The Potential of Higher Plants as a Source of New Drugs

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Abstract. The plant kingdom is still an untapped reservoir of new molecules with therapeutic potential. A selection of bioactive plant constituents recently discovered are presented with focus on new drugs or lead compounds in an advanced state of development. Obtaining pure new biologically active substances from plants remains a complex task. Biological and chemical screenings are complementary approaches for the rapid detection and isolation of new interesting plant constituents. Biological screening followed by activity-guided fractionation has been successfully used in our laboratories for the discovery of new antifungal metabolites and inhibitors of enzymes involved in the aetiology of prostate hyperplasia. High-performance liquid chromatography (HPLC) coupled to UV spectroscopy (LC/UV), mass spectrometry (LC/MS), and magnetic resonance (LC/NMR) proved to be highly efficient for the chemical screening of crude plant extracts. These hyphenated techniques were extensively used for the investigation of polyphenols with monoamine-oxidase inhibitory (IMAO) properties in Gentianaceae species.

1. Introduction

For a long time, plants have been the almost exclusive therapy available to humans. With the development of medicinal chemistry in the early nineteenth century, plants were also the first source of substances to be developed as drugs. Nowadays, in spite of the tremendous development of synthetic pharmaceutical chemistry and microbial fermentation, 25% of prescribed medicines in industrialized countries are from plant origin and some 120 plant-derived compounds from ca. 90 plant species are used in modern therapy. Classical examples of drugs of plant origin include the antimalarial agent quinine from the bark of Cinchona officinalis (Rubiaceae), the analgesics codeine and morphine from Papaver somniferum (Papaveraceae), atropine from Atropa belladonna and other Solanaceae species, and the cardiac glycoside digoxin from Digitalis sp. (Scrophulariaceae). Over the last decade, there has been a resurgence of interest in plants as a source of new therapeutic agents. Major pharmaceutical companies are increasingly introducing plant extracts and plant metabolites into high-throughput screening programs for the discovery of new leads. Among the ca. 400000 plant species on the earth, only a small percentage have been phytochemically investigated and the fraction submitted to biological or pharmacological screening is even smaller. Moreover, plant extracts contain up to several thousands of

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different secondary metabolites. Thus, any phytochemical investigation of a given plant will reveal only a narrow spectrum of its constituents. The plant kingdom thus represents an enormous reservoir of pharmacologically valuable molecules to be discovered [1][2].

2. New Drugs Derived from Plant Metabolites

During the last decades, work on natural compounds has been particularly successful in the field of anticancer drug research. Thus, in the United States of America, more than 60% of the approved anticancer drugs between 1983 and 1994 are of natural origin [3]. Among them, several are plant secondary metabolites or molecules derived from plant constituents [4]. The bisindole alkaloids vinblastine (1) and vincristine (2) from the Madagascar periwinkle (Catharanthus roseus, Apocynaceae; Fig. 1) which were already developed as effective anticancer drugs in the 1960s are still of great value in the treatment of leukaemia. Moreover, a semisynthetic derivative, vinorelbine (3, 5-nor-anhydrovinblastine, Navelbine®), has been recently developed particularly for the treatment of breast cancer.

The diterpenoid paclitaxel (4), previously known as Taxol®, was discovered as part of an NCI (National Cancer Institute)-sponsored program. It was isolated for the first time from the stem bark of the Pacific yew Taxus brevifolia (Taxaceae) in the late 1960s, but has since been found in other yew species such as the European yew T. baccata. Major supply problems have hampered, however, the development of this product and approval by the FDA was only obtained in 1992. While Taxol® was initially used for the treatment of ovarian cancer resistant to chemotherapy, its therapeutic applications are in the process of spreading to other gynecologic cancers. Paclitaxel possesses a unique mode of action. In contrast to other antimitotic drugs, it enhances both the rate and yield of microtubule assembly which leads to the formation of abnormal arrays or bundles of tubulin. Paclitaxel occurs almost exclusively in the stem bark of yews and at very low concentrations. Moreover, a total synthesis is impracticable on an industrial scale. The supply problem has been finally overcome by the development of a semisynthetic approach from 10-deacetylbaccatin III, a more accessible congener found in the needles. This strategy has also given access to structural analogues, one of which, docetaxel (5, Taxotère®), has been recently commercialized and appears to be even more active than paclitaxel [5].

Camptothecin derivatives are the most recent plant-derived substances to be used in cancer therapy. The monoterpennoid alkaloid camptothecin (6) has been isolated in the late 1960s from the Chinese ornamental tree Camptotheca acuminata (Nyssaceae). However, despite potent antitumor properties, the clinical success remained moderate owing to toxic effects and poor solubility. Interest for camptothecin was revived with the discovery of its novel mode of action in 1985 based on the inhibition of topoisomerase I, an enzyme involved in several DNA transactions. Considerable efforts have since been made to find more active and less toxic structural analogues. Topotecan (7, Hycamtin®) has been approved in May 1996 by the FDA for the treatment of advanced ovarian cancers that have resisted to other chemotherapy drugs. In June 1996, injectable irinotecan (8) HCI was also approved for the treatment of metastatic cancer of the colon or rectum [6].

Further plant-derived agents are currently in investigational use for the treatment of cancer. This is in particular the case of homoharringtonine (9) from Cephalotaxus harringtonia (Cephalotaxaceae) which has shown activity against various leukaemias. Not only new molecules have a potential as leads. Well-known compounds can be promising as well. Thus, betulinic acid (10), a common constituent of birch trees (Betula sp., Betulaceae), proved recently to exhibit potent antitumor activity. This metabolite is considered as a candidate of interest for the treatment of melanoma [7].

In the last decade, plant products have also played a role in the development of new antimalarial agents as illustrated by the discovery and development of artemisinin (11). Artemisinin, a sesquiterpene lactone containing an endoperoxide group, was isolated in 1972 by Chinese scientists from qinghao (Artemisia annua, Aster-
Table. Most Frequently Prescribed Plant Extracts in Germany in 1996

| Plants                      | Vernacular names | Indication                          | Turnover (million DM) |
|-----------------------------|------------------|-------------------------------------|-----------------------|
| Ginkgo biloba               | Ginkgo           | cerebrovascular and peripheral insufficiency | 461                   |
| Aesculus hippocastanum      | Horse Chestnut   | venous insufficiency                 | 114                   |
| Crataegus sp.               | Hawthorn         | cardiontonic                         | 65                    |
| Hypericum perforatum        | St. John’s Wort  | depression                           | 59                    |
| Urtica dioica               | Nettle           | urological problems                  | 35                    |
| Echinacea sp.               | Echinacea        | immunostimulant                      | 34                    |

Plants have not only a therapeutic potential as a source of pure, chemically defined active principles. The use of extracts is appropriate for plants exhibiting weaker and/or less specific pharmacological activities and if the active principles are as yet unknown. Moreover, the therapeutic effect may result of the additive action of several active principles. To ensure a constant quality and therapeutic efficacy, it is, however, essential that such extracts are being standardized for their...
content of active principles. When active principles are not known with certainty, those compounds have to be selected which are the most representative of the chemical composition of the extract. The most frequently prescribed plant extracts in Germany are listed in the Table. Over the last few years, ginkgo (Ginkgo biloba, Ginkgoaceae) and St. John’s Wort (Hypericum perforatum, Gutiferae) preparations have become enormously popular in most western countries.

The ginkgo or maidenhair tree is the sole survivor of the family Ginkgoaceae that flourished during the Cretaceous period, 80 million years ago. The ginkgo tree was mentioned in a Chinese medicinal book in 2800 B.C., and is still part of the Chinese pharmacopoeia as an antiasthmatic and antitussive drug. With a turnover of more than 500 million dollars, standardized leaf extracts of Ginkgo biloba are now among the best-selling drugs in the world. Ginkgo preparations are widely used in the treatment of cerebrovascular and peripheral circulatory disorders of the elderly. Clinical efficacy of ginkgo is mainly due to ginkgolides (19–22), a group of unique diterpenes which selectively inhibit the platelet activating factor (PAF). Bilobalide, a sesquiterpene with neuroprotective properties, and various flavonoids with free-radical-scavenging activity may also play a significant role [10].

According to a recent estimation, ca. 4% of the world’s population suffers from depression. The market for synthetic drugs used in the treatment of depression is several billion dollars per year, but the safety of some of them is a matter of controversy. In this context, growing attention is paid to plant preparations, which appear to be of great value in the treatment of light to middle depressive states. Although the use of Hypericum perforatum to cure melancholia was recommended by Paracelsus and although this indication was documented in ancient German medicinal treatises, the antidepressive properties of H. perforatum have been only recently rediscovered. There is now increasing clinical evidence for the beneficial effect of Hypericum extracts in light to medium depressive states. In spite of extensive phytochemical and pharmacological investigations, the mode of action and the active principles are still uncertain. In fact, different mechanisms are likely to be involved. Thus, xanthones and flavonoids demonstrated inhibitory properties towards monoamine oxidase A (MAO A), an enzyme which plays a key role in the regulation of some neurotransmitters. Extracts also demonstrated in vitro activity on the serotonin uptake in synaptosomes and inhibition of flumazenil binding on the benzodiazepine receptor of the GABA_A (α-aminobutyric acid) complex [11].

4. Strategies for the Discovery of New Lead Compounds

As already mentioned, the plant kingdom represents a largely unexplored reservoir of pharmacologically valuable compounds to be discovered. However, not every one of the 400,000 different species can be submitted to a complete panel of pharmacological and biological assays. The selection of the plants to be studied is therefore a factor of crucial importance. Besides random collection of plant material, targeted collection based on consideration of chemotaxonomic relationships and the exploitation of ethnobotanical information is currently carried out. Ethnopharmacological screens taking into account the empirical knowledge of traditional medicine appear to be the most likely to yield pharmacologically active compounds. In addition, field observation may be useful in screening programs aimed at antimicrobial or insect-deterrent/insecticidal activities.

Despite of the development of powerful chromatographic and spectroscopic techniques, developing a new drug from a plant remains a challenge. This process, which is summarized in Fig. 2, requires a multidisciplinary collaboration of botanists, pharmacognosists, pharmacologists, and chemists. When searching for active plant metabolites, biological screening followed by activity-guided fractionation is the standard procedure. Simple and inexpensive bioassays have been introduced in phytochemical laboratories for rapid screening of crude plant extracts. Bioassays also serve as a guide during the isolation process. Thus, all fractions are biologically evaluated, and those continuing to exhibit activity are carried through further isolation and purification until pure active principles are obtained. In this way, different properties and types of ailment, including microbial afflictions and parasitic diseases, can be investigated. This approach is illustrated by the investigations carried out in our institute for discovering new antifungal compounds and inhibitors of 5α-reductase and aromatase, two enzymes which are involved in the aetiology of benign prostatic hyperplasia.

4.1. Antifungal Compounds

The increasing incidence of mycoses associated with AIDS and also those arising after treatment by immunosuppressive drugs has given fresh impetus to the search for novel antifungal agents. There are few really effective antifungal preparations currently indicated for the treatment of systemic mycoses and their efficacy is rather limited. Another area which is badly in need of new lead compounds is
agrochemicals. Consequently, the investigation of higher plants for antifungal properties is of great importance at the moment.

For the isolation of active compounds by activity-guided fractionation, bioautography is the method of choice. This technique combines TLC with a bioassay in situ and allows localization of active constituents in a plant extract. Spore-producing fungi, such as Aspergillus, Penicillium, and Cladosporium spp., can all be employed as target organisms in direct bioautographic procedures. After migration and drying of the TLC solvent, the plates are sprayed with a mixture of the microorganism and the nutrition medium. They are then incubated in a humid atmosphere. Zones of inhibition appear where fungal growth is prevented by the active components of the plant extract [12]. Bioautography with Cladosporium cucumerinum has been used successfully in our laboratory for several years, and a large number of fungicidal natural products of different origins and chemical structures have been isolated [13].

Since direct bioautography is not possible with yeasts such as Candida albicans, a simple and rapid agar overlay assay has been developed [14]. This contact bioautography technique relies on the transfer of active compounds from the stationary phase into the agar layer (which contains the microorganism) by a diffusion process. After incubation, the plate is sprayed with methylthiazolyltetrazolium chloride (MTT) which is converted into a MTT formazan dye by the fungus. Inhibition zones are observed as clear spots against a purple background.

Several antifungal compounds have recently been isolated in our laboratory using the bioautographic technique to track the activity during the separation process. For example, a lipophilic crude extract of whole plants of Valeriana capensis (Valerianaceae), collected in Malawi, exhibited activity against C. cucumerinum. Fractionation by a combination of column chromatography on silica gel, liquid-solid extraction, and semipreparative HPLC on RP-18 provided the active compound valtrate (23), together with several inactive valepotriates. Valepotriates are well known from Valeriana species, such as V. officinalis, but the antifungal properties of valtrate had not been previously noticed. Valtrate inhibited the growth of C. cucumerinum at 1 μg. High structural specificity was observed, since the isomer iso-valtrate as well as dihydrovaltrate were completely inactive. In a dilution assay using solid media, the minimal inhibitory concentrations of 23 were 10 μg/ml against C. albicans and Aspergillus fumigatus, and 20 μg/ml against Trichophyton mentagrophytes. As valtrate exhibited noteworthy activity against C. cucumerinum, in vitro, it was tested in vivo against other plant-pathogenic fungi. Valtrate was active against Cercospora arachidicola, a pathogenic fungus for the peanut plant, Erysiphe graminis, a fungus which infects barley plants and Venturia inequalis. Since the activity of 23 against E. graminis was comparable to that of the commercial product Calixin®, valtrate may become of interest as an agricultural fungicide [15].

4.2. Search for Active Compounds in Epilobium Species for the Prevention and the Treatment of Prostatic Hyperplasia

It is recognized that testosterone and some of its metabolites are implicated in the development of benign prostatic hyperplasia. Thus, inhibitors of 5α-reductase (which metabolizes testosterone into dihydrotestosterone) or aromatase (which converts testosterone into 17β-estradiol) play a potential role in the treatment of this disease and provide ideal targets for therapeutics. Various species of the genus Epilobium (Onagraceae) have found application in popular medicine in Europe.
for the management of prostatic complaints, and efficacy of willow herb in the treatment of miction problems has been recorded. As part of our studies on *Epilobium* species, we observed that the aqueous-methanolic extract of *Epilobium cape-ense*, an African willow herb species collected in Malawi, inhibited both aromatase and α-reductase. Activity-guided isolation afforded the two macrocyclic ellagitannins oenothine A and oenothine B (24) as the main constituents responsible for the inhibition of the two enzymes. Oenothine B which was the most active against α-reductase with an IC₅₀ of 0.44 μM was also found in other *Epilobium* species, including *E. parviflorum* which is commercialized in Switzerland for the preparation of infusions, and the common Alpine plant *E. angustifolium* (Fig. 3). Although other pathways might also be important in the development of the hyperplastic condition of the prostate, these two compounds go at least some way towards explaining the folkloric use of *Epilobium* species for prostate disorders [16].

4.3. Chemical Screening with LC-Hyphenated Techniques

In the biological screening approach, the number of available targets is limited. Moreover, bioassays are quite often not predictive for clinical efficiency. As further drawback, the bioassay-guided fractionation strategy can lead to the frequent reisolation of known metabolites. The chemical screening of crude extracts, therefore, constitutes an efficient complementary approach allowing localization and targeted isolation of new types of constituents with potential activities. The potential of the chemical screening strategy has been considerably increased by the recent development of hyphenated techniques, able to provide efficient separation of the metabolites and valuable structural information on-line at the same time. HPLC (high-performance liquid chromatography), which is the best-suited technique for the separation of crude plant extracts, can be coupled with spectroscopic methods providing structural information on separated compounds.

HPLC coupled with UV photodiode array detection (LC/UV) has been used since more than a decade by phytochemists for screening extracts and is now widely spread in many laboratories. The UV spectra of natural products give useful information on the type of constituents and also, as it is the case for polyphenols, information on the oxidation pattern.

HPLC coupled to mass spectrometry (LC/MS) has been introduced more recently [18]. MS is one of the most sensitive methods of molecular analysis. Moreover, it has the potential to yield information on the molecular weight as well as on the structure of the analytes. Due to its high power of mass separation, very good selectivities can be obtained. The coupling between LC and MS has not been straightforward, since the normal operating conditions of a mass spectrometer (high vacuum, high temperatures, gas-phase operation, and low flow rates) are diametrically opposed to those used in HPLC, namely liquid-phase operation, high pressures, high flow rates, and relatively low temperatures. Because of the basic incompatibilities between HPLC and MS, on-line coupling of these instrumental techniques has been difficult to achieve, and to cope with these different problems, different LC/MS interfaces have been built up. Each of these interfaces has its own characteristics and range of applications, and several of them are suitable for the analysis of plant secondary metabolites. In our approach to LC/MS, mainly used for the HPLC screening of crude plant extracts, three interfaces, thermospray (TSP), continuous flow FAB (CF-FAB), and electrospray (ES) have been used. They cover the ionization of relatively small nonpolar products (aglycones, 200 u) to high-polar molecules (glycosides, 2000 u). LC/TSP-MS allowed a satisfactory ionization of moderately polar constituents such as polyphenols or terpenoids in the mass range of 200–800 u. For larger polar molecules such as saponins (MW > 800 u), ES is the methods of choice. HPLC coupled with nuclear magnetic resonance (LC/NMR), despite being known for over fifteen years, has not been yet a widely accepted technique, mainly because of its lack of sensitivity. However, the recent progress in pulse field gradients and solvent suppression, the improvement in probe technology and the construction of high-field magnets have given a new impulse to this technique [19]. LC/NMR has an important potential for on-line structure identification of natural products. Indeed, NMR spectroscopy is by far the most powerful spectroscopic technique for obtaining detailed structural information about organic compounds in solution. While the LC coupling itself was rather straightforward compared to LC/MS, the samples are flowing in a non-rotating glass tube (60–180 μl) connected at both ends with HPLC tubing, the main problem of LC/NMR was the difficulty of observing analyte resonances in the presence of the much larger resonances of the mobile phase. This problem was even worsened in the case of typical LC reversed-phase-operating conditions, where more than one protonated solvent was used and where the resonances changed frequencies during the analysis in gradient mode. These problems have now been overcome thanks to the development of fast reliable and powerful solvent suppression techniques. Thus, in reversed HPLC conditions, non-deuterated solvents such as MeOH or MeCN can be used, while water is replaced by D₂O. High-quality ¹H-NMR spectra can now be recorded in both stop-flow and on-flow modes, while also 2D-NMR spectra can be obtained in the stop-flow mode. A general setup of the LC/UV/MS and the LC/NMR configuration used is presented in Fig. 4.

4.4. Investigation of Polyphenols with IMAO Properties in Gentianaceae by LC-Hyphenated Techniques

The enzyme monoamine oxidase (MAO) plays a key role in the regulation
of certain physiological amines. Disturbances in MAO levels have been reported in a series of disorders, in particular depression and anxiety. In this context, considerable interest has recently focused on xanthones, as several of these polyphenols showed strong reversible inhibitory properties on MAO, with some selectivity towards MAO A isoenzyme [20]. Xanthones occur only in a limited number of plant families. Xanthone-O-glycosides are found in two families only (Gentianaceae and Polygalaceae) while C-glycosides and aglycones are more widely distributed among angiosperms, ferns, and fungi. The use of LC/MS combined with LC/UV has been applied in our laboratories for the systematic investigation of the xanthones of numerous Gentianaceae species. These coupled techniques allowed a rapid screening of a great number of species and furnished useful information with a minute amount of vegetable material. In many cases, full structural determination online was possible. In some cases, however, additional information was needed, and the extracts of different Gentianaceae plants have been analyzed also by LC/NMR and LC/MS/MS. In order to illustrate this approach, analysis of the methanolic extract of Gentiana ottonis from Chile is presented in some detail [21].

The LC/UV analysis exhibited peaks with UV spectra characteristic for secoiridoids, flavones, and xanthones. The LC/TSP-MS analysis allowed the attribution of molecular weights of all these compounds (Fig. 5). The secoiridoid 25 exhibited [M + H]+ and [M + NH4]+ ions at m/z 375 and 392 together with a fragment at 213 characteristic for the loss of an hexosyl moiety. These MS information suggested that 25 could be swertiamarin, a widespread secoiridoid of the Gentianaceae family. Compounds 26 and 27 presented all fragments characteristic for C-glycosides (losses of 90 and 120 u). According to their UV spectra, 26 and 27 (Mw 446 and 448) were tri- and tetraoxoglycosylated C-glycoside flavones, respectively. Xanthones 28–31 presented all similar UV spectra, suggesting an identical oxidation pattern. Compounds 28 and 29 presented both intense ions at m/z 261, characteristic for tetrahydroxylated xanthones. Substance 28 exhibited also a protonated molecular ion [M + H]+ at m/z 423. This suggested that 28 was the corresponding glucoside of aglycone 29. The LC/TSP-MS spectra of 30 and 31 indicated the presence of another couple of related xanthones with a common aglycone ion at m/z 275, characteristic for substitution by one methoxy and three hydroxy groups.

To confirm these attributions and to obtain more structure information on-line, the same extract of G. ottonis was submitted to an on-line LC/1H-NMR analysis. The same LC conditions as for the LC/UV/MS analysis were used, except that the water of the LC gradient system was replaced by D2O. However, the quantity of extract injected onto the column was increased to 0.4 mg, because of the relative insensitivity of LC/NMR compared to LC/UV and LC/MS detection. As the extract of G. ottonis was rather complex, stop-flow measurements were needed to obtain clear 1H-NMR spectra. The acquisition of the LC/1H-NMR spectra with solvent suppression was then carried out for each constituent until a satisfactory signal-to-noise ratio was obtained for the peak of interest. To illustrate the type of results obtained, the LC/1H-NMR spectra of four types of metabolites are displayed (Fig. 6). 1H-NMR data enabled the definitive identification of the secoiridoid glycoside 25 as swertiamarin, confirming thus the attribution made according to the LC/UV/MS results.

The xanthone-O-glycoside 30 (Mw 436) presented signals characteristic for an O-glucosyl moiety (δ3.3–5.1) and one methoxy group (δ3.96). Aromatic signals confirmed a 1,3,5,8-substitution pattern for 30. The LC/1H-NMR spectrum of 31, aglycone of 30, also exhibited a pair of meta- and ortho-coupled protons as well as a

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**Fig. 5. LC/UV/MS analysis of the crude methanolic extract of Gentiana ottonis**

**UV spectra and TSP-MS ions**

25 [M+H]⁺ = 375 [M+Na]⁺ = 387 (t: 162)
26 [M+H]⁺ = 467 [M+Na]⁺ = 479 (t: 180, 0-120)
27 [M+H]⁺ = 449 [M+Na]⁺ = 461 (t: 162)
28 [M+H]⁺ = 422 [M+Na]⁺ = 434 (t: 152)
29 [M+H]⁺ = 261 [M+Na]⁺ = 273 (t: 162)
30 [M+H]⁺ = 375 [M+Na]⁺ = 387 (t: 162)
31 [M+H]⁺ = 275 [M+Na]⁺ = 287 (t: 162)

**UV trace (254 nm)**

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![Diagram](image_url)
methoxy group. However, with respect to 30, one of the ortho-protons was shifted upfield indicating a glycosylation on the B-ring at C(5) or C(8). A careful comparison of the LC/UV data with authentic samples allowed finally the identification of 31 and 30 as 1,5,8-trihydroxy-3-methoxyxanthone (bellidifolin) and 1,5-dihydroxy-3-methoxy-8-O-glucosylxanthone (8-O-glucosyldesmethybellidifolin), respectively. Similar deductions allowed the identification of 29 and 28 as 1,3,5,8-tetrahydroxyxanthone (desmethybellidifolin) and 1,3,5-trihydroxy-8-O-glucosylxanthone (8-O-glucosyldesmethybellidifolin), respectively.

In the case of the flavone C-glycoside 26 ($M_w$ 446), the position of the hydroxy and methoxy substituents could be established from LC/UV/MS and LC/$^1$H-NMR data. On the other hand, these data were not sufficient to ascertain the position of C-glycosylation. An LC/MS/MS experiment was therefore performed on the $[M+H-120]^+$ion. Fragments were detected at $m/z$ 191 and 163, characteristic for C(6)-glycosylated flavones. Indeed, the flavone C-glycoside 27 ($M_w$ 448) was identified as the common 5,7,3',4'-tetrahydroxy-6-C-glucosylflavone (isorientin).

This example demonstrates that LC/NMR and LC/MS/MS constitute a powerful complement to LC/UV/MS. The combined use of all these hyphenated techniques allow efficient structure identification of the main constituents of an extract on-line.

5. Conclusion

Natural products will continue to function as very important lead compounds. At the same time, they will be essential for the identification of new biological targets and the validation of new assays. In the future, combination of simple biological assays enabling rapid screening of plant extracts with powerful hyphenated analytical techniques will provide, at an increasing rate, new active compounds with novel structures. The ultimate success of such research will, however, depend on the effective collaboration between chemists, biologists, and pharmacologists. Close cooperation between the pharmaceutical industry and universities is also essential for the efficient investigation and development of new leads. Only if such collaborations exist, promising molecules will find an application as drugs one day.