Übersichtsarbeit | ***Review Article***

Schweiz. Zschr. GanzheitsMedizin 2009;21(6):300–306. © Verlag für GanzheitsMedizin, Basel. www.ganzheitsmedizin.ch

Hoodia: A Herb Used in South African Traditional Medicine – A Potential Cure for Overweight? Pharmacognostic Review of History, Composition, Health-Related Claims, Scientific Evidence and Intellectual Property Rights

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Background: Within the last decade, the crude drug *Hoodia* and preparations derived from *Hoodia* [*Hoodia gordonii* (MASSON) SWEET ex DECNE] have become increasingly popular. These food supplements – sold partly via the Internet – are promoted as appetite suppressants for weight reduction. This succulent plant is consumed by South African natives, the San, to stop thirst and hunger during hunting. **Objective:** To review current knowledge on origin, chemical constituents, ethnopharmacology and pharmacology of *Hoodia*. Historical development and intellectual property rights are addressed as well. **Method:** Systematic analysis of the scientific literature on *Hoodia* found in major electronic databases. **Results:** A considerable number of patents have been deposited for hoodia, which is claimed to suppress appetite, develop antidiabetic activity and protective effects against gastric acid secretion. The originally planned development of *Hoodia* as a pharmaceutical was abandoned in 2004, at which time *Hoodia* was classified as a functional food and temporarily suspended by the end of 2008. Knowledge on its chemical composition focuses on pregnane glycosides, one of which is regarded as the active principle. Analytical methods which enable screening of the crude drug and formulations thereof have been devised. A huge amount of food supplements claiming to contain *Hoodia* turned out to lack any of its pregnane constituents and must be regarded as adulterations. Studies on the above-mentioned beneficial health claims are scarce. The metabolic stability of the main steroidal glycoside and its interaction with drug-metabolizing enzymes were assessed in vitro. In vivo, *Hoodia* was shown to reduce caloric uptake and body weight after either intracerebroventricular injection or oral ingestion. However, neither clinical nor toxicity data have been published to date. Two cases of adverse reactions (anticholinergic syndrome, acute hepatitis) upon intake of *Hoodia*-containing preparations have been reported. **Conclusion:** Current knowledge on *Hoodia* and its products is incomplete. The phytochemical profile needs to be studied in more detail for further classes of compounds besides the well-investigated pregnane glycosides. There are no reliable data on toxicity, safety and clinics. Moreover, the *Hoodia* issue is intrinsically tied to questions concerning the Convention of Biological Diversity and protection of species: The benefit-sharing agreements signed with the San are to be respected and permits from the authorities are required for collection, culture, transport or export because *Hoodia* is a protected plant.

Keywords: *Hoodia*, San, appetite suppression, safety, quality control, pharmacognosy

The succulent *Hoodia* has been used by the San, indigenes from Southern Africa, for generations as an appetite suppressant and thirst quencher during famine and low food supply [1]. From ancient times, the San have made use of the plant's properties which allow them to endure long hunting expeditions with fewer provisions [2]. This traditional knowledge has been kept among the indigenes and was passed on from generation to generation by word of mouth until the Council for Scientific and Industrial Research (CSIR) in South Africa became acquainted with this information. In the early sixties, an investigation was launched at the CSIR to determine the nutritional value and also any possible long-term toxic effects of "food from the veld" [3]. More than 1000 species of wild South African plants – among them *Hoodia* species – known to be used as indigenous "bush foods" were screened [3]. This research aimed to inform the South African Defence Force about the toxic and nutritional properties of wild foods and so to ascertain their suitability for the army [4]. As a result, the CSIR patented the oxypregnane glycoside P57AS3 which was considered to be the active constituent of *Hoodia gordonii* [5]. Since then the publicity of *Hoodia* began to develop with big expectations in the plant to be promoted successfully as anoretic drug. Several herbal weight-loss products were formulated hitherto and are sold as OTC dietary supplements [5] but to date pharmaceutical industry has failed to

Hoodia: Natürliche Heilkraft zur Gewichtsreduktion aus der Traditionellen Medizin Südafrikas? Ein Review zu Geschichte, Zusammensetzung, Wirkversprechen, wissenschaftlicher Evidenz und Fragen des geistigen Eigentums

Hintergrund: Die pflanzliche Droge *Hoodia* sowie Zubereitungen, die aus *Hoodia* (*Hoodia gordonii* (MASSON) SWEET EX DECNE.) gewonnen werden, haben in den letzten zehn Jahren immer mehr an Bedeutung gewonnen. Diese Nahrungsergänzungsmittel werden teilweise über das Internet verkauft und als Appetit zügelnde Präparate zur Gewichtsreduktion beworben. Das Wissen um die sukkulente Pflanze stammt von Eingeborenen, dem Stamm der San. Diese leben seit Jahrhunderten im Grossraum Südafrika und verwenden *Hoodia* als Bestandteil ihrer traditionellen Medizin zur Unterdrückung von Durst und Hunger während ihrer Jagdausflüge. **Zielsetzung:** Es soll eine Übersicht gegeben werden hinsichtlich des derzeit verfügbaren Wissens über Herkunft der Stammpflanze, chemische Zusammensetzung, Ethnopharmakologie und Pharmakologie von *Hoodia*. Darüber hinaus werden die historische Entwicklung und rechtliche Fragen hinsichtlich des geistigen Eigentums beleuchtet. **Methoden:** Systematische Auswertung der wissenschaftlichen Literatur zu *Hoodia* aus den gängigen elektronischen Datenbanken. **Ergebnisse:** Bisher wurde eine Reihe von Patenten zu *Hoodia* erteilt, von der behauptet wird, sie zügle den Appetit, besässe anti-diabetische Aktivität und zeige gastro-protektive Effekte infolge übermässiger Magen-

säuresekretion. Die ursprünglich geplante Entwicklung von *Hoodia* als Arzneimittel wurde 2004 aufgegeben, in die Kategorie Nahrungsergänzungsmittel verschoben und mit Ende 2008 vorübergehend eingestellt. Die Kenntnis über die chemische Zusammensetzung konzentriert sich auf Pregnanglykoside, von denen eine Verbindung als verantwortlich für die Wirkung angesehen wird. Es wurden analytische Methoden entwickelt, die Screening-Untersuchungen der pflanzlichen Droge sowie von Formulierungen daraus erlauben. Bei einer grossen Anzahl von Nahrungsergänzungsmitteln, die überprüft wurden und die vorgaben, *Hoodia* zu enthalten, konnten keine Pregnanglykoside detektiert werden. Diese Präparate gelten somit als Verfälschungen. Die Datenlage zu den behaupteten gesundheitszuträglichen Wirkungen ist dünn. Es wurden die metabolische Stabilität des Hauptsteroidglykosids und dessen Wechselwirkung mit metabolisierenden Enzymen in vitro gemessen. In vivo zeigte diese Verbindung eine Reduktion der Kalorienaufnahme und des Körpergewichts nach intracerebroventrikularer Injektion oder oraler Gabe. Bis heute sind weder zu Klinik noch zur Toxikologie Daten in wissenschaftlich referierten Zeitschriften veröffentlicht. Berichte über unerwünschte Wirkungen nach der Einnahme von *Hoodia*-haltigen Präparaten liegen in zwei Fällen vor (anticholinerges Syndrom, akute Hepatitis). **Schlussfolgerungen:** Die gegenwärtige Datenlage zu *Hoodia* und Produkten daraus ist unzureichend. Das phytochemische Profil muss neben den bisher gut untersuchten Pregnanglykosiden noch eingehend auf weitere Substanzklassen überprüft werden. Es gibt keine verlässlichen Angaben zu Toxizität, Sicherheit und Klinik. Der Fall *Hoodia* ist untrennbar verbunden mit Fragen, die die Convention of Biological Diversity (CBD) und den Artenschutz betreffen: Die mit den San unterzeichneten Übereinkommen zur Aufteilung eines potentiellen Gewinns sind international zu respektieren, ebenso wie die Tatsache, dass für Aufsammlung, Kultivierung, Transport oder Export behördliche Genehmigungen eingeholt werden müssen, da *Hoodia* unter Schutz steht.

Schlüsselwörter: *Hoodia,* San, Appetitzügler, Sicherheit, Qualitätskontrolle, Pharmakognosie

put a registered herbal remedy to the market. The present paper reviews the current scientific knowledge on *Hoodia* **(Fig. 1)** in terms of phytochemistry, scientific evidence and health-related claims. A historic overview about the succulent and its development as potential anoretic cure is given and intellectual property rights are addressed.

Historical development

The commercialisation of biodiversity in Southern Africa was the topic of a PhD study performed by Wynberg at the University of Strathclyde, Scotland, who laid down her compilation up to the year 2004 in a detailed overview [4]. According to Wynberg, the San **(Fig. 2)** represent the oldest human inhabitants in Southern Africa living in small nomadic groups as hunters and gatherers for thousands of years. A long history of dispossession and relocation has accompanied the San which started with their persecution upon colonisation in 1652 followed by discrimination along with other people of colour during South Africa's apartheid regime and which continues today through permanent political marginalization [4]. At present, the approximately 90.000 San in Southern Africa mainly live in the Kalahari Desert and its surrounding regions in Namibia, Botswana and, to a lesser extent, in South Africa. The San as well as other indigenous peoples in the region have been using *Hoodia* and related species as a food and, especially, as a drink substitute and appetite suppressant, as well as for a variety of other purposes [4].

The first reference to the use of *Hoodia* dates back to 1796 [6], whereas its use as thirst quencher and appetite suppressant was recorded centuries later [7, 8]. The above mentioned CSIR, South Africa's national laboratory, had been established in 1945 by an act of Parliament in order to engage in industrial and scientific development to improve the quality of life of African people [9]. This organisation obtained information about the properties of the plant during a project on edible wild plants and, therefore, included *Hoodia* species in this project in 1963 [4]. Even though information from literature and laboratory tests on mice suggested *Hoodia* as a promising non-toxic appetite suppressant scientific evidence to file for a patent was insufficient at that time. The issue was postponed until further investigations including isolation and structure elucidation led to a "revival": more than 30 years later, in 1995, the CSIR was assigned a patent in South Africa which guarantees the use of the active components of the plant – referred to as "P57" – responsible for suppressing appetite. This was followed by a patent on pharmaceutical compositions with appetite suppressant activity granted by the World Intellectual Property Organisation in 1998 [10]. In 1998, the CSIR licensed use of P57 to Phytopharm, a British pharmaceutical research company specialised in the development of phytomedicines [4,9]. The aim was to promote the worldwide development and marketing of the patented extract P57 from *Hoodia* for suppressing appetite, treatment of eating disorders, adipositas and type-II-diabetes. The realisation of this ambitious project required the involvement of a solvent partner, therefore, Phytopharm sub-licensed the pharmaceutical giant Pfizer in the very same year [4]. Press releases launched by Phytopharm reported on completed pre-clinical studies (October 1998) and on a proof-of-principle clinical study with three successfully completed stages [11]. Although Phytopharm and Pfizer agreed on a future development program for P57 in July 2002, only one year later Pfizer decided to discontinue its involvement upon the merger with Pharmacia, which resulted in the shutdown of its Natureceuticals group [4]. All rights were returned to Phytopharm who began discussions with potential licensing partners to develop the extract as a weight-control food supplement.

In December 2004, Phytopharm entered together with Unilever into a licence and joint development agreement for the *Hoodia* extract [12], its development as a pharmaceutical ceased. The both companies aimed at bringing a new weight management product to the functional food market. The collaboration comprised a five-stage programme including safety and efficacy studies. In September 2007, Phytopharm announced the successful progress into stage three, the final stage prior to submission for regulatory approval [13]. However, data of a clinical study using *Hoodia* extract in a drink-based product led Unilever to conclude that it is unsuitable to move forward with the product concept [14]. In December 2008, a mutual termination agreement was concluded between the parties and all the original Phytopharm patents and rights reverted to Phytopharm [14,15,

Source: Ch. Reisch

Fig. 1. *Hoodia gordonii* – natural habitat and cultivation site in Biedouw-Valley, South Africa.

16]. Even though Phytopharm's functional food programme was negatively impacted by the Unilever decision not to proceed, the company believes that the pre-clinical and clinical data of the *Hoodia* extract encourage to continue with further studies on obesity, as well as for pharmaceutical and veterinary applications [14]. Presently Phytopharm is in early stage discussions with a number of interested partners. Expenditure on the *Hoodia* programme will be limited until a satisfactory business proposition emerges [16,17].

Intellectual property rights

When the patent was awarded to the CSIR in 1998, this happened without the knowledge of the San [18]. They first learned of the patent through a Phytopharm press release [9]. Feeling exploited and disappointed, the San started opposition to the *Hoodia* patent and accused the CSIR and Phytopharm of biopiracy. Represented by the South African San Council, they filed suit against the CSIR and its licensees [9] which, in March 2003, resulted in the signing of an agreement between the two parties to share any royalties from potential sales of drugs or other products derived from *Hoodia* [4,19]. The benefit sharing was arranged according to the Convention on Biological Diversity (CBD) implemented 1992 at the Earth Summit in Rio de Janeiro [20]. This "Global Convention" has 190 parties and aims to achieve three objectives [20]:

- The conservation of biological diversity
- The sustainable use of its components
- The fair and equitable sharing of benefits from the use of genetic resources.

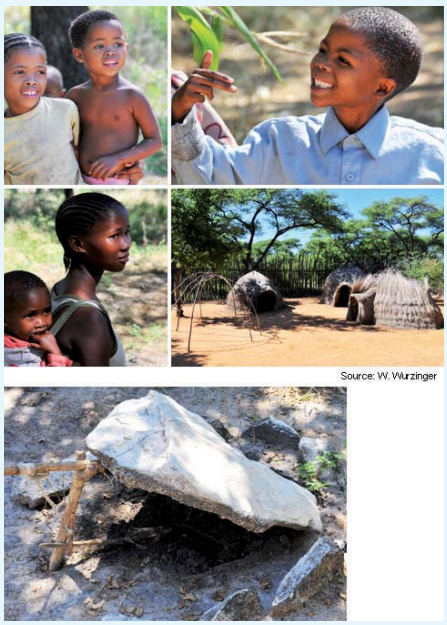
Under the terms of the agreement, the CSIR will pay the San 8% of all payments it receives from its licensee, as well as 6% of all royalties once the drug is commercialised [18]. The money would be paid into a San-controlled Trust, tasked and committed to equitable distribution of this money amongst the San peoples [20].

The *Hoodia* case attracted international attention because of its potential to reduce appetite, because of being derived from an African plant, and, because it was one of the first times that holders of traditional knowledge were given a share of the potential profits of products derived from that knowledge. However, besides issues regarding patent law discussed in literature [9,2], the benefit sharing agreement between the CSIR and the San implies further substantial political, environmental and ethical questions in intellectual property law. Martin and Vermeylen analyse whether or not intellectual property rights can be used to advance the development of indigenous peoples while at the same time conserving their culture and their knowledge of nature [18]. Schroeder and Chennells deal with the question whether benefit sharing could help the San who are exposed to serious poverty, resulting in malnutrition and avoidable illnesses, to overcome the lack of access to essential health care [20].

Plant origin

The genus *Hoodia* is classified as one of the stapeliads, a group of stem succulents belonging to the family Apocynaceae. They were formerly part of the family Asclepiadaceae, but are now assigned within the tribe Ceropegieae of the subfamily Asclepiadoideae to the Apocynaceae [21]. The first *Hoodia* species to be described were *H. pilifera* and *H. gordonii,* which were published initially as *Stapelia* species in the second half of the 18th century. In the 19th century, *Stapelia pilifera* L. f. was moved to a new genus *Trichocaulon*, and *Stapelia gordonii* was published as *Hoodia gordonii* MASSON [21]. According to a recent revision by Bruyns [22], the *Trichocaulon* species were regrouped into the genus *Hoodia*.

From the older literature it is clear that *Hoodia pilifera (=Trichocaulon piliferum = Stapelia pilifera)* was the species of choice for use as a substitute for food and water given the vernacular name "ghaap" [21]. The larger, hard-spined and more bitter tasting species *Hoodia gordonii* is reported to be considered worthless in some regions, whereas in the Kalahari the pealed, juicy young shoots were eaten – raw and cooked – although it could not be utilised in times of draught [21].



Source: W. Wurzinger

Fig. 2. San in a farm of the Ombili foundation and trap for hunting as used by the San, Omuramba Ovambo valley, Namibia.

However, the existing literature mainly deals with *H. gordonii,* and, to a lesser extent with *H. pilifera*. In common with other *Hoodia* species, *H. gordonii* is a multi-stemmed succulent with thick, erect, cylindrical, fleshy and fairly hard, glabrous, grey-green to grey-brown stems [23]. The tubercles are prominent, fused in their lower halves into 11–17 obtuse angles along stem, each tipped with a sharp spine 6–12mm long [23]. *H. gordonii* has flesh-coloured blooms as large as 75mm with an odour that resembles to rotten meat [24]. Due to its spines it is by mistake often referred to as "cactus". The cultivation of the slow growing plant is not easy and must be started from seeds [21,24]. Moreover, several *Hoodia* species are known to have small and widely dispersed populations [25], some of them are listed as rare or vulnerable in Red data lists [26].

The planned commercialisation and the wild harvesting of *H. gordonii* are considered as serious threat to rare *Hoodia* species which might be mistaken for *H. gordonii.* The danger of overexploitation led to the inclusion of *Hoodia* species to Appendix II of the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES) in 2005 [24, 27]. Anyone wishing to cultivate or harvest wild *Hoodia* species outside of South Africa must register for a CITES permit [24]. In South Africa, *Hoodia* species are protected and permits are required from the authorities for the collection, cultivation, transport or exporting of the plants [21]. In 2005, the Cape Ethno Botanical Growers Association was founded due to threat of *Hoodia* becoming extinct [28] with the aim to guarantee the supply with plant material and to prevent unregulated collection upon the increasing interest in the commercial application of *Hoodia*. In 2006, this organisation merged with the Southern African *Hoodia* Growers Association in order to include *Hoodia* cultivators from Namibia and Botswana [28]. This newly formed Southern African *Hoodia* Association signed a profit sharing agreement with the San in February 2006 [19,28].

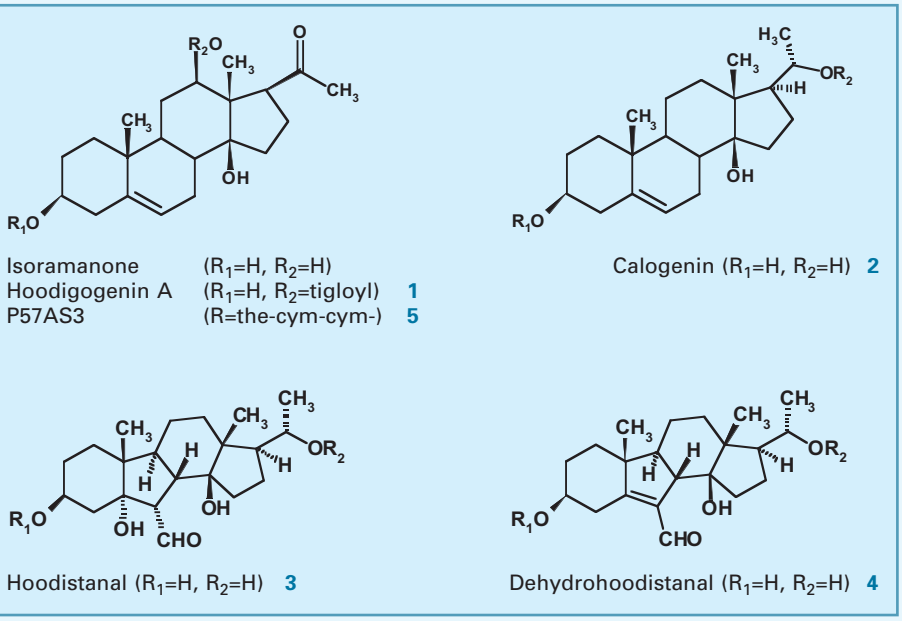


Fig. 3. Skeletal structures of *Hoodia* constituents.

Phytochemistry and quality control

The phytochemical papers published hitherto focus on the two species *H. gordonii* and *H. pilifera* [3,21,29–36]. About forty different pregnane glycosides have been isolated and structurally elucidated so far comprising the aglycones hoodigogenin A (1), calogenin (2), hoodistanal (3) and dehydrohoodistanal (4) (Meaning of the numbers in brackets – see **Fig. 3**).

Hoodigogenin A (1) is a 3β,12β,14β-trihydroxy-pregn-5-en-20-one with a tigloyl ester substitution in position 12 which is unique from *Hoodia* [36]. The derivatives of hoodigogenin A represent 3β-O-glycosides with a chain consisting of two to five sugar moieties named hoodigosides A–K [21,32], W and X [36] and gordonosides A–L [30]. The distinction between these closely related compounds is made by the sugars, mainly D-glucose as well as 6-deoxy- and 2,6-dideoxy sugars such as D-thevetose, D-cymarose, D-oleandrose, D-digitoxose and 3-O-methyl-6-deoxy-D-allose [21,33]. One of the first hoodigosides to be published and patented was named P57AS3 (5), it is regarded as the active principle in *Hoodia* and sometimes referred to as P57. In comparison to hoodigogenin A (1), calogenin (2) lacks the hydroxygroup in position 12β and exhibits position 20 reduced to a hydroxyl function instead of the ketone. A number of bisdesmosides (substitution in positions 3 and 20) and one monodesmoside (substitution in position 3) have been isolated and called as hoodigosides L–V [32], Y and Z [36]. Most characteristic for the genus *Hoodia* are the rare 6-5-6-5 fused ring sterols hoodistanaloside A and B which are the first two naturally occurring glycosides comprising a 5(6→7)abeosterol aglycone (3, 4) [36]. A summary of the isolated compounds is given in **Table 1**.

The limited availability of the plant material due to the above-mentioned reasons and the increasing popularity leads to the problem of adulterations. In the US for example, more than 100 products are currently marketed as tablets, capsules, liquid gels, liquid tinctures, snack bars, juice, powders, protein shakes, lollipops, tea and coffee [37]. Such *Hoodia* products – partly offered on the Internet – are outside the profit sharing agreement, which is appealed against by lawyers representing the San [19]. As the supply of authentic *H. gordonii* cannot match the demand for all these preparations, adulterations by other species or even genera occur [37]. Consequently, analytical techniques have been developed based on the acquired knowledge on the plant's composition in order to detect appearing adulterations. HPLC-UV

Tab. 1. Constituents identified in *Hoodia*

Synonym according to Reference	Ref.	No in Ref.	MW	Aglycone	R_1	R_2
Gordonoside A Hoodigogenine A	30 31	1 1a	430	Hoodigogenine A	H	tigloyl-
Hoodigoside A	31	1	734	Hoodigogenine A	the-cym-	tigloyl-
P57AS3 Compound 1 Formula 6	31 3 33	12 1 6	878	Hoodigogenine A	the-cym-cym-	tigloyl-
Hoodigoside B	31	2	894	Hoodigogenine A	the-the-cym-	tigloyl-
Hoodigoside C Gordonoside C	31 30	3 3	1022	Hoodigogenine A	the-cym-cym-cym-	tigloyl-
Hoodigoside D	31	4	1038	Hoodigogenine A	the-the-cym-cym-	tigloyl-
Compound 2	3	2	1022	Hoodigogenine A	cym-the-cym-cym-	tigloyl-
Hoodigoside E Gordonoside H	31 30	5 8	1040	Hoodigogenine A	glc-the-cym-cym-	tigloyl-
Hoodigoside F	31	6	1084	Hoodigogenine A	glc-ole-the-cym-cym-	tigloyl-
Hoodigoside G	31	7	1084	Hoodigogenine A	glc-cym-the-cym-cym-	tigloyl-
Hoodigoside H	31	8	1068	Hoodigogenine A	glc-cym-cym-cym-cym-	tigloyl-
Hoodigoside I	31	9	1068	Hoodigogenine A	glc-ole-cym-cym-cym-	tigloyl-
Hoodigoside J	31	10	1154	Hoodigogenine A	glc-ole-dig-cym-cym-	tigloyl-
Hoodigoside K	31	11	898	Hoodigogenine A	glc-glc-cym-	tigloyl-
Hoodigoside L	32	1	1206	Calogenin	(4-O-tigloyl)-the-ole	glc-glc-glc-
Hoodigoside M	32	3	1124	Calogenin	the-ole-	glc-glc-glc-
Hoodigoside N	32	4	638	Calogenin	the-ole-	H
Hoodigoside O	32	5	1044	Calogenin	(4-O-tigloyl)-the-ole	glc-glc-
Hoodigoside P	32	6	1190	Calogenin	(4-O-tigloyl)-ole-cym	glc-glc-glc-
Hoodigoside Q	32	7	1350	Calogenin	(4-O-tigloyl)-the-cym-cym-	glc-glc-glc-
Hoodigoside R	32	8	1334	Calogenin	(4-O-tigloyl)-ole-cym-cym-	glc-glc-glc-
Hoodigoside S	32	9	1478	Calogenin	(4-O-tigloyl)-ole-cym-cym-cym-	glc-glc-glc-
Hoodigoside T	32	10	1316	Calogenin	(4-O-tigloyl)-ole-cym-cym-cym-	glc-glc-
Hoodigoside U	32	11	1478	Calogenin	(4-O-tigloyl)-cym-cym-cym-cym-	glc-glc-glc-
Hoodigoside V Compound 2	36 32	6 2	882	Calogenin	(4-O-tigloyl)-the-ole-	glc
Hoodigoside W	36	1	1022	Hoodigogenine A	ole-the-cym-cym-	tigloyl-
Hoodigoside X	36	2	796	Isoramanone	the-cym-cym-	H
Hoodigoside Y	36	5	800	Calogenin	the-ole-	glc
Hoodigoside Z	36	7	1026	Calogenin	(4-O-tigloyl)-the-the-ole-	glc
Hoodistanaloside A	36	8	914	Dehydrohoodistanal	(4-O-tigloyl)-the-ole-	glc
Hoodistanaloside B	36	9	896	Hoodistanal	(4-O-tigloyl)-the-ole-	glc
Gordonoside B	30	2	1022	Hoodigogenine A	the-ole-cym-cym-	tigloyl-
Gordonoside D	30	4	992	Hoodigogenine A	dig-ole-cym-cym-	tigloyl-
Gordonoside E	30	5	1006	Hoodigogenine A	ole-ole-cym-cym-	tigloyl-
Gordonoside F Formula 9	30 33	6 9	1006	Hoodigogenine A	ole-cym-cym-cym-	tigloyl-
Gordonoside G Formula 10	30 33	7 10	1006	Hoodigogenine A	cym-cym-cym-cym-	tigloyl-
Gordonoside I	30	9	1136	Hoodigogenine A	dig-ole-ole-cym-cym-	tigloyl-
Gordonoside L Formula 11	30 33	10 11	1150	Hoodigogenine A	ole-cym-cym-cym-cym-	tigloyl-
Formula 7	33	7	1018	Hoodigogenine A	cym-mda-cym-cym-	tigloyl-
Formula 8	33	8	992	Hoodigogenine A	ole-dig-cym-cym-	tigloyl-
Formula 12	33	12	1022	Hoodigogenine A	ole-mda-cym-cym-	tigloyl-

cym: β-D-cymarose; dig: β-D-digitoxose; glc: β-D-glucose; mda: 3-O-methyl-6-deoxyallose; ole: β-D-oleandrose; the: β-D-thevetose;
Ref: reference; MW: molecular weight

[38], HPLC-MS [39], UPLC-UV-MS [37] and HPTLC [5] are useful methods to perform qualitative analysis and to quantify respective steroid glycosides [40] from *H. gordonii* preparations. The new methods developed for chemical fingerprint analysis allow a quick and reliable assessment of various matrices: *Hoodia* species, plants from genera related to *Hoodia* and dietary supplements that claim to contain *H. gordonii* may be screened. According to Rumalla et al., the HPTLC analysis of thirteen commercially available dietary supplements confirmed the presence of *H. gordonii* for only two samples, eleven products did not show any of the scrutinised pregnane glycosides [5]. Quantification analyses showed variability and big differences in the contents: an extract of dried *H. gordonii* was determined by 2.1% of total steroid glycosides [40]. The content of the single compound P57AS3 **(5)** was found to be 0.05% and 0.005% in two *H. gordonii* plant samples. Two of ten commercially available dietary supplements which claimed to consist of *H. gordonii* contained 0.17% and 0.005% of P57AS3, but in the remaining eight preparations it was not detectable at all [39]. These data show the diverse quality of the offered products and should raise the consumer's awareness of potential adulterations because they represent a potential health risk.

Effects, mode of action, clinical trials

The main reason why *Hoodia* became so popular within the last decade is its use for suppressing appetite. Various patents were filed comprising extracts, constituents and preparations of *H. gordonii* which cover suppression of appetite, anti-diabetic activity and treatment of gastric acid secretion damage. However, there is little data on *Hoodia*'s mechanism of action even though this would be of substantial interest. The metabolic stability of P57AS3 **(5)** in human liver microsomes and its interaction with drug metabolising enzymes were determined [41]. Intestinal transport of P57AS3 was studied in the Caco-2 cell model of intestinal transport and absorption [41]. The authors conclude that the intestinal transport of P57AS3 is mediated by P-glycoprotein and multidrug resistance-associated protein transporters. The compound was metabolically stable and showed weak inhibition of CYP 3A4 [41].

A study in rats showed that the intracerebroventricular injection of P57AS3 (0.07 mg **5** per injection) reduced the food-intake during 24h after extract application by 40–60%. The effect was dose-dependent and suggested a likely central (CNS) mechanism of action for P57AS3 [42]. In a later study this compound was applied orally to rats over a three-day period (6.25–50 mg/kg). Compared to the animals who were either treated with the vehicle or with the appetite suppressor fenfluramine food consumption and body mass gain of the P57AS3 treated rats decreased significantly during a monitoring period of eight days [3].

The utmost recent patent filed by Unilever reports on polysaccharides obtainable from plants of the Asclepiadoideae subfamily *(Hoodia, H. gordonii, Stapelia)* which are said to exhibit a not otherwise specified immunostimulating effect [43].

According to the author's knowledge, no papers in peer-reviewed journals have been published to date on clinical trials with *Hoodia*. The only available information are press releases by Phytopharm which report on a double-blind, placebo-controlled clinical study on overweight male volunteers who showed a statistically significant reduction in the average daily calorie intake and in body fat [11,13]. There is scarce evidence in literature about serious adverse effects. A recent publication from Italy reports on preparations containing *Hoodia* and concomitant drugs related to one case of acute hepatitis and one case of anticholinergic syndrome [44].

Recently a monograph of *H. gordonii* has been prepared and compiled by Van Wyk. The monograph on general description, identity/quality, use/efficacy and safety is planned to be published in the African Herbal Pharmacopoeia by the third quarter of 2009 [45].

Conclusions

Hoodia has been of increasing interest within the past decade due to its attractive indication profile. It originates from Southern African indigenes, the San, who have been using the plant since centuries as thirst and appetite quencher. The South African Council for Scientific and Industrial Research (CSIR) together with the British company Phytopharm have been aiming at the development of *Hoodia* as pharmaceutical or food supplement but were not successful to date. Meanwhile a considerable amount of patents has been issued protecting the rights on an extract and compounds out of *Hoodia* for its appetite reducing, anti-diabetic and gastro-protective activity. Benefit sharing agreements with the San have been signed in order to share in profit from cultivation and potential commercialisation of *Hoodia*. To prevent the slow-growing plant from over exploitation and to guarantee sustainable supply, *Hoodia* species were included into Appendix II of the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES). Collection, cultivation, transport and export are subjected to strict rules which need to be respected by all countries who signed the Convention of Biological Diversity (CBD). However, obesity concerns many people in the civilized countries and as presently only few drugs are available to treat this condition efficiently a break-through would open a big potential market. Some institutions see this chance and provide *Hoodia* preparations disregarding the above-mentioned patents and agreements even though there are no data on successful clinical studies. Preparations are available in Europe and the US. Valuable phytochemical investigations focusing on one class of compounds, the pregnane glycosides, allow the quality control of the crude drug and preparations containing *Hoodia*. The results of these screenings give rise to serious concern about the safety of such products as a considerable amount seems to lack *Hoodia*. Even though *Hoodia* itself might be safe, if slim-down products claimed to contain *Hoodia* obviously lack this

agent, what else do these preparations contain? This involves a clear safety risk and has to be assessed critically. The consumers' attention should be drawn to the fact that they run danger to be affected by adverse reactions due to unspecified constituents with a completely unknown chemical and pharmacological profile. Who would take the responsibility in this case?

Apart from this ethical issue, several other questions remain open: Why did two big companies who participated in the development abandon? Why did they not succeed in publishing data about safety, toxicology and clinics? Does *Hoodia* have an effect or not? Which other compounds are contained in *Hoodia* and what effects/adverse effects do they have? To date, we are not able to answer these questions but suppliers, customers as well as governments should not forget about the sensitive background of this potential "slimming agent".

Acknowledgements

My thanks go to Prof. K. Eloff, Prof. B-E. Van Wyk and Dr. T. Brendler for their willingness and promptness to answer my questions concerning the *Hoodia* monograph in the African Herbal Pharmacopoeia. Dr. F. Petersen took his time to discuss the *Hoodia* issue with me, which helped a lot. I am deeply indebted to DI. W. Wurzinger and Dr. Ch. Reisch for providing me with photographs.

References

1 Van Wyk BE: A review of Khoi-San and Cape Dutch medical ethnobotany. J Ethnopharmacol 2008;119:331–341.
2 Dolder F: Traditional Knowledge and Patenting: The Experience of the Neemfungicide and the Hoodia Cases. Biotechnology Law Report 2007;26(6):583–590.
3 Van Heerden FR, Horak RM, Maharaj VJ, Vleggaar R, Senabe JV, Gunning PJ: An appetite suppressant from Hoodia species. Phytochemistry 2007;68:2545–2553.
4 Wynberg R: Use of Traditional Knowledge of Hoodia Species in the Development of an Appetite Suppressant. The Journal of World Intellectual Property 2004;7(6):851–876.
5 Rumalla CS, Avula B, Shukla YJ, Wang YH, Pawar RS, Smillie TJ, Khan IA: Chemical fingerprint of Hoodia species, dietary supplements, and related genera by using HPTLC. J Sep Sci 2008;31:3959–3964
6 Masson F: Stapelia Novae: On a Collection of Several New Species of That Genus. London, 1796.
7 Marloth R: In: The Flora of South Africa with Synopsis of the South African Genera of Phanerogamous Plant. Vol. III, Wheldon and Wesley, London, 1932.
8 White A, Sloan BL: The Stapelieae. Vol III, 2nd edition, Abbey San Encino Press, Pasadena, California, 1937.
9 Moyer-Henry K: Patenting Neem and Hoodia: Conflicting Decisions Issued by the Opposition Board of the European Patent Office. Biotechnology Law Report 2008;27(1):1–10.
10 Van Heerden FR, Vleggaar R, Horak RM, Learmonth RA, Maharaj V, Whittal RD: Steroidal glycosides, methods for their production and preparation, pharmaceutical compositions containing them, and their use as appetite suppressants. 1998: patent; WO9846243.
11 Phytopharm pld, Successful Completion of Proof of Principle Clinical Study of P57 for Obesity, Press release, 5 Dec 2001; available at: www.Phytopharm.co.uk/press (accessed Sept 14th 2005).
12 Phytopharm and Unilever enter into a Licence and Joint Development Agreement for Hoodia gordonii Extract, Press release, 15 Dec 2004; available at: www.phytopharm.co.uk/news/newsreleases (accessed May 18th 2009).
13 Phytopharm, Portfolio, Weightmanagement Hoodia extract; available at: www.phytopharm. com/portfolio/?id=2244 (accessed May 18th 2009).
14 Neutraceuticals World, Braking News, Unilever abandons hoodia project; available at: http://www.nutraceuticalsworld.com/news/2008/11/26 (accessed June 24th 2009).
15 Phyotpharm, News, News Releases, Unilever returns rights to Hoodia extract, Press release, 12 Dec 2008; available at: www.phytopharm.com/news/newsreleases/?id=16553 (accessed June 24th 2009).
16 Phyotpharm, News, News Releases, Interim Management Statement for the three month period ended 31 December 2008, Press release, 17 Feb 2009; available at: www.phytopharm.com/news/newsreleases/ ?id=16706 (accessed June 24th 2009).
17 Phyotpharm, News, News Releases, Interim Results for the six months ended 31 March 2009, Press release, 20 May 2009; available at: www.phytopharm.com/news/newsreleases/?id=17403 (accessed June 24th 2009).
18 Martin G, Vermeylen S: Intellectual Property, Indigenous Knowledge, and Biodiversity. Capitalism Nature Socialism 2005;(16)3:27–48.
19 Anonymous: Protecting traditional knowledge: the San and hoodia. Bulletin of the World Health Organization 2006;84(5):345.
20 Schoeder D, Chennells R: Benefit sharing and access to essential health care: a happy marriage? Medicine and Law 2008;27(1):53–69.
21 Van Heerden FR. Hoodia gordonii: A natural appetite suppressant. J Ethnopharmacol 2008; 119:434–437.
22 Bruyns PV: A revision of Hoodia and Lavrania (Asclepiadaceae-Stapelieae). Botanische Jahrbücher 1993;115:145–270.
23 Bruyns PV: Stapeliads of Sothern Africa and Madagascar. Vol.1. Umdaus Press, Pretoria, 2005, 4–8.
24 Lee RA, Balick MJ: Indigenous use of Hoodia gordonii and appetite suppression. Explore 2007;3(4):404–406.
25 Van Wyk BE: A broad review of commercially important Southern African medicinal plants. J Ethnopharmacol 2008;119:342–355.
26 Golding J: Southern African Plant Red Data Lists. Southern African Biodiversity Network Report No. 14 2002: SABONET, Pretoria.
27 CITES species database, Hoodia gordonii; available at: www.cites.org/eng/resources/ species.html (accessed June 23rd 2009).
28 The ABS Capacity Development Initiative for Africa, Cape Town Workshop 11/2006; available at: www.abs-africa.onfo/capetown_221106. html (accessed June 22th, 2009).
29 Horak RM, Maharaj V, Hakkinen J: Steroidal glycosides or plant extracts for treatment of gastric acid secretion damage. 2001: patent; EP1099444.
30 Dall'Acqua S, Innencenti G: Steroidal glycosides from Hoodia gordonii. Steroids 2007;72:559–568.
31 Pawar RS, Shukla YJ, Khan SI, Avula B, Khan IA. New oxypregnane glycosides from appetite suppressant herbal supplement Hoodia grodonii. Steroids 2007;72:524–534.
32 Pawar RS, Shukla YJ, Khan IA. New calogenin glycosides from Hoodia gordonii. Steroids 2007;72:881–891.
33 Abrahamse SL, Povey KF, Rees DD. Appetite suppressant compositions. 2007: patent; WO 2007096239.
34 Shukla YJ, Fronczek FR, Pawar RS, Khan IA. Hoodigogenin A from Hoodia gordonii. 2008: Acta Cryst E64; o1643–o1644.
35 Avula B, Wnag YH, Pawar RS, Shukla YJ, Smillie TJ, Khan IA. Identification and structural characterization of steroidal glycosides in Hoodia gordonii by ion-trap tandem mass spectrometry and liquid chromatography coupled with electrospray ionization time-of-flight mass spectrometry. Rapid Com Mass Spec 2008;22:2587–2596.
36 Shukla YJ, Pawar RS, Ding Y, Li XC, Ferreira D, Khan IA. Pregnane glycosides from Hoodia gordonii. Phytochemistry 2009;70:675–683.
37 Avula B, Wang YH, Pawar RS, Shukla YJ, Smillie TJ, Khan IA: A rapid method for chemical fingerprint analysis of Hoodia species, related genera, and dietary supplements using UPLC-UV-MS. J Pharm Biomed Anal 2008;48:722–731.
38 Avula B, Wang YH, Pawar RS, Shukla YJ, Khan IA: Chemical Fingerprinting of Hoodia Species and Related Genera: Chemical Analysis of Oxypregnane Glycosides Using High-Performance Liquid Chromatography with UV Detection in Hoodia gordonii. Journal of AOAC International 2007;90(6): 1526–1531.
39 Avula B, Wang YH, Pawar RS, Shukla YJ, Schaneberg B, Khan IA: Determination of the Appetite Suppressant P57 in Hoodia gordonii Plant Extracts and Dietary Supplements by Liquid Chromatography/Electrospray Ionization Mass Spectrometry (LC-MSD-TOF) and LC-UV Methods. Journal of AOAC International 2006;89(3):606–611.
40 Janssen HG, Swindells C, Gunning P, Wang W, Grün C, Mahabir K, Maharaj VJ, Apps PJ: Quantification of appetite suppressing steroid glycosides from Hoodia gordonii in dried plant material, purified extracts and food products using HPLC-UF and HPLC-MS methods. Anal Chim Act 2008;617;200–207.
41 Madgula VLM, Avula B., Pawar RS, Shukla YJ, Khan IA, Walker LA, Khan SI: In Vitro Metabolic Stability and Intestinal Transport of P57AS3 (P57) from Hoodia gordonii and its Interaction with Drug Metabolizing Enzymes. Planta Med 2008;74:1269–1275.
42 MacLean DB, Luo LG: Increased ATP content/ production in the hypothalamus may be a signal for energy-sensing of satiety: studies of the anorectic mechanism of a plant steroidal glycoside. Brain Res 2004;1020:1–11.
43 Abrahamse SL, Van Adrichem JA, Van Der Burg-Koorevaar MCD, Koek JH: Edible product having an immunostimulating effect. 2009: patent; WO2009071425.
44 Menniti-Ippolito F, Mazzanti G, Santuccio C, Moro PA, Clapai G, Firenzuoli F, Valeri A, Raschetti R: Surveillance of suspected adverse reactions to natural health products in Italy. Pharmacoepidemiology and Drug Safety 2008;17: 626–635.
45 Van Wyk BE. Hoodia gordonii. In: Eloff JN, Brendler T, Gurib-Fakim A, Phillips LD (Eds.). The African Herbal Pharmacopoeia. Association for African Medicinal Plants Standards (AAMPS), Reduit, Mauritius (in press).

Disclosure Statement

The author declares that no financial or other conflict of interest exists in relation to the content of this article.

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