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Natural products in drug discovery

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Natural products have been the single most productive source of leads for the development of drugs. Over a 100 new products are in clinical development, particularly as anti-cancer agents and anti-infectives. Application of molecular biological techniques is increasing the availability of novel compounds that can be conveniently produced in bacteria or yeasts, and combinatorial chemistry approaches are being based on natural product scaffolds to create screening libraries that closely resemble drug-like compounds. Various screening approaches are being developed to improve the ease with which natural products can be used in drug discovery campaigns, and data mining and virtual screening techniques are also being applied to databases of natural products. It is hoped that the more efficient and effective application of natural products will improve the drug discovery process.

Natural products have been the source of most of the active ingredients of medicines. This is widely accepted to be true when applied to drug discovery in 'olden times' before the advent of high-throughput screening and the post-genomic era: more than 80% of drug substances were natural products or inspired by a natural compound [1]. It is, however, arguably still true: comparisons of the information presented on sources of new drugs from 1981 to 2007 [2,3] indicate that almost half of the drugs approved since 1994 are based on natural products. Thirteen natural-product-related drugs were approved from 2005 to 2007 [3], and, as pointed out by Butler [3], five of these represented the first members of new classes of drugs: the peptides exenatide and ziconotide, and the small molecules ixabepilone, retapamulin and trabectedin (Fig. 1).

These recently approved natural-product-based drugs have been described extensively in earlier reviews [2–5]. They include compounds from plants (including elliptinium, galantamine and huperzine), microbes (daptomycin) and animals (exenatide and ziconotide), as well as synthetic or semi-synthetic compounds based on natural products (e.g. tigecycline, everolimus, telithromycin, micafungin and caspofungin) (Fig. 1). They cover a range of therapeutic indications: anti-cancer, anti-infective, anti-diabetic, among others, and they show a great diversity of chemical structures. The chemical properties of the small-molecule natural products that have recently been developed into drugs have been analysed [6]. Half of them were found to be closely compliant with Lipinski's Rule of Five for orally available compounds, but the remainder had higher molecular weights, more rotable bonds and more stereogenic centres, although they retained relatively low log *P* values. It is clear that, on average, natural products are more readily absorbed than synthetic drugs.

Despite these advantages and the past successes, many large pharmaceutical companies have decreased the use of natural products in drug discovery screening. This has been because of the perceived disadvantages of natural products (difficulties in access and supply, complexities of natural product chemistry and inherent slowness of working with natural products, and concerns about intellectual property rights), and the hopes associated with the use of collections of compounds prepared by combinatorial chemistry methods (for further discussion, see Refs. [5,7–10]).

Over a 100 natural-product-derived compounds are currently undergoing clinical trials and at least a 100 similar projects are in preclinical development (Table 1). Most are derived from leads from plants and microbial sources (see also Ref. [3]). The projects based on natural products are predominantly being studied for use in cancer or as anti-infectives, but many other therapeutic areas are

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TABLE 1

Drugs based on natural products at different stages of development

Development stage	Plant	Bacterial	Fungal	Animal	Semi-synthetic	Total[a]
Preclinical	46	12	7	7	27	99
Phase I	14	5	0	3	8	30
Phase II	41	4	0	10	11	66
Phase III	5	4	0	4	13	26
Pre-registration	2	0	0	0	2	4
Total	108	25	7	24	61	225

Source: *Pharmaprojects* database (March 2008).

[a] This does not include reformulations of existing products (66 such products were listed).

represented (Table 2). Seven years ago, a similar analysis of the same database [11] identified 312 projects, indicating a drop of about 30% in natural-product-based development projects between 2001 and 2008. There is, however, also a growing interest in the possibility of developing products that contain mixtures of natural compounds from traditionally used medicines [12], and a defined mixture of components extracted from green tea (Veregen™) has been approved by the FDA and has recently come on the market.

Improving access to natural products

One analysis of newly introduced drugs states that only sorafenib has reached the market from an origin in high-throughput screening of combinatorial chemistry libraries [2]. With the growing realisation that the chemical diversity of natural products is a better match to that of successful drugs than the diversity of collections of synthetic compounds [13,14], the interest in applying natural chemical diversity to drug discovery appears to be increasing once again [15].

As noted above, most of the leads from natural products that are currently in development have come from either plant or microbial sources. Earlier publications have pointed out that relatively little of the world's plant biodiversity has been extensively screened for bioactivity and that very little of the estimated microbial biodiversity has been available for screening [8,16]. Hence, more extensive collections of plants or further advances in the ability to culture microbes could provide many novel chemicals for use in drug discovery assays.

In the microbial area, the main sources to date have been fungi and terrestrial actinomycetes. There is growing interest in samples from marine actinomycetes [17–19], particularly with the discovery of species unique to the marine environment and the demonstration that they can produce chemically novel bioactive metabolites. For example, salinosporamide A (Fig. 2) from *Salinospora tropica* potently inhibits the 20S proteasome and has anti-cancer activity in experimental models [18]; it is undergoing clinical trials. Many technical hurdles still have to be overcome before wide-scale bioprospecting in marine bacteria is a realistic activity [19].

Another marine source of bioactive compounds that is receiving increasing attention is cyanobacteria [20]. These have yielded curacin A and dolastatin 10 (Fig. 2) which are being evaluated as anti-cancer agents or have triggered the creation of analogues with better drug-like properties. Over 120 cyanobacterial alkaloids were published between 2001 and 2006, and they have wide structural diversity and a variety of biological actions, such as cytotoxicity, sodium channel modulation, anti-fungal and inhibition of proteases.

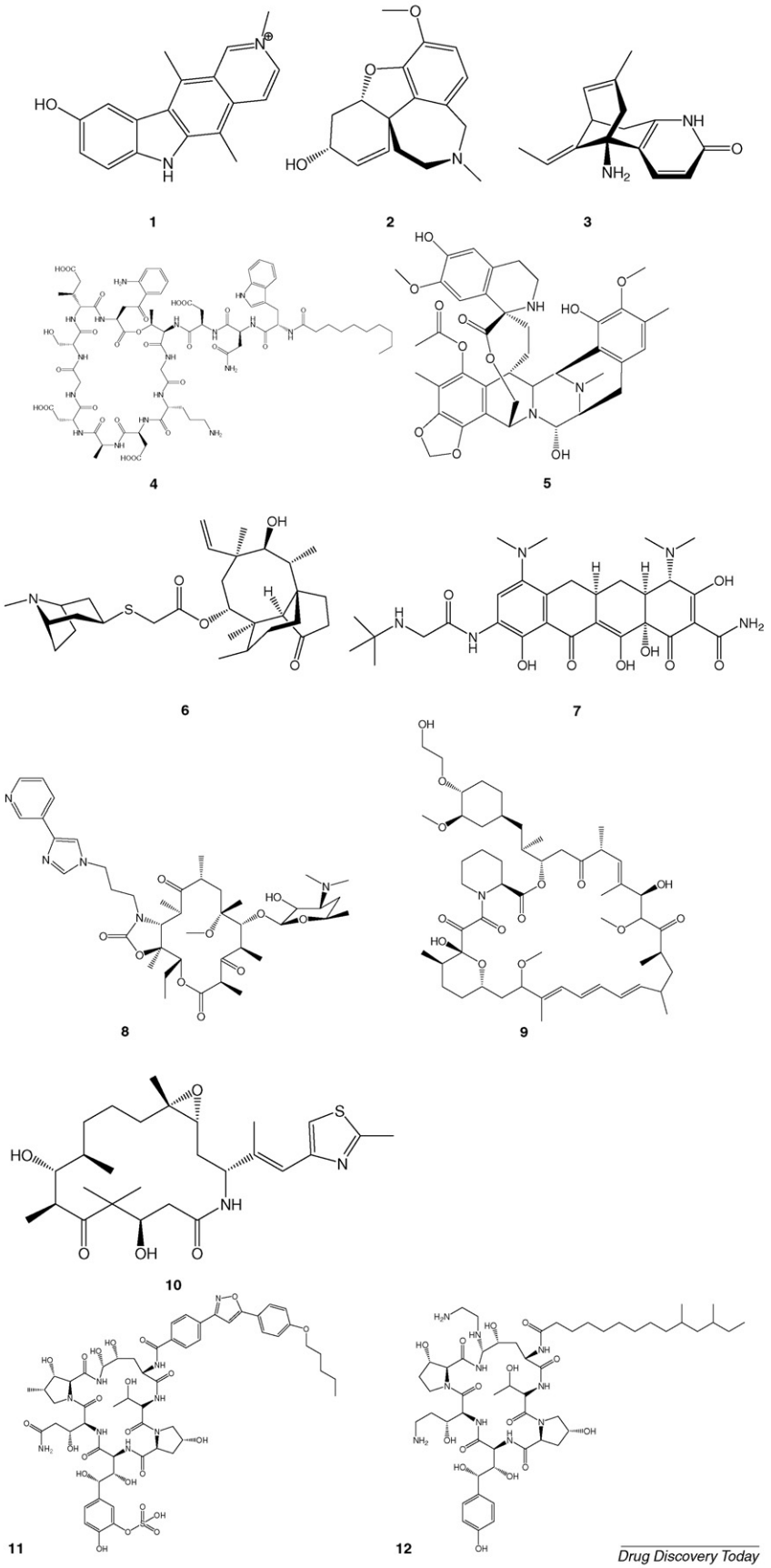
Although the mostly untapped microbial diversity of marine environments is recognised, continued productive use of terrestrial bacteria has been limited by difficulties in culturing the vast majority of species. This has led to the interest in various genetic manipulation techniques such as combinatorial genetics [16,21].

TABLE 2

Therapeutic categories of natural product-derived drugs at different stages of development

Therapeutic area	Preclincal	Phase I	Phase II	Phase III	Pre-registration	Total
Cancer	34	15	26	9	2	86
Anti-infective	25	4	7	2	2	40
Neuropharmacological	6	3	9	4	0	22
Cardiovascular/gastrointestinal	9	0	5	6	0	20
Inflammation	6	2	9	1	0	18
Metabolic	7	3	6	1	0	17
Skin	7	1	2	0	0	10
Hormonal	3	0	2	1	0	6
Immunosuppressant	2	2	0	2	0	6
Total	99	30	66	26	4	225

Source: *Pharmaprojects* database (March 2008).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Most of the research in this area focuses on polyketide pathways in bacteria or fungi [22], and this has led, for example, to the creation of rapamycin analogues with a range of activities [23]. There are, however, concerns about the applicability of the approach [24] and many of the specialist biotech companies that were founded to exploit the technology have not survived. Molecular biological techniques have also been applied to use bacteria to produce drug-like isoprenoid compounds originally isolated from plants [25], and to produce novel flavanones and dihydroflavonols [26]. A bioinformatics approach has also been used to predict which microbes will produce novel chemicals on the basis of the gene sequences encoding polyketide synthesis; this has led to the discovery of novel compounds with potential anti-fungal and anti-cancer activities [27].

More recently, a metagenomics approach has been used to access a wider range of synthetic capabilities from bacteria [28,29]. This involves sampling all the bacterial DNA from an environmental sample and cloning the DNA in host organisms such as *E. coli*. Recombinant bacteria can then be cultured and tested for the expression of bioactive metabolites. Similar work has explored the peptide synthetase genes and polyketide synthase genes of cyanobacteria [30]. The metagenomics approach has led to the discovery of novel compounds with antibiotic activity, the turbomycins [31] (Fig. 2).

Another approach is to adapt the strategy long used to improve the activity of naturally occurring antibiotics by applying combinations of synthetic and enzymatic methods to produce complex natural products. 'Mutasynthetic' methods [32] have been used to create macrocyclic compounds related to the antibiotic daptomycin (Fig. 1) and the anti-cancer compound cryptophicin (Fig. 2) [33], and vancomycin (Fig. 2) analogues have been made with the aid of oxidative modifications carried out by cytochrome P450 enzymes [34].

Natural products have inspired many developments in organic chemistry [35,36], leading to advances in synthetic methodologies and to the possibility of making analogues of the original lead compound with improved pharmacological or pharmaceutical properties [37]. Natural product scaffolds have also been well recognised as being 'privileged' structures in terms of their ability to be the basis for successful drugs. Such scaffolds are being used as cores of compound libraries made by combinatorial techniques. There are several examples of libraries based on alkaloids, polyketides, terpenoids [38] and flavonoids [39]. There is also a description of computational methods to compare the natural product likeness of compound libraries [40]. With the application of various techniques to create analogues and derivatives of natural products, it becomes possible to derive novel compounds that can be patented, even when the original structure was previously disclosed.

New approaches to the value of natural products

With advances in fractionation techniques to isolate and purify natural products (e.g. counter-current chromatography [41]) and in analytical techniques to determine structures [7,21], screening of natural product mixtures is now more compatible with the expected timescale of high-throughput screening campaigns. Singh and Barrett [7] point out that pure bioactive compounds can be isolated from fermentation broths in less than 2 weeks and that the structures of more than 90% of new compounds can be elucidated within 2 weeks. With advances in NMR techniques, complex structures can be solved with much less than 1 mg of compound. Quinn *et al.* [42] recently demonstrated that it is possible to prepare a screening library of highly diverse compounds from plants with the compounds being pre-selected from an analysis of the Dictionary of Natural Products to be drug-like in their physicochemical properties. It will be interesting to see if such a collection proves to be enriched in bioactive molecules.

Several alternative approaches are also being explored in efforts to increase the speed and efficiency with which natural products can be applied to drug discovery.

Activity profiling of extracts

Because it is extremely time-consuming and expensive to create extensive collections of isolated and structurally characterised natural products (the example mentioned above [42] had only 814 different compounds), there is an attraction to screen the mixtures of compounds obtained from extracts of plant material or from microbial broths. But it is not always easy to select extracts from primary screens that are likely to contain novel compounds with the desired biological activity. The concept of 'differential smart screens' approached this by screening extracts of unknown activity against pairs of related receptor sites. By the comparison of the ratios of the binding potencies at the two receptor sites for a known selective ligand and for an extract, it was shown to be possible to predict which extract was likely to contain components with the appropriate pharmacological activity [43]. The technique, as described, is limited to a relatively small number of target sites, but the concept has been extended in a different therapeutic area by the use of antisense RNA against specific therapeutic targets to enhance the sensitivity of the modified cells to compounds acting at those targets. This was used to screen fermentation broths for antibacterial activity following inhibition of fatty acid synthesis [44]. The use of whole-cell screens with the antisense silencing technology was very productive and has led to the discovery and characterisation of the novel antibiotics platensimycin and platencin (Fig. 2) [45].

A different approach to the same area is the 'chemical-genetics profiling' carried out in yeasts [46]. This exploits a panel of yeast strains with selective mutations that highlight sensitivities to particular drugs. By building up a database of the effects of a wide range of known compounds, it is possible to interrogate drugs with unknown mechanisms or mixtures of compounds such as natural product mixtures. The technique highlighted unexpected similarities in

FIGURE 1

Contributions from small-molecule natural products to new medicines. Plant-derived compounds: (**1**) elliptinium for cancer, (**2**) galantamine and (**3**) huperzine-A for Alzheimer's disease; microbially derived compounds: (**4**) daptomycin, an antibiotic; the marine anti-cancer compound (**5**) trabectidin (ecteinascidin 743); and natural product derivatives: the antibiotics (**6**) retapamulin, (**7**) tigecycline and (**8**) telithromycin, (**9**) the immunosuppressant everolimus, (**10**) the anti-cancer agent ixabepilone, and the anti-fungal agents (**11**) micafungin and (**12**) caspofungin.

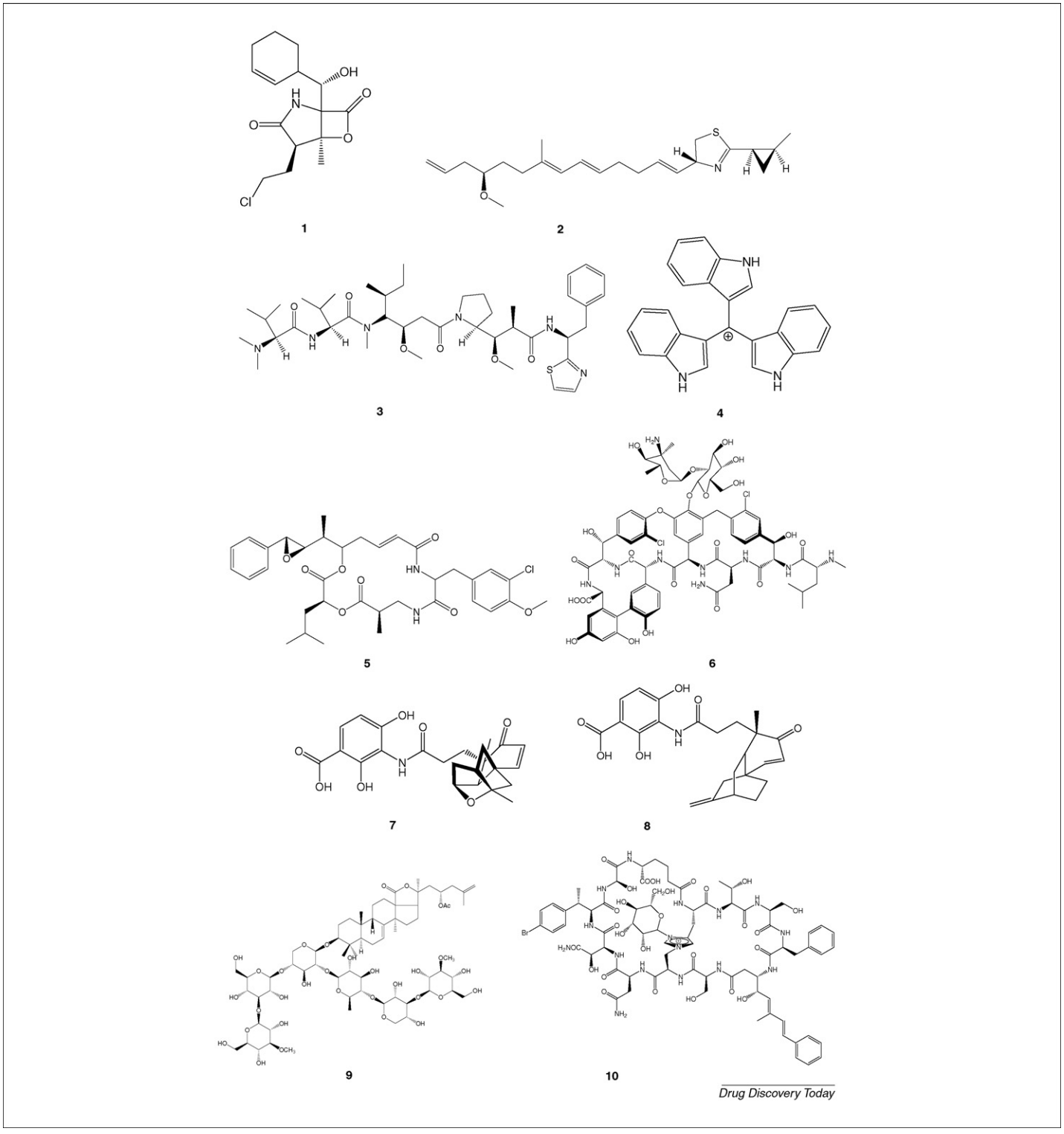

FIGURE 2

Natural products – recently discovered and/or in development. (**1**) Salinosporamide A; (**2**) curacin A; (**3**) dolastatin 10; (**4**) turbomycin A; (**5**) cryptophicin; (**6**) vancomycin; (**7**) platensimycin; (**8**) platencin; (**9**) stichloroside; (**10**) theopalauamide.

molecular effects of unrelated drugs (e.g. amiodarone and tamoxifen) and also revealed potential anti-fungal activity of crude extracts. This activity was confirmed by isolation and testing of defined compounds, stichloroside and theopalauamide (Fig. 2). Because these compounds are not structurally similar, they would not have been expected to act via the same biological target.

Exploiting leads from traditional medicines

Although there are key examples of traditional medicines that have led to modern drugs, the traditional approach of bioassay-guided fractionation can be laborious, and it is also dependent on the availability of a convenient assay. There are several publications [47–50] suggesting the value of data-mining approaches to

pinpoint the active ingredients in traditional Chinese medicines (TCM). These are based on assuming that the biological effects of a mixture of herbal extracts will still vary in a quantitative manner with the relative amounts of the constituents, leading to the concept of quantitative composition–activity relationships [47]. They also seem to be making the assumption that the activity of a complex TCM preparation can be associated with a relatively small number of components or even with a single component. Several traditionally used preparations were analysed. In one, 12 separate TCM preparations were spilt into 6 fractions by chromatography and the relative amounts of each fraction measured. The activity under test was the ability of the TCM to lower blood cholesterol in rats. Different computational methods (including multiple linear regression, artificial neural networks and a stepwise causal adjacent discovery algorithm) were used to analyse the relation between variations in components and activity [47]. Two fractions were predicted to be synergistic in activity and this was confirmed through *in vivo* tests. The comparisons were, however, performed with only a single dose and it is difficult to conclude that there was true synergism. Another example concerned the ability of different versions of the same TCM to reduce the consequences of myocardial ischemia and reperfusion injury [47]. Twenty-four different samples were analysed chemically and pharmacologically: the computer-based analysis of causal relationships highlighted two peaks that were then analysed by HPLC and LC–MS and found to contain two known active ingredients. In a further example, several preparations of ginseng (*Panax ginseng*) were analysed for their content of nine chemicals previously proposed to be associated with the biological activity of the plant extract [48]. The preparations were tested for effects on the proliferation of the breast cancer cell line MCF-7. Depending on the level of significance set for the computer analysis, either one or a group of two to three components were predicted to be associated with anti-proliferative effects. Unfortunately, the bioassay appeared not to be sensitive enough to provide data to confirm the predictions. In a different approach, Random Forest methods were used to examine possible links between identified constituents of TCM preparations and biological targets [50,51]. This allowed linkages to be suggested between broad classes of traditional preparations and known therapeutic targets, and it enabled some predictions to be made, including preparations that may have anti-viral activities.

There has been a different approach to make use of a database of active structures from TCM preparations [51,52]. By a 'reverse docking' method, the active ingredients were screened *in silico* for the ability to bind to sites on proteins in the structural database. Although this was suggested to be a means to predict the biological mechanisms for the isolated natural products, it assumes that the compounds are entering cells (most of the proteins being tested being intracellular) and it ignores the fact that most of the known drug targets are proteins, such as G-protein-coupled receptors, whose structures have not been determined. A somewhat similar approach has been used with other plant chemicals including those from Western herbal remedies [53].

Biology-oriented synthesis

As mentioned earlier, natural products have been used to inspire the synthesis of small but highly diverse chemical libraries for screening [38,39]. These still have to be used in a random screening approach. Structural information from natural products has been used differently to create a way to focus on the most relevant part of chemical space for a particular assay through what has been called biology-oriented synthesis [54,55]. All of the ~150,000 structures from the CRC Dictionary of Natural Products were reduced to ~25,000 simple two-dimensional scaffolds that were then clustered in a 'parent–child' relationship [54]. This allowed easy selection of related structures to base library creation for focused screening. It also facilitated the selection of chemically simpler scaffolds that could be expected to maintain the ability to support the desired biological activity. When combined with the authors' complementary approach of clustering biological targets through similarities in binding sites [56], this method was demonstrated to result in quite selective and potent enzyme inhibitors being found from testing of a very small number of compounds: selective inhibitors of 11β-hydroxysteroid dehydrogenase 1 [54], potent, selective and novel inhibitors of various protein phosphatases [55], and anticholinesterase compounds derived from lead structures that inhibited Cdc25A phosphatase [57].

Integration of in silico *screening and natural products*

Facilities for high-throughput screening are now available in academic labs as well as in drug companies; however, the cost of random screening of very large collections of compounds can be prohibitive, and it makes sense to use *in silico* or virtual screening where possible to filter down the number of compounds used in real screens [58]. Whereas the Dictionary of Natural Products gives structural information on ~150,000 different compounds that could be used in virtual screening, the compounds would still have to be physically available for any predicted activity to be confirmed through testing in a relevant assay. As mentioned above, clustering of chemically related scaffolds can be very useful in guiding the synthesis of new compounds, but obviously there is a delay and expense in the synthesis. In an attempt to combine the advantages of virtual screening of chemically diverse natural products and their synthetic analogues with the rapid availability of physical samples for testing, an academic collaboration has established the Drug Discovery Portal (see http://www.ddp.strath.ac.uk/). This brings together a wide variety of compounds from academic laboratories in many different institutions in a database that can be used for virtual screening. Academic biology groups can also propose structures as targets for virtual screening with the Portal's database (and with conventional commercially available databases). When hits are predicted from the *in silico* screening, they can be sourced from the originating chemist for confirmatory tests. Often, there is an immediate link to expertise for the preparation of analogues to help start a lead optimisation programme. Access to the Portal is free for academic groups and the continued expansion of the chemical database means that there is a valuable and growing coverage of chemical space through many novel chemical compounds. Although the compounds in the Portal's database will generally have already been disclosed in a thesis or in a chemistry journal, very few of them have been previously tested for biological activity. This is a common feature of known natural products: of the ~150,000 structures in the CRC Dictionary of Natural Products only ~1% of them

have any biological test results ascribed to them in the MDL Drug Data Report database (see Ref. [55]).

Natural products as pharmacological tools

There are many historical examples in which the natural product has not just been the medicinal product but has also helped reveal a novel aspect of physiology. For example, digitalis from foxglove showed the role of sodium-potassium-ATPase; morphine pointed the way to the receptors affected by endogenous opioids; muscarine, nicotine and tubocurarine helped explore the different types of acetylcholine receptors, and so on [1,10]. More recently, there has been interest in systematically searching for small-molecule inhibitors of key steps in biochemical processes (chemical genetics) [58]. Given that many assays involve identifying phenotypic changes in living cells (as opposed to binding interactions with isolated proteins), it is probable that natural products will provide useful probes for such studies [6,10]. Moving beyond observations of phenotypic changes to defining the alterations in gene expression or protein function that are responsible will require advances in transcriptomic (e.g. Ref. [59]) and proteomic [60] methods.

Conclusions

Despite a period in which pharmaceutical companies cut back on their use of natural products in drug discovery, there are many promising drug candidates in the current development pipeline that are of natural origin. Technical drawbacks associated with natural product research have been lessened, and there are better opportunities to explore the biological activity of previously inaccessible sources of natural products. With the increasing acceptance that the chemical diversity of natural products is well suited to provide the core scaffolds for future drugs, there will be further developments in the use of novel natural products and chemical libraries based on natural products in drug discovery campaigns.

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