

***Hoodia*, a case study at CSIR**

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Abstract

An appetite suppressant agent from *Hoodia* developed by CSIR scientists, promises to become the first natural food ingredient for weight management based on a plant indigenous to the African continent. The research programme that led to this potential product started at CSIR in 1963, and today includes major multi-national companies, farmers and communities. An analysis of the key innovative steps in the research programme illustrates the value of combining modern science and ancient knowledge on the use of South Africa's rich biodiversity.

Hoodia illustrates the potential of bioprospecting to produce significant economic and social benefits for a nation. The processes leading to the creation and protection of intellectual property, licensing to commercial partners and the benefit-sharing agreement with the San people, custodians of indigenous knowledge on the use of *Hoodia*, are discussed.

1. Introduction

South Africa has a long history of natural products chemistry, typically based on the investigation of the biological properties of the chemical components isolated from indigenous plants. This work was often stimulated by reports of livestock losses on farms as a result of ingestion of toxic plants. Research on indigenous plants led to international acclaim, e.g. South African scientists were the first to discover the presence of fluorine-containing plant metabolites, now known to cause photo-sensitisation in sheep. During times of drought, domestic animals were especially prone to ingestion of highly toxic indigenous plants, often containing highly active cardiotoxins.

Indigenous plants have always formed part of the diet of communities in rural areas. During the early sixties, an investigation was launched to determine the nutritional value and also any possible long-

term toxic effect of 'food from the veld'. The National Food Research Institute of the CSIR, one of the institutes now incorporated into CSIR Biosciences, led this investigation.

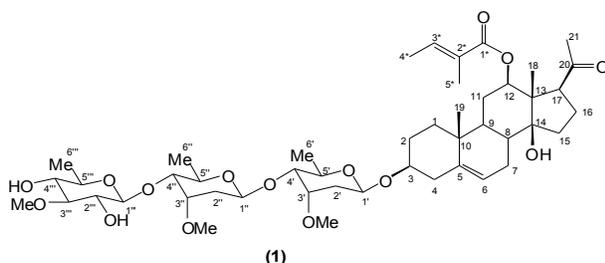
The genus *Hoodia* was studied because certain species of this succulent plant were reported to be used by indigenous people as a substitute for food and water (Marloth, 1932). A CSIR scientist who studied the biological effects of extracts of this plant on small laboratory animals, observed that the animals lost their appetite, accompanied by a loss of weight, with no apparent toxic effects. This was 1963 - the first, scientifically-validated observation of appetite suppression caused by extracts derived from *Hoodia*.

The following six years witnessed attempts by leading CSIR scientists to isolate and identify the chemical substance responsible for the appetite suppressant effect of extracts of the *Hoodia* plant. However, the repertoire of chromatographic and spectroscopic techniques available to chemists and biochemists during the sixties were simply not sufficient to allow progress. The project was moth-balled from about 1970.

During 1983, 20 years after the *Hoodia* research started at CSIR, the organisation acquired state-of-the-art nuclear magnetic resonance spectrometry for the identification of chemical structures of complex natural products. This provided the stimulus to re-launch the investigation of the appetite suppressant properties of the *Hoodia* plant. The main task ahead at this stage was to isolate the active principles in purified fractions, through sequential process of solid-liquid extraction and liquid-liquid partitioning of extracts, guided by bio-assaying in the animal model. Active fractions were separated into several individual components through repeated chromatographic separation and testing in the animal model. Eventually, one of the active compounds was identified as 3β-[β-D-

thevetopyranosyl-(1→4)-β-D-cymaropyranosyl-(1→4)-β-D-cymaropyranosyloxy]-12β-tigloyloxy-14β-hydroxypregn-5-en-20-one (1) using proton and carbon-13 n.m.r. spectroscopy, fast-atom bombardment mass spectrometry, accompanied by chemical hydrolysis studies (Maharaj *et al*, 2007). Sequence information on the sugars of the glycosides and the substitution pattern of the aglycone were deduced from 2-dimensional long-range carbon-13-{H} chemical shift experiments (HMBC).

The compound had the remarkable ability to reduce the food intake of laboratory animals, accompanied by weight loss. The results of this stage of the investigation were as exciting as the original observation in 1963: a new chemical entity was discovered, representing a family of molecules not known before to have appetite suppressant properties.



Since the earliest observation of the appetite suppressant effect of extracts of *Hoodia* in 1963, scientists realised the enormous economic potential of their discovery and kept it a closely guarded secret, while continuing their scientific investigations. During 1993, the CSIR recognised the tremendous value that can be unlocked should it be able to bring the country's rich biodiversity, indigenous knowledge and capacity for scientific innovation, together in a comprehensive bioprospecting programme. It was important to demonstrate the strategic benefit that will accrue to the country as a result of commercialisation of biodiversity products. *Hoodia* was selected as an ideal case study to demonstrate the viability of this ambitious plan, which was without precedent at the time. This lead provided the opportunity to address many key issues of importance to a successful bioprospecting venture (cf. Table 1).

Table 1

The final product must address a major market need (in excess of US\$1 billion)

Goal: to demonstrate value of medicinal plants to the economy of South Africa, through the establishment of new businesses locally.

Requirement for world-class scientific innovation, suitable for international patenting and subsequent licensing to a multi-national company.

Goal: demonstrate that South Africa can be a productive source of intellectual property in demand by multinational companies

Based on utilisation of an indigenous plant that can be cultivated by local farmers and communities as part of production system for the product (i.e. not a synthetic production process)

Goal: prove the potential of medicinal plants to contribute to diversification of local agriculture through new agro-processing opportunities

Based on a plant used traditionally by communities

Goal: learn how to establish benefit-sharing models with owners of indigenous knowledge in support of government legislation on the topic

2. Results

The *Hoodia* research programme already spans 40 years at CSIR and is still ongoing. The programme has already yielded both direct and indirect benefits.

A. Direct benefits

A decision was made to develop *Hoodia* as a food ingredient for weight management. The estimated market size for new weight management agents is in excess of US\$ 3 billion per year. It can be reasonably expected that the commercial production of the active extracts will provide an opportunity to establish a sizable local manufacturing business.

The CSIR's invention based on *Hoodia*, has been patented in most countries of the world (van Heerden *et al*, 1998). The successful licensing of this technology, involving overseas multinational companies, was a significant milestone in the development of *Hoodia* to date. In addition to direct financial benefits in the form of milestones and royalties should the product be successfully commercialised, the licensing agreement allowed the transfer of world-class good farming and manufacturing technology to South Africa.

Hoodia is a scarce succulent plant not easily cultivated. The CSIR's licensee has transferred technology for the controlled horticulture of the plant to South Africa, in line with the requirements for Good Farming Practice. Currently *Hoodia* is being cultivated as part of this programme on different sites in arid regions of the country. Local communities are involved in the cultivation programme.



Figure 1. *Hoodia* cultivation site

Technology for the processing of *Hoodia*, in conformance with Good Manufacturing Procedures (GMP), has been established at the CSIR. The licensee has constructed a Clinical and Botanical Supplies Unit for processing the plant to produce high quality material for testing in the clinic.

Hoodia is still in the process of development and is not expected to be a commercial product before a further two to three years. In anticipation of a successful outcome of clinical trials, the CSIR has entered into a benefit sharing agreement with the San people. This agreement is one of the first examples of its kind anywhere in the world.

The licensing agreement provided valuable opportunities for local scientists at CSIR and a number of research institutes to participate in the ongoing research programme.

B. Indirect benefits

The progress with *Hoodia* to date already positioned South Africa as a country with the scientific and technological capability to produce leads of interest to multinational companies. The CSIR is currently involved in a number of collaborations with the industry interested in future inventions that might flow from its investigation of the possible commercial use of the country's indigenous plants and knowledge on the use thereof.

3. Conclusions

The ongoing bioprospecting activities of the CSIR have produced a rich portfolio of drug candidates, including potential new treatments for diseases such as malaria, HIV, asthma, diabetes and inflammation. The further development of these candidates benefit substantially from the product development platform that resulted from the *Hoodia* research programme.

4. References

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van Heerden *et al.* Pharmaceutical compositions having appetite suppressant activity. PCT application WO 98/46243 and corresponding patents / patent applications. Filed: 15 April 1998

5. Acknowledgments

We would like to thank the CSIR Parliamentary Grant (PG) for funding and Phytopharm plc for the transfer of GMP technology to the CSIR.