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Review Article

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PHARMACOGNOSY OF THE HERBAL MEDICINE *Hoodia gordonii* (HOODIA), A TRADITIONAL APPETITE SUPPRESSANT

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ABSTRACT

Obesity is now at epidemic proportions throughout the world. It is known to be associated with a number of diseases and is one of the leading preventable causes of death worldwide. Development of herbal and synthetic agents for the treatment of obesity represents a potential multi-billion dollar market. Previously marketed herbal and synthetic weight loss medications have suffered from serious potential adverse reactions. *Hoodia gordonii* is a cactus-like plant traditionally used by natives of Africa to suppress hunger pangs during long hunting trips. Constituents of hoodia may represent anti-obesity lead compounds that work by mechanisms not previously exploited. Two multi-national pharmaceutical companies have invested several tens of millions of dollars in development of these agents. By fractionation of extracts of hoodia, and biological assay of the fractions, the14-β hydroxy pregnane glycoside P57 has been isolated. A number of studies have provided support for development of the crude plant extract and isolation of P57 into clinically useful appetite suppressants for the treatment of obesity. Some controversy surrounds the development of hoodia into commercial medicinal or dietary substances, due to potential infringement on "traditional intellectual property". Furthermore, questions remain regarding the efficacy of these preparations, their mechanism of biological action, and their safety. The present review summarizes the current knowledge surrounding these questions, within a historical context of drug development.

Keywords: *Hoodia gordonii,* Appetite Suppressant, Pharmacognosy, P57, Plant Steroidal Glycoside.

INTRODUCTION

Excessive body weight is known to be associated with a number of diseases, such as diabetes and heart disease, and is one of the leading preventable causes of death worldwide.[1] Reduction in caloric intake is one of the mainstays of reducing excessive body weight. However, many individuals have difficulty adhering to a reduced calorie diet. For this reason, there is considerable demand for products that can decrease appetite. Previously popular herbal and synthetic weight-loss products, such as ephedra, phenylpropanolamine, and sibutramine have been found to be associated with serious adverse effects. Phenylpropanolamine has been removed from the market in a number of countries due to increased risk of hemorrhagic stroke.[2] The more recently developed anti-obesity drug sibutramine has also been withdrawn from the market due to adverse cardiovascular events.[3] Ephedra (*Ephedra sineca*) plant material, which has been widely used in herbal weight loss products, has similarly been associated with adverse cardiovascular and central nervous system events.[4] This has led to a ban on its use in the United States. Ephedra alkaloids, sibutramine, and phenylpropanolamine are all sympathomimetic agents, and may produce side effects typical of stimulants, such as nervousness, insomnia, hypertension, and irregular heartbeat. For the preceding reasons, a weight loss product that does not work by sympathomimetic action is desirable. The herbal medicine commonly called "hoodia" may be a viable alternative, and many hoodia-containing preparations have been extensively marketed.[5] More than 100 products have been marketed in formulations ranging from tablets and tinctures to protein shakes and lollipops.[6] Much of the early marketing notoriously occurred through spam email.

Hoodia is derived from plants in the genus *Hoodia*, especially *Hoodia gordonii*. *H. gordonii* was discovered and described by Col. Robert Gordon Jackson in 1779. It was initially identified as a member of the closely related genus *Stapelia* and named *Stapelia gordonii* in his honor. Later it was moved to the genus *Hoodia*, which itself was named in honor of Van Hood, a renowned succulent grower of the 19th century.

Hoodia species are found in the arid west of Southern Africa and Namibia. Common names for the plant include Bushman's hat, queen of the Namib, and xhoba. Hoodia has traditionally been used by the San people of South Africa and Namibia to suppress appetite and thirst during long hunting trips in the Kalahari desert.[7] Hoodia species are in the Apocynaceae, or dogbane family, within the subfamily Asclepiadoideae. The general growth pattern is as a small shrub-like succulent (up to 1 m high) with large flowers

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(up to 75 mm) which often have a strong carrion smell. This smell attracts flies and other pollinators. They are very tolerant to harsh growing conditions, growing in temperature extremes of -3°C to +40°C in dry sands and stony soils. Initial growth form occurs as a single stem, which branches as the plants mature. Asclepiadoideae contains close to 3000 species within 415 genera. Its members range in form from lianas to trees. They are mostly tropical or warm temperate, with distribution largely in Africa and South America. Modern plant systematics puts hoodia into the subfamily (often referred to as family) Asclepiadaceae.[8] Hoodia belongs to the tribe Stapeliae within Asclepiadeaceae. The various species of Stapeliae have the general appearance of a cactus, being leafless and succulent. Spines on the stem of the plant (spiny tubercles) provide further resemblance to cacti (Figure **1**). Although hoodia species resemble cacti (Cactaceae), they are not closely related, but rather owe their similar morphology to convergent evolution.

Figure 1. A young *Hoodia gordonii* growing in its natural environment. Flies have been attracted to the plant by the carrion-like smell of the flowers, and may help pollinate it.

**Image copyright Martin Heigan, 2006. Used with permission.*

MODERN DISCOVERY OF ACTIVITY

In the early 1960s The Center for Scientific and Industrial Research (CSIR) of South Africa began investigations into the nutritional properties and possible long term toxicity of plants traditionally used as indigenous subsistence "bush foods". In these studies it was found that extracts of *Hoodia* species, particularly *H. gordonii* and *H. pilifera* possessed appetite suppressant effects.[9] Fractionation of the extracts coupled with bioassay of the fractions provided unique pregnane glycosides (Figure II). It was found that rats administered these compounds showed a reduction in food intake and a decrease in body mass. This research resulted in the award of a patent for appetite suppression in 1998.[10] Further patents for antidiabetic action and prevention of gastric damage caused by aspirin have also been granted.[11,12] The appetite suppression patent was assigned to Phytopharm, LLC. Phytopharm licensed the rights to commercially exploit hoodia to the pharmaceutical company Pfizer in 1998.

Some criticism has been lobbied at CSIR by the Working Group of Indigenous Minorities in Southern Africa (WIMSA) for misappropriation of intellectual property rights of the native San people (i.e. "biopiracy"). WIMSA was established in 1996 at the request of the San people in South Africa, Botswana, Namibia, Zambia, and Zimbabwe to provide a platform for their communities to express their concerns and advocate for their rights.[13] It has been reported that CSIR was originally informed of the appetite suppressant activity by members of the San, and thus commercialization of hoodia warrented just compensation for those peoples.[14]

WIMSA was influential in effecting a "benefit sharing" agreement between the CSIR and the San representatives in 2003. This agreement is widely acknowledged to be one of the most important examples of an indigenous people obtaining financial benefits through a benefit sharing agreement.[15] Benefit sharing is a term popularized by the Convention on Biological Diversity (CBD) adopted at the 1992 Earth Summit in Rio de Janeiro, Brazil.[16] Signatories of the CBD require users of plant and animal resources to share the benefits with those who provide knowledge of and access to genetic resources. As a result of this agreement, a San Hoodia Trust was founded and charged with acting on behalf of WIMSA to ensure the proper distribution of financial benefits derived from Hoodia.

In contrast to Phytopharm's patent for appetite suppression from hoodia extract, use of the plant itself is not protected. For this reason there have been a profusion of commercial products claiming to contain hoodia, although this claim is often suspect. Lack of standardization of active constituents, lack of control of purity, and lack of control over manufacturing conditions are some of the obstacles to rational comparision of the commercial products.

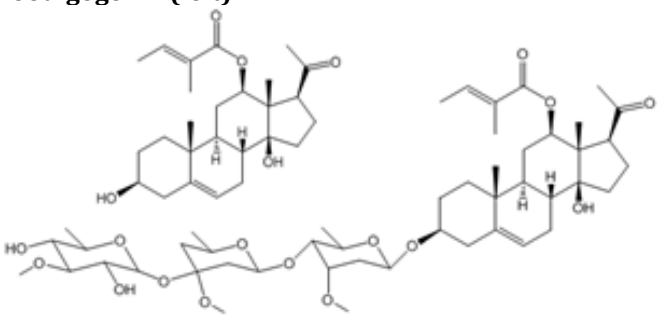
Pfizer returned development rights to Phytopharm in 2003 without commercializing hoodia, and stopped efforts to further develop it as a pharmaceutical. A spokesperson for Pfizer stated that development was halted due to difficulty of synthesizing hoodia. Given the potential multi-billion dollar market for an effective diet aid, it seems surprising that synthetic difficulty alone might be a primary reason to abandon hoodia. However, Jasjit S. Bindra, a lead researcher on hoodia at Pfizer, acknowledged that early clinical trials showed that hoodia could be a potent appetite suppressant, but there were indications of effects on the liver that could not be easily removed from the supplement. He concluded that "Clearly, hoodia has a long way to go before it can earn approval from the Food and Drug Administration. Until safer formulations are developed, dieters should be wary of using it".[17] In 2005, Phytopharm granted an exclusive license for the use of hoodia extract to Unilever plc, the global consumer products company and owner of a number of the world's leading brands.[18] Unilever paid $12.5 million for this right.

Although hoodia and its constituents have been apparently extensively studied by pharmaceutical and consumer product companies, only limited information about efficacy of appetite suppression is available in the open literature. There have been no peer-reviewed controlled trials of its efficacy. Uilever abandoned plans to use hoodia in a range of diet products in 2008, after investing €20 million in R&D. According to Unilever, these plans were abandoned because " our clinical studies revealed that products using hoodia would not meet our strict standards of safety and efficacy".[19]

BIOLOGICALLY ACTIVE CONSTITUENTS

H. gordonii extract has been found to contain a variety of steroid glycosides, fatty acids, plant sterols, and alcohols. The steroid glycosides are the constituents most likely responsible for appetite suppression (Figure **2**). Specifically, the 14β-hydroxy pregnane glycoside known as H.g.-12 or P57 ((3β,12β,14β)-3-[(O-6-Deoxy -3-O-methyl -β-D-gluco-pyranosyl-(1→4) -O-2,6-dideoxy -3-O-methyl -β-D-ribo-hexopyranosyl-(1→4) -2,6-dideoxy -3-O-methyl -β-D-ribo-hexopyranosyl)oxy] -14-hydroxy -12-[[(2E) -2-methyl-1-oxo-2-butenyl]]oxy]pregn-5-en-20-one) is thought to be the main active constituent. Hoodigogenin A ((12-O-β-tigloyl-3β, 14β-dihydroxy-pregn-5-ene-20-one)) the aglycone of P57[20] is common to various glycosides found in hoodia. Hoodigogenin A is an unusual pregnane derivative, containing the previously unknown structural elements of *cis*-fusion of rings C and D of the steroid skeleton and a tiglic acid functionality at C12[21]. There are at least 20 compounds present in *H. gordonii* that are analogs or epimers of hoodigogenin A. Additional glycosides have been found that are based on a second backbone, caligogenin[22]. The contribution of these compounds to biological activity, if any, is currently unknown.

Figure 2: The putative main active constituent of *Hoodia gordonii*,P57 (right) and its aglycone, Hoodigogenin (left)



One reason for the lack of information on the biological activity of hoodia glycosides is their lack of availability, since *H. gordonii* is a protected species and the yield of extraction is only between 0.003% and 0.02%. As an effort to increase availability of the compounds, the aglycone of the natural 14β-hydroxy pregnane glycosides (hoodigogenin A, Figure II) was recently synthesized in 3% overall yield from commercially obtainable starting materials.[23]

MECHANISM OF APPETITE SUPPRESSION

The mechanism by which hoodia may produce appetite suppression is not currently understood, although there have been a number of studies directed at elucidating it. The original patent for the appetite suppressant effects postulates agonist activity at melanocortin-4 receptors (MCR-4), neuropeptide-Y receptors, or via cholecystokinin (CCK). The melanocortin system has been increasingly studied for its role in obesity[24], but its relationship to any constituent of hoodia remains to be convincingly demonstrated. The structural resemblance of P57 to the cardiac glycosides has also suggested to some workers that it may act through modulation of Na^+/K^+ ATPase activity.[25] However, initial competitive binding studies on membranes of the kidney, gut, and brain failed to demonstrate inhibition of oubain binding or find Na^+/K^+ ATPase activity. It has recently been found that one of the steroid glycosides (P57) purified from *H. gordonii* caused CCK secretion *ex vivo* in rat intestine and *in vitro* in a human enteroendocrine cell line.[26] CCK has previously been found to produce appetite suppression via a central nervous system mechanism involving the vagus nerve. It was demonstrated that P57 activates the human bitter taste receptors TAS2R7 and TAS2R14, and that a nonspecific bitter receptor antagonist abolished H.g.-12 mediated CCK release. This information taken together may indicate that CCK is important in the mechanism of producing satiety. Other evidence that hoodia produces its action through a central mechanism has been provided by a study of the intracerebroventricular administration of P57 to rats.[25] In this study moderate food deprivation of the animals led to a reduction of hypothalmic ATP, which could be reversed by P57. P57 was found to increase the concentration of ATP in the hypothalamus by 50-150% in rats. These observations led the investigators to hypothesize that a key mechanism of hypothalmic regulation of food intake is altered intracellular concentrations of ATP. The authors point out that this does not preclude a partially peripheral action for P57 as well. This study found that food intake was decreased by 50-60% in a dose-dependent manner, and that this effect lasted for 24-48 hours.

Some encouragement for the hypothesis that ATP regulation is associated with the appetite suppressant action of hoodia is provided by studies with another herbal medicine, the ayurvedic herb *Coleus forskohlii*. This plant has also been shown to activate the production of ATP, and has been found in limited clinical trials to have a beneficial effect on weight in overweight individuals.[27,28]

EVIDENCE OF EFFICACY

No evidence has been published in peer-reviewed journals that hoodia is an effective appetite suppressant in humans.[29] In 2001, Phytopharm announced the completion of an initial study involving 60 healthy overweight subjects, but it has not published details.[30] This was a double-blind, placebo-controlled study. It was divided into 3 stages. Initially safety, tolerability, and pharmacokinetics were evaluated in 30 men for increasing single doses and repeat dosing. In the final stage of the study, caloric intake for 19 overweight men was evaluated over 15 days in both twice-daily dosing and placebo control groups. Men in the treatment group were reported to have achieved a significant reduction of body fat by 1 kg, as well as a 30% reduction in caloric intake. The very limited duration of the study, the limited number of participants, and the fact that the data has not been published in an open forum make a true evaluation of this study impossible.

Several animal studies have provided evidence that supports activity of hoodia as a diet aid. When P57 was administered to rats by oral gavage at 6.25-50 mg/kg all doses resulted in a decrease in food consumption over an eight day period.[9] A decrease in body mass was also observed. Compared to the appetite suppressant fenfluramine (15mg/kg), there was an overall decrease in body weight. This study was relatively small, but has generated great interest in the pharmacological action of hoodia.

Interesting results were obtained in another study that examined the effect of *H. gordonii* supplementation on broiler chickens.[31] Supplementation of feed with 300mg hoodia meal per day reduced the weight of fat pads by 40%, while having no effect on food intake, growth rate, feed conversion ratio, or live weight. This result contrasts to the studies that demonstrate an apparent increase in

satiety, but still shows a beneficial effect on reduction of fatty tissue. Further unpublished studies are claimed to show that food intake inhibition and weight loss are independent of the nutrient content of diet and also occur in animals that overfeed on a highly palatable diet.[25]

SAFETY PROFILE OF HOODIA

As with the mechanism and efficacy of hoodia, only limited data is available on potential toxicity of the plant or its constituents. Extract of *H. gordonii* was recently studied for evidence of genotoxicity, as part of an overall safety assessment for its use in consumer products.[32] In three separate assays (a bacterial mutation test, an *in-vitro* gene mutation assay in mouse lymphoma cells, and an *in-vivo* bone marrow micronucleus assay in mice) no evidence for genotoxicity was found. *In-vitro* cytotoxicity was also not observed for P57 or 10 other glycosides isolated from *H. gordonii.* This study involved a variety of mammalian cell lines (SK-MEL, KB, BT-549, SKOV-3, VERO, and LLC-PK1) and did not show inhibition of growth up to a highest concentration of 25 μg/ml.[20] 30 day toxicological studies in rats also failed to find evidence of significant toxicity.[25]

A study of the metabolic stability of P57 and its interaction with drug metabolizing enzymes found that it weakly inhibited cytochrome P450 3A4 in human liver microsomes with an IC_{50} of 45 μM. The activity of CYP1A2, 2C9, and 2D6 was not affected.[33] A second characterization of the *in-vitro* pharmacokinetic properties of P57 found that it strongly inhibited CYP3A4 activity.[34] Since a large proportion of clinically used drugs and a number of xenobiotics are metabolized by CYP3A4, there may be a significant possibility of drug-herbal or herbal-herbal interactions when products containing hoodia are coadministered with other drugs/herbal medicines. Additional pharmacokinetic evaluation of P57 examined its transport across excised porcine intestinal and buccal tissue, and compared it to that of the plant extract.[35] In this study, it was found that P57 transport across intestinal mucosa was very low, but was significantly higher in a secretory versus absorptive direction. This is in agreement with the results of another study using Caco-2 cell monolayers.[34]

Evidence of active transport of P57 by P-glycoprotein (P-gp) and multidrug resistance-associated (MRP1/MRP2) proteins was also provided by the decrease in transport after treatment with P-gp and MDR inhibitors. A further interesting result of the former study was the observation that absorptive transport across intestinal tissue of P57 from the crude plant extract was slightly higher than transport of the pure compound. This may indicate that other components of the plant extract are inhibiting efflux, and have implications for differences in the pharmacology of the crude extract compared to the isolated active constituent P57. Bioavailability of P57 may be strongly affected by conditions in the stomach and intestine. Support for efficacy of buccal versus oral administration was also provided by this study. In another study it was found that oral administration of a methanolic extract equivalent to 25 mg/kg of P57 to female CD1 mice resulted in a moderate 47.5% bioavailability and a peak plasma level at 0.6 hours.[36] Intravenous administration of P57 gave a plasma clearance rate of P 1.09 L/h/kg. Distribution was rapid, with rapid elimination within 4 hours. The highest levels were found in the kidney, followed by liver and brain. P57 was not detected in the brain after oral administration.

CONSERVATION STATUS OF HOODIA SPECIES

Hoodia cultivation thus far has not been easy, although there have been some notable attempts.[5] The limited number of plants in the wild cannot sustain a large commercial market and any future commercialization will depend on the availability of cultivated plants or synthetic derivatives. Populations of various hoodia species may be at risk for a number of reasons. They have relatively limited distribution, are slow-growing, and are increasingly sought for the herbal drug market. Hoodia is listed in Appendix II to the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES). Appendix I of CITES list species that are the most endangered. Appendix II lists species that are not now threatened with extinction, but may become so unless trade is closely controlled. CITES controls trade of "All parts and derivatives except those bearing a label 'Produced from *Hoodia* spp. material obtained through controlled harvesting and production in collaboration with the CITES Management Authorities of Botswana/ Namibia /South Africa under agreement no. BW/NA/ZA xxxxxx".[37]

Hoodia juttae is a hoodia species that is listed by the International Union for Conservation of Nature (IUCN) in the Red list of Threatened Species.[38] It is noted to be known from 9-18 subpopulations with extent of occurrence < 10,000 km^2 and area of occupancy suspected to be < 5,625 km^2. When IUCN evaluated *H. juttae* in 2004, it was placed under the category of "Least Concern", meaning that the population is assumed to be stable at present. However, it was further noted that this status may rapidly change if people begin collecting this species for its appetite suppressant qualities. Two other Namibian species of Hoodia (*H. ruschii* and *H. triebneri*) were given the same status, with similar cautions about population stability.

OTHER SPECIES OF HOODIA WITH POTENTIAL ACTIVITY

At least 10 species of Hoodia are recognized in Namibia, and are distinguished primarily by their flowers. *Hoodia currorii* (Namib Hoodia or "Ghaap") is a species that flowers only after rain. Namib hoodia is bitter but edible. One of its names is ghaap, which means veld food, and it has been used as a traditional medicine for its appetite suppressant properties as well as to relieve high blood pressure.

Different varieties of *Hoodia* are eaten fresh as raw foods by natives within their growth range. They may form a "convenient emergency food and moisture source in harsh arid environments".[39] After removing the spines with a stone, the stems may be eaten like a cucumber. The taste is said to be bitter and the texture mucilaginous. *H. flava* (yellow-flowered ghaap) is used in a similar manner for both food and appetite suppressant activity. *H. officinallis* has been used to treat tuberculosis and was once imported into the United States as a treatment for hemorrhoids. *H. pilifera* was the original species whose extract was determined to have appetite suppressant effects on rats. It has been reported to be preferred by natives, who disparage *H. gordonii* as fit only for livestock.

ANALYTICAL METHODS FOR IDENTIFICATION AND QUANTIFICATION OF CONSTITUENTS

Due to the rapid increase in the amount of hoodia being sold as commercial weight-loss preparations, there has

been much speculation as to the purity of the formulation, the identity of species, and the concentration of putatively active constituents. According to a United States Food and Drug Administration spokesman, a large percentage of products sold as herbal dietary supplements either contain dangerous undeclared ingredients or may be entirely fraudulent. Consumers have little trust in the claims made by weight loss products in general[5]. This suspicion may be well founded, since in a preliminary evaluation by Unilever of ten products claimed to be hoodia, only 4 contained significant amounts of it, while 4 contained only small amounts, and 2 contained none at all. In an analytical study of 35 commercially available hoodia dietary supplements, only 9 were found to contain P57[6]. Of these 9 products, concentrations of 0.016 mg/average weight of dosage form, 1.201 mg/average weight dosage form, and 54 μg/ml were found for 3 of the formulations. Five of the formulations were found to contain P57 below the limits of quantification. A number of analytical methods have been developed for the analysis of the constituents of hoodia. Recently an HPLC-ESI-MS/MS method for the quantification of the Hoodia steroid glycosides in plasma was reported. The method was validated to a limit of quantification of 0.04 ng/ml in porcine plasma collected in a pharmacokinetics study.[40] Other quantitative analytical methods have been developed for plant material , formulations, and extracts using HPLC-UV and HPLC-MS.[41-43] NMR, HPTLC, and UPLC-UV-MS techniques have also been developed for the fingerprinting and differentiation of *H. gordonii*, *H. currorii, H. parviflora,* and *H. rushii* species.[6,44,45] Identification and structural characterization of steroidal glycosides in hoodia has been accomplished by electrospray ion-trap tandem mass spectrometry (ESI-MS/MS) and high performance liquid chromatography coupled with electrospray ionization time-of-flight mass spectrometry (LC/ESI-TOFMS).[46]

CONCLUSION

Although the lack of toxicity observed for hoodia is encouraging, the lack of direct evidence for efficacy means that the preparations cannot be recommended. The observation that 2 multinational corporations have spent more than $30 million USD on development gives some support for the conjecture of utility in treatment of obesity by hoodia. However, the fact that both corporations have abandoned development indicates serious difficulties to develop medications based on the plant. Additionally, evidence of inhibition of CYP3A4 means that there may be potential problems for drug-drug or herb interactions. Finally, the observation of differences in the pharmacokinetic profiles between the plant extract and the pure isolates shows that care must be taken in comparison of studies that have used either one or the other.

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