Are scientists barking up the wrong tree to "scientifically validate" traditional medicines?

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Highlights

Core findings

- Traditional healing is a holistic system and researching this is not straightforward
- Scientists unknowingly undertake a reduction approach to prove efficacy
- This is incorrectly quoted as “scientific validation of traditional medicines”
- Products from *Hoodia*, *S. ilicifolius*, *L. javanica* and *E. elephantina* are discussed
- The commercialized studies are illustrations of this misconception by scientists

ABSTRACT

In South Africa it is estimated that at least 70% of South Africans consult one of the more than 200 000 Traditional Healers in the country. Clearly traditional health practitioners in South Africa play a crucial role in providing primary health care to the majority of the population. This knowledge system together with South Africa's unique biodiversity provides valuable resources for scientists to undertake research in search of new pharmaceuticals, nutraceuticals and cosmeceuticals. Scientists often refer to this as "scientific validation of traditional medicines" which can be misleading to holders of the traditional knowledge since traditional health practitioners treat their patients holistically using traditional medicines consisting of one or more plant species. Four case studies i.e. appetite suppressant form *Hoodia gordonii*, monatin from *Sclerochiton ilicifolius*, mosquito repellent from *Lippia javanica* and the treatment of benign prostate hyperplasia (BPH) and male pattern baldness from *Elephantorrhiza elephantina* which were either commercialized or close to commercialization are described and in all cases these have followed the classical drug discovery or product development route. These case studies have led to the realization that the traditional use of the plants were not exactly the same as the commercialized use. Often the scientists select plants based on traditional use and through scientific intervention discover similar biological activities or different biological activities of the plant species or constituents thereof. The scientific discoveries are further developed and the route to commercialization requires huge investment, time and resources. Hence it could be concluded that the approach has not been to scientifically validate the traditional uses of plants or traditional medicines. As scientists we need to be responsible when utilizing traditional knowledge in our research approaches and it is important to share benefits with the owners of indigenous knowledge.

KEY WORDS

Appetite suppressant, *Elephantorrhiza elephantina, Hoodia gordonii*, *Lippia javanica*, monatin, mosquito repellent, scientific validation, *Sclerochiton ilicifolius*, traditional medicines, sweetener

1. INTRODUCTION

Southern Africa is blessed with a rich plant biodiversity of more than 24 000 indigenous plants, representing about 10% of all higher plants on although the land surface is less than 2.5 % of the Earth (Germishuizen and Meyer, 2003). This includes an entire floral kingdom (Cape Floristic Region), one of the richest and most diverse succulent flora on earth (Goldblatt, 1997; Goldblatt and Manning, 2002). An important feature of Southern Africa's botanical wealth is the high endemism – more than half of our indigenous plants occur exclusively within the confines of its borders (Gibbs Russell, 1984, 1987; Goldblatt, 1997).

Many developing countries have vast resources of medicinal plants which are used in traditional medicines. A large proportion of the population rely heavily on traditional practitioners and medicinal plants to meet primary health care needs (WHO, 2004). It is estimated that at least 80% of the population in Africa consult Traditional Health Practitioners (THPs). Traditional healing is a holistic system of treating a patient and therefore the translation of traditional medicines into modern therapeutic agents is not necessarily a straightforward process. In South Africa it is estimated that at least 70% of all South Africans consult one of the more than 200 000 Traditional Healers in the country (Abdool Karim et al., 1992; Kale, 1995). Clearly, THPs in South Africa play a crucial role

in providing primary health care to the majority of the population. They are often the first health care providers, especially in rural areas, and deeply interwoven into the fabric of cultural and spiritual life.

Undoubtedly these two resources provide scientists with an excellent opportunity towards identifying and developing plant based medicines especially for the pharmaceutical industry. These are often in the form of herbal extracts which may be mixtures of plants and single chemical entities. Single chemical entities are lead compounds that lend themselves towards medicinal chemistry endeavours with the ultimate goal of commercializing these (David et al., 2015; Ngo et al., 2013). Scientists frequently rely on the traditional use of medicinal plants and through interpretation of the reported use, identify a disease or therapeutic area for which research is undertaken to try and prove at the first stage, its efficacy. There are vast number of reported studies which have focused on biological evaluation of single plant species as well as a collection of species in an attempt to prove efficacy refer to this as “scientific validation of traditional medicines”. Some notable and extensive studies are the screening of 21 medicinal plants for the treatment of Alzheimer’s disease through the inhibition of acetyl cholinesterase (Amoo et al., 2012), antibacterial (Buwa and van Staden, 2006; Eloff, 1999; Grierson and Afolayan, 1999; van Vuuren, 2008), anti-inflammatory (Dzoyem and Eloff, 2015; Fawole et al., 2010; Fawole et al., 2009; Luseba et al., 2007), antimalaria (Clarkson et al., 2004a; Pillay et al., 2008; Prozesky et al., 2001), lavacidal (Maharaj et al., 2012; Mavundza et al., 2013), antidiabetic (van de Venter et al., 2008), wound healing (Steenkamp et al., 2004), anticancer (Bisi-Johnson et al., 2011; Fouche et al., 2008). Despite these extensive studies, no single lead was identified through these research endeavours that

was further developed and commercialized. This leads to the question as to whether this is part of the natural drug discovery paradigm or whether scientists are interpreting the traditional use correctly and undertaking biological assays using the correct screening and appropriate models. These may be regarded as a reductionist approach.

A broad overview of commercially important southern African medicinal plants was also reported by van Wyk (van Wyk, 2008). Of the various species described perhaps it is *Harpagophytum procumbens* (Burch.) DC. ex Meisn*, Pelargonium sidoides* DC and *Aspalathus linearis* (Burm. f.) that have the greatest impact on the international markets. In addition these species have the most relevant scientific data which are the closest or substantiates their traditional uses. In the case of *P. sidoides* there are several *in vitro* and clinical studies which proves efficacy closely aligned to its traditional use (Brendler and van Wyk, 2008; Kayser and Kolodziej, 1997) i.e. treatment of infections of the upper respiratory tract. The same for *H. procumbens* which is traditionally used for the relief of minor joint pain as well as the relief of mild digestive disorders such as bloating and flatulence. Mild analgesic and anti-inflammatory properties have been reported in several clinical studies (Chrubasik et al., 2003) closely related to its traditional use.

The Council for Scientific and Industrial Research (CSIR) with its clear mandate to undertake translational research and ultimate commercialization has a proven track record in the successful commercialization or attracting international multinational companies in investing in the development of natural product leads. Four well known case studies which have been commercialized or were close to this i.e. *Hoodia gordonii* (Masson) Sweet ex Decne as an appetite suppressant or treatment of obesity, *Sclerochiton ilicifolius* A.Meeuse as a source of a naturally occurring high intensity non-

carbohydrate sweetener*, Lippia javanica* (Burm.f.) Spreng as a mosquito repellent and *Elephantorrhiza elephantina* (Burch.) Skeels for the management of male pattern baldness, are discussed in the context of their scientific research and commercialization with relation to their traditional uses. In all cases the obtained scientific efficacy data provided evidence for uses that were not identical to the traditional use of these plants. Some showed related uses while others showed different uses that were discovered by the scientists.

2. *Hoodia gordonii* (Ghaap)

The case of *Hoodia* (Figure 1A) has been extensively published both in the media and reported in journal articles. This includes articles on the chemistry [(van Heerden et al., 2007) Patent No WO 98/46243] , production (Knight et al., 2012), *in vitro* and *in vivo* efficacy and toxicity (Orsi et al., 2011), review articles on the development and commercialization of *Hoodia* (Vermaak et al., 2011) as well and the benefit sharing models with knowledge holders *viz* the San People and Khoi-San (Wynberg, 2004). The research was aimed at the development of *Hoodia* as an appetite suppressant for the management of obesity. However, of most relevance are the reported clinical studies on *Hoodia,* specifically the one significant peer review manuscript which reports on the clinical efficacy of *Hoodia* as an appetite suppressant undertaken by the licensee, Unilever (Blom et al., 2011). In the study there were no serious adverse events (SAE) but *Hoodia* extract was less well tolerated than the placebo due to episodes of nausea, emesis and disturbances of skin sensation. Blood pressure, pulse, heart rate, bilirubin and alkaline phosphatase showed statistically significant ($p<0.05$) increases in the *Hoodia*

A

B

C

D

Fig. 1. A: *Hoodia gordonii* in flower and under cultivation, B: *Leaves of Sclerochiton ilicifolius* and the plant in its natural environment C: *Lippia javanica* leaves and plants under cultivation D: *Elephantorrhiza elephantina* plant and sliced rhizomes.

group. Mean effects on *ad libitum* energy intake and body weight did not differ significantly between the *Hoodia* extract and placebo treatment groups ($p>0.05$). However, 14 other clinical studies were completed which were not published in peer review journals mainly by work undertaken by Pfizer, as an earlier licensee. One of these as reported by the CSIR provided contradicting efficacy results (Maharaj, 2011). This was a randomised, double-blind, placebo-controlled, 15 day repeat dose study, with a single dose escalation stage, to establish the pharmacokinetics, safety, tolerability and effects of the *Hoodia* extract in healthy male subjects. In the study mean calorie intake in all meals was lower for the *Hoodia* extract compared to the placebo (Figure 2).

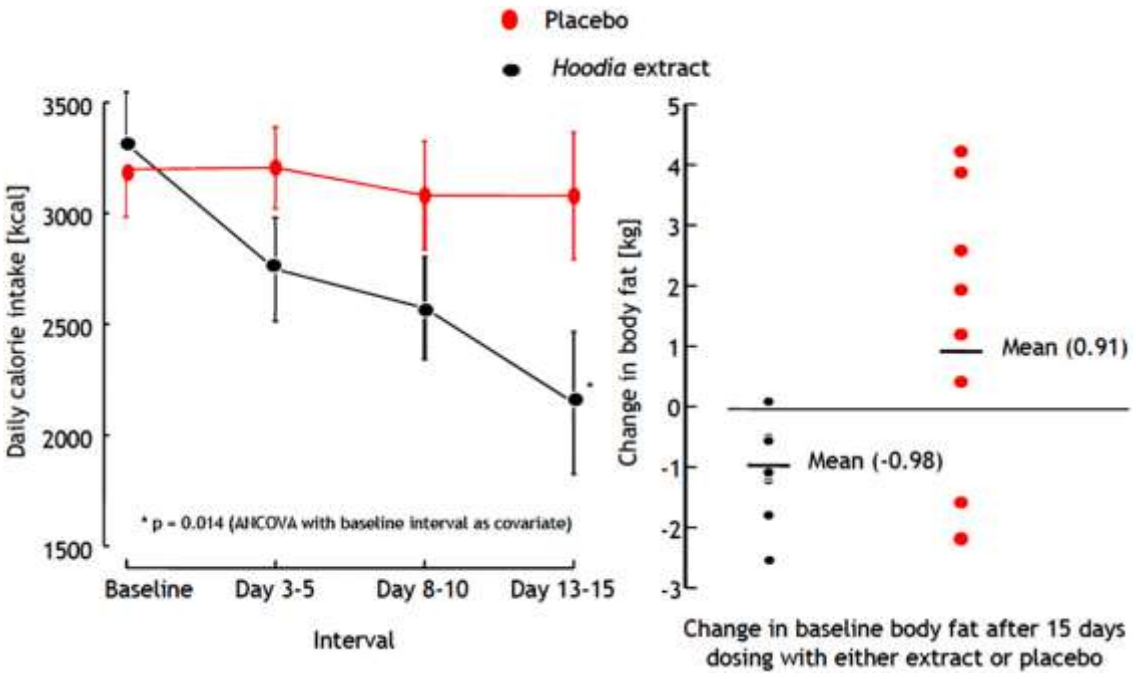

Fig. 2. Graphs showing clinical efficacy of Hoodia extract (taken as a screen shot from CSIR confidential reports on clinical trials conducted by licensee).

The difference was statistically significant for dinner calorie intake and for total calorie intake (p = 0.032 and 0.036 respectively). There was a statistically significant difference for the change from baseline in the body fat content (BFC) between the groups (p = 0.035) with the *H. gordonii* extract having the lower BFC on day 16. The conclusion from the study was that a short term oral administration of *H. gordonii* concentrated extract caused a clear reduction in food intake. Administration for 15 days caused a substantial reduction in calorie intake, however it was associated with mild side effects (paraesthesia, headache, taste perversion, vasodilatation, somnolence and isolated reversible hyperbilirubinemia).

Based on these finding whether positive or not, one would question how does this impact or relate to the traditional use of the plant by the indigenous communities, especially the San People and the Khoi-San? Careful interrogation of the history of use of *Hoodia* at the time when research was initiated at the CSIR in the early 1960s indicates that the plant, *Trichocaulon piliferum* (Linne´ fil) N. E. Brown was researched based on its traditional use as a source of food and water (Marloth, 1932). It was recorded that the plant had an insipid, yet cool and watery taste, and was eaten by the natives for the purpose of quenching their thirst (Pappe, 1862). The plant has been reported to be edible in its raw state or preserved in sugar (White and Sloane, 1937) and has been described as the ‘real ghaap’ of the natives, who used it as a substitute for food and water (Marloth, 1932). It was the report by Marloth (Marloth, 1932) who observed that the plant has the ability to “remove pangs of hunger” information that further inspired the research as a potential appetite suppressant. *H. gordonii* was later researched and developed after the *Trichocaulon* species was reclassified as *Hoodia.* Subsequent to the publicity of *Hoodia*

being licenced to multinational companies and the patenting in 1998, there have been many reports, mainly on the internet and more recent publications that state that the "indigenous communities use the plant as an appetite suppressant and on long hunting trips to stave of hunger when food supplies were low" (Vermaak et al., 2011). This information on the traditional use did not predate the patent filing date (van Heerden, 2008) and international licensing as a result caused significant confusion especially with the holders of the traditional knowledge.

Although it is clear that the actual recorded traditional knowledge on the use of the plant is not the same as the research that led to the discovery of its appetite suppressant properties, it is acknowledged that the information on the traditional use mainly as a source of food and water led to the discovery that was patented. Could it be then said that the discovery of the appetite suppressant properties of the plant was serendipitous or scientific innovation? Nevertheless the case study of Hoodia is a clear example of how researchers can mislead traditional knowledge holders by undertaking research to "scientifically validate traditional medicines" while conducting other scientific studies.

3. *Sclerochiton ilicifolius* (Molomo monate)

Monatin, (Indol-3-yl)-2-amino-4-carboxy-4-hydroxypentanoic acid (Figure 3), is a naturally occurring high intensity sweetener isolated from the bark of the roots of *S. ilicifolius,* a spiny-leafed hardwood shrub growing in the rocky hills of the Limpopo Province in South Africa (Figure 1B) (Maharaj et al., 2018). The relative sweetness of the 2S,4S monatin isolated from the natural plant was reported in 1992 to be 1200 to 1400-fold more intense than that of sucrose although synthetic 2R,4R monatin, was reported later to have a more intense sweetness than the 2S,4S isomer i.e. up to 2700 times that

of 5% sucrose [(Vleggaar et al., 1992) Patent No. WO2003059865 A1, 2003]. The research that led to the identification of the compound started at the National Food Research Institute (NFRI) of the CSIR which launched an investigation into non–carbohydrate sweeteners from South Africa's indigenous plants in the early 1970's.

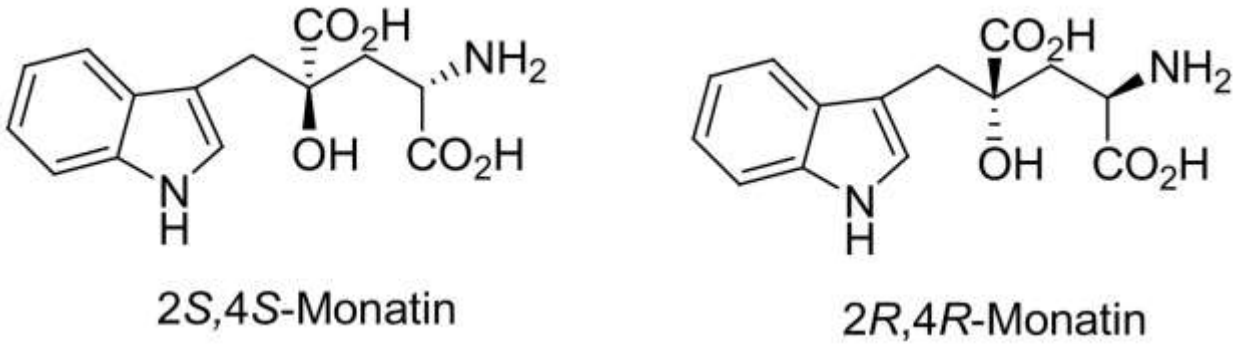

Fig. 3. Monatin stereoisomers.

The indigenous name of the plant *molomo monate* (which directly translates to "sweet mouth") encouraged scientists to investigate the properties of the plant. The first sample from which an aqueous extract was produced for research purposes was collected in 1974. The CSIR protected its invention by filing SA patent 88/4220 on June 1988 titled "high intensity sweetener" and a number of corresponding patents internationally (Van Wyk and Ackerman, 1990) Patent No US 4975298]. In July 1989, the intellectual property (IP) relating to "Monatin" including the controlling the patent was transferred to Technifin, a CSIR owned company that specialises in the commercialisation of Intellectual Property by licensing. Two communities from the Lephalale area in Limpopo received milestone payments from the CSIR resulting from the development of the non-carbohydrate sweetener (https://www.csir.co.za/csir-shares-milestone-payments-two-lephalale-communities).

There is limited documented information on the traditional use of *S. ilicifolius. Molomo monate* is known generally all over the Limpopo Province, particularly by practitioners of traditional medicine and those who collect and /or sell it. Most of these groups mention the sweet taste as an identification character. The various language groups in the province call the medicine by the same name spelt in their respective languages. For example *molomo monate* (Sepedi), *mulomo munandi* (Luvenda) and *mlomo mnandi* (Ndebele). There are other names used for the same medicine that are more related to the way the users interpret the way they know it to work. Some of these names describe other uses of *molomo monate.* The common root of the name indicates that it originated either from Sepedi or Ndebele languages. THPs who know and use more than one type do not attach much significance to the taste of *molomo monate* except as a diagnostic feature. They believe that there is a *molomo monate* for every place that should not necessarily be *Schlerochiton ilicifolius*. Some practitioners combine the types or use one type with other medicines. All people who know *molomo monate* associate it with its medicinal use. They say the name means that using the medicine makes one's words "sweet" and "convincing". Most of them believe the name refers only to the medicinal use, not the taste. They, still refer to the sweet taste as an important feature of the medicine. Emphasis on medicinal use does, to a large extent, seem to underplay the association of the name to the taste of the plant. As little information is available regarding the origin of the medicinal use, it is likely that this may be an innovation from the fact that it was "sweet". The relationship of traditional medicine with the Doctrine of Signatures, postulated by Paracelsus, has been established (Mabogo, 1990). According to this doctrine, all those plants not necessarily used as food were created to be useful as

medicines, and the Creator put some pointers (signatures) to show humans what the plant should be used for in terms of health. So, plants with heart-shaped leaves are useful as treatments for heart related diseases, while those with reddish sap could be used for illnesses that involve blood. In the same way plants with a sweet taste may be used in relation to various types of sweetness including that of the mouth. This is further complicated by the fact that both the taste and the medicinal effect are described in the same way. The term *monate* does not necessarily only mean sweet, but has other meanings such as, “interesting”, “enjoyable”, “delicious” and other such words (https://www.indifferentlanguages.com/translate/sesotho-english/monate).

In the case of monatin once again the main traditional use of the plant is not directly related to the discovery of a non-carbohydrate high intensity sweetener. There is no doubt that the traditional use has led to the discovery whereas the discovery may have been serendipitous and through scientific innovation.

4. ***Lippia javanica*** **(Fever tree)**

Lippia javanica (Burm.f.) Spreng also commonly known as the Fever tree (Figure 1C) has been listed as a commercially important southern African medicinal plant (van Wyk, 2008). The plant has been thoroughly researched for its pharmacological properties based on its traditional use. Its traditional use is not restricted to use in specific applications but used in a wide variety of ailments as well as a food and beverages (Maroyi, 2017b). Pharmacological studies amongst others include anti-cancer activity, antidiabetic, antiplasmodial, antioxidant, antimicrobial, antiviral activities and its pesticidal

effect (Maroyi, 2017b). Of relevance, more recent reports on its traditional use (2011) now include the repelling of mosquitos and not only restricted to the reported use on the treatment of malaria (Mavundza et al., 2011).

Since 1991, the CSIR has been undertaking research on *L. javanica* as a mosquito repellent, and based on the active ingredients that is not found in any of the current commercial repellents on the market led to the invention of a novel product. The phytochemical research, conducted over many growing seasons on plants from diverse ecosystems, led to the identification of chemotypes of the species with superior repellent properties. The volatile components of the plant were isolated and the chemical constituents identified (Fouche et al., 2002).

The efficacy (or effectiveness at producing a result) of the essential oil and active components were evaluated at the South African Bureau of Standards (SABS) using olfactometer tests. Using a standard protocol with the yellow fever mosquito (yellow fever is an acute viral haemorrhagic disease), it was demonstrated that the products are significantly more efficient at repelling and expelling mosquitoes when compared with the current products on the market. Both repellency and expellency are important qualities. Repellency is the ability to prevent mosquitoes from entering an area; expellency is the ability to drive or force mosquitoes from an area (Maharaj, 2008). A licensing agreement with Zollhaus International (Pty) Ltd has paved the way for marketing of mosquito repellent products, thereby realising the commercial benefit of this local essential oil (Maroyi, 2017b). The product is currently marketed by Zollhaus International (Pty) Ltd and is commercially available (http://www.fever-tree.co.za/index.php) in a few prototypes

(Figure 4). The CSIR has made royalty payments to the indigenous knowledge holders based on the commercial success (https://www.csir.co.za/more-royalties-paid-indigenous-knowledge-holders).

Fig. 4. Commercial products of Fever-Tree, 2019.

Most of the documented traditional use of the *L. javanica* as a mosquito repellent appears to have been published after its commercialization as a repellent. While the plant is used in malaria endemic areas and for the treatment of fevers, most of the early research focused on trying to prove its antiplasmodial properties and less on its efficacy as a repellent (Clarkson et al., 2004b; Ludere et al., 2013; Prozesky et al., 2001). Perhaps this should have been the focus of researchers as traditional healers seek the commercial

success of products based on their knowledge and often the risky pharmaceutical approach is one followed by researchers.

5. *Elephantorrhiza elephantina* (Elandsboontjie)

Elephantorrhiza elephantina (Burch.) Skeels (Figure 1D) is a member of a small and purely African genus represented by nine species on the continent (Germishuizen and Meyer, 2003; Glen, 2003). The genus name *"Elephantorrhiza"* means "elephant root" and is based on the large underground stem common to most members of the genus (Maroyi, 2017a). Its traditional use is for a wide range of human diseases and ailments including dermatological diseases, gastrointestinal system disorders, sexual dysfunction, sexually transmitted infections, and wounds. The rhizome decoction of *E. elephantina* is widely used by small-scale farmers in Botswana and South Africa as ethno-veterinary medicine for cattle, goats, horses, pigs, poultry, and sheep (Maroyi, 2017a).

There are several reports on the scientific research on trying to establish and prove efficacy through pharmacological studies. In a most recent review by Maroyi (2017), research on its anthelmintic, anti-bacterial, anti-fungal, anti-inflammatory, antinociceptive, anti-plasmodial activity, antioxidant properties, antirickettsial and anti-babesial activities are well summarized. Many of these studies are based on trying to provide scientific evidence which substantiate the traditional use of the plant, however, no significant discovery was made that would warrant its development and commercialization.

The CSIR filed a patent [(Fouche et al., 2015) Patent No US 9,061,023 B2] on the extracts of *E. elephantina* for the management and treatment of benign prostatic hyperplasia (BPH). The research has shown that the extract has potent activity in inhibiting the 5-alpha reductase enzyme which is responsible for converting testosterone to dihydrotestosterone (DHT) a causative factor in the progression of BPH (McConnell et al., 1992). In addition the mode of action of inhibitors of the 5-alpha reductase enzyme could also be used for the treatment of male pattern baldness (Ellis and Sinclair, 2008) which led the CSIR to developing the extract of the plant for the management and treatment of male pattern baldness. The discovery was licensed to Afriplex a South African botanical manufacturing company (https://www.csir.co.za/csir-and-afriplex-partners-bringing-health-solutions) and the product is currently traded as Folicin A/T for BPH and male pattern baldness (https://afriplex.co.za/what-we-do/product-manufacturing/active-ingredients/).

This is a unique case in which the product developed specially for BPH and male pattern baldness has no documented traditional use of the plant for these indications or maybe even related to these. However there may be undocumented use of the plant for “bladder or urinary” problems based on its anti-bacterial properties (Maroyi, 2017a) which led the scientists to follow this route. It can be considered that this discovery may have been entirely through scientific innovation. Nevertheless, the traditional use of the plant led researchers to undertake several scientific studies which led to the use for treating BPH and male pattern baldness that was commercialized.

6. Conclusion

Researchers commonly use information from indigenous knowledge systems, typically the traditional use of medicinal plants as a resource for the discovery of pharmaceuticals, nutraceuticals and more recently cosmeceuticals. The four case studies on *Hoodia*, Monatin from *S. ilicifolius*, mosquito repellent from *L. javanica* and the treatment of BPH and male pattern baldness from *E. elephantina* which were either commercialized or close to commercialization have all followed the classical drug discovery or product development route. In these cases it was shown that the ultimate use of the commercializable product may not have been a direct interpretation of the traditional use of the plant. Traditional healing is a holistic system of treating a patient therefore the translation of traditional medicines into modern therapeutic agents is not necessarily a straightforward process. In this context the claim by many researchers to "scientifically validate traditional medicines" may in fact be misleading and may be further compounded when scientists often interpret the names given to medicinal plants or traditional medicines literally, when they may represent metaphors describing their biological, psychological and/or spiritual effects. The major gap that exists is designing appropriate studies or guidelines towards authentication of traditional medicines for their formal incorporation into health care systems. In the conventional approach discussed in this article scientists and traditional health practitioners / indigenous communities should ensure appropriate benefit sharing arrangements are in place.

ABBREVIATIONS USED

SABS - South African Bureau of Standards

CSIR – Council for Scientific and Industrial Research

THP – Traditional Health Practitioners

BPH – Benign prostatic hyperplasia

DHT – Dihydrotestosterone

NRFI - National Food Research Institute

SAE - Serious adverse events

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