

Chapter 2

The Chemical Diversity of Bioactive Molecules and Therapeutic Potential of Medicinal Plants

K.G. Ramawat, S. Dass and Meeta Mathur

Abstract The therapeutic use of herbs is as old as human civilization and has evolved along with it. The vast majority of people on this planet still rely on their indigenous system of medicine and use herbal drugs. The Indian and Chinese systems of medicine are well established with written records going back around 3000 years. Medicinal plant drug discovery continues to provide new and important leads against various pharmacological targets including cancer, malaria, cardiovascular diseases and neurological disorders. Interest in herbal drugs and natural medicine is undergoing a renaissance at the present time. The medicinal properties of plants are due to the presence of active principles. These bioactive secondary metabolites are synthesized by two principal pathways: shikimic acid or aromatic amino acid, and mevalonic acid. Alkaloids, phenolics and terpenoids constitute many pharmacologically active compounds. Several natural-product drugs of plant origin have either recently been approved by the US Food and Drug Administration (FDA), including arteether, galanthamine and triptopium, or are in clinical trials. Although drug discovery from medicinal plants continues to provide an important source of new drug leads, this work is constrained by the unavailability of sufficient plant material, selection and implementation of appropriate high-throughput screening bioassay and the production of bioactive compounds in large quantities. This article reviews the use of herbs in traditional systems and bioactive therapeutic molecules responsible for this activity.

Keywords Herbal drugs · Traditional medicine · Secondary metabolites · Alkaloids · Terpenes · Polyphenolics

2.1 Introduction

The world's population will be more than 7.5 billion in the next 10 to 15 years. This increase in population will occur mostly in the southern hemisphere, where 80%

K.G. Ramawat (✉)

Laboratory of Biomolecular Technology, Department of Botany, M.L. Sukhadia University, Udaipur-313001, India,
e-mail: kg_ramawat@yahoo.com

of the population still relies on a traditional system of medicine based on herbal drugs [1]. As civilizations grew from 3000 BCE onwards in Egypt, the Middle East, India and China, the uses of herbs became more sophisticated and written records were prepared. The specific plants to be used and the methods of application for particular ailments were passed down through oral history. Later on, information regarding medicinal plants was recorded in herbals [2]. Historically, herbal drugs were used as tinctures, poultices, powders and teas followed by formulations, and lastly as pure compounds. Medicinal plants or their extracts have been used by humans since time immemorial for different ailments and have provided valuable drugs such as analgesics (morphine), antitussives (codeine), antihypertensives (reserpine), cardiotonics (digoxin), antineoplastics (vinblastine and taxol) and anti-malarials (quinine and artemisinin). Some of the plants which continue to be used from Mesopotamian civilization to this day are *Cedrus* spp., *Cupressus sempervirens*, *Glycirrhis glabra*, *Commiphora wightii* and *Papaver somniferum* [1, 3, 4]. About two dozen new drugs derived from natural sources were approved by the FDA and introduced to the market during the period 2000–2005 and include drugs for cancer, neurological, cardiovascular, metabolic and immunological diseases, and genetic disorders [5]. Seven plant-derived drugs currently used clinically for various types of cancers are taxol from *Taxus* species, vinblastine and vincristine from *Catharanthus roseus*, topotecan and irinotecan from *Camptotheca accuminata*, and etoposide and teniposide from *Podophyllum peltatum* [6]. It is estimated that the worldwide market potential for herbal drugs is around US\$40 billion [6]. A similar situation also exists for plant-based food additives, fragrances and biopesticides. Mostly, herbal drugs are collected from the wild, and relatively few species are cultivated. Overexploitation of plants, particularly when roots, tubers and bark are used for commercial purposes, has endangered 4,000 to 10,000 species of medicinal plants [7]. To counter overexploitation of natural resources and the consequent threats to biodiversity, alternative biotechnological methods and sustainable practices have been recommended. Several world organizations and governments have established guidelines for the collection and utilization of medicinal plants [8, 9].

2.2 Traditional Use of Medicinal Plants

Traditional medicine is the sum total of the knowledge, skills and practices based on the theories, beliefs and experiences indigenous to different cultures used in the maintenance of health, prevention of diseases and improvement of physical and mental illness. In practice, traditional medicine refers to the following components: acupuncture (China), Ayurveda (India), Unani (Arabic countries), traditional birth attendant's medicine, mental healer's medicine, herbal medicine, and various forms of indigenous medicine. Complementary or alternative medicine refers to a broad set of healthcare practices that are not part of a country's own tradition and are not integrated into the dominant healthcare system. Traditional medicine has maintained its popularity in all regions of the developing world, and its use is rapidly spreading in industrialized countries [1]. Knowledge of plants and of healing have been

closely linked from the time of human beings' earliest social and cultural groupings. The medicine man was usually an accomplished botanist. Even in historical times, botany and medicine continued to be virtually one and the same discipline until about 1500 CE, when they began to separate from their close association, to the advantage of both sciences.

Knowledge of the medicinal plants used in the drugs of traditional systems of medicine (TSM) has been of great significance, especially as a lead for the discovery of new single-molecule medicines for modern system of medicine. To determine the chemical nature of such compounds, isolation of a substance in pure form using various separation techniques, chemical properties and spectral characteristics are a prerequisite for establishing its correct structure. Thus, medicinal plants are used in crude or purified form in the preparation of drugs in different systems. In countries like India, China and others with well-founded traditional systems of medicine, plant-based formulations occupy an important place in health management [1–10]. However, the recent broadening of the horizons of drug discovery, due to advances in instrumentation and bioinformatics (computational methods), has opened up new avenues for use of this knowledge in drug development research [2–5]. Structural novelty and new modes of action are common features of plant drugs. This has been shown by anticancer agents like vinblastine, vincristine and paclitaxel, cardiovascular agents like forskolin, anti-HIV agents like calanoid, and antihyperlipidemic agents like guggulsterones.

2.3 Ancient Systems of Medicine

2.3.1 *Traditional Indian Medicine*

The word Ayurveda is derived from 'Ayur', meaning life, and 'veda', meaning knowledge. Ayurveda means the science of life. It is an ancient system of health care and longevity. Ayurveda takes a holistic view of human beings, their health and illness. It aims at positive health, which has been defined as a well-balanced metabolism coupled with a healthy state of being. Disease, according to Ayurveda, can arise from the body and/or mind due to external factors or intrinsic causes. Ayurvedic treatment is aimed at the patient as an organic whole and treatment consists of the salubrious use of drugs, diet and certain practices. This doctrine was conceived when science was not developed enough to understand even the human body, let alone drug molecules [6–11].

Ayurveda, perhaps the most ancient of all medicine traditions, is probably older than traditional Chinese medicine. The origin of Ayurveda is lost in prehistoric antiquity, but its characteristic concepts appear to have matured between 2500 and 500 BCE in ancient India. The earliest references to drugs and diseases can be found in the Rigveda and Atharvaveda, dating back to 2000 BCE. Atharvaveda, comprised of 6599 hymns and 700 prose lines, is considered as the forerunner of Ayurveda.

The ‘Samhitas,’ or encyclopedia of medicine, were written during the postvedic era, and include ‘Charak Samhita’ (900 BCE), ‘Sushruta Samhita’ (600 BCE) and ‘Ashtang Hridaya’ (1000 CE). Later on, many more treatises were prepared and the use of medicinal plants is described in ‘Nighantu Granthas’ between the 7th and 16th centuries. The most basic concept of Ayurveda is that all living beings derive their subsistence from three essential factors (three doshas), namely vaata, pitta and kapha, which operate in unison. It believes that the human body is composed of living and non-living environments including earth, water, fire, air and space. Illness is the consequence of imbalance between the various elements, and it is the goal of treatment to restore this balance [11, 12].

Ayurvedic drugs are also attracting much attention for diseases for which there are no or inadequate drugs for treatment in modern medicine, such as metabolic and degenerative disorders. Most of these diseases have multifactorial causation, and there is a growing realization that in such conditions, a combination of drugs, acting at a number of targets simultaneously, is likely to be more effective than drugs acting at one target. Ayurvedic drugs, which are often multicomponent, have a special relevance for such conditions [12]. For various reasons, Ayurveda has not incorporated much of modern science/scientific tools. Investigation of the biological activity of multicomponent Ayurvedic drugs will bring Ayurveda into the mainstream of scientific investigations.

2.3.2 *Traditional Chinese Medicine*

Traditional Chinese medicine (TCM) has been in practice for more than 200 years and includes acupuncture, massage (tuina), breathing exercise (qi gong) and dietary therapy. TCM has been an integral part of China’s healthcare system along with conventional Western medicine. TCM products were safe and effective for the treatment of many human diseases before Western medicine was introduced in China. Famous texts in TCM include the *Yellow Emperor’s Inner Classic* (Hung Di Nei Jing; ~200 BCE to 100 CE), *Divine Husband-man’s Classic of Materia Medica* (Shen Nong Ben Cao Jing; 25-220 AD) and cold-induced disorders (Shang han Lun; 220 AD). The most complete reference to Chinese herbal prescriptions is *Chinese Materia Medica*, published in 1977. It lists nearly 6000 drugs, of which 480 are of plant origin. This ancient system of medicine, believed to be more than 5000 years old, is based on two separate theories about the natural laws that govern good health and longevity, namely ‘Yin and Yang’, which are in opposition to each other, and the five elements (wu xing). The five-element theory is similar to the four humours and elements of the Greeks or the three humours of Ayurveda. The five elements are earth, metal, water, wood and fire, each of which is linked to the main organ systems of the body—spleen, lungs, kidney, liver and heart, respectively. It considers that an unbalanced diet, lifestyle or environment will disrupt the body balance, which in turn manifests as symptoms of diseases. The aim of the practitioner of TCM is to restore health by removing the cause, correcting abnormal functioning,

opposing the imbalance and normalizing the flow of energy. *Angelica polymorpha* var. *sinensis*, *Artemisia annua*, *Ephedra sinica*, *Paeonia lactiflora*, *Panax ginseng*, *Rheum palmatum* and *Peuraria lobata* constitute the important medicinal plants of TCM [3, 13, 14].

2.3.3 Traditional Egyptian Medicine

Although Egyptian medicine dates from at least 3000 BCE, the last known and most important pharmaceutical record is the *Papyrus Ebers* (1500 BCE). Use of *Ricinus communis* seeds, *Citrilus colocynthes*, *Senna alexandrina* and *Prunica granatum* roots in large quantities is mentioned in the ancient Egyptian literature. These uses were later documented by the Greek physician Dioscorides (100 CE). Writings of the Greeks, such as Hippocrates (460–377 BCE) and Galen (130–200 CE), also used parts of the *Papyrus Ebers*. Therefore Greek, and ultimately modern, medicine has its origin in Egyptian or Nile Valley civilization [15].

2.3.4 Traditional Arabic Medicine

The Babylonians, Assyrians and Sumerians comprise one of the oldest civilizations, and several plants were domesticated during this early period. Several medicinal plants are mentioned in civil laws carved on stone and commissioned by the King of Babylon (1700 BCE). The Arabs established drugstores in the eighth century, and the Persian pharmacist Avicenna described all Greco-Roman medicine in his book *Canon of Medicine*. This text forms the basis of distinct Islamic healing system known today as Unani-Tibb. *Papaver somniferum* was known to the Sumerians in 4000 BCE as *hul gil* (joy plant). The most frequently used medicinal plants in the Middle East are: *Allium cepa*, *Astracantha gummifera*, *Carthamus tinctorius*, *Carum carvi*, *Ferula asafoetida*, *Lawsonia inermis*, *Papaver somniferum*, *Peganum harmala*, *Prunus dulcis*, *Prunica granatum*, *Salvadora persica*, *Senna alexandrina*, *Sesamum indicum*, *Trachyspermum ammi*, *Trigonella foenum-graecum* and *Vitis vinifera* [3, 16].

2.3.5 African, European and Other Traditional Systems of Medicine

Africa is considered the cradle of *Homo sapiens*' emergence. Though traditional African medicine is the oldest and perhaps the most diverse of all healthcare systems [3], detailed documentation on the use of medicinal plants in Africa is lacking. With rapid urbanization, traditional oral knowledge is dwindling fast, e.g. knowledge of traditional oral knowledge of the Khoisan, the Nguni and the Sotho-speaking peoples [17]. Traditional African medicine is holistic, involving both body and

mind. Famous African medicinal plants include *Acaccia senegal* (source of gum Arabic), *Aloe ferox*, *Aloe vera*, *Artemisia afra*, *Asplanthus linearis*, *Boswellia sacra*, *Catha edulis*, *Commiphora myrrha*, *Harpagophytum procumbens*, *Catharanthus roseus*, etc.

Like Africa, South American countries are also rich in biodiversity and diverse healing cultures, but information on the use of medicinal plants is sparse. The famous medicinal plants from this region are *Cinchona pubescens*, *Erythroxylum coca*, *Ilex paraguariensis*, *Paullinia cupana*, *Spilanthes acmella* and *Uncaria tomentosa*. The European healing system is believed to have originated with Hippocrates (460–377 BCE) and Aristotle (384–322 BCE). Subsequent naturalists like Theophrastus (~300 BCE), Dioscorides (100 CE) and the pharmacist Galen (130–200 CE) recorded the use of medicinal plants. The philosophy was based on the belief that the body is composed of earth, wind, fire and water, similar to the Indian system [14]. The famous book *De Materia Medica* by the Greek physician Dioscorides was the standard reference in Europe for more than 1000 years. The use of herbal teas and decoctions is still very popular in Europe, e.g. teas prepared from *Humulus lupulus*, *Rosmarinum officinalis*, *Hypericum perforum* and *Valeriana officinalis* [14].

Though traditional and alternative medicine and its practitioners exist in Europe, it is not officially recognized and is punishable under the law in France, Italy, Spain and other countries, while it is unregulated in UK. This requires provisions in pharmacopoeias to include herbal drugs. Allopathic medicine is practiced predominantly in developed countries, and herbal drugs are categorized as food supplements and are not reimbursed by the social security system.

2.4 Exploration of Medicinal Plants

Plants are a great source of therapeutic molecules. In the early 20th century, taxonomic surveys established the identity of plants, followed by ethnomedical surveys documenting the use of plants as medicine and other uses. The identification of active principles of medicinal plants leads to the use, misuse and abuse of substances of vegetal origin. The use may be curative (e.g. vincristine and vinblastine, reserpine, ephedrine, aspirin, morphine, digoxin) or narcotic abuse (cocaine, morphine and cannabis), and misuse has made several plants endangered species, e.g. *Podophyllum hexandrum*, *Taxus baccata*, *Coptis teeta*, *Picrorhiza kurroa* and *Nardostachys jatamansi* [18]. This overexploitation has resulted in depletion in germplasm resources, particularly in Third World countries, and urgently warrants the development of alternative biotechnological methods for micropropagation, the study of seed and reproductive biology, and, last but not least, social awareness [11]. It is estimated that approximately 1500 plant species in India are threatened including 124 endangered species [19]. About 250,000 species of higher plants are yet to be investigated for pharmacological activity. Plants can be a source of effective remedies for Alzheimer's, Parkinson's, epilepsy, migraine, arthritis and schizophrenia. Increased demand for natural drugs has led to the domestication of several plants such as

Catharanthus roseus and *Taxus baccata*, and several others (*Psoralea corylifolia*, *Carthamus tinctorius*) are being evaluated for agronomic traits [9, 11, 20].

Secondary metabolites have evolved in nature in response to needs and challenges of the plant environment. Nature has been carrying out its own combinatorial chemistry for over three billion years [21]. The total number of natural products produced by plants has been estimated at over 500,000 [22]. Ethnobotanical and traditional usage of medicinal plants serves as a source of information for the isolation of active compounds, e.g. as direct therapeutic agents (D-tubocurarine from *Chondrodendron tomentosum*), as the starting drug for semisynthesis (diosgenin from *Dioscorea floribunda*), the model drug for new synthetic drugs (cocaine from *Erythroxylum coca*), for the synthesis of local anaesthetics and, lastly, as taxonomic markers for identification [2, 3, 23]. Drug discovery from plants requires the combined efforts of botanists, pharmacognosists, phytochemists and other scientists to screen the products. Improvements in isolation techniques to meet the demand for pharmacology, the generation of large numbers of samples from correctly identified plants from the tropics for high-throughput screening, elaborate arrangements for preclinical (pharmacology, toxicology, pharmacokinetics and drug delivery) and, lastly, for clinical trials are required for drug development. This process may take more than 10 years [24].

2.5 Approaches to Drug Discovery

Isolation of compounds in their pure form and evaluating them for their pharmacological properties leading to drug discovery is a long, tedious, time-consuming and expensive path. Drug discovery from natural sources has become very expensive (currently estimated at US\$500 million) and time consuming (5 to 6 years in the 1980s to 15 to 22 years in the 21st century). Two-thirds of the cost goes to leads that fail during the clinical trials [25]. Fifty percent of all potential drugs fail because of adsorption, distribution, metabolism, excretion or toxicity problems [26]. Due to the long periods involved in discovery and preclinical and clinical trials, which require large numbers of volunteers (1000 to 5000 for long-term effects), many companies have abandoned the search for natural products and turned their attention towards combinatorial chemistry and modification/analogue synthesis of existing drugs. Therefore, the new approaches like metabolomics and high-throughput screening (HTS) are used to screen and evaluate several metabolites in a short time.

In the postgenomic era, pharmaceutical researchers are evaluating vast numbers of protein sequences to formulate novel strategies for identifying valid targets and discovering leads against them [27]. Modern drug discovery often involves screening small molecules for their ability to bind to a preselected protein target. Drug discovery can also involve screening small molecules for their ability to modulate biological pathways in cells or organisms, without regard to any particular protein target. Thus, the establishment of various techniques of the genomic sciences, such as rapid DNA sequencing, together with combinatorial chemistry, cell-based assays

and automated HTS, has led to a new concept of drug discovery [28]. In this concept, interaction between biologists and chemists, as well as scientific reasoning, has been replaced by a very high number of samples processed. With rapid industrialization, an HTS system has been developed to screen not just a few hundred but hundreds of thousands of chemical compounds in a short amount of time. HTS was created in the early 1990s for the rapid screening of large numbers of extracts/compounds. This requires the identification of disease-specific targets by basic research or by a genomic approach, which is used to design/develop a bioassay used in the HTS system [29]. Under an HTS setup, large numbers of hypothetical targets are incorporated into cell-based assays and exposed to large numbers of compounds representing numerous variations on a few chemical themes. It is assumed that this experimental design would be suitable to identify many substances, which can modify the target in question. Such molecules are then isolated in greater quantity and evaluated on more complex models (cells, animals) to a certain efficacy. About 50 million screening tests have been conducted so far using different molecules, different concentrations and different bioassays [28]. These technologies generated vast amounts of information on natural products obtained from plants and microorganisms and have had a historic impact on modern medicine.

New bioactive molecules are desirable to pharmaceutical companies for their growth and economic viability. Previously, the search for new bioactive molecules was carried out either by activity-based separation and purification or by pure compounds obtained through slow and tedious chemical methods. These methods were time consuming, yielded a small number of products, and resulted in the failure of the product/process using critical evaluation parameters at various stages of clinical/toxicological tests. The history of gene expression analysis began when laboratory methods were developed to examine the expression of individual known genes. The northern blot technique, developed in the late 1970s, hybridizes labelled DNA or RNA probes of known genes to RNA blots. The resulting expression patterns of mRNA transcripts can then be read [30]. Now technology has reached its pinnacle where large numbers of genes can be sequenced or gene products can be analyzed. The ability to rapidly survey and compare gene expression levels between reference and test samples using new technology such as differential display, READS (improved differential display), expressed sequence tag (EST), serial analysis of gene expression (SAGE), and DNA microarray has made drug discovery genome oriented. By comparing gene products of two samples it is possible to identify gene products or disease targets. To find new drugs in the postgenomic era, pharmaceutical researchers must evaluate vast numbers of protein sequences and formulate novel intelligent strategies to identify valid targets and discover promising molecules against them. This is helpful in the identification of small molecules that selectively target proteins. By identifying protein function first, efficacy is gained that makes it possible later on to focus resources on protein families of interest [27]. Although the sequencing of the human and other genomes is a result of the synergy between innovations in automation and bioinformatics, it is in principle a breakthrough in synchronous use and process management. New technologies offer rapid and simultaneous analysis of the sequence and function of all genes in the genome.

Mass sequencing is done today in factory-like setups, with many to several hundred sequencers running 24 h, 7 d a week [31]. The companies involved in such work are Incyte Pharmaceuticals, Human Genome Sciences, Millennium, and PE Celara. These known sequences will be useful in the rapid drug discovery for target diseases and in the identification of lead molecules [29].

2.6 Bioactive Molecules of Medicinal Plants

Plant cells produce two types of metabolites. Primary metabolites are involved directly in growth and metabolism, viz. carbohydrates, lipids and proteins. Primary metabolites are produced as a result of photosynthesis and are additionally involved in cell component synthesis. Most natural products are compounds derived from primary metabolites such as amino acids, carbohydrates and fatty acids and are generally categorized as secondary metabolites. Secondary metabolites are considered products of primary metabolism and are generally not involved in metabolic activity viz. alkaloids, phenolics, essential oils and terpenes, sterols, flavonoids, lignins, tannins, etc. These secondary metabolites are the major source of pharmaceuticals, food additives, fragrances and pesticides [4, 6, 32, 33].

In general, primary metabolites obtained from higher plants for commercial use are high-volume, low-value bulk chemicals. They are primarily used as industrial raw materials, foods or food additives such as vegetable oils, carbohydrates (sucrose, starch, pectin and cellulose) and proteins. It is the medicinal plants that are rich in secondary plant products, and it is because of these compounds that these are termed 'medicinal' or 'officinal' plants. These secondary metabolites exert a profound physiological effect on mammalian systems; thus they are known as the active principle of plants. With the discovery of the physiological effect of a particular plant, efforts are being made to know the exact chemical nature of these drugs (called active principle) and, subsequently, to obtain these compounds by chemical synthesis [4].

Here we present a brief account of physiologically active primary and secondary metabolites, and more prominent compounds belonging to the alkaloid, terpenoid and phenolic groups. This will provide readers an overview of the biosynthesis, diversity and distribution of such compounds.

Besides secondary plant products, several primary metabolites exert strong physiological effects. In this category, proteins are the principal compounds having such diverse functions as blood agglutinants from Fabaceae, hormones (e.g. insulin), various snake venom poisons, ricin from *Ricinus communis*, and abrine and precatorine from *Abrus precatorius*. Other examples of primary metabolites exerting a strong physiological effect include certain antibiotics, vaccines and several polysaccharides acting as hormones or elicitors [34, 35].

The carbon skeleton of all the compounds are derived from carbohydrates synthesized by photosynthesis. The synthesis of various classes of secondary metabolites from primary metabolites is presented in schematic form in Fig. 2.1. The majority

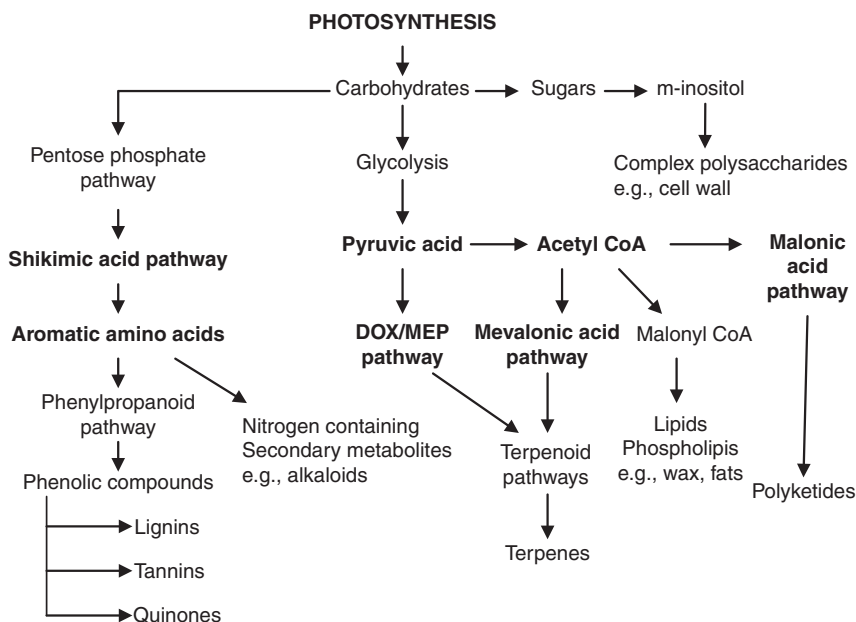


Fig. 2.1 Principal biosynthetic pathways leading to synthesis of secondary metabolites

of secondary metabolites are synthesized via two principal biosynthetic pathways: (1) shikimic acid pathway producing a pool of aromatic amino acids, which in turn are converted into diverse compounds such as phenolics (lignins, tannins, quinones) and alkaloids [36], and (2) acetyl-CoA mevalonic acid pathway, leading to a vast array of terpenoids [37].

2.6.1 Alkaloids

Around 12,000 alkaloids of various types have been known to occur in all land plants, including more than 150 families. The important families are Apocynaceae, Papaveraceae, Fabaceae, Ranunculaceae, Rubiaceae, Rutaceae, Solanaceae, and less common lower plants and fungi (ergot alkaloids). In plants, alkaloids generally exist as salts of organic acids like acetic, oxalic, citric, malic, lactic, tartaric, tannic and other acids. Some weak basic alkaloids (such as nicotine) occur freely in nature. A few alkaloids also occur as glycosides of sugar such as glucose, rhamnose and galactose, e.g. alkaloids of the solanum group (solanine), as amides (piperine), and as esters (atropine, cocaine) of organic acids [4, 38].

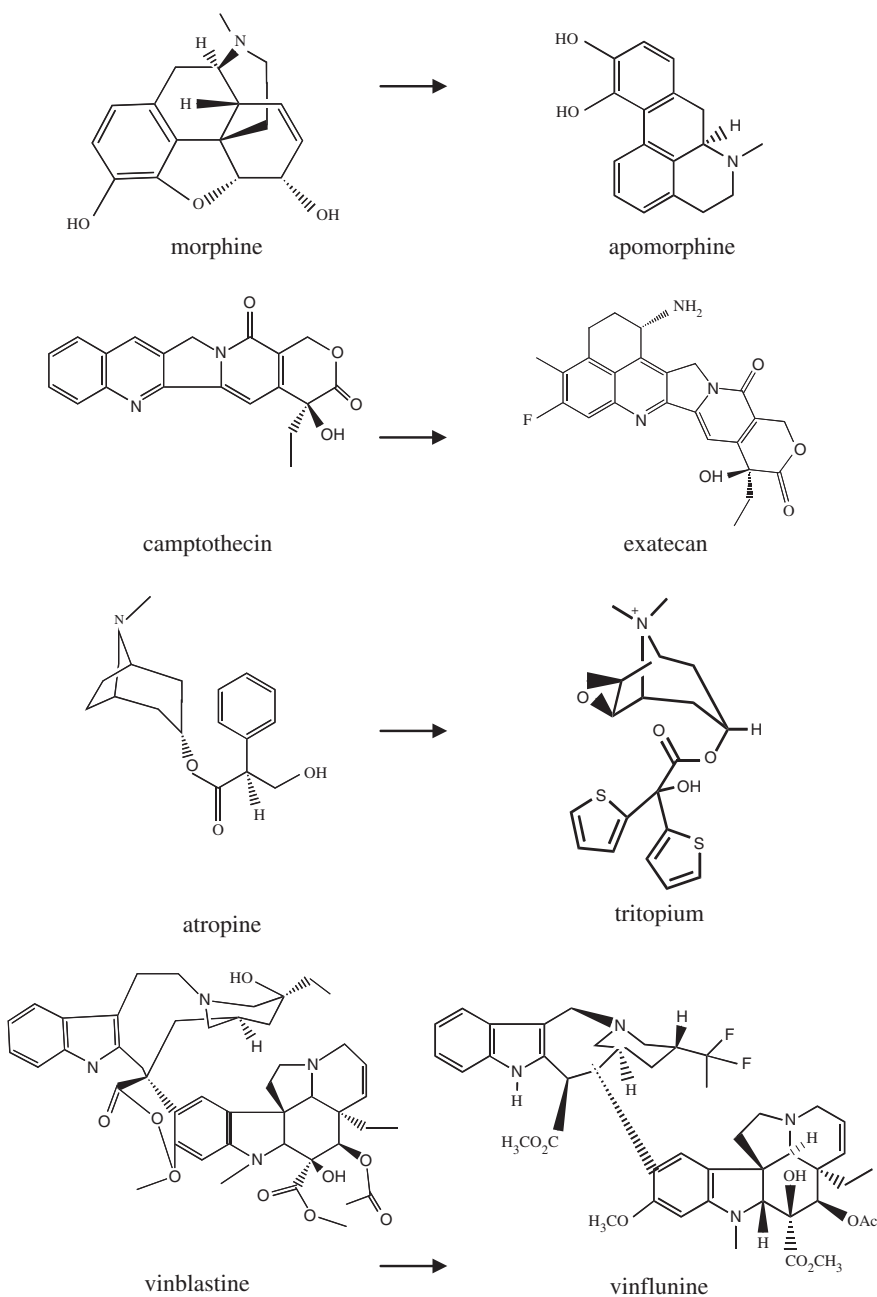
In plants, alkaloids may be present systematically in whole plants, or they may be accumulated in large amounts in specific organs like roots (aconite, belladonna), stem bark (cinchona, pomegranate) and seeds (nux vomica, *Areca*). In angiosperms, alkaloids are more common in dicots than in monocots.

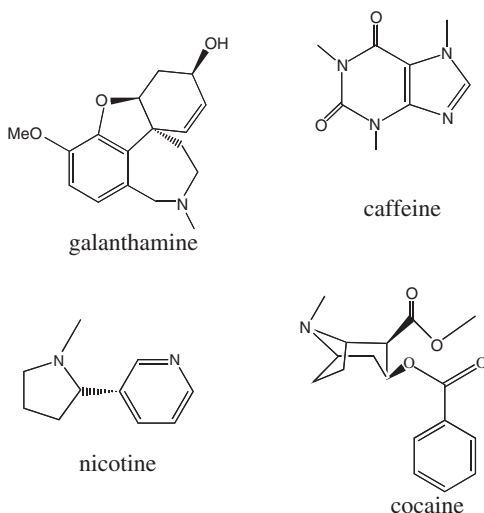
Alkaloids have known to humans for several centuries. They are a diverse group of low-molecular-weight, nitrogen-containing compounds found in about 20% of plant species (Fig. 2.2). Morphine, an alkaloid from latex of the opium poppy, was isolated by F.W. Serturmer in 1806, whose structure could be confirmed in 1952 due to the stereochemical complexity of the molecule [39]. Later on, other alkali-like active principles were isolated and identified, e.g. narcotine in 1817 by Robiquet, emetine in 1817 by Pelletier and Magendie, and so on. The term 'alkaloid' was coined by W. Meibner, a German pharmacist, meaning 'alkali like'. Later it was demonstrated that the alkalinity was due to the presence of a basic nitrogen atom. The first alkaloid synthesized was coniine in 1886 by Ladenburg, which had already been isolated in 1827 [4].

According to Pelletier [40] "an alkaloid is a cyclic organic compound containing nitrogen in a negative oxidation state which is of limited distribution among living organisms". Sometimes it is not possible to draw a clear line between true alkaloids and certain plant bases. Simple bases, such as methylamine, trimethylamine and other straight-chain alkylamines, are not considered alkaloids. Other compounds such as betaines, choline and muscarine (present in fig agaric, *Amanita muscaria*) are also excluded from alkaloids by some experts. These compounds are synthesized from amino acids and categorized as biological amines or protoalkaloids because their nitrogen is not involved in a heterocycle system. Similarly, polyamines (putrescine, spermine, spermidine) are also excluded. Some authorities even exclude the phenylalkylamines, such as β -phenylethylamine (mistletoe, *Viscum album*; barley, *Hordeum vulgare*), dopamine (banana, *Musa sapientum*), ephedrine (Ma huang, *Ephedra sinica*), mescaline (peyote, *Lophora williamsii*) and tryptamine (*Acacia* species). Widely distributed vitamin B₁ (thiamine) is not categorized as an alkaloid even though it contains a nitrogen in heterocycle and has physiological activity. Similarly, purine-based compounds (caffeine, theophylline, theobromine) are also excluded by some workers, as they are not derived from amino acids [4]. However, a neutral compound such as colchicine from autumn crocus (*Colchicum autumnale*), in which the nitrogen is present in an amide group, is an alkaloid because of other traits like medicinal properties and restricted distribution in plants. Other examples of neutral compounds such as alkaloids are piperine from black pepper (*Piper nigrum*), indicine-n-oxide (*Heliotropium indicum*), di-n-oxide trilupine (*Lupinus barbariger*, *L. laxus*), betaines e.g. stachydrine (*Medicago sativa*) and trigonelline (in fenugreek, garden peas, oats, potatoes, coffee, hemp) [4].

The potent physiological activity of many alkaloids has also led to their use as pharmaceuticals, stimulants, narcotics and poisons. Alkaloids currently in clinical use include the analgesics morphine and codeine, the anticancer agent vinblastine, the gout suppressant colchicine, the muscle relaxant (+) tubocurarine, the antiarrhythmic ajmalicine, the antibiotic sanguinarine and the sedative scopolamine. The plant alkaloids like caffeine in tea and coffee and nicotine in all preparations (smoking, chewing) of tobacco are widely consumed daily [4].

Piperidine alkaloids such as coniceine, coniine and *N*-methyl coniine are present in *Conium maculatum*. Apart from tobacco alkaloids, nicotinic acid and its derivatives are a major pyridine alkaloid present in plants. The most commonly occurring

**Fig. 2.2** Alkaloids

**Fig. 2.2** (continued)

compound is trigonelline (*N*-methyl-nicotinic acid), which is present in *Trigonella foenum-graecum*. Anticholinergic alkaloids hyoscyamine, atropine and hyoscyne (scopolamine) are found principally in plants of the family Solanaceae. *Datura* species contain more than 30 alkaloids. *D. stramonium* and *D. innoxia* are the main sources of hyoscyamine and scopolamine respectively. Other species known to contain tropane alkaloids are *Atropa belladonna* (Deadly nightshade), *Hyoscyamus niger* (Henbane), *H. muticus*, *Dubosia* hybrids, *D. myoporoides* and *D. leichhardtii* [41]. Nicotine and tropane alkaloids are formed in the roots and transported to the aerial parts of the plant [42]. The tropane alkaloids possess an 8-azabicyclo octane nucleus and are found in plants of three families, Solanaceae, Erythroxylaceae and Convolvulaceae. The attractive berries of these plants contain these alkaloids, which are toxic. Fewer than three berries of Henbane (*Hyoscyamus niger*) or deadly nightshade (*Atropa belladonna*), both of which contain scopolamine and hyoscyamine, can cause death in infants. Both the tropane ring moiety of the tropane alkaloids and the pyrrolidine ring of nicotine are derived from putrescine by way of *N*-methyl putrescine (Fig. 2.3). Because putrescine is metabolized to polyamines such as spermidine and spermine, the *N*-methylation of putrescine catalysed by putrescine *N*-methyltransferase is the first committed step in the biosynthesis of these alkaloids [43, 44].

Galanthamine hydrobromide is an Amaryllidaceae alkaloid obtained from *Galanthus* and *Crinum* species that has been used traditionally in Russia, Bulgaria and Turkey for neurological conditions. It is currently obtained by synthesis and used as an acetyl cholinesterase inhibitor in the treatment of Alzheimer's disease [45].

Cocaine in Coca (*Erythroxylum coca*) was the first local anaesthetic to be discovered. Leaves of a few species of *Erythroxylum*, indigenous to Peru and Bolivia,

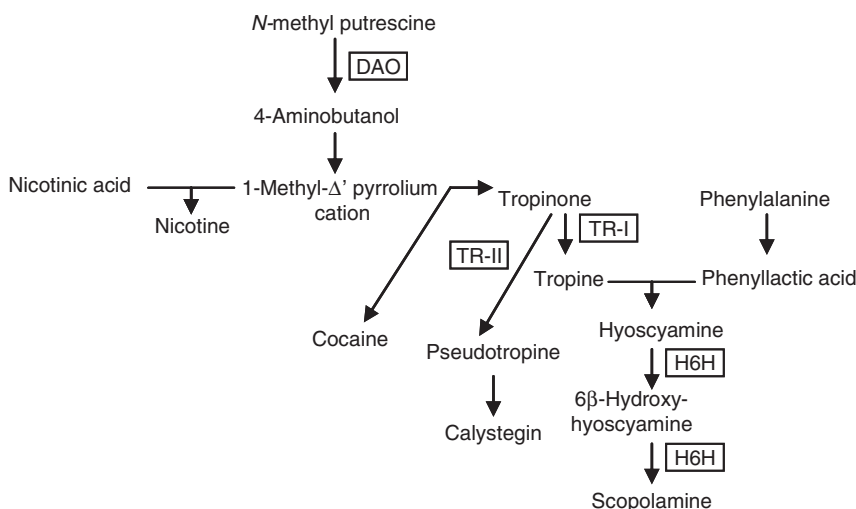


Fig. 2.3 Biosynthesis of tropane alkaloids from N-methyl putrescine

contain 0.6 to 1.8% cocaine. The leaves of the plant have been used for centuries by natives to increase endurance and to promote a sense of well-being. Cocaine was isolated in 1859 by A. Niemann for its central-nervous-system-stimulating activity, which can lead to dependence liability; cocaine has been a drug of abuse. These alkaloids are synthesized from tropic acid. Outside the Solanaceae, tropane alkaloids occur in two other plant families. Within the Erythroxylaceae, the genus *Erythroxylon* comprises about 200 widely distributed, tropical species found mainly in S. America and Madagascar. *E. coca* is the only plant currently cultivated for cocaine production.

About 2500 benzyl isoquinoline alkaloids have been isolated from diverse taxa, including well-established drugs like morphine, sanguinarine, berberine and palmatine. The biosynthesis of these alkaloids begins with the conversion of tyrosine into dopamine and 4-hydroxyacetaldehyde [39]. Isoquinoline-type alkaloids show strong pharmacological activities like those of morphinan-, protoberberine- and benzophenanthridine-type alkaloids, and they are widely distributed in the plant kingdom, mainly in Papaveraceae, Berbidaceae, Ranunculaceae and Menispermaceae.

The opium poppy (*Papaver somniferum*) is one of the oldest cultivated plants. The therapeutic use of latex obtained from unripe capsules of poppy was recorded by Theophrastus in the third century BCE. Dioscorides (100 CE) described the curative properties of the opium poppy and presented the different uses for both latex and extracts of whole plants. Laticifers are found associated with the vascular bundle in plant parts. The morphinan alkaloids, morphine, codeine and thebaine, are found both in roots and in aerial plant parts and specifically accumulate in vesicles within laticifers. Details of opium alkaloid biosynthesis, the enzymes involved and localization are given elsewhere [39], [46–48]. These alkaloids are used in modern

medicine for the treatment of pain, cough and diarrhoea. Two new semisynthetic derivatives of age-old drugs, morphine and atropine, have been developed and are being used clinically for Parkinson's disease and for chronic obstructive pulmonary disease, respectively. Apomorphine hydrochloride [49] is a dopamine receptor agonist, while triotropium bromide is derived from atropine [50].

The antimalarial activity of the alkaloid quinine obtained from the bark of *Cinchona* species (*C. ledgeriana*, *C. pubescens* and *C. officinalis*) has been known for many centuries. Besides their pharmaceutical use, *Cinchona* alkaloids are also used in the food and soft drink industry because of their bitter taste [4].

Terpenoid indole alkaloids comprise a group of about 3000 compounds with well-known compounds such as antineoplastic agents vinblastine and camptothecin, the antimalarial drug quinine and the rat poison strychnine. Terpenoid indole alkaloids consist of an indole component provided by tryptamine and a terpenoid moiety derived from secologanin. Tryptophan, a shikimic acid biosynthetic pathway product, is converted to tryptamine by tryptophan decarboxylase (TDC). The biosynthesis of these alkaloids is discussed elsewhere in detail [39, 42], [51–53]. New derivatives of vinblastine and camptothecin are currently in clinical trials for their anticancer properties, such as vinflunine and exatecan, respectively [2]. Besides vincristine and vinblastine, *Catharanthus roseus* is famous for its more than 100 secologanin-derived monoterpene indole alkaloids (MIAs). The monomeric MIA ajmalicine is used in the treatment of circulatory disorders, whereas the heterodimeric MIAs vinblastine and vincristine are powerful antitumour drugs [54].

Purine alkaloids are widely distributed within the plant kingdom (Fig. 2.2) and have been detected in at least 90 species belonging to 30 genera. Caffeine and theobromine, methylated derivatives of xanthine, are generally the main purine alkaloids and are regularly accompanied in low concentrations by the two methylxanthines theophylline and paraxanthine, as well as by methylated uric acids such as theacrine, methylxanthine and liberine. Purine alkaloids, being present in tea and coffee, are widely consumed in the human diet across the continents. Plant species from different families are made into a pleasant stimulant, e.g. coffee (*Coffea arabica*, *C. robusta*), tea (*Camellia sinensis*), cocoa (*Theobroma cacao*), mate (*Ilex pguariensis*) and cola (*Cola nitida*) [55].

2.6.2 Phenolics

Simple phenolics are termed compounds and have at least one hydroxyl group attached to an aromatic ring, e.g. catechol. Most compounds having a C_6C_1 carbon skeleton, usually with a carbonyl group attached to the aromatic ring, are phenolic compounds [56].

Simple phenylpropanoids are defined as secondary metabolites derived from phenylalanine, having a C_6C_3 carbon skeleton, and most of them are phenolic acids, e.g. cinnamic acid, *o*-coumaric acid, *p*-coumaric acid, caffeic acid and ferulic acid [57]. A simple phenylpropanoid can conjugate with an intermediate from

the shikimic acid pathway, such as quinic acid, to form compounds like chlorogenic acid. Phenolic compounds having a $C_6C_3C_6$ carbon skeleton include flavonoids (including anthocyanins) and isoflavonoids.

Phenolic compounds are generally synthesized via the shikimate pathway (Fig. 2.4), but the polyketide pathway can also provide some phenolics, such as orcinols and quinones. Phenolic compounds derived from both pathways are quite common, e.g. flavonoids, stilbenes, pyrones and xanthenes [58].

The shikimate pathway, a major biosynthetic route for both primary and secondary metabolism, starts with phosphoenol pyruvate and erythrose-4-phosphate and ends with chorismate [59]. Chorismate is an important branching point since it is the substrate for all subsequent products (Fig. 2.4) [60]. A great diversity of phenolic compounds are synthesized through these intermediate products, e.g. phenylalanine is a common precursor for C_6C_3 and $C_6C_3C_6$ compounds, and their polymers such as tannins and lignins [38].

Resveratrol (3, 5, 4'-trihydroxystilbene) is an oligomeric polyphenol found as dimer, trimer and tetramer in the families Vitaceae, Dipterocarpaceae, Cyperaceae, Gnetaceae and Leguminosae. Resveratrol is synthesized from phenylalanine, mediated by the enzyme stilbenes synthase, while chalcone synthase converts phenylalanine into flavonoids. Resveratrol is implicated in the prevention of cancer and

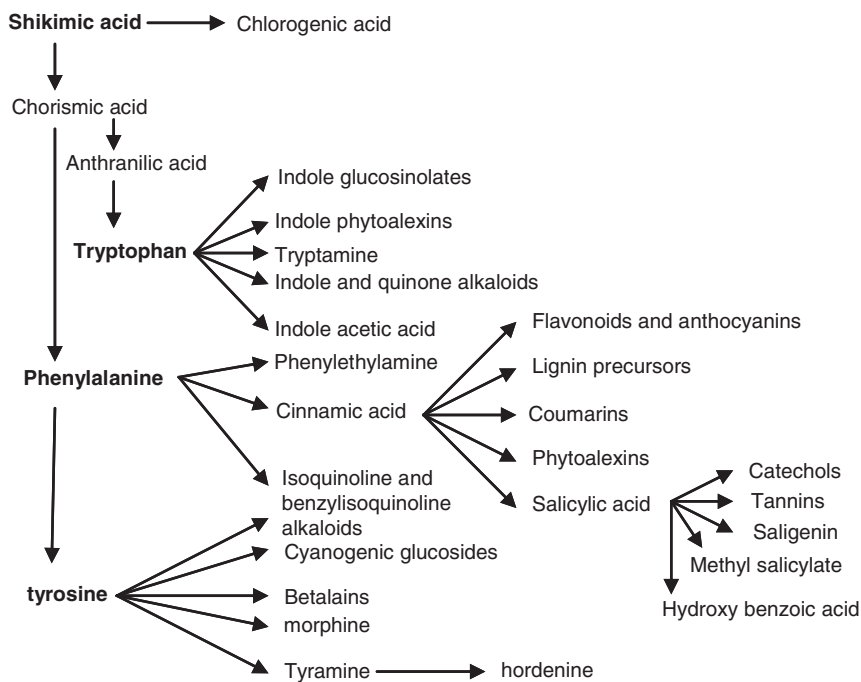


Fig. 2.4 Biosynthesis of diverse phenolic compounds from pool of amino acids formed by shikimic acid pathway

cardiovascular diseases in vasoprotection and neuroprotection [61–63]. The details about the mode of action of resveratrol are discussed in reviews on resveratrol [62–64].

The phenolic group includes metabolites derived from the condensation of acetate units (e.g. terpenoids), those produced by the modification of aromatic amino acids (e.g. phenylpropanoids, cinnamic acids, lignin precursors, hydroxybenzoic acids, catechols and coumarins), flavonoids, isoflavonoids and tannins. The phenolics derived from aromatic amino acids, and their precursors, are just some of the very wide range of compounds (Fig. 2.5) derived from shikimic acid [57]. A phenyl group having three carbon side chains is known as a phenylpropanoid, such as hydroxycoumarins, phenylpropenes and lignans. The phenylpropenes are important components of many essential oils, e.g. eugenol in clove oil (*Syzygium aromaticum*) and anethole and myristicin in nutmeg (*Myristica fragrans*) [65].

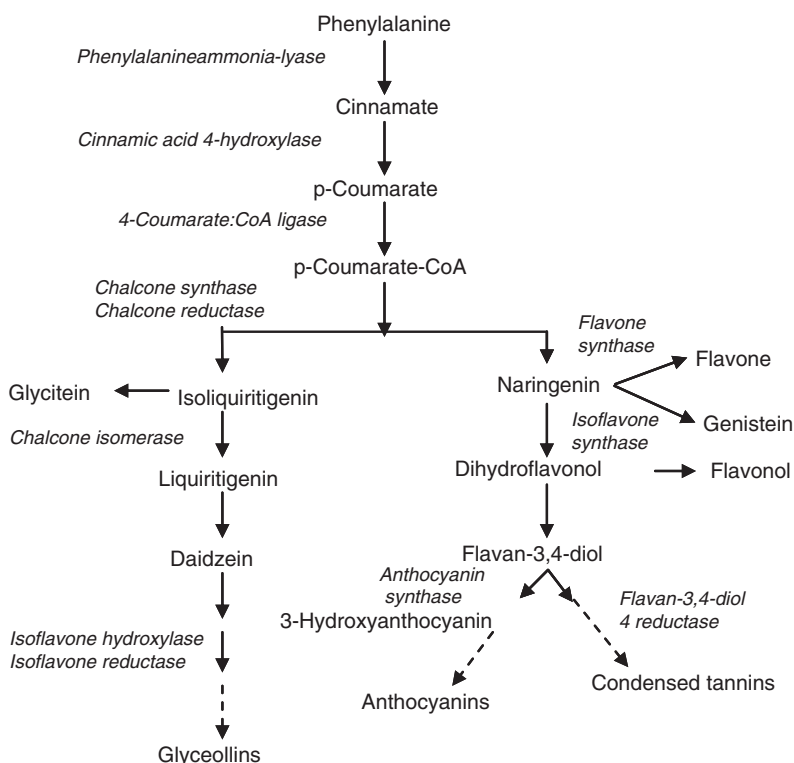


Fig. 2.5 Biosynthetic pathway of major flavonoids and anthocyanins

Flavonoids have two benzene rings attached by a propane unit and are derived from flavones. They are found throughout the plant kingdom, whereas isoflavonoids are more restricted in distribution, and are present in the family Fabaceae, in which they are widely distributed and function as antimicrobial, anti-insect compounds,

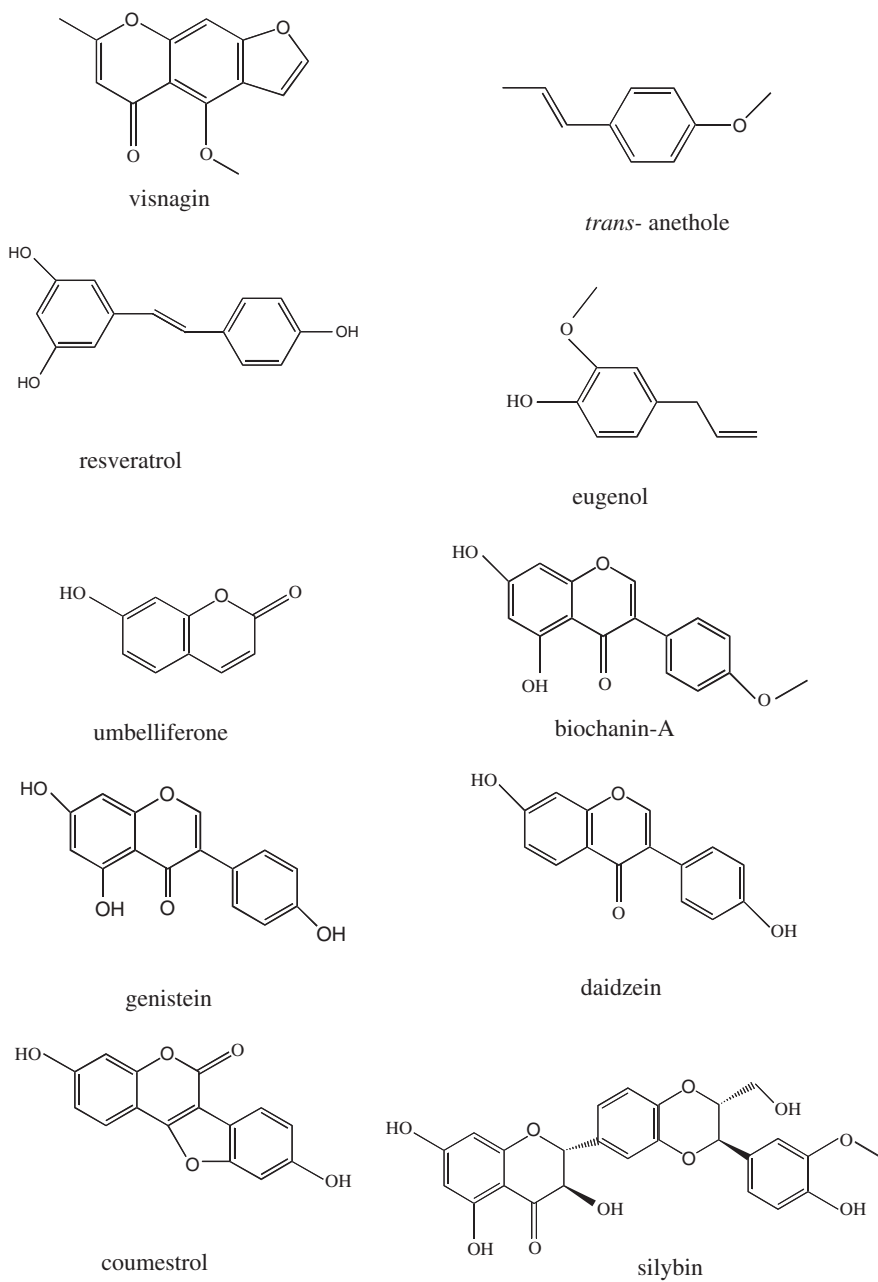
as an inducer of nodulation genes of symbiotic *Rhizobium* bacteria, or as allelopathic agents [66]. Flavonoids are brightly coloured compounds generally present in plants as their glycosides. Different classes within this group differ by additional oxygen-containing heterocyclic rings and hydroxyl groups and include the chalcones, flavones, flavonols, flavanones, anthocyanins and isoflavones. Anthocyanins impart red and blue pigment to flowers and fruits and can make up as much as 30% of the dry weight of some flowers. Flavanones, flavonols and anthocyanins normally exist as their glycosides. The isoflavonoids are rearranged flavonoids, in which this rearrangement is brought about by a cytochrome P-450-dependent enzyme which transforms the flavanones' liquiritigenin or naringenin into the isoflavones daidzein or genistein, respectively. Simple isoflavones such as daidzein, and coumestans such as coumestrol, have sufficient estrogenic activity to seriously affect the reproduction of grazing animals and are known as phytoestrogens [56]. Isoflavones exhibit estrogenic, antiangiogenic, antioxidant and anticancer properties [66, 67].

Major sources of isoflavones for humans are pulses, particularly soybeans and chick peas [68]. Epidemiological studies suggest a link between consumption of soy isoflavones and reduced risks of breast and prostate cancers [66–68]. Isoflavones also possess other health-promoting activities, such as chemoprevention of osteoporosis, and prevention of postmenopausal disorders and cardiovascular diseases [69, 70]. Phenoxodiol, a synthetic analogue of diadzein, is being developed as a therapy for cervical, ovarian, prostate, renal and vaginal cancers and induces apoptosis through inhibition of antiapoptotic proteins [71]. The other important compounds (Fig. 2.6) in this group include quercetin (flavonoid), silybin (flavonolignan) and genistein (isoflavone).

2.6.3 Terpenes

The functional diversity of chemicals within plants is best demonstrated by terpenoids. More than 30,000 terpenoids [72] have been identified. The terpenes have a simple unifying feature by which they are defined and by which they may be easily classified. This generality, referred to as the isoprene rule, was postulated by Otto Wallach in 1887. This rule describes all terpenes as having fundamental repeating 5-carbon isoprene units [73]. Thus, terpenes are defined as a unique group of hydrocarbon-based natural products that possess a structure that may be hypothetically derived from isoprene, giving rise to structures that may be divided into isopentane (2-methylbutane) units.

The actual biosynthesis route to terpenes is not so simple. Two different biosynthetic pathways produce the main terpene building block, isopentenyl diphosphate (IPP). The first classical biosynthetic route is known as the MVA (mevalonic acid) pathway. This takes place in the cytosol, producing sesquiterpenes [54, 76]. It is now known that the actual 5-carbon building blocks *in vivo* are the interconvertible isomers isopentenyl pyrophosphate (IPP) and dimethylallyl pyrophosphate (DMAPP). These two building blocks are condensed together in a sequential fashion by the

**Fig. 2.6** Phenols

action of enzymes called prenyltransferases. The products include geranyl, farnesyl and geranyl geranyl pyrophosphate, squalene and phytoene, which are the direct precursors of the major families of terpenes. The key intermediate in the process was mevalonic acid (MVA), a 6-carbon compound. MVA is formed by the enzymatic reduction of the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA), which in turn is formed by the head-to-tail condensation of three molecules of acetate. MVA is enzymatically converted to IPP with the loss of carbon dioxide, and subsequently IPP and DMAPP are incorporated directly into cholesterol.

The second biosynthesis route to terpenes is referred to as either the MEP (methylerythritol-4-phosphate) or DOX (1-deoxy-D-xylulose) pathway [74]. When first discovered, this new plastid-bound pathway was distinct biochemically and was identical to that found in bacteria and probably is a legacy of prokaryotic endosymbiotic ancestors [75]. In this case, IPP is derived, not from MVA, but from 1-deoxyxylulose 5-phosphate (1-DXP), formed from the glycolytic intermediates glyceraldehyde 3-phosphate and pyruvate. The key step in the biosynthesis is the skeletal rearrangement and reduction of 1-DXP to form 2C-methylerythritol 4-phosphate (MEP) using the biological reducing agent NADPH as cofactor. MEP is converted to IPP via a chemical sequence involving the removal of three molecules of water. Thus, in higher plants, there are two pathways for generating terpenes. Here, IPP is formed in the chloroplast, mainly for the synthesis of more volatile mono- and diterpenes (Fig. 2.7). The evidence indicates that there may be sharing of intermediates across these pathways, a sort of biosynthetic crosstalk [77]. Various classes of terpenes classified by the number of 5-carbon units are given in Fig. 2.8. In plants, the MEP pathway leads to monoterpenes, diterpenes, the prenyl side chains of chlorophylls and carotenoids as well as to the phytohormones such as abscisic acid, gibberellins and *trans*-cytokinins. The first of the seven enzymatic steps of the MEP pathway is catalysed by the enzyme 1-deoxy-D-xylulose 5-phosphate synthase [54]. The monoterpenoids are major components of many essential oils and are economically important as fragrances and perfumes. Common acyclic compounds include myrcene, geraniol and linalool. Cyclic structures include menthol, camphor, pinene and limonene (Fig. 2.8).

Sesquiterpenes, C₁₅ or compounds having 3-isoprene units, exist in aliphatic bicyclic and tricyclic frameworks. A member of this series, farnesol, is a key intermediate in terpenoid biosynthesis. Arteether is derived from artemisinin, a sesquiterpene lactone isolated from *Artemisia annua*, and currently used as an antimalarial drug (Fig. 2.8). Several derivatives of artemisinin are in various stages of clinical trials as antimalarial drugs in Europe [78] and as antineoplastic agents (see Chap.11).

The diterpenes are not considered essential oils and constitute a component of plant resins because of their higher boiling point. These are composed of four isoprene units. Gibberellic acid, a plant growth regulator, and taxol are diterpenes.

Triterpenes, C₃₀ compounds, are composed of six isoprene units and are biosynthetically derived from squalene. These are high-melting-point colourless solids and constitute a component of resins, cork and cutin. Triterpenoids produce several

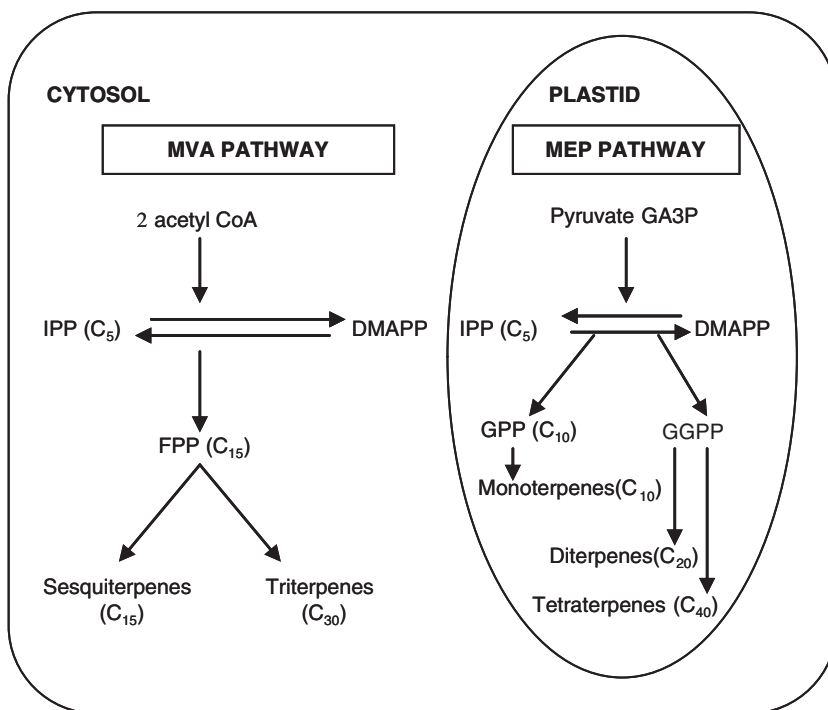
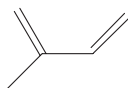


Fig. 2.7 Cytosolic MVA and plastidial MEP pathways for the synthesis of Terpenoids

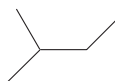
pharmacologically active groups such as steroids, saponins and cardiac glycosides. Azadirachtin, a powerful insect antifeedent, is obtained from seeds of *Azadirachta indica*. Other triterpenes include the limonins and the cucurbitacins, which are potent insect steroid hormone antagonists [79].

All plant steroids hydroxylated at C_3 are sterols. Steroids are modified triterpenes and have profound importance as hormones (androgens such as testosterone and estrogens such as progesterone), coenzymes and provitamins in animals. Many progesterones are derived semisynthetically from diosgenin. Saponins are C_{27} steroids widely distributed in monocot families like Liliaceae, Amaryllidaceae and Dioscoreaceae, and in dicot families, e.g. Scrophulariaceae and Solanaceae. Saponins are composed of two parts: the glycone (sugar) and the aglycone or genin (triterpene). Commercially important preparations based on saponins include sarsaparilla root (*Sarsaparilla*), licorice (*Glycyrrhiza glabra*), ivy leaves (*Hedera*), primula root (*Primula*) and ginseng (*Panax ginseng*). The ammonium and calcium salt of glycyrrhizic acid are referred to as glycyrrhizins. They are 50 to 100 times sweeter than sucrose [80].

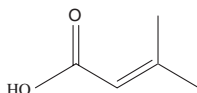
Isoprene unit



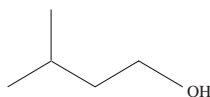
isoprene



isopentane

Hemiterpenes C₅

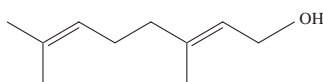
senecioic acid



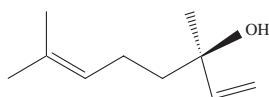
isoamyl alcohol

Monoterpenes C₁₀

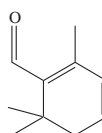
α-pinene



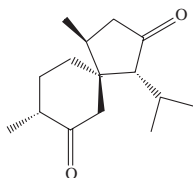
geraniol



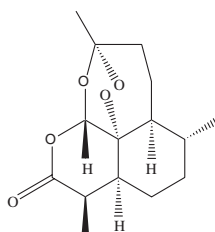
linalool



safranal

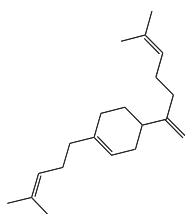
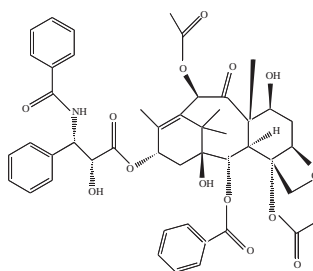
Sesquiterpene C₁₅

acorone

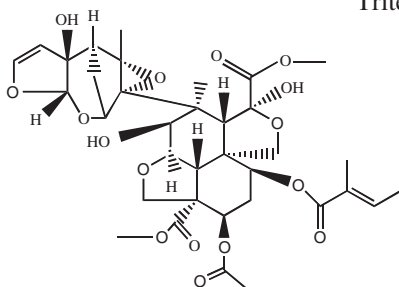


artemisinin

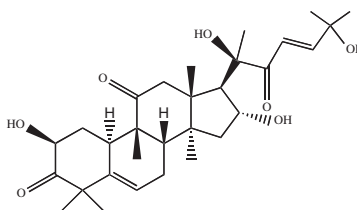
Fig. 2.8 Basic building unit and various classes of terpenes

Diterpene C₂₀*p*-camphorene

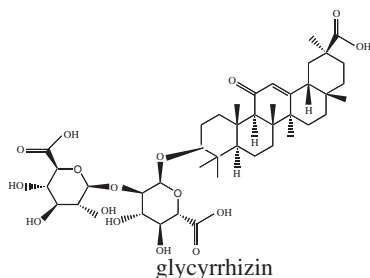
taxol

Triterpene C₃₀

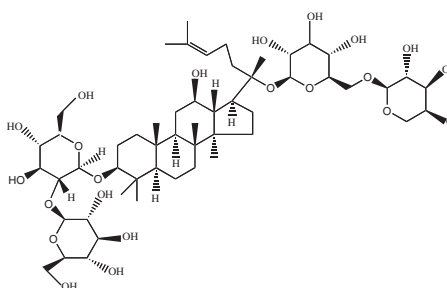
azadirachtin



cucurbitacin-D



glycyrrhizin



ginsenoside rb2

Fig. 2.8 (continued)

2.7 Conclusion

The therapeutic potential of herbs has been well recognized by various indigenous systems of medicine. Besides their therapeutic use, herbs are disease preventors and also used as cosmetics, dietary supplements and for reducing obesity. The priority of developed countries is different from that of developing countries in relation to medicinal plants. Developed countries are looking for leads to develop drugs from medicinal plants, while developing countries would like to have cheap herbal formulations as these countries cannot afford the long path of drug discovery using pure

compounds. The indigenous system of medicine is officially recognised in India. The government funds education on this system, reimburses the cost of treatment by this system, and approves drugs based on Ayurvedic formulations.

About one-fourth of the drugs approved during the period 1981–2002 was either natural products or based on natural products [81]. Despite the ups and downs in funding for drug discovery from medicinal plants, new drugs that are in the pipeline for approval by the US FDA include morphine-6-glucoronide (a derivative of morphine with fewer side effects than morphine), vinflunine (a modification of vinblastine for cancer), exatecan (an analogue of camptothecin for cancer) and calanolide A (a dipyrano coumarin from *Calophyllum lanigerarum* var *anstrocoriaceum*, an anti-HIV drug).

Drug discovery from medicinal plants has traditionally been lengthier and more complicated than other drug discovery methods. As a result, many pharmaceutical companies have reduced their efforts and funding for natural-product research. Overexploitation of medicinal plants in developing countries needs proper attention to conserve biodiversity while at the same time catering to the needs of herbal drugs by sustainable utilization and production. Current research in drug discovery from medicinal plants involves a multidisciplinary approach combining botanical, phytochemical, biological and molecular techniques. There is a need to improve technology for the rapid isolation of active compounds in large quantities for evaluation with the scientific collection of plant material and maintenance of biodiversity. It is also desirable to have collaborative work with profit-sharing agreements between leading institutes, pharmaceutical companies of developed countries, and organizations in developing countries where most medicinal plants are still unexplored.

Acknowledgements Research on medicinal plants in the laboratory is supported by funds from the UGC-DRS programme and the DST-FIST programme.

References

1. Ramawat KG, Goyal S (2008) The Indian herbal drugs scenario in global perspectives. In: Ramawat KG, Merillon JM (eds) *Bioactive Molecules and Medicinal Plants*. Springer, Berlin Heidelberg New York, p 323
2. Balunas MJ, Kinghorn AD (2005) *Life Sci* 78:431
3. Gurib-Fakim A (2006) *J Mol Asp Med* 27(1):1
4. Ramawat KG (2007) Secondary metabolites in nature. In: Ramawat KG, Merillon JM (eds) *Biotechnology: Secondary Metabolites*. Science Publishers, Enfield, CT, p 21
5. Chin YW, Balunas MJ, Chai HB, Kinghorn AD (2006) *AAPS J* 8:E239
6. Patwardhan B, Vaidhya ADB, Chorghade M (2004) *Curr Sci* 86:789
7. Canter PH, Thomas H, Ernest E (2005) *Trends Biotechnol* 23:180
8. Kathe W (2006) Revision of the “Guidelines on the conservation of medicinal plants” by WHO, IUCN, WWF and TRAFFIC: process and scope. In: Bogers RJ, Craker LE, Lange D (eds) *Medicinal and Aromatic Plants*. Springer, Dordrecht, The Netherlands, p 109
9. Merillon JM, Ramawat KG (2007) *Biotechnology for medicinal plants: research needs*. In: Ramawat KG, Merillon JM (eds) *Secondary Metabolites: Plants and Microbes*, 2nd edn. Science Publishers, Enfield, CT, p 1

10. Jia W, Zhang L (2005) Challenges and opportunities in the Chinese herbal drug industry. In: Demain AL, Zhang L (eds) *Natural Products: Drug Discovery and Therapeutic Medicine*. Humana, Totowa, NJ, p 229
11. Ramawat KG, Sonie KC, Sharma MC (2004) Therapeutic potential of medicinal plants: an introduction. In: Ramawat KG (ed) *Biotechnology of Medicinal Plants: Vitalizer and Therapeutic*. Science Publishers, Enfield, CT, p 1
12. Dev S (2006) *Selection of Prime Ayurvedic Plant Drugs Ancient-Modern Concordance*. Anamaya, New Delhi
13. Zhang L, Zia W (2007) Chinese herbal drug industry: past, present and future. In: Ramawat KG, Merillon JM (eds) *Biotechnology: Secondary Metabolites: Plants and Microbes*, 2nd edn. Science Publishers, Enfield, CT, p 417
14. Chevallier A (1996) *The Encyclopaedia of Medicinal Plants*. Dorling Kindersley, London, p 17
15. Heinrich M, Barnes J, Gibbons S, Williamson EM (2004) *Fundamentals of Pharmacognosy and Phytotherapy*. Churchill Livingstone, Elsevier, UK
16. Theis N, Lerdau M (2003) *Int J Plant Sci* 163:S93
17. Taylor JLS, Rabe T, McGaw LJ, Jager AK, Staden JV (2001) *Plant Growth Regul* 34:23
18. Gupta R, Chadha KL (1995) Medicinal and aromatic plants research in India. In: Chadha KL, Gupta R (eds) *Advances in Horticulture: Medicinal and Aromatic Plants*, vol 11. Malhotra, New Delhi, p 429
19. Nayar MP, Sastry ARK (1987) Red Data Book of Indian Plants, vol II. In: Nayar MP, Sastry ARK (eds) *Botanical Survey of India*. Calcutta, p 142
20. Croteau R, Ketchum EB, Long RM, Kaspera R, Wildung MR (2006) *Phytochem Rev* 5:75
21. Holland HD (1998) *Science* 275:38
22. Mendelson R, Balick MJ (1995) *Econ Bot* 49:223
23. Wagle A, Kelkar GD, Heble MR (2007) Production of steroids and saponins. In: Ramawat KG, Merillon JM (eds) *Biotechnology: Secondary Metabolites: Plants and Microbes*, 2nd edn. Science Publishers, Enfield, CT, p 209
24. Reichert JM (2003) *Nat Rev Drug Discovery* 2:1
25. Wilson EK (2002) *Chem Eng News* 80:35
26. Demain AL, Zhang L (2005) Natural products and drug discovery. In: Demain AL, Zhang L (eds) *Natural Products: Drug Discovery and Therapeutic Medicine*. Humana, Totowa, NJ, p 3
27. Betz SF, Baxter SM, Fetrow JS (2002) *DDT* 7:865
28. Drews J (2000) *Science* 287:1960
29. Kessmann H, Schnurr B (2002) Industrial strategies for the discovery of bioactive compounds from plants. In: Oksman-Caldentey KM, Barz WH (eds) *Plant Biotechnology and Transgenic Plants*. Dekker, New York, p 45
30. Lennon GG (2000) *DDT* 5:59
31. Bertels S, Formann S, Jas G, Bindseil KU (2000) Synergistic use of combinatorial and natural product chemistry. In: Grabley S, Thierike R (eds) *Drug Discovery from Nature*. Springer, Berlin Heidelberg New York, p 72
32. Ravishankar GA, Bhagyalakshmi N, Ramachandra Rao S (2007) Production of food additives. In: Ramawat KG, Merillon JM (eds) *Biotechnology: Secondary Metabolites: Plants and Microbes*, 2nd edn. Science Publishers, Enfield, CT, p 103
33. Pal A (2007) Production of insecticides. In: Ramawat KG, Merillon JM (eds) *Biotechnology: Secondary Metabolites: Plants and Microbes*, 2nd edn. Science Publishers, Enfield, CT, p 131
34. Audi J, Belson M, Patel M, Schier J, Osterloh J (2005) *J Am Med Assoc* 294:2342
35. Ramos MV, Sampaio AH, Cavada BS, Calvete JJ, Grangeiro TB, Debray H (2001) *Glyco-conjugate J* 18: 391
36. Mustafa NR, Verpoorte R (2007) *Phytochem Rev* 6:243
37. Eisenreich W, Bacher A, Arigoni D, Rohdich F (2004) *Cell Mol Life Sci* 61:1401
38. Wink M (2000) *Biochemistry of Plant Secondary Metabolism: Annual Plant Review*, vol 2. Academic, Sheffield, UK, p 151
39. Facchini PJ (2001) *Annu Rev Plant Physiol Plant Mol Biol* 52:29

40. Pelletier SW (1982) The nature and definition of an alkaloid. In: Pelletier SW (ed) *Alkaloids: Chemical and Biological Perspectives*. Wiley, New York
41. Oksman-Caldentey KM (2007) *Curr Pharma Biotech* 8:203
42. Rothe G, Hachiya A, Yamada Y, Hashimoto T, Drager B (2003) *J Exp Bot* 54:309
43. Gomez-Galera S, Peiacho AM, Gene A, Capell T, Christou P (2007) *Plant Cell Rep* 26:1689
44. Sato F, Hashimoto T, Hachiya A, Tamura K, Choi KB, Morishige T, Fujimoto H, Yamada Y (2001) *PNAS* 98:367
45. Howes MJR, Houghton PJ (2003) *Phytother Res* 17:1
46. Facchini PJ, Hagel M, Liscombe DK, Loukantana N, MucLeod BP, Samamani N, Zulak KG (2007) *Phytochem Rev* 6:97
47. Weid M, Ziegler J, Kutchan TM (2004) *PNAS* 38:13957
48. Bird DA, Franceschi VR, Facchini PJ (2003) *Plant Cell* 15:2626
49. Deleu D, Hanssens Y, Northway MG (2004) *Drugs Ag* 21:377
50. Koumis T, Samuel S (2005) *Clin Ther* 27:377
51. Heijden RVD, Verpoorte R, Ten Hoopen HJG (1989) *Plant Cell Tiss Org Cult* 18:231
52. Verpoorte R, Contin A, Memelink J (2002) *Phytochem Rev* 1:13
53. Memelink J, Kijne JW, Van der Heijden R, Verpoorte R (2001) *Adv Biochem Eng/Biotech* 72:105
54. Oudin A, Courtois M, Rideau M, Clastre M (2007) *Phytochem Rev* 6:259
55. Eteng MU, Eyong EU, Akpanyung EO, Agiang MA, Aremu CY (1997) *Plant Foods Hum Nutr* 51:231
56. Dewick PM (2002) *Medicinal Natural Products*. Wiley, West Sussex, UK
57. Bennett NR, Wallsgrove RM (1994) *New Phytol* 127:617
58. Bruneton J (1999) *Pharmacognosy Phytochemistry Medicinal Plants*, 2nd edn. Lavoisier, Paris
59. Herrmann KM, Weaver LM (1999) *Annu Rev Plant Physiol Mol Biol* 50:473
60. Mustafa NR, Verpoorte R (2005) *Planta* 222:1
61. Ates O, Cayli S, Altinoz E, Gurses I, Yucel N, Sener M, Kocak A, Yologlu S (2007) *Mol Cell Biochem* 294:137
62. Delmas D, Jannin B, Latruffe N (2006) *Mol Nutr Food Res* 49:377
63. Vitrac X, Krissa S, Decendit A, Deffieux G, Merillon JM (2004) Grapevine polyphenols and their biological effects. In: KG Ramawat (ed) *Biotechnology of Medicinal Plants*. Science Publishers, Enfield, CT, p 33
64. Baur JA, Sinclair DA (2006) *Nat Rev* 5:493
65. Archer AW (1988) *J Chromatogr* 438:117
66. Dixon RA, Sumner LW (2003) *Plant Physiol* 131:878
67. Dixon RA, Ferreira D (2002) *Phytochem* 60:205
68. Lamartinier CA (2000) *Am J Clin Nutr* 71:1705S
69. Alekel DL, St Germain A, Pererson CT, Hanson KB, Stewart JW, Toda T (2000) *Am J Clin Nutr* 72:844
70. Uesugi T, Toda T, Tsuji K, Ishida H (2001) *Biol Pharm Bull* 24:368
71. Kamsteeg M, Rutherford T, Sapi E et al (2003) *Oncogene* 22:2611
72. Buckingham J (1998) *Dictionary of Natural Products*. Chapman & Hall, London
73. Croteau R (1998) *Discoveries Plant Biol* 1:329
74. Lichtenthaler HK, Rohmer J, Schwender J (1997) *Physiol Plant* 101:643
75. Cvejic JH, Rohmer M (2000) *Phytochem* 53:21
76. Janses BJM, de Groot A (2004) *Nat Prod Rep* 21:449
77. Jux A, Gleixner W, Boland W (2001) *Angew Chem Int Ed Engl* 40:2091
78. van Agtmael MA, Eggelte TA, van Bostel CJ (1999) *Trends Pharmacol Sci* 20:199
79. Miro M (1995) *Phytother Res* 9:159
80. Brielmann HL, Setzer WN, Kaufman PB, Kirakosyan A, Cseke LJ (2005) *Phytochemicals: the chemical components of plants*. In: Cseke LJ, Kirakosyan A, Kaufman PB, Warber SL, Duke JA, Brielmann HL (eds) *Natural Products from Plants*. Taylor Francis, Boca Raton, FL, p 1
81. Newmann DJ, Cragg GM, Snader KM (2003) *J Nat Prod* 66:1022



<http://www.springer.com/978-3-540-79115-7>

Herbal Drugs: Ethnomedicine to Modern Medicine

Ramawat, K.G. (Ed.)

2009, XXII, 402 p., Hardcover

ISBN: 978-3-540-79115-7