenolic content of 1.55 mg/l GAE and pH of 2.5. It was found to inhibit the electrophoretic movement of the LDL-cholesterol and thus the juice has the capability to inhibit the oxidation of LDL-particles in a similar manner to red wine. In vitro studies show that cranberry juice has antioxidative effects on the LDL oxidation processes. The effect is stronger with higher concentration of cranberries. The antioxidative effect of a cranberry sample of 100 g is similar to that of a 1 mg dose of Vitamin C or 3.7 mg dose of Vitamin E. The juice increased the expression of LDL-receptors in hepatocytes and increased the capability of the hepatocytes to intake cholesterol in correlation to juice sample size (Chu and Liu 2005). This indicates that cranberry juice can have a positive effect on the removal of extra cholesterol from blood plasma and can act as an inhibitor of heart and coronary diseases.

There are still other health effects found with berries. The long-chain carbohydrates extracted from the seeds of black currant can inhibit the attachment of ulcer bacteria (*Helicobacter pyroli*) to the walls of stomach. A number of epidemiological studies (Arts and Hollman 2005) show that there is a relationship between the intake of phenolic compounds from daily food, such as fruits and vegetables, and a reduced risk of cardiovascular diseases and lung cancer. These health effects seem to be related to the antioxidant activity of the phenolic compounds protecting the body tissues against oxidative stress (Prior 2003). The cancer-preventive properties can be attributed to mechanisms such as cell cycle arrest, apoptosis, altered cellular signaling, and induction of detoxifying enzymes (Chen and Kong 2004). A clinical study showed that high intake of certain flavonoids (flavonols and flavanones) could protect against coronary heart disease, stroke, lung cancer, prostate cancer, asthma and type-2 diabetes (Knekt et al. 2002).

3.8 Health-Promoting By-Products from Forest Industries

Of the various chemical products, including health-promoting compounds, produced from the sixteenth century to the middle of the nineteenth century in the area which now is Finland, wood tar was the most important commercial product.

Tar was used mainly for painting wooden ships but was also used as a health product. Other examples of health-promoting products from trees with ancient traditions are birch bark tar, birch sap juice and pine inner bark.

Today, bioactive compounds from trees are produced in Europe in large amounts. They include compounds that are marketed world-wide as ingredients in so-called dietary supplements and in functional foods. In this section, the development of three products, xylitol, sitosterol and sitostanol, and HMR lignan is described and the development of other products from knots and bark is discussed.

3.8.1 Xylitol – A Caries-Preventing Sugar

Xylitol (Fig. 3.3), produced by acid hydrolysis of xylans, the dominating hemicellulose in deciduous trees, followed by reduction of xylose, was developed as a health product in Finland in the 1970s when research at University of Turku found that xylitol can inhibit tooth decay (Sheinin and Mäkinen 1976). Commercial production of xylitol began in Kotka, Finland, by the Finnish Sugar Company. Xylitol-containing chewing gum was developed and marketed as a product promoting dental health. Since then, xylitol has been found also to inhibit ear infections in children (Uhari et al. 1996). After approval by the United States Food and Drug Administration (US FDA) in 1986, xylitol has spread world-wide, and is now used as a specialty sweetener in large variety of food products.

3.8.2 Sitosterol/Sitostanol for Reducing Blood Serum Cholesterol

Sitosterol (Fig. 3.4), the dominating sterol in plants, including trees, was known already in the 1950s to inhibit the absorption of cholesterol into the blood stream (Miettinen et al. 1995). By the early 1970s sitosterol was being produced in France from tall oil, a by-product from the pulp industry, when it was used mainly in the cosmetic industry. Sitosterol production from sulfate soap, a by-product from chemical pulping, was developed in Finland in the 1970s, and a production plant was built at a pulp mill in Lappeenranta. In 1995, the company Raisio in Finland announced a new margarine product, named Benecol®, containing sitostanol fatty

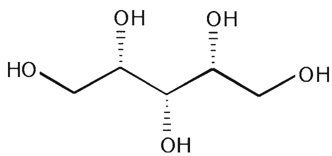


Fig. 3.3 Chemical structure of xylitol

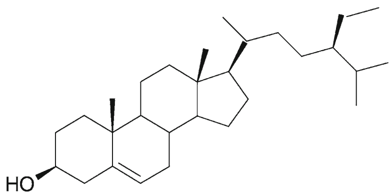


Fig. 3.4 Chemical structure of sitosterol

acid ester as the active ingredient. Sitostanol is the saturated analogue to sitosterol and is produced by catalytic hydrogenation of sitosterol. The Benecol® margarine marketed as a cholesterol-lowering functional food, attracted large attention all over the world.

Today, there are a large variety of Benecol® products: cream cheese, pasta, yoghurts, sour milk, meat products, etc. Several competitors to Benecol® have arisen based on sitosterol fatty acid esters, or mere sitosterol, using the same cholesterol-lowering arguments in their marketing. The total annual production of sitosterol for use in functional foods now exceeds 10,000 t.

3.8.3 HMR Lignan – A New Anticarcinogen and Antioxidant from Spuce Knots

The lignan 7-hydroxymatairesinol (HMR) (Fig. 3.5) is the predominant lignan in spruce wood. It was first identified and its chemical properties described in 1957 (Freudenberg and Knof 1957). Already in the 1970s and 1980s HMR and other spruce lignans were studied at Åbo Akademi. In the early 1990s, researchers at University of Turku tested of HMR for its biomedical properties, initially for its possible estrogenic effects on fish (Mellanen et al. 1996). However, such effects were not found, but when the compound was studied in a breast cancer test, a positive response was obtained. This led Hormos Medical Ltd, a biotechnology company in Turku, to develop HMR as a health product. Further tests were made on rats and significant inhibition of breast cancer growth was documented (Saarinen et al. 2000).

A new and exceptionally rich source of HMR was discovered in 1998, when a knot from a spruce tree (Fig. 3.5) was analyzed at Åbo Akademi. The knot contained as much as 10% lignans and over 7% of HMR. Further research has shown that knots in spruce trees (*Picea abies*) contain on average about 10% of lignans, of which HMR makes up 70–85% (Willför et al. 2003). The variation between knots is large; values ranging from 6% to 29% have been found (Fig. 3.5). The lignan concentrations are 100–500 times higher in the knots than in the surrounding normal stem wood. Spruce trees in Northern Finland contain considerably larger amounts of lignans than trees in south Finland (Piispanen et al. 2008).

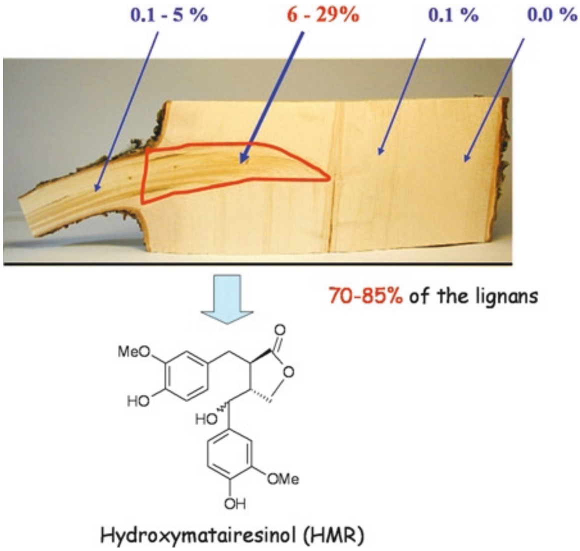


Fig. 3.5 Typical distribution of lignans in spruce wood (*Picea abies*)

The HMR research at University of Turku and Åbo Akademi, and further toxicological and clinical studies undertaken on behalf of Hormos Medical Ltd., provided the necessary data for an application to the U S Food and Drug Administration (FDA). HMR was approved by the FDA to be marketed as dietary supplement in 2004. Hormos Medical then sold a world-wide production and marketing license to Linnea S.A., a phyto-pharmaceutical manufacturing company based in Locarno, Switzerland.

The HMRlignan™ was launched as a dietary supplement on the market in 2006. HMR is a direct, effective precursor to the lignan enterolactone. There is good scientific support also for the statements that plant lignans have a positive influence on the development of breast, prostate and colon cancer which rely specifically on estrogens in order to progress. Lignans can also help to maintain good cardiovascular health and can moderate other estrogen-dependent health problems such as menopause symptoms and osteoporosis (see www.hmrlignan.com).

Production of HMR started in 2005. Spruce chips were taken from a paper mill in northern Finland and processed in southern Finland where clean knot material was separated according to a patented process. The knot material was then delivered to Switzerland where the knots were extracted and the HMR purified by precipitation.

The next stage in the HMR product development is to obtain clearance for using HMR as ingredient in health foods. Research at Åbo Akademi has recently uncovered that HMR exists naturally in cereals, where it is often the predominant lignan, and in oilseeds and nuts (Smeds et al. 2007). This new finding that HMR is a common lignan in foods validates that it is a good choice for inclusion in health foods.

3.8.4 Other Potential Bioactive Compounds from Knots and Bark

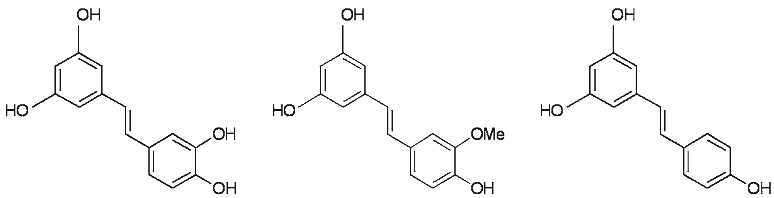
Research on polyphenols in knots started at Åbo Akademi in 1998 and has since become extensive (Holmbom et al. 2007). Knots in about 60 tree species other than spruce have been investigated. In almost all of the species the knots have been found to contain substantially higher concentrations of polyphenols than ordinary stem-wood, for many species 20–100 times more. Knots of softwood species commonly contain 5–15% (w/w) of polyphenols, with lignans as the dominating group. Some tree species also contain large amounts of flavonoids and stilbenes. These studies have documented that knots constitute a very rich source of a wide variety of polyphenols, maybe the richest source in all of nature.

Bark, the protective ‘skin’ of trees is also a rich source of bioactive compounds. Bioactive bark products are already on the market. Pycnogenol is the trade name for extract from bark of the maritime pine (*Pinus pinaster*) growing in the region near to Bordeaux in France. It contains a complex mixture of phenolic compounds, mainly procyanidins and bioflavonoids. It is a powerful antioxidant and is said to be good for cardiovascular health, skincare, diabetes health and inflammations, among others.

Spruce (*Picea* spp.) bark contains large amounts of stilbenes, such as piceatannol (also named astringenin), its methyl ether and resveratrol (Fig. 3.6). Resveratrol which is present also in red wine and other plant extracts is presently of great interest in research because it has been found to extend the lifespan of cells and even mammals and may be developed to an anti-aging drug (Bauer et al. 2006).

3.8.5 Concluding Remarks

Trees live much longer than almost all other organisms and cannot run or move away from threats. They can persist for centuries in a single, fixed location. It is not surprising that trees contain higher concentrations of protective and defensive substances than annual plants. These compounds have been created by natural



Piceatannol (Astringenin) Methyl piceatannol (Isorhapontigenin) Resveratrol

Fig. 3.6 Stilbenes that can be extracted from spruce bark evolution during millions of years to protect the trees from micro-organisms, herbivores, insects and other dangers. The chances of finding more health-promoting compounds in trees seem good.

3.9 Health Benefits of Volatile and Non-Volatile Terpenoids in Some Cupressaceae

Plants produce an imposing variety of chemicals, called secondary products, which are not directly involved in metabolic pathways, but nonetheless have important biological and ecological functions and include substances that protect plants by various means (Harborne and Tomas-Barberan 1991). The terpenoids form by far the largest group. They are highly lipophilic, open chain to ring compounds built from multiples of the 5-carbon (C_5). About 35,000 terpenoids have been described to date, with the huge variation arising mainly from different combinations of isoprene units and stereoisomerism (Connolly and Hill 1991). Terpenoid compounds are ubiquitous in algae, lower plants and especially abundant in conifers and several aromatic angiosperm families. They occur as highly volatile, often pleasant-smelling compounds called essential oils (mostly C_{10} and C_{15} compounds), semi-solid oleoresins (mostly C_{10}, C_{15} and C_{20} compounds) and solid resins (mostly C_{20} compounds in conifers and C_{30} compounds in angiosperms) (Steele et al. 1995). Their main uses include additives to food and beverages in pure form, as herbs and spices which contain numerous essential oils, in folk medicine as well as pharmaceutical preparations including the commercially important anticancer drug Taxol and the antimalarial drug artemisinin (McGarvey and Croteau 1995). Effects of volatile essential oils that permeate the forest atmosphere on mental health have been recorded. Antimicrobial activity and immuno-modulation of terpenoids present in volatile essential oils and resins has also been shown in a number of scientific publications (Yatagai et al. 1995; Barrero et al. 2003). Throughout history, man has found different and varied health and well-being uses for volatile and non-volatile terpenoid extracts from plants in general and forest trees, especially conifers, in particular. Fragrant resins have been employed for thousands of years in making perfumes, unguents and disinfectants by virtually all advanced cultures that had access to these resources. Resin burnt as incense both for religious rites and in traditional medicine is again also frequently recorded in the literature (Claisse 1985; Buhagiar et al. 2000).

The Cypress family (*Cupressacea*e), one of seven in the *Gymnospermae*, is a large widespread family comprising seven subfamilies, 30 genera and over 130 species including recent grouping of members of the *Taxodiaceae* such as the redwoods *Sequoia*, *Sequoiadendron* and *Taiwania* within this family. The largest genera are *Juniperus* (60 spp.), *Cupressus* (15–22 spp.), *Callitris* (16 spp.), *Thuja* (5 spp.) and *Chamaecyparis* (7 spp.). Phylogenetic relationships between members of the Cypress family are useful tools in the search for bioactive principles since these usually occur in related genera (Farjon et al. 2002).

Since antiquity, cypress family members have been important sources of durable wood, as well as resin and essential oils since their wood resists fungal and insect attack. It is recorded that Cicero paid enormous sums of money for table tops made from the wood of one particular species. Their resins are very fragrant when burnt and indeed the resin of some family members was burnt as incense in ceremonial gathering, some of which may have served as mass healing sessions. It is evident that very early on in man's history someone had made the connection that this healing effect was due to something 'magical' present in the wood or resin, and burning them gave these extraordinary properties. A good few cypress family members are mentioned in ancient texts including Egyptian herbals, the Bible, Theophrastus' *Historia Plantarum* (Enquiry into Plants), Ayurvedic literature and Chinese herbals. The essential oil and resin-producing species of a number of cypress family genera such as *Thuja*, *Cupressus* and *Tetraclinis* are additionally given the name of Tree of Life (*Arbor Vitae* in Latin or *Shagjaret al. Hajat* in Arabic) attesting to the life-preserving importance attached to these species in the past. Some of the beneficial properties will now be reviewed.

3.9.1 Health Benefits Reported in the Literature

Volatile monoterpenoid constituents including those of conifer resins are now known to induce various physiological, emotional and behavioral responses. Yatagai et al. (1985, 1995) refer to the beneficial effects of terpenoid emissions in forest air even when present at extremely low concentration ranges of 10–1,000 ppb. Specifically, a low concentration of alpha-pinene reduces tension and mental stress, improves physical and mental health, and helps quick recovery from fatigue. Conversely, high concentrations of the same monoterpenoid result in increased fatigue and the accumulation of stress. Given that volatile terpenoids have an effect that relieves stress and depression; it is perhaps no coincidence that the Etruscans and the Romans buried their dead under Cypress trees, a tradition that carries on in Mediterranean cemeteries to this day.

The use of terpenoid additives in food as a flavor enhancer and long-term preservative to prevent spoilage in stored food also goes back in antiquity. Neolithic pottery dating back to 5000 BC has been shown to have contained resinated wine with a non-conifer resin added to prevent *Acetobacter* from turning wine into vinegar (McGovern et al. 1996). And to this day, resinated wines are still produced for exactly the same reason, but often employing resin from pines and other conifers including that from the sandarac tree *Tetraclinis articulata*. The flavoring of food and gin with berries from *Juniperus communis* can also be mentioned in this context, and it is now known that the monoterpenes such as alpha-pinene, beta-pinene and borneol present in juniper berry and leaf oils, are bactericidal. Conifer resins also contain a variety of diterpene resin acids such as communic acid, which has been shown to have antimicrobial properties (Merzouki et al. 1997; Muhammad et al. 1995).

The ethno-botanical repertoire of some cultures includes varied and sometimes ingenious applications of terpenoid-rich extracts for treating many body aliments and diseases both in humans and in veterinary care. They have been applied externally as disinfectants, parasiticides, antiseptics and stimulants as well as internally for intestinal parasites, diarrhea, flatulence and respiratory problems. Some have been used for thousands of years as perfume, incense and embalming fluid and medicinally as a pain killer, to reduce spasms and fever, to heal wounds and as an ointment for sores, as a sweating stimulant and as a local stimulant to mucous membranes and to neutralize bad breath in oral hygiene (Prendergast et al. 1998). The medicinal action and properties of different oils and resins derived from members of the cypress family are equally versatile. Thus *Cupressus sempervirens* essential oil is described as astringent, antiseptic, deodorant, diuretic, diaphoretic, tonic, expectorant and rubefacient. Sandarac resin derived from the cypress family genera *Tetraclinis* and *Callitris* is reportedly used in the treatment of acute diarrhea, roundworm and tapeworm infestations, hemorrhoids, respiratory ailments, against hemorrhage, in dental fillings, diabetes mellitus, hypertension and cardiac diseases, skin diseases and to treat nervous disorders including depression (Ait Igri et al. 1990; Merzouki et al. 1997; Ziyyat et al. 1997; Eddouks et al. 2002).

The cellular, sub-cellular and biochemical effects of monoterpenoid, sesquiterpenoid and diterpenoid components in the volatile and non-volatile fractions of conifer oleoresin are equally varied. The effect of monoterpenoids on pathogenic and non-pathogenic bacteria and fungi has also been extensively studied and demonstrated both for non-conifer and conifer extracts (Chanegriha et al. 1994). The diterpenoids present in a number of conifers have repeatedly been shown capable of controlling pathogenic fungi and various authors have attributed their use in nature as antifungal agents. Muhammad et al., (1995), report on the isolation of potent antibacterial diterpenes from bark and leaves of *Juniperus procera* namely (+)-E-communic acid, (+)-Z-communic acid (labdane diterpenes) and totarol (totarane diterpenes), amongst others. Totarol is a highly hydrophobic bacteriostatic diterpenoid originally isolated from *Podocarpus* species (Totara pine) that has been found to have potent activity on *Mycobacterium* species – the causative agent of tuberculosis. Evans et al. (2000), also report on the antibacterial activity of totarol, its chemical analogues and derivatives, on drug resistant gram-positive bacteria (lactamase-positive and gentamycin-resistant *Enterococcus faecalis*, penicillin-resistant *Streptococcus pneumoniae* and methicillin-resistant *Staphylococcus aureus* (MRSA)). Pimarane diterpenoids isolated from North American white cedar (*Thuja occidentalis, Cupressaceae*) have also been shown to possess a range of biological activity including anti-tuberculosis effect and inhibitory effects on growth of fungal mycelium (Chang et al. 2000).

Apart from antimicrobial activity, additional bioactive properties are reported for diterpenoid compounds isolated from cypress family tree species. Shimizu et al. (1988) report on the anti-inflammatory effect of topically applied crude extracts of the conifer *Cryptomeria japonica* containing several types of pimarane diterpenoids. Similar immunomodulatory effects are reported for a number of pimarane diterpenoids isolated from leaves and wood of *Tetraclinis articulata* (Barrero et al. 2003). Minami et al. (2002) report on the antitumor and antiviral potential of labdane-type diterpenes isolated from *Pinus luchensis* but known to be present also in several members of the *Cupressaceae*. Other diterpenoids present in cypress family members as well as angiosperms have been found to induce massive cell death by apoptosis in a range of cancer cells by causing G_0/G_1 or G_2/M cell cycle arrest, DNA fragmentation into nucleosomal fractions, accumulation of cells with sub-G_1 DNA content and appearance of nuclear condensation, all being features typical of apoptosis (Dimas et al. 2001).

Bioprospecting for drugs is attracting increasing interest from drug companies. Given the huge number of terpenoid chemicals produced by plants, the range of cellular targets that they affect and the fact that certain terpenoid constituents appear repeatedly in those extracts that have medicinal applications, the importance of this class of secondary products to human health and well being, is bound to increase.

3.10 Conclusions

Forests are a rich renewable source of health-promoting and medicinal products. Not only the trees but also berries, nuts and mushrooms in forests contain a multitude of natural bioactive compounds which can be used in health-promoting products and medicines. In addition to the main structural components that trees contain, namely cellulose, hemicelluloses and lignin, thousands of bioactive compounds have been identified.

Forest products have always had a key role in traditional medicine which continues to be of great importance, especially in developing countries. In the industrialized countries, the pharmaceutical industry is again increasingly looking at plant-derived natural drugs. Plant-derived compounds help to build a bridge between the traditional medical drugs in developing countries and the modern pharmaceuticals in the developed countries. Plant-derived bioactive compounds serve especially as preventive agents helping to maintain health.

Today bioactive compounds from forests have been developed and are produced in Europe in large amounts for worldwide markets. New health-promoting products could be produced in large quantities especially from knots and bark. The research tools necessary for exploring these possibilities have developed dramatically during the last 30–50 years and continue to improve. We are confident that there are good prospects for identifying and exploiting further chemicals and products from temperate forests.

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