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Muthi to medicine

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Abstract

The limited commercial opportunity for bioprospecting for isolated pure natural compounds or their derivatives from plants for novel pharmaceuticals is discussed. A broad overview of the key research inputs involved in the commercialisation of indigenous medicinal plants as botanical medicines is given to assist young researchers in contextualising research from an industry perspective, and to encourage university–industry collaboration. Compliance with the Biodiversity Act of 2004, and the regulations under this Act is stressed. The chain of research and development (R&D) activities is briefly described including ethnobotanical research, raw material supply, identification of active compounds, extract development, absorption studies, formulation development, *in vitro*, *in vivo*, and clinical safety and efficacy studies, and protection of intellectual property. Ultimately obtaining international marketing authorization for a novel botanical medicine is a lengthy and costly undertaking, with high risk of failure. Elements of botanical medicine R&D can be applied to functional foods, novel foods and personal care products, which can reach the market faster and with less risk than botanical medicines.

Keywords: Botanical medicine; Commercialisation; *Harpagophytum procumbens*; *Hoodia gordoniii*; New drug discovery; *Pelargonium sidoides*; Product development; *Sceletium tortuosum*; University–industry collaboration

1. Introduction

This short communication for the South African Journal of Botany's special edition on economic botany is intended to provide researchers, particularly young postgraduate students who have little or no exposure to industry, with a broad overview of the key research inputs involved in the commercialisation of indigenous medicinal plants as botanical medicines, and to afford an insight into the many entry points where scientific research contributes value along the commercial value chain from raw material through to manufactured, marketed product. Informed by the research inputs that contribute to the research and development (R&D) of a botanical product, researchers interested in the practical application and economic potential of their research are encouraged to develop university–industry collaborations early on to ensure they are addressing an identified market need as well as downstream regulatory requirements. All researchers active in scientific work on useful plants of South Africa should work closely with their institutions' technology transfer offices to protect commercially important new intellectual property prior to presentation or publication in the public domain.

It is an essential prerequisite that all research on South African plants must be fully compliant with local laws and regulations. The United Nations Convention on Biological Diversity (CBD) was one of the major outcomes of the Earth Summit in Rio de Janeiro in June 1992, and as a signatory to the CBD South Africa enacted the National Environmental Management: Biodiversity Act (10 of 2004), known as 'the Biodiversity Act', or more popularly as "NEMBA". This law provides for the management and conservation of South Africa's biodiversity including the protection of species and ecosystems that warrant national protection, the sustainable use of indigenous biological resources, the fair and equitable sharing of benefits arising from bioprospecting involving indigenous biological resources, and for the establishment

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and functions of a South African National Biodiversity Institute. NEMBA defines "bioprospecting" in relation to indigenous biological resources as meaning any research on, or development or application of, indigenous biological resources for commercial or industrial exploitation, including:

(a) The systematic search, collection or gathering of such resources or making extracts from such resources for purposes of such research, development or application;
(b) The utilisation for purposes of such research or development of any information regarding any traditional uses of indigenous biological resources by indigenous communities; or
(c) Research on, or the application, development or modification of, any such traditional uses, for commercial or industrial exploitation.

Access and benefit-sharing regulations under NEMBA were gazetted on 8 February 2008 (Regulations Gazette number 30739) (Government Gazette, 2008). These regulations make a distinction between the 'discovery' phase of a bioprospecting project, for early-stage academic or industrial research that is being done prior to identifying a commercial opportunity, and the 'commercialisation' phase when a commercial opportunity has been identified, and further research is being done to advance a commercial venture. The Minister of Water and Environmental Affairs is responsible for issuing permits for bioprospecting and export purposes. Foreign nationals may only apply for permits jointly with a South African collaborator. An export permit must be obtained for the export of any indigenous biological resource when research on the material is to be conducted outside of South Africa, or when the material is to be commercialised outside of South Africa, and this export must be deemed to be in the public interest. The regulations also specify the criteria for material transfer agreements.

On the 8th of December 2009, HG&H Pharmaceuticals (Pty) Ltd became the first company to be granted an integrated export and bioprospecting permit, Permit No. IEP0001. This permit, signed by the Minister of Water and Environmental Affairs, is for research into, and export of, *Sceletium tortuosum* (L.) N.E. Br. In applying for the permit the company demonstrated it had successfully concluded the first South African prior informed consent benefit-sharing agreement with indigenous knowledge holders, through an agreement with the South African San Council signed on 21st February 2008. This agreement includes payment over three years of up-front amounts prior to commercialisation of product, and a defined percentage on all future income to be derived from the commercialisation of *Sceletium*. The up-front amounts and percentage royalty have not yet been made public. In addition to its ethical approach in recognising the rights of indigenous knowledge holders, the company had addressed environmental sustainability of wild plant resources by only utilising cultivated *Sceletium tortuosum* for all research and export purposes.

The Nagoya Protocol, a supplementary agreement to the CBD, was adopted at the 10th meeting of the Conference of the Parties to the Convention on 29 October 2010 in Nagoya, Japan, and South Africa became a signatory on 11 May 2011. The Nagoya Protocol outlines the legal procedures for access to genetic resources, access to indigenous knowledge associated with genetic resources, and the sharing of benefits arising from the utilization of genetic resources and indigenous knowledge.

The prior informed consent of communities holding traditional knowledge must be obtained and benefits, both monetary and non-monetary, arising from utilisation of that knowledge must be shared with the indigenous knowledge holders. The Protocol also obliges a user country to obtain formal informed consent from a provider country prior to accessing indigenous genetic resources or indigenous knowledge.

2. Pharmaceuticals

Pharmaceuticals based on isolated pure natural compounds or their derivatives represent the pinnacle of scientific, technical and commercial value-addition for natural products, and the commercial returns may be substantial: by definition a blockbuster pharmaceutical generates US$1 billion or more in annual sales. Important pharmaceuticals originally discovered from African plants include physostigmine, a reversible acetylcholinesterase inhibitor from *Physostigma venenosum* Balf. from Nigeria, Cameroon and Gabon, used in treating Alzheimers Disease (Orhan et al., 2009), and the vinca alkaloids, including vincristine and vinblastine, that revolutionised the treatment of acute leukaemia in children, derived from the Madagascar periwinkle, *Catharanthus roseus* (L.) G.Don. Although originally endemic to Madagascar (Foster, 2010), *Catharanthus roseus* is now a pan-tropical ornamental and naturalised species.

Although most of the active ingredients in medicines have historically been natural products from botanical and microbial sources (Sneader, 1996), and natural products continue to form a productive source of new drugs (Newman and Cragg, 2007; Butler, 2008), the age of blockbuster drugs seems to largely be over. The international pharmaceutical sector is presently unable to deliver enough new products to market to generate revenues sufficient to sustain its own growth, and nearly all major drug developers are critically examining current R&D practices (Kaitlin, 2010). FDA approvals of new drugs in the United States reached a 24-year low in 2007 (Li and Vederas, 2009), and only three in 10 new products actually generate revenues equal to or greater than the pharmaceutical industry R&D costs (Kaitlin, 2010).

It would seem that bioprospecting activities by universities and local research organizations, for new drug discovery, including using ethnobotanically-directed approaches to bioprospecting, have very little chance of achieving commercial success. Nonetheless such groups would stand more chance of success if they could pool resources and work towards a common goal: isolating, characterising and validating lead compounds that are likely to be suitable for development into pharmaceuticals or botanical medicines that address unmet therapeutic needs for prevalent communicable diseases of Africa. Translational research – defined as the movement of discoveries from basic research to application at the clinical level (Ruttenberg et al., 2007) – is a growing field of research, and the establishment of a South African centre of