

Review

***Hoodia gordonii* in the treatment of obesity: A review**

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According to data from the World Health Organization (WHO), one billion adults that are approximately overweight currently exist in the world, of which three hundred million are obese. These numbers led to the finding that obesity appears as a major global epidemic, affecting countries in all stages of development. In Brazil, about 13% of the population is now considered obese and estimates suggest that by the year 2025, the country will be fifth in the world in obesity ranking. Although some herbal medicines are recommended in the treatment, numerous natural products are used indiscriminately to prevent, reduce or delay weight gain; there are no studies of its therapeutic efficacy and safety. Among these stands out the *Hoodia gordonii* commercial powder, a native plant of Africa, with purported appetite inhibitory action attributed to the active glycoside P57, which was sold freely until its ban by the Brazilian National Sanitary Surveillance Agency (ANVISA) in February 2007 because of the absence of scientific proofs of its efficacy and safety. In addition, information on its mechanism of action in inhibiting appetite and thirst are scarce, and its possible relation with leptin and insulin involved in the neuroendocrine regulation of appetite and satiety.

Key words: *Hoodia gordonii*, obesity, herbal medicine, treatment.

INTRODUCTION

According to data from the World Health Organization (WHO, 2010), one billion adults that are approximately overweight currently exist in the world, of which three hundred million are obese. These numbers led to the finding that obesity appears as a major global epidemic, affecting countries in all stages of development. In Brazil, about 13% of the population is now considered obese and estimates suggest that by the year 2025, the country will be fifth in the world in obesity ranking (Brasil, 2009; Ogden et al., 2006).

Considering that obesity is a multifactorial disorder, that is, several factors are involved in their occurrence including cultural, genetic, psychological, metabolic, endocrine and environmental factors. Treatment and therapeutic approach should also be performed by a multidisciplinary staff.

Although some herbal medicines are usually recommended for the treatment, numerous natural products are used indiscriminately to prevent, reduce or delay weight gain; there are no studies of its therapeutic

efficacy and safety. Among these stands out the *Hoodia gordonii* (*Apocinaceae*, sub-family *Asclepiadaceae*) powder, a plant native to Africa, with purported appetite inhibitory action attributed to the active glycoside P57, which was sold freely until its ban by the National Sanitary Surveillance Agency (ANVISA) in 2007 because of the absence of scientific proofs of its efficacy and safety (Anvisa, 2007). In recent years, there has been a growing interest in the plant reflected in the rising of numerous commercial products based on *H. gordonii* in different presentations. However, the binomial supply or demand has created an unbalanced situation due to its limited availability in relation to the large consumption of the plant, causing the worrying possibility of tampering, especially the cactus *Opuntia ficus*, popularly known as cactus.

So far, there are no scientific studies related to the chemical constituents (nutrients and anti-nutrients) present in the *H. gordonii* commercial powder, as well as its efficacy and toxicity. Further investigations are needed on its mechanism of action in inhibiting appetite and thirst, and their possible relationship with the hormones insulin and leptin involved in regulating appetite and satiety.

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LITERATURE REVIEW

Obesity

Concept

Obesity is characterized by excessive accumulation of body fat. For diagnosis in adults, the most commonly used parameter is the body mass index (BMI). BMI is calculated by dividing body weight by their squared height. It is the standard used by the World Health Organization (WHO) (WHO, 2010), which identifies normal weight when the result of calculating the BMI is between 18.5 and 24.9. To be considered obese, the BMI should be above 30 (Abeso, 2010; Sbem, 2010; WHO, 2010).

Thus, overweight and obesity in the population are currently defined as "a weight that is above what is considered healthy for a specific height" (CDC, 2010), using the various anthropometric parameters available for evaluation.

Etiology

There are many causes of obesity. The excess weight may be linked to the genetic heritage of the person, bad eating habits or, for instance, the endocrine disorders (Sbem, 2010). Considering that the genetic heritage of human kind cannot have undergone major changes during interval of a few decades, certainly environmental factors must explain this epidemic. When evaluating a clinically obese patient, however, one should consider that several predisposing genetic factors may be playing a significant role in determining energy imbalance of overweight (Coutinho, 2007).

Moreover, it is known today from the investigation of physiology and the neuroendocrine regulation of appetite and satiety that the obesity epidemic is a result of the combination of racial factors, genetic and cultural environment by creating the so-called obesogenic environment (Apovian, 2010).

Prevalence and progression

Obesity has reached epidemic proportions globally, with more than one billion adults that are overweight, of which 300 million are clinically obese. Obesity rates have tripled compared with 1980 data, collected in the countries of North America, UK, Eastern Europe, Middle East, Pacific Islands, Australia and China. However, the increase in those rates is faster in developing countries than in the developed countries (Opas/OMS, 2003).

In the last research conducted in the U.S., the National Health and Nutrition Examination Survey (NHANES) showed that rates of obesity among adults are 32.2% in men and 35.5% in women (Flegal et al.,

2010). Studies present the United States as the country of the highest rates of obesity among the population

(Fabricatore et al., 2008; Houston et al., 2008; Ogden et al., 2006), however, recent data suggest that other countries have already exceeded U.S. rates, like China among children, and Australia and the UK among women (Popkin, 2010).

Brazil has about 18 million people considered obese. Adding the total number of overweight individuals, the amount increases to 70 million, which is double compared to three decades ago (Sbem, 2010).

Recent data show currently that in Brazil; approximately 13% of adults are obese, with the highest rates among women (13.6%) than men (12.4%). These data show great concern since the first assessment in 2006 show growth rates for each year (Brasil, 2009).

Problems associated

Obesity and overweight produce adverse metabolic effects on blood pressure, cholesterol levels and blood triglycerides and insulin resistance. Health problems are not fatal, but extremely debilitating. WHO report in 2002 estimated that all over the world, 2.5 million people die each year due to overweight (Opas/OMS, 2003).

Obesity is linked to some of the most prevalent diseases in modern society, with greater risk associated with development of diabetes mellitus. Furthermore, the mortality risk increases even more for obese people who are smokers (Francischi et al., 2000). Other medical conditions such as biliary diseases, osteoarthritis, heart disease and some cancers also have relationship with obesity (Bray, 2004; Thande et al., 2008).

Economic impacts

Obesity accounts for 2 to 7% of the total cost of health care in developing countries. The true costs of this epidemic are undoubtedly much higher, since not all disease associated with obesity is included in these statistics (Opas/OMS, 2003).

Data show that in the United States in 1998, medical expenses related to obesity including hospital patients or outpatients and prescriptions, were approximately 78.5 billion dollars, estimating \$147 billion in 2008 (Finkelstein et al., 2009).

Brazil occupies the sixth place in the global ranking of countries with problems of obesity. The direct costs associated with this disease, including hospitalizations, medical consultations and prescriptions reach 1.1 billion dollars per year, equivalent to 12% of the total annual expenses of Unified Health Services (SUS) with hospitalizations (Gigante et al., 2009).

Treatments to reduce obesity

The treatments involve a balanced diet, physical exercise

often, drug therapy and behavioral change related to the eating habits (Francischi et al., 2000). Suggestions for reversal of the obesity epidemic include public health campaigns, medical programs and community supported by changes in food industry, aiming changes in eating patterns and lifestyle. Community programs structured physical activity, inside and outside of work can also assist in a healthier lifestyle (Apovian, 2010).

Therapeutic options for these patients include various agents promoting weight loss. The main study drugs are sibutramine (serotonin reuptake inhibitor) and orlistat (lipase inhibitor), catecholaminergic agents (or amfepramone diethylpropion, fenproporex, mazindol and ephedrine-caffeine combination), serotonergic drugs (fenfluramine, fluoxetine) and other drugs with some action in weight loss (metformin, topiramate and bupropion) (Halpern and Mancini, 2005).

Besides these, it is assumed that self-medication with "natural products" slimming has increased considerably in recent years because the population in general believes that these drugs will not bring harm to health. The herbal drugs used for reference are: artichoke (*Cynara scolymus*), aloin (*Aloe vera*), boldo (*Peumus boldus*), coot (*Baccharis sp*), cascara sagrada (*Rhamnus purshiana*), *Centella asiatica*, citrin extract (*Garcinia sp*), chlorella (*Chorella pyrenoidosa*), Maytenus (*Maytenus ilicifolia*), spirulina (*Spirulina maxima*), *Fucus sp. guarana (Paullinia cupana)*, false ginseng (*Pfafia paniculata*), glucomannan (*Amorphophallus konjac*) jurubeba (*Solanum paniculatum*), passionflower (*Passiflora alata*) and senna (*Cassia angustifolia*) (Azeredo et al., 2005). In addition, other products such as *Hoodia gordonii* have been consumed for the same purpose, without however, being scientific proof of its efficacy and safety.

Finally, the current perception of fat cell as an endocrine organ, in addition to contributions from the intestine and pancreas, helps us understand the origins of the neuroendocrine regulation of appetite and satiety by substances such as leptin, insulin and ghrelin, representing a field of possibilities in the treatment of obesity (Apovian, 2010; Bays, 2004).

Hormones involved in neuroendocrine regulation of appetite and satiety

Leptin

Leptin (Greek mites = thin) is a protein composed of 167 amino acids with a structure similar to cytokines and is mainly produced in the adipose tissue which is responsible for the control of food intake, acting in cells of the hypothalamus in the central nervous system (Reseland et al., 2001). The action of leptin in the hypothalamus in mammals, promotes reducing food intake and increase energy expenditure, in addition to regulating neuroendocrine function and energy metabolism (Auwerx and Staels, 1998; Friedman and Halaas, 1998).

Leptin reduces appetite from the inhibition of appetite-related neuropeptides such as neuropeptide Y (NPY),

and also stimulates the expression of anorexigenic neuropeptides: hormone α -melanocyte-stimulating (α -MSH), corticotropin-releasing hormone (CRH) and substances synthesized in response to amphetamine and cocaine (CART) (Elmqvist et al., 1998; Friedman and Halaas, 1998). Thus, high levels of leptin reduces food intake while low levels induces hyperphagia (Romero and Zanesco, 2006).

However, leptin blood levels increased much (hyperleptinemia), found mainly in obese people, may indicate a condition of leptin resistance state similar to insulin resistance that occurs in diabetes mellitus. In this condition, the high leptin levels are associated with hyperphagia and obesity (Considini et al., 1996).

Studies with rats have shown that leptin activates a potassium channel ATP-sensitive, indicating that this channel may function as molecular target of the hormone in hypothalamic neurons (Spanswick et al., 1997).

Insulin

Insulin is a protein composed of two chains (A and B) with 21 amino acids in each, linked by two disulfide bonds. The amino acid composition is variable for different animals, but in each chain 10 residues are common, and few essential for biological activity. The insulin molecule exists as a monomer only at low concentrations (<0.1 mM or ~ 0.6 mg/mL). Under physiological conditions, insulin is normally maintained at concentrations below 10 to 3 mM, to ensure their circulation, and exerts its biological activity as a monomeric molecule. For concentrations above 0.1 mM, it occurs in insulin dimerization (Chien, 1996).

It is the most anabolic hormone known and essential to the maintenance of glucose homeostasis, growth and differentiation. Insulin regulates glucose homeostasis at several levels, reducing its production by the liver (via decreased gluconeogenesis and glycogenolysis) and increasing capture peripheral, mainly in muscle and adipose tissue. Insulin also stimulates lipogenesis in the liver, adipocytes and reduces lipolysis, and increases the synthesis and inhibits protein degradation (Carvalho et al., 2002).

Insulin produced by beta cells and its serum concentration is also proportional to adiposidade (Halpern et al., 2004). With its anabolic effect, insulin increases glucose uptake, and the fall of blood glucose is a stimulus for increased appetite (Woods et al., 1998). The recent discovery receptors for insulin in the brain demonstrated its essential function in the central nervous system to stimulate satiety and energy expenditure, in addition to regulating action of leptin (Hallschmid and Schultes, 2009; Schwartz, 2000).

Ghrelin

Ghrelin (English grow = growth) is a gastrointestinal

hormone identified in the stomach of rats, which has as one of its main functions the increased secretion of growth hormone (GH) (Kojima et al., 1999; Kojima et al., 2001). It is a peptide composed of 28 amino acids, produced primarily by cells of the gastrointestinal tract (Bednarek et al., 2000; Kojima et al., 1999).

Ghrelin is directly involved in regulating short term energy balance and is one of the most important factors to the top of food intake. Its concentration remains high during periods of fasting and periods prior to meals, falling immediately after feeding, which suggests a neural control. Besides increasing the appetite, it also stimulates the digestive secretions and gastric motility (Konturek et al., 2004; Nakazato et al., 2001).

Animal studies indicate that leptin signaling plays an important role in the hypothalamic centers that regulate food intake and adiposity, suggesting its participation in stimulus to start a meal (Nakazato et al., 2001; Romero and Zanesco, 2006).

The plasma concentration of ghrelin decreases after meals rich in carbohydrates, while the elevation of insulin, however, increased levels are found after meals rich in animal protein and lipids, accompanied by mild insulin increase (Erdmann et al., 2004; Salbe et al., 2004).

Hoodia gordonii (Apocinaceae)

Taxonomic information

Hoodia is a plant of the order of Gentianales, family of Apocinaceae, sub-family of Asclepiadaceae. This family consists mainly of medicinal plants (herbs) and shrubs with white sap, comprising about 250 genera and 2000 species, some of which possess succulent stems and thorns, similar to cacti with leaves pequenas (University of Hawaii, 2007; Van Heerden, 2008). The genus *Hoodia* has several species, especially *H. gordonii*, *H. pilifera*, *H. lugardii* and *H. ruschii* main research subjects (Archer and Victor, 2003; Chow et al., 2005; MacLean and Luo, 2004).

In common with other species of the genus, *Hoodia gordonii* is succulent and fleshy, with several erect and cylindrical rods varying in color from gray-green to gray-brown and flower-shaped crown with about 100 mm. The tubers are prominent, fused in their lower halves of stems 11 to 17 at obtuse angles, and each end of a very sharp thorn 6 to 12 mm (Bruyns, 2005). Due to their prickly appearance, the plant *H. gordonii* is often referred to as "cactus" or "cactus of the desert" by the press, although in reality, it cannot be characterized as a true cactus that belongs to the family *Cactaceae* (Van Heerden, 2008).

There are currently 13 species (*H. alstonii*, *H. currorii*, *H. Dreger*, *H. flava*, *H. gordonii*, *H. juttae*, *H. mossamedensis*, *H. officinalis*, *H. parviflora*, *H. pedicellata*, *H. pilifera*, *H. ruschii*, and *H. triebneri*) and *H. gordonii* which are of primary interest because of their

anorectic properties (Avula et al., 2007; Van Heerden et al., 2007).

Distribution

The *Hoodia* plant is native to Africa, being found in the deserts of Namibia and the Kalahari. The species *Hoodia gordonii* (Figure 1) is grown mainly in South Africa, Namibia, Botswana and Angola, by the San people, a tribe whose indigenous inhabitants are known as Bushmen. These Indians call the plant xhoba (WHO, 2003).

In South Africa, *Hoodia* species are protected, and permits are required by official bodies for the collection, cultivation, transportation or export of plants. They are related to plant slow-growing, and difficult to culture. Its limited number available cannot sustain a strong market, which in future will depend on plants grown for the marketing purposes (Van Heerden, 2008).

Currently, *H. gordonii* is listed as a species at risk of extinction and its export is tightly controlled by the South African government and by international agreements to protect plant species (Avula et al., 2008).

History

For thousands of years, the San people, one of the oldest inhabitants of southern Africa, took pieces of *H. gordonii* bitten during the hunt. For several days of hunting without food and water, they ingested the plant just to satisfy hunger, inhibit appetite and keep the provision (WHO, 2003). Apparently, the plant sap relieves the sensation of hunger during long trips in search of indigenous hunting (Bruyns, 2005).

This effect of suppression of appetite aroused scientific interest and in the 60s of the twentieth century, the Council for Scientific and Industrial Research (CSIR), located in South Africa, isolated and patented an appetite suppressing molecule present in *H. gordonii*, called P57. Later in 1997, the CSIR licensed the rights to the molecule P57 British Company Phytopharm. After initial tests, the drug seemed promising and part of Phytopharm sold the rights to Pfizer pharmaceutical industry for 21million dollars. The companies expected the drug to revolutionize the market for slimming products which moved about 9.5 billion dollars at the time. However, a protest international companies was accused of biopiracy and began a long legal battle between business and the CSIR on one side and San people on the other; the division of profits from the exploitation and marketing of *Hoodia* (WHO, 2003).

In 2002, Pfizer released the rights to the *Hoodia*, claiming that the development of the P57 had been suspended because of difficulty in their synthesis and evidence of side effects in mice, caused by other



Figure 1. *Hoodia gordonii* (Hübner. and Tränkle, 2004).

components of the extract could not be easily removed (Bindra, 2005). According to Jasjit Bindra, head of research for hoodia at Pfizer, "surely, Hoodia has a long way to go before it can receive the approval of the North American Food and Drug Administration (FDA). Until safer formulations are developed, people Interested in the diet should avoid its use. "

Finally in March 2003, after years of negotiation, an agreement was reached between the parties. Under terms of the agreement, the CSIR will pass to the San people, 8% of all payments received from licensing to Phytopharm, and 6% of all royalties that the CSIR receives on drug will be commercially available. It is hoped that in future, the transfer will be 10 to 12 million dollars per year (WHO, 2006).

Today the great interest in the inhibitory properties of *Hoodia* appetite, gives an intense demand for products based on the plant. It is estimated that only in the U.S. market are available for marketing products in over 100 different presentations (tablets, capsules, gels, juices, powders, teas, and others) which contain the plant in its composition (Avula et al., 2008). So the high demand in contrast to the scarce supply have created a scenario in which the adulteration of products for other species such as *O. ficus* and even other species of the genus *Hoodia* has become a real possibility (Avula et al., 2007; Avula et al., 2008; Rader et al., 2007; Van Heerden, 2008).

Chemical composition of the extracts of Hoodia

Various active components were isolated by researchers from CSIR and have been revealed in recent patents (Bronner, 2005; Gardiner et al., 2006; MacLean, 2006; Raskin et al., 2006; Rifkin, 2005; Van Heerden et al., 2004; Verdegem et al., 2008). However, the supposed active component present in extracts from *H. gordonii* is a steroidal glycoside trirabinosídeo, 14-OH, 12-tigloilpregnane (MW = 1008), known as P57 (Figure 2), responsible for appetite suppressing (MacLean and Luo, 2004).

The putative active component in extracts of *H. gordonii* is a trirhabinoside, 14-OH, 12-tigloyl pregnane steroidal glycoside (MW = 1008). The core steroid, particularly regarding the 14-OH substitution, is somewhat similar to other cardenolides (MacLean and Luo, 2004). The 14-glucoside is not unique to *H. gordonii*, which is also found in other species of the genus as *H. curreri*, *H. macranth*, *H. parviflora*, and *H. pilifera ruschii* (Avula et al., 2007; Avula et al., 2008; Van Heerden et al., 2007).

Recently, ten new derivatives C (21)-steroid, called gordonisides were isolated from chloroform extracts obtained from aerial *H. gordonii*. The new compounds were based on 3-beta, 14-beta-hydroxy-pregn-5-en-17-22 betaona (Dall'acqua and Innocenti, 2007).

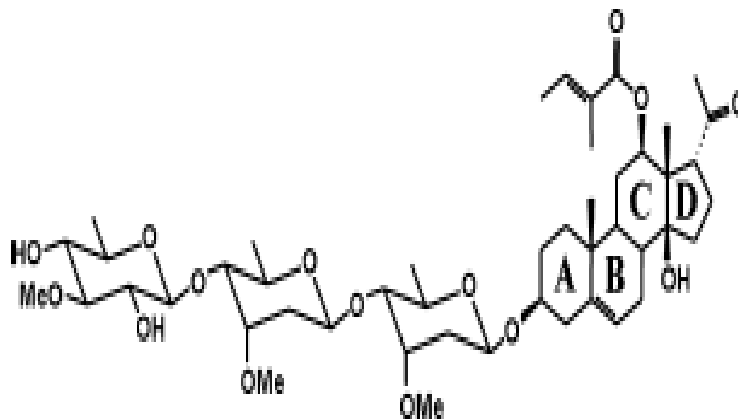


Figure 2. Structure of glycoside P57. Steroidal glycoside trirabinoside, 14-OH, 12-tigloilpregnane (Janssen et al., 2008).

Also, shoot were isolated on eleven new oxipregnanos, glucosides with the basic structure 12-O-beta-called tigloil isoramano hoodigosides. Their structures were determined by chemical evidence and magnetic resonance nuclear (Pawar et al., 2007).

Information regarding the chemical composition (proteins, carbohydrates, lipids, vitamins, fiber, polyphenols, nitrate, oxalic acid, lectins, saponins and digestive enzyme inhibitors) which may be present in *H. gordonii*, are scarce and sometimes non-existent.

Pharmacological effects of extracts of *Hoodia gordonii*

Long-term biological assays not published by companies Phytopharm and Pfizer, with extracts of the dried sap of the plant, which contained not only P57 but also multiple components, were conducted with obese diabetic Zucker rats. The results showed anorexic activity and reversal of diabetes, maintained during the administration of doses. Other tests reveals that the inhibition of feeding and weight loss are independent of the nutrient content of the diet and also occur in overfed animals with a highly palatable diet (MacLean and Luo, 2004). In addition, Phytopharm announced short-term studies in humans, during which the extract of *H. gordonii* was well tolerated (MacLean and Luo, 2004).

Trichoplusia ni larvae fed a diet containing latex of *H. gordonii* (1,000 ppm) showed no inhibition of growth and reproduction remained unchanged as compared to larvae treated with control diet (Chow et al., 2005).

Intracerebroventricular injections of steroidal glycoside P57AS3 (P57), isolated and purified extracts of *H. gordonii* in rats showed that the compound has a likely mechanism of action in the central nervous system. The results showed that the compound increased the content of ATP in hypothalamic neurons by up to

150%, and within 24 h, reduction of food intake by 60% (MacLean and Luo, 2004).

Works using rats demonstrated that treatment with purified extracts of *H. gordonii* containing active glycosides in the diet or administered by gavage were effective in reducing weight (Tulp et al., 2001; Tulp et al., 2002; Van Heerden et al., 2007).

Studies with mammals including humans have shown that the compound P57 was able to reduce gastric acid secretion, allowing its use in formulations for treatment of disorders and diseases related to excessive gastric secretion (Hakkinen et al., 2004). Moreover, supplementation of the diet of broiler chickens with powdered *H. gordonii* at concentrations 000 to 500 mg/animal / day, showed no change in food consumption during 30 days of experiment (Mohlapo et al., 2009).

Accordingly, Holt (2006) formulations containing *H. gordonii* and other herbal medicines are able to control obesity and suppress appetite, and aid in the treatment of metabolic disorders associated with obesity. The San people for thousands of years consumed *H. gordonii* due to the supposed effects of inhibition of hunger and thirst (WHO, 2006).

Scientific research

Despite the great commercial interest by *H. gordonii*, as evidenced by the large consumption in the form of capsules, there are few reports about the plant. Some sought to elucidate the components ativos (Pawar et al., 2007; Shukla et al., 2009), while others devoted themselves to understanding the mechanism of appetite suppression (Dall'acqua and Innocenti, 2007; MacLean and Luo, 2004).

Currently, due to the high possibility of fraud and adulteration of products marketed as *H. gordonii*, most studies are aimed at developing analytical

methods, mainly using high performance liquid chromatography for identification of glycosides characteristic and confirm the authenticity of commercial samples (Avula et al., 2006; Avula et al., 2007; Avula et al., 2008; Janssen et al., 2008).

With regard to the side effects and chronic effects from ingesting *H. gordonii*, there are no reports in the literature. This fact led to the banning of advertising and handling in Brazil by the Brazilian Sanitary Surveillance Agency (ANVISA) in 2007 (Anvisa, 2007).

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