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Drug makers are starting to revisit the promise of treatments derived from naturally grown materials, writes Andrew Jack

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In a laboratory near Shanghai's futuristic magnetic levitation train track, dozens of scientists are studying how to convert medicines described in Chinese texts written 2,000 years ago into modern western treatments

The Shanghai Institute of Materia Medica (Simm), founded in the 1930s and reinforced through co-operation with international pharmaceutical companies over the past decade, is one of many organisations that hope for fresh medical breakthroughs inspired by ancient lore.

Alfred Hofmann, the Swiss chemist who first isolated LSD from a fungus in 1938 and died aged 102 last week, was a west-ern pioneer in the field. He lived just long enough to witness the subject. after most companies had turned their backs during the latter part of the last century. "He was part of the ergot [fun-

gus] school, which isolated and modified toxic compounds to give us very important drugs - to induce birth contractions, stop bleeding and treat Parkinson's disease," says Paul Herrling, head of corporate research at Novartis, the pharmaceutical group that absorbed Sandoz, Hofmann's long-standing employer.

On paper, the appeal of studying the natural compounds used by traditional peoples to develop modern medicines is clear. Their

## Medicine looks back to its roots, barks, moulds and leaves

use of local plants and products over many generations ought to provide valuable clues and short cuts for modern drug developers around the world.

The approach has led to the emergence of a number of significant treatments, from the historical development of aspirin as a painkiller derived from willow bark to the recent launch outside Asia of the anti-malarial artemether, identified from a Chinese plant used for centuries to treat fevers

In practice, however, the adaptation of such substances to western medicine has proved difficult. One issue is that much medicinal knowledge was and continues to be lost with modernisation, especially in African and Latin Amer ican tribal cultures where nothing was written down.

Even where there are texts and continued practice, notably in Indian Ayurvedic and Chinese traditional medicine, they typically use plant compounds that contain a complex mix of different and often unstable substances, in varying concentrations, which may operate on different disease "targets" in a person. "Traditional medicines can be

very dangerous," says Mr Herrling. "Practitioners had no concept of statistics or of long-term consequences such as treatments that may cause cancer when used over many years."

By contrast, the western pharmaceutical industry - reinforced by regulatory requirements operates by isolating, extracting and purifying compounds that work on a single target, ensuring that they can be consistently reproduced and scrupulously tested for safety and efficacy.

Testing traditional medicines is like jumping into the water without knowing quite where you are going." says Yongning Chen, a professor from Simm. The process is so complex and quite time consuming, especially for pharmaceutical companies with short time lines [to bring drugs to the market]."

Phytopharm of the UK has suffered repeated losses and financial restructuring because of set-

backs in its attempts to commercialise products such as Hoodia. a weight-loss extract from a plant used by the San bushmen of the Kalahari. "Regulators need to be convinced," says Daryl Rees. Phytopharm's chief executive. "We realised that - quite rightly - there was no quick way of get ting things through.

But if aligning traditional medicine to western practice has proved difficult, a more promising approach has come from recently rekindled interest in developing new drugs derived from naturally occurring compounds - as opposed to the many drugs manufactured from artificially created compounds.

Companies such as <u>Chi-Med</u> in China and Nicholas Piramal in India developed some of their more promising leads from natural compounds that have no link to historical treatments.

Statins, the best-selling cholesterol-lowering drugs, were originally isolated from mould. Cyclosporin, used to prevent the rejection of transplanted organs. was derived from a Norwegian soil sample. Tamiflu, the bestselling antiviral drug for influenza - heralded as the first "designer drug" specifically engineered to fit its target - is synthesised from a starting material derived from the Chinese star anise plant.

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recent study published by Α David Newman from the natural products branch at the US National Cancer Institute estimated that of 1,000 new chemical registered entities during 1981-2006, more than one-quarter

## 'Big pharmaceutical companies viewed natural compounds as old-fashioned and cumbersome. Now they are coming back'

were natural products or derivatives. For cancer drugs, the proportion was nearly half.

Until recently, drug companies tried to take a different approach. "A decade ago, the big pharmaceutical companies viewed natu ral compounds as old-fashioned and cumbersome, and they got out," says Tony Buss, chief executive of MerLion, a Singaporebased business with a library of 500,000 natural product com-pounds. "Now they are coming back to knock at our door."

While a few large companies, including Novartis and Merck. retained their libraries, most others sold them off, including GlaxoSmithKline, which spun out some of the assets that were merged into MerLion in 2002 but has since become a client.

The declining attention to natural compounds came at a time of apparent breakthroughs in alternative techniques including combinatorial chemistry, which

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created complex compounds, and high-throughput screening, which rapidly tested them against disease targets.

The problem was that these approaches have failed to achieve significant results. Increases in both the number of experimental compounds and spending on research and development have not resulted in a rise in the number of successfully developed new medicines. The renewed interest in natural compounds reflects a realisation that they too can be screened using newer and more effective techniques.

They are particularly promising for anti-infectives and antibiotic drugs to treat diseases that were abandoned by many pharmaceutical companies because of limited commercial potential. Now the rise of drug resistance and the emergence as a public concern of MRSA and other hospital-acquired infections has sparked fresh attention and made the market more attractive.

It is still a long way from being fully developed. Jean-Pierre Garnier, chief executive of GSK, doubts whether there will be a big return to natural products. "The industry has always actively pursued them, but there is a lot of pessimism because the pay-out has been modest," he says. "We have contracts but I can't say we will get back into it full-time."

Going back to nature may offer no quick, easy or universal fix. But Phil Dudfield, an executive at BioFocus DPI, another company in the field, argues that now "few would question the great benefit of having natural products as part of a balanced portfolio of research strategies".



For flu relief: star anise

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