

peptides like PR39 will be significantly less toxic than conventional competitive proteasome inhibitors because they are much more specific. 'If it [PR39] constitutes a 'novel' and less toxic proteasome inhibitor, it could be great,' says Alexander. 'What I would like to see is how they will be able to deliver a small molecular weight inhibitor *in vivo*,' wonders Grisham, 'that is always, of course, the bugaboo in drug discovery.'

### Peptoids, perhaps

The next step for investigators will be to learn exactly why PR peptides are substrate-specific *in vivo*. Knowing more about the molecular mechanism-of-action will enable them to model even better compounds. Gaczynska anticipates that peptoids, derivatives of peptides, can be made to bind to the proteasome even faster, stronger and with better specificity. This might still

be a long way off, she says, but 'it is very promising, and what is important here is it is a new idea of proteasome inhibition'.

### References

- 1 Gaczynska, M. *et al.* (2003) Proline- and arginine-rich peptides constitute a novel class of allosteric inhibitors of proteasome activity. *Biochemistry* 42, 8663–8670
- 2 Adams, J. (2003) Potential for proteasome inhibition in the treatment of cancer. *Drug Discov. Today* 8, 307–315

# Pharmacists seek the solution of a shaman

Marcus Anhäuser, BMN News

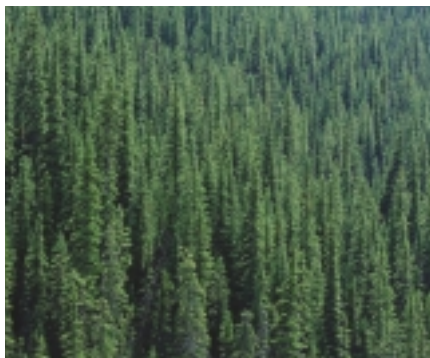
A traditional healer's prescription from the highlands of Mexico could make an effective addition to the therapeutic armament against diabetes, claims a German phytopharmacist.

Traditional healers in the highlands of Mexico can taste whether a patient has diabetes. If a patient shows typical symptoms, like strong thirst, the urge to urinate, tiredness and loss of weight, the healer will taste the blood or urine of the patient. 'If it is sweet, he knows what to do,' said Helmut Wiedenfeld, a Phytopharmacist at the University of Bonn (<http://www.uni-bonn.de>).

### It's all in the blood

Sweet blood, better known in Western medicine as diabetes, is not rare in the Mexican highlands. 'In some villages, eight in ten adults suffer from diabetes mellitus,' Wiedenfeld said. A high sugar diet has recently spread to the region, particularly since sweet soft drinks entered villages in most remote valleys.

'It is tremendous, the kids drink it like water, sometimes two liters a day,' he



said. Diabetes mellitus is recognized as the fourth highest cause of mortality globally. Mexico itself is the country with the fourth highest frequency of the disorder in the world.

According to World Health Organization predictions (<http://www.who.org>), there will be 11.7 million diabetic patients in Mexico by 2025, which means every seventh Mexican will have the disorder. But a shaman would be a hopeless healer if he did not provide medicine. The Mexican healers prescribe a drink called 'Agua de Uso,' meaning water for daily use, Wiedenfeld has found. Patients have to

drink half a litre of this liquid per day, and Wiedenfeld is busy working out what it contains.

### The magic ingredient

The healers, called curanderos, use local plants that have been used for generations to treat diabetes. About 880 plants worldwide are believed to possess hypoglycemic activity, 343 of which have been reported in the scientific literature. 'But most are just anecdotal stories or poorly tested,' said Wiedenfeld. In Mexico, an estimated 400 plants are used in the treatment against diabetes.

Wiedenfeld knows three of these that work. Shamans always use one plant, no mixtures, which made it easier for the German to investigate. At first he tested a plant called *Equisetum myriochaetum*, the traditional name of which is 'cola de caballo', the Mexican word for the English family name it belongs to – horsetail. Ethnopharmacologically it is reported to show activity against kidney disease.

'The healers, especially in the southern Mexican state of Guerrero, use a water decoction to treat diabetes', explains Wiedenfeld. In other words, they boil the aerial part of the dried plant in water.

Wiedenfeld tested this extract alongside a butanolic extract in a rat model of type 2 diabetes [1], the type of diabetes that results from a combination of tissue resistance (or insensitivity) to insulin action and an inadequate compensation of insulin secretion. Type 2 diabetes accounts for nearly 90% of all diabetes cases.

### Antidiabetics

Together with Adolfo Andrade Cetto from the National University of Mexico (<http://www.unam.mx>) and colleagues from the Mexican National Medical Center, Wiedenfeld showed three years ago that the medicine lowers plasma glucose level within three hours of administration, making it as effective as the reference drug glibenclamide, which is the most commonly used antidiabetic tablet [1].

In 2002 the team conducted a pilot study of eleven type-two diabetic patients [2], the extract being administered as recommended by the shamans: 'Except that in our study the dose was adjusted for the weight of each patient,' said Wiedenfeld. As in the rats, the data reveal that plasma glucose levels declined significantly. It is the first report showing the hypoglycemic effect in humans. 'Insulin level did not change,

implying that the mechanism-of-action is not glibenclamide-like as we thought after the study with rats,' said Wiedenfeld. That means that the effect is not due to stimulation of insulin secretion. They identified the active component as a flavonol glycoside, a Kaempferol derivative, which is not surprising: 'Kaempferol derivatives have already been described as hypoglycemic active,' said Wiedenfeld.

Meanwhile, the team successfully tested two other plants in rat models: *Cecropia obtusifolia* – traditionally called 'Guarubo' or 'Chancarro' – and, more recently, *Acosmium panamense*, a tropical leguminous tree. This contains 'a substance with a new structure,' which Wiedenfeld will present at the Society for Medicinal Plant Research annual congress in Kiel, Germany (31 August – 4 September 2003; <http://www.ga-online.org>).

### No side effects

Medicines like glibenamides are known for gastrointestinal, dermatological or haematological side effects but researchers who have examined the history of Mexican plant remedies have found no such effects. Wiedenfeld's pilot study showed no short-term adverse reactions to patients. Corranderos know their patients and their medicines well. For instance, the healers know exactly how to eliminate toxic alkaloids or how to get the glycosides, the substances that are effective. 'It is like a field study over generations,' says Wiedenfeld.

Wiedenfeld and his team have been working for about six years on this topic and are now in negotiation with pharma companies, which could produce the medicine or conduct the studies needed for approval; two companies are interested but first they have to know whether the wild plants are eligible for cultivation. 'Without cultivation there is no guarantee of getting consistent concentrations and quality of the active agent,' explains Wiedenfeld. New cultures are also needed because using the wild stocks might mean eradicating them.

Another problem that Wiedenfeld is aware of is biopiracy. Most of the researchers involved in these studies are Mexican, he says, and the laboratory they work in is sponsored by one of the interested companies. 'We have a contract that the people in the villages will get their profit,' he said. 'That does not mean that the company will abandon its gain. It is a case of give and take,' he said.

Finally, if everything works, the healer's medicine will help not just his people in the remote villages in the highlands of Mexico but also the populations in the West who supply Mexicans with a steady supply of soft drinks.

### References

- 1 Andrade Cetto, A. *et al.* (2000) Hypoglycemic effect of *Equisetum myriochaetum* aerial parts on streptozotocin diabetic rats. *J. Ethnopharmacol.* 72, 129–133
- 2 Revilla, M.C. *et al.* (2002) Hypoglycemic effect of *Equisetum myriochaetum* aerial parts on type 2 diabetic patients. *J. Ethnopharmacol.* 81, 117–120

## Conference reports

*Drug Discovery Today* Publications is pleased to publish the highlights from international conferences. Conference participants who wish to cover a particular meeting should contact:

Dr Christopher Watson, *Drug Discovery Today*, 84 Theobald's Road, London, UK WC1X 8RR  
e-mail: [DDT@drugdiscoverytoday.com](mailto:DDT@drugdiscoverytoday.com)