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From traditional Chinese medicine to rational cancer therapy

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Many natural products and derivatives thereof belong to the standard repertoire of cancer chemotherapy. Examples are *Vinca* alkaloids, taxanes and camptothecins. In recent years, the potential of natural products from plants, notably from medicinal plants used in traditional Chinese medicine (TCM), has been recognized by the scientific community in the Western world. To provide an example of the most recent developments in this field, we have selected several compounds, namely artesunate, homoharringtonine, arsenic trioxide and cantharidin, that are found in natural TCM products and that have the potential for use in cancer therapy. Controlled clinical studies have shown that homoharringtonine and arsenic trioxide can exert profound activity against leukaemia. Increased knowledge of the molecular mechanisms of TCM-derived drugs and recent developments in their applications demonstrate that the combination of TCM with modern cutting-edge technologies provides an attractive strategy for the development of novel and improved cancer therapeutics.

East meets West

Traditional Chinese medicine (TCM) has held, and still holds, an important position in primary health care in rural areas of China and is also appreciated in urban and well-developed areas because of its 5000-year-old tradition. Recently, the Chinese government has undertaken enormous efforts to modernize TCM by investing capital in scientific research and in the economical exploitation of TCM. In the Western world, interest in TCM stems from the hope that it might complement Western medicine. The history, philosophy, theory and practice of TCM have been recently reviewed [1–3].

Medicinal herbs have played an important role in Western medicine from ancient to modern times. However, medicinal plants gradually lost their importance as pharmaceutical synthetic chemistry progressed in Western countries during the 20th century. Currently, there is a revival of interest in medicinal plants and an increasing scientific interest in bioactive natural products as chemical lead compounds for the generation of semi-synthetic derivatives.

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During the past decades, interest in medicinal plants has followed two separate paths, either toward complementary medicine, which will not be discussed here, or toward Western science and medicine, which represents a mechanism-centred approach. Rather than the analysis of the patient in his or her entirety, as is the case in the practices of TCM and complementary medicine, in Western medicine it is the disease that is analyzed at the cellular, molecular and pharmacological level (see Box 1).

TCM and pharmacology

At the pharmacological level, different areas of classical pharmacy focus on medicinal herbs, for example, phytochemistry, pharmacognosy and phytotherapy (see Glossary). Secondary metabolites, which are – in contrast to primary metabolites – not essential for the nutrition of plants, are produced by an organism as a defence against competitors, herbivores and pathogens and as signal compounds that attract insects for reproduction. Therefore, secondary metabolites represent an important part of plants' life strategies for maintaining survival and reproductive fitness [4]. Interestingly, many secondary metabolites of plants exert pharmacological features. The exploitation of these beneficial effects is the goal of molecular pharmacology of natural products.

Natural products are among the major players in pharmacology in general and in cancer research in particular. A considerable portion of anti-tumour agents currently used in the clinic are of natural origin. Naturally occurring

Glossary

Alternative medicine: any of the various healing or disease-treatment systems that are not included in the traditional medical curricula taught in the Western world.
Complementary medicine: any of the practices of alternative medicine that are accepted and utilized by mainstream medical practitioners.
Pharmacognosy: the biochemistry and pharmacology of drugs of natural origin (e.g. medicinal plants and spices).
Phytochemistry: the chemistry of secondary metabolites and isolated chemical entities found in medicinal plants. This field is easily compatible with molecular pharmacology, molecular biology and pharmacogenomics.
Phytotherapy, or phytomedicine: treatments using entire plants, aromatic essential oils and herbal or floral extracts that are applied as herbal teas, via massage as packs or wraps or in therapies using water, steam or inhalation.
Traditional Chinese medicine (TCM): TCM comprises the use of medicinal products from plants, animals and minerals, acupuncture and other practices. In this article, we focus only on herbal medicine (*ben cao*, 本草). Herbal prescriptions that consist of a varying number of different medicinal plants are used as extracts, decoctions and teas.

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Box 1. Controversies in TCM

Western medicine versus Chinese medicine; TCM is frequently regarded with some scepticism by Western academic medicine because

- TCM represents a holistic approach that treats the entire human body, whereas Western science and medicine is focused on mechanisms: Rather than the analysis of the patient in his/her entirety, it is only the disease that is analyzed at the cellular, molecular and pharmacological level.
- Scientific evidence of efficacy and safety is frequently missing in TCM, and so quality management needs to be improved. False TCM preparations on the market further weaken the reputation of TCM in the scientific communities outside China.

Another controversy in TCM is about the use of complex mixtures of medicinal plants in contrast to isolated, bioactive, single natural products. Composite and complex TCM remedies (*fu-fang*, 複方) might act in a synergistic fashion to increase therapeutic effects. On the other hand, these combined remedies might reduce adverse side effects on healthy tissues. Even with the current methodology of academic phytochemistry and pharmacology, it is still difficult to identify and prove the synergistic or antagonistic effects of dozens of chemical constituents in herbal composite prescriptions.

drugs that are part of the arsenal in the war against cancer include *Vinca* alkaloids (vincristine, vinblastine, vindesine, vinorelbine), taxanes (paclitaxel, docetaxel), podophyllotoxin and its derivative (etoposide, teniposide), camptothecin and its derivatives (topothecan, irinothecan), anthracyclines (doxorubicin, daunorubicin, epirubicin, idarubicin) and others. In fact, half of all anti-cancer drugs approved internationally between the 1940s and 2006 were either natural products or their derivatives and were developed on the basis of knowledge gained from small molecules or macromolecules that exist in nature [5].

Accordingly, considerable experience with traditional folk medicines might facilitate the identification of novel agents. At some point during the development of synthetic chemistry in the 20th century in industrialized countries medicinal herbs gradually lost importance. However, bioactive plant constituents have recently experienced an impressive revival as lead compounds for the generation of semi-synthetic derivatives [5]. This has caused phytochemists and pharmacognosticists to use the principles of modern life sciences to investigate natural products used in TCM.

The attractiveness of TCM in China and throughout the world has led to enormous efforts to systematically investigate the scientific basis of TCM. Modern pharmacological disciplines, including phytochemistry, pharmacognosy and phytotherapy, provide the scientific methodology and technology to facilitate this transition. This concept is supported by the fact that numerous standard cytostatic drugs established for many years in clinical oncology are derived from natural sources. Here, we review the efforts to scientifically investigate the efficacy of TCM by using artesunate, homoharringtonine, arsenic trioxide and cantharidin as our main examples.

Classical targets for TCM-derived drugs applied in tumour therapy

Anti-cancer drugs target DNA either directly (e.g. platinum compounds and alkylating agents) or indirectly by inhibition of DNA-metabolizing functions. Other targets for anti-cancer drugs are proteins involved in cell division or in cell signalling related to proliferation or cell death. Standard tumour chemotherapy comprises several natural products, and many of them are derived from or have a direct relationship to TCM. Although this fact might not be well recognized in the Western academic world, it speaks impressively for the power and the potential of TCM.

Classical targets for natural compounds that were derived from TCM include DNA topoisomerases. DNA topoisomerase I (topo I) induces DNA single-strand breaks during transcription and DNA replication to reduce the torsion tension of super-coiled DNA. Camptothecin is a valuable natural product that inhibits the ligation of DNA after topo I-mediated strand breaks [6]. This compound was isolated from the Chinese 'happy tree', *Camptotheca acuminata* (喜樹). Topotecan (Hypocamptin) and irinotecan (Campto), which are semi-synthetic derivatives of camptothecin, have entered clinical routine treatment for ovarian cancer and colon cancer, respectively.

DNA topoisomerase II (topo II) induces DNA double-strand breaks (DSBs) and thus reduces torsion tension in DNA during replication and the condensation of chromosomes in the nucleus during cell division. The topo II-induced DSBs are transient, and they are immediately repaired by topo II itself. The religation function of topo II can be blocked by topo II inhibitors. As a consequence, DSBs are held open for longer periods, and this eventually leads to the activation of the apoptotic pathway [7]. Established topo II inhibitors are etoposide (Vepesid) and teniposide (VM-26), which are semi-synthetic derivatives of podophyllotoxin. This toxin was first identified in a plant (*Podophyllum peltatum*) that Native Americans used to treat warts. Podophyllotoxin is also found in *Podophyllum emodi var. chinense* (鬼臼), a medicinal plant from China [8].

Other plant poisons target mitotic-spindle proteins and microtubuli of the cytoskeleton. Microtubuli are integral components of the mitotic-spindle apparatus, which is necessary for the separation and distribution of chromosomes to daughter cells during cell division [9]. This process requires a dynamic balance between assembling and disassembling of microtubuli. Compounds that disturb this balance cause interruption of mitosis and lead to cell death. The alkaloids vinblastine and vincristine from the Madagascar periwinkle (*Catharanthus roseus*, 長春花) are natural products that bind to β-tubulin and inhibit microtubule assembly. Vindesine and vinorelbine are novel *Vinca* alkaloid derivatives with improved clinical features for tumour therapy [10].

Taxanes such as paclitaxel were originally isolated from *Taxus brevifolia*. Paclitaxel is also present in high amounts in *Taxus chinensis* (红豆杉) [11]. Paclitaxel and its derivative docitaxel stabilize microtubules and thereby inhibit their disassembly (Figure 1a).

Novel targets for TCM-derived natural compounds

Natural products from TCM represent a valuable source for the identification of small-molecule inhibitors against novel targets for medicine, especially for cancer therapy (see Table 1 for a compilation of TCM-derived drugs).