

Mother Nature's Drug Cabinet



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The endeavours of drug discovery have long relied upon Mother Nature for inspiration. Lately, though, pharmaceutical companies are less and less willing to take on the challenge of finding and developing new, natural product based drugs and this, despite some encouraging results from the scientific world.

A quite extraordinary tree can be found growing in the southern part of China; natives call it “Xi Shu”, the happy tree. It’s not, however, the tree that is happy but people who have for centuries benefited from treatments and remedies made from its bark. *Camptotheca acuminata*, Xi Shu’s Latin name, made its grand appearance on the international medical stage when, during the 1950s, a huge screening programme to find substances with anti-cancer activities from natural products was initiated by the US-based National Cancer Institute (NCI).

Scientists at the NCI isolated a quinoline alkaloid, named it “camptothecin” and subsequently discovered that the compound is effectively inhibiting DNA topoisomerase I, which is an important enzyme involved in cell division. By binding to topoisomerase I and DNA, camptothecin stabilises the complex and thus prevents DNA re-ligation. This leads to DNA damage and ultimately, results in the death of the cell by apoptosis. Conveniently, this is exactly the fate you would want to befall a malicious cancer cell. Today, camptothecin analogues with optimised pharmacological properties are one of the most commonly prescribed anti-cancer drugs available. Topotecan is one such example, and is used as a standard treatment for ovarian and small cell lung cancer; similarly, irinotecan is useful in treating metastatic colorectal cancer.

How is it then that plants are so “willing” to benefit human well-being? Well, perhaps they aren’t really all that accommodating after all, as many of those ‘natural products’ are secondary metabolites and are made by the plant either to get rid of predators (toxins), to attract insects (pheromones), fight bacterial or fungal infection (phytoalexins) or to inhibit competition from rival plants (allelochemicals). As plants haven’t (yet) invented any escape tactics they have to stand their ground and fight against their enemies using “chemical warfare”. As such, the repertoire of pharmacologically interesting compounds that plants produce increases, unsurprisingly, with the species richness of a plant’s environment. The greater the presence of potential foes, the greater the chemical arsenal to annihilate them!

It’s all about secondary metabolites

During the last few decades, natural products, either derived from microorganisms, terrestrial plants or marine life forms, have been a major source for lead compounds in drug discovery and drug design. In their 2007 paper “Natural Products as Sources of New Drugs over the Last 25 Years” (spanning the period from 1981-2006), David Newman and Gordon Cragg found that of 155 FDA-approved small molecule anti-cancer drugs, 47% were either natural products or directly derived there-

from (*J Nat Prod*, 70:461-77). The authors also noted, however, a “current low level of natural product-based drug discovery programs in major pharmaceutical houses”. The same was still found to be true by Jesse Li and John Vederas two years later (*Science*, 325:161-5). In 1990, they claim that 80% of drugs were either natural products or analogues inspired by them. Subsequent years, however, saw the expansion of synthetic medicinal chemistry, which led to a decline of that figure to 50%. Nevertheless, in 2008, of the 225 drugs being developed, 164 were of natural origin, with 108 being derived from plants, 25 from bacterial sources, 7 from fungal and 24 from animal sources. And, to throw some more numbers around, of the 108 plant-based drugs, 46 were in preclinical development, 14 in phase I, 41 in phase II, 5 in phase III and two had already reached pre-registration stage. Between 2005 and 2007, of 13 natural product derived drugs that received their FDA approval, five were first members of brand new drug classes (*Drug Discov Today*, 13:894-901).

According to Li and Vederas, there are two major issues that make natural products less favourable as a source of new drug discovery: technical difficulties and the pharmaceutical paradigm. In most cases, it’s an exceptionally long and difficult path from finding, isolating and purifying a potentially biologically active substance

to ultimately marketing and selling a natural product based drug.

Pretty hard to handle

Many things have to be taken into consideration along the way. Some exotic plants, for example, are hard to come by (local governments may have prohibited the export of samples) or there could be seasonal or environmental variations within a species' chemical composition; in the worst case scenario, a certain plant could be on the brink of extinction or could be driven to the edge during drug development. In the late 1980s, for example, it was estimated that 360,000 Pacific yew trees, *Taxus brevifolia*, would have to be cut down annually to isolate enough taxol from the bark to enable treatment of all melanoma cases in the US. Nowadays, taxol is mainly produced by plant cell fermentation using a specific *Taxus* cell line. The yews are safe now.

On top of the access issue, quite a number of natural products stand out as having inauspicious features, such as poor sol-

ubility and permeability and also exhibit a high potential for adverse side-effects. This means an awful lot of work, time and money have to be invested in product development before a drug comes onto the market. And with looming patent expiration fears hanging like a spectre over the shoulder of many drug companies (sales revenue can drop by as much as 80%), many pharmaceutical concerns seem to be geared to choosing the quickest way out. And one of those quick ways out is high-throughput screening of massive libraries of diverse but purely synthetic compounds (*Science*, 325:161-5). In contrast to natural products, those compounds are usually very easy to make and modify, however, their comparative success rates are pretty low. Only one compound, sorafenib, has so far been found and made ready for the market using this approach (*J Nat Prod*, 70:461-77).

And more dark clouds are gathering over Mother Nature's drug cabinet. Last year, voices were raised that natural products are not optimal as drug sources

anyway. Using network analysis, Stuart Schreiber of the Broad Institute of Harvard and MIT and colleagues argue that "natural products target proteins with a high number of protein-protein interactions and that these protein targets have higher network connectivity than diseased genes" (*J Am Chem Soc*, 132:9259-61). Simply put, natural products hit too many targets. The authors go on to suggest that "additional sources of small molecules will be required" referring to the above mentioned concept of "diversity-oriented synthesis" (short DOS) – the creation of combinatorial libraries of diverse small molecules for biological screening (*Nat Chem Biol*, 1, 74-84).

Provocative views

However, not everyone in the field shares Schreiber's opinion. Samuel Danishefsky, a highly awarded chemistry professor from the Columbia University, and Derek Lowe, writer of the blog "In the Pipeline", disagree. In fact, neither of them sees the future of new drug discovery resting



Not only pretty but medically useful, too
Madagascar Periwinkle

photo: Fotolia/mislain

solely with DOS. Lowe is concerned that “the chemical space DOS covers doesn’t necessarily overlap very well with the space occupied by potential drugs”. “Chemical space”, for that matter, is defined as “all possible small organic molecules”. Estimations of its number go as high as 10^{60} or in real words: a decillion (*Med Res Rev*, 16: 3-50). Lowe even goes as far as calling Schreiber’s article a “provocative paper”. Danishefsky, however, still finds something positive between the lines, “The paper admirably serves to refocus reader interest on small-molecule natural products as well as synthesis. That’s all to the good.” (*Chemical & Engineering News*, 88(27):8).

Wormwood vs. malaria

And there are more good things. Natural products are sometimes the source of exciting, Hollywood-worthy stories, too. Take, for example, artemisinin, a compound isolated from the common herb *Artemisia annua* or annual wormwood. It has been used in Chinese traditional medicine for centuries with the earliest recorded use dating as far back as 200 BC for the treatment of many diseases, including malaria. In 1960, the Chinese Army set up a research project to screen traditional remedies for their anti-malarial activities. First isolated from its leaves in 1972, artemisinin was found to be more effective and rapid in action than any other drug previously known, and that is the case to this day, but the Chinese kept it a secret until they finally published their results in the *Chinese Medical Journal* in 1979 (*Chin Med J*, 92(12):811-6). Even though its exact mode of action is still unclear, an artemisinin derivative, in combination with a partner drug, is standard treatment for falciparum malaria worldwide. Research into its anti-cancer activity was launched in 2005.

Then there’s the mamala tree, *Homolanthus nutans*, rooted in Western Samoa. When ethno botanist Paul Alan Cox observed that village healers used the tree’s bark to treat hepatitis, he immediately sent a sample to the NCI where a compound with anti-HIV activity was isolated and described in 1992 (*J Med Chem*, 35(11):1978-86). Research showed that this compound, named “prostratin”, is a potent protein kinase C activator. Functionally, prostratin does not only inhibit HIV replication, it also activates dormant HI-viruses, so the immune system can recognise the viral invader in infected CD4+ positive T-cells and render it harmless, which is something that no other currently available compound is able to do.

Furthermore, in what can be regarded as a landmark event in drug discovery and development, two separate agreements were signed to share potential drug profits between drug developers and the people of Samoa. The Aids Research Alliance of America wants to give 20% of their profits back and the University of Berkeley, where the gene sequence of prostratin is currently being analysed, even offered a generous 50%. It’s really too bad that, according to www.clinicaltrials.gov, prostratin is currently not even in a clinical trial!

The French paradox

Things are, however, looking better for another interesting natural compound. Resveratrol, first isolated from *Veratrum album* (white hellebore), is currently represented in several clinical trials for the treatment of diabetes. But this phytoalexin, also found in the skin of red grapes, is said to have even more miraculous powers. It is held responsible for what has become known as the “French paradox”. In regions where people tend to drink more red wine, their lives appear to last quite a bit longer. Several model organisms including yeast, fruit fly, *C. elegans* and a short-lived fish by the name of *Nothobranchius furzeri* seem also to confirm this empirical observation (*Nature* 425(6954): 191-6, *Nature* 430(7000): 686-9, *Current Biology*, 16(3): 296–300). Unfortunately, to date, it hasn’t officially been replicated in humans. And the compound recently suffered yet another setback, when UK pharma giant GlaxoSmithKline “terminated its phase IIa study of SRT501 in advanced multiple myeloma” due to “a potential to indirectly exacerbate a renal complication common in this patient population”. In 1997, a mouse model study had suggested that topical applications of resveratrol

were able to prevent skin cancer (*Science*, 5297(275):218-20).

So, whilst maybe not every natural product has the potential to save humankind, Mother Nature does still have a few tricks up her sleeve as latest research results reveal. Genistein, for example. It’s a phytoestrogen found in soybeans and lupin but was initially isolated from the Dyer’s broom (*Genista tinctoria*). The compound mainly acts as a tyrosine kinase inhibitor but it is also able to inhibit the mammalian hexose transporter Glut1 (*J Biol Chem*, 271(15):8719-24). Recent research by the Brian Bigger group at the University of Manchester has shown in a mouse model of Sanfilippo, an untreatable mucopolysaccharide disease affecting one in 89,000 children in the UK, that high doses of genistein have had a dramatic effect. In experiments, where the drug was administered over a nine-month period, the isoflavone significantly delayed disease onset and corrected behavioural defects like mental decline (*PLoS ONE*, 5(12)e14192). It’s only a matter of time before the first clinical trials begin to recruit patients.

Sweet results and sweet research

Another genistein-derived drug, imaginatively named KBU2047, has already proven its clinical benefits in phase II trials. When the drug was administered before prostate cancer surgery, metastasis could be effectively prevented. Presenting his team’s results at a recent conference in Philadelphia, Raymond Bergan of the Northwestern University enthused, “This is the first time that it has been possible to inhibit prometastatic pathways in humans by targeted therapeutics for any cancer type” and he goes on to speculate that “a similar therapy could have the same effect on the cells of other cancers.” That, of course, still remains to be seen.

But it’s not only those notorious secondary metabolites that are pharmacologically active; plant hormones may also promote human health. Abscisic acid is known to positively affect the anti-inflammatory response and recently, in an EC-funded project conducted in the US, it was shown exactly how this works. Abscisic acid binds to a totally different receptor domain than commonly prescribed drugs, like the synthetic drug Avandia, thereby revealing a brand spanning new therapeutic target (*J Biol Chem*, Nov 18, Epub ahead of print). Those results are all the “sweeter” as recently the European Medicines Agency (EMA) has recommended that Avandia be sus-

pended from the market due to a high potential for severe side effects.

Other “sweet” things are going on at the University of Helsinki, where glycyrrhizin, the sweet-tasting compound of the liquorice plant (*Glycyrrhiza glabra*), serves as the research subject for Ari Rouhiainen. First described in 1809, glycyrrhizin has been used for several years to treat hepatitis in Japan. And only a few years back, it was even associated with HMGB-1, one of the major damage-associated molecular pattern (DAMP) molecules that once again play a role during the inflammatory response (*Nature*, 418(6894):191-5). Rouhiainen states, “We have used glycyrrhizin to inhibit HMGB1 binding to its cell surface receptors that in turn inhibits motility of cancer and immune cells.” But what are the future prospects of a liquorice-inspired drug? Rouhiainen explains, “Although it is not a specific inhibitor of HMGB1, it has advantages to be the first clinically-used HMGB1 blocking drug: it has been used for a long time in Japan to treat hepatitis, it is well tolerated in humans and its effects have been shown in many studies by independent research groups *in vitro* and *in vivo*.”

So it's very obvious that plants do make many medically useful compounds but apart from testing promising new natural products for their disease-fighting abilities, methods to improve production and delivery of already successfully employed drugs are on the horizon, too.

Halogenated plants

In a fascinating approach to “reshaping the natural synthetic pathway” of secondary metabolites, the group around Sarah O'Connor at the MIT in Boston, was recently able to promote the production of rare (halogenated), pharmacologically more effective variants of vinblastine. Vinblastine, an alkaloid isolated from the Madagascar periwinkle (*Catharanthus roseus*), is currently in use for the treatment of testicular cancer or Hodgkin's lymphoma. The drug binds to tubulin and thereby, inhibits the assembly of microtubules during the M-phase of the cell cycle. However, by introducing prokaryotic genes that code for halogenases

to hairy root cultures, the periwinkle cells produce high amounts of chlorinated and brominated alkaloids all by themselves (*Nature*, 468:561-7). The next goal is targeted at engineering an entire periwinkle plant.

A unique head start

To counteract the poor bioavailability of many natural products, delivery options are being optimised, too. Recently, Cerulean Pharma, a company specialising in nanopharmaceuticals, raised \$24 million to further develop their anti-cancer drug CRLX101. This drug, currently in phase 1b/2a clinical trial, consists of our favourite happy tree isolate, camptothecin coupled to a cyclodextrin-based polymer, which self-assembles into nanoparticles. Administration of this nanopharmaceutical is said to increase target specificity and

tumour cell exposure to the drug, while decreasing side effects (*Genetic Engineering News*, Nov 2010, www.genengnews.com). In not completely unrelated news, Chanda *et al.* from the University of Missouri, fairly recently, discovered the secret ingredient for making

gold nanoparticles without using dangerous levels of toxic chemicals. And you're probably wondering what on earth it could be? The answer is of course... cinnamon (*Pharm Res*, 2010 Sep 25, Epub ahead of print).

Back in 2006, Samuel Danishefsky and Rebecca Wilson wrote, “We hope and expect that enterprising and hearty organic chemists will not pass up that unique head start that natural products provide in the quest for new agents and new directions in medicinal discovery” (*Acc Chem Res*, 39:539-49). And, indeed, it looks like Mother Nature still has quite a few surprises in store for us. With less than 10% of all the estimated 250,000 higher plants screened for biological activity, so far, and a few of them still waiting to be discovered somewhere in the deepest jungles of Borneo, just maybe there's still a good chance we will eventually find what we are so desperately looking for. Anything still seems possible if only ‘big pharma’ could be persuaded it was worth getting back to nature once again...

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photo: Fotolia/Yvonne Begianski

Is this candy or the next liquorice-inspired drug?