E

WIPO

WIPO/GRTKF/IC/5/13
ORIGINAL: Spanish
DATE: May 12, 2003

WORLD INTELLECTUAL PROPERTY ORGANIZATION
GENEVA

INTERGOVERNMENTAL COMMITTEE ON INTELLECTUAL PROPERTY AND GENETIC RESOURCES, TRADITIONAL KNOWLEDGE AND FOLKLORE

Fifth session
Geneva, July 7-15, 2003

PATENTS REFERRING TO *LEPIDIUM MEYENII* (MACA): RESPONSES OF PERU

Document submitted by the Delegation of Peru

1. On May 9, 2003, the Delegation of Peru submitted a document within the framework of the fifth session of the Intergovernmental Committee on Intellectual Property and Genetic Resources, Traditional Knowledge and Folklore.

2. The document entitled "Patents referring to *Lepidium Meyenii* (Maca): Responses of Peru" is reproduced in the form it which was received and is published in the Annex.

3. The Intergovernmental Committee is invited to take note of this document and its Annex.

[Annex follows]

ANNEX

I. INTRODUCTION

(i) Aim

1. The aim of this report is to describe the results of the technical and legal analysis carried out in relation to patents referring to *Lepidium meyenii* (or "maca"). Similarly, an attempt is made to draw attention to a series of elements and problems associated with this type of patents of particular importance for Peru.

(ii) Description of the problems

2. The patents referring to *Lepidium meyenii* or maca are one more example, among many which exist, of how the intellectual property system– by means of patents – is based, mainly in the United States, on the privatization of biological and genetic components and materials in isolation, as part of larger inventions. In this case, these are resources in relation to which Peru (as the country of origin) has a series of rights which are not taken into account or respected. This same case refers to knowledge which, although difficult to document, has been broadly used by old Peruvians for a long period of time. This is obvious owing to the fact that many food-related, nutritional and medicinal uses of maca, claimed in these patents, have traditionally been used by the indigenous peoples of Peru.

3. This situation is in no way particular to Peru. In the final analysis, various countries with a high concentration of biological diversity and industrial and commercial potential suffer exactly the same problem as regards the way in which the intellectual property system, and patents in particular, are used. In this connection, some of the conclusions and final recommendations of this report are possibly valid outside the specific situation in Peru relating to *Lepidium meyenii*.

(iii) INDECOPI initiative

4. At the beginning of 2002, a number of institutions such as the ANDES Association, PROBIOANDES, ETC GROUP, and certain public sector institutions, drew attention to the patents granted in the United States of America for inventions relating to maca. Faced with the possible rights infringed in Peru as the country of origin, the assignment of rights of its indigenous peoples as holders of their ancestors' knowledge over different uses of maca and the possible commercial effects which these patents might have on Peruvian producers and exporters of maca, the *National Institute for the Defense of Competition and Protection of Intellectual Property* (INDECOPI) took the initiative, in the middle of 2002, to convene a working group in order to analyze the patents granted and the applications pending, which refer to *Lepidium meyenii* and its consequences and, similarly, to assess alternatives for dealing with them.

(iv) Content of the report

5. The report is divided into ten sections or subjects which, in turn, have been subdivided owing to their degree of complexity and specificity. A first part deals with questions of context and the standard-setting policy framework within which the problem of patents relating to maca is presented. A second part describes *Lepidium meyenii* and provides an idea of its botanical, biological, commercial and other value.

II. BRIEF DESCRIPTION OF THE CONTEXT: PATENTS, BIOLOGICAL DIVERSITY AND "BIOPIRACY"

(i) A general overview

6. Access to and the use and appropriation of biological materials (and related indigenous knowledge) originating from developing countries with great biological wealth on the part of institutions from developed countries constitutes a permanent very old process, which has been widely documented.

7. The use of less obvious and sufficiently more mechanisms than force and the physical control of these materials is, by contrast, a much more recent phenomenon. Intellectual property and, in particular, patents (specifically in the field of biotechnology) form part of mechanisms through which the law legitimizes certain methods of property assignment.

8. In the past few years, this direct or indirect appropriation of biological materials and indigenous knowledge through the use of patents has become known as "biopiracy." Biopiracy is at the very basis of the dispute over whom and under what circumstances rights over inventions and products derived from biological materials may be invoked, based in many cases on the use of indigenous knowledge associated therewith. This has been accentuated much more since the entry into force of the *Convention on Biological Diversity* (CBD) in 1993, in a context in which certain basic principles have been established, providing access to these resources and knowledge, and legitimizing and regulating their use.

9. As one of its main tasks, the CBD seeks to balance the lack of equilibrium between those who are able to use biological resources and their components (the industrialized countries) for commercial and industrial purposes, and those who do not have such capacities but do have the raw material, i.e. these resources and their components (developing countries). For this purpose, the CBD establishes rules and principles on the conditions for this access and use, and as to how the benefits derived from such use should be shared in a fair and equitable manner.

(ii) Intellectual property rights; patents

10. The common aim of intellectual property rights is to provide compensation for the creative and intellectual efforts of human beings, both in artistic and scientific terms. This need to compensate creative efforts has been recognized as *a fundamental right* since the 1948 Universal Declaration of Human Rights.

11. Copyrights, patents, trade secrets, marks and breeder's rights are some of the basic instruments and tools of intellectual property. Each of them has been designed over time to protect the interests and property of authors, inventors, entrepreneurs and improvers.

12. Patents were devised in the fifteenth century in England as a means of rewarding the creative capacity of inventors. With the passing of time, a regulatory system for patents has been put in place with elements of national scope and others of international scope. It is universally recognized that an invention may be patented in any technological field, provided that it is novel, involves an inventive step and is industrially applicable. The owner of a patent is entitled to exclude third parties from using, marketing and generally exploiting a

particular invention, without his authorization. As a counterpart to this exclusive right and in order to promote continual scientific and technological progress, an inventor must describe his invention and disclose it so that the process of creation and human innovation continues therefrom.

13. Technology, which originally concentrated on the improvement of equipment, tools, devices and the processes for their generation, has begun to develop in fields in which work is done directly with biological material. Biotechnology and, in particular, genetic engineering are based on the possibilities for manipulating biological or living material and transforming it for commercial and industrial purposes. The system of patents has certainly been obliged to respond and adapt itself to this new situation.

14. Countries have advanced in different ways as regards whether they allow the legal protection of inventions derived from biotechnology. Whereas understandably developed countries, which have led this technological revolution, have demonstrated their much greater determination to authorize patents for these inventions, less developed countries have expressed a number of reservations. With the adoption of the World Trade Organization (WTO) Agreement on Trade-Related Aspects of Intellectual Property, certain minimum standards were established for the protection of the intellectual property rights enshrined therein. Although the scope of these standards continues to be discussed, as a general rule countries allow biotechnology inventions to be patented (some with more limitations than others).

(iii) Biological diversity and its importance

15. In simple terms, it is recognized that biological diversity constitutes the material basis for the survival of a life on earth and, in particular, for the maintenance of human life. As a source of medicines, food, clothing, seeds, pollenators, biological controllers and, *inter alia*, environmental services, biological diversity – at an ecosystemic level, of species and geneses – is essential for satisfying the basic needs of survival and comfort of human kind.

16. The importance of biodiversity can be measured from an economic perspective (the global market for genetic resources and products derived therefrom varies between US$ 500 and 800 billion, including in this calculation the biotechnology sector, the agriculture industry, cosmetic sector, horticulture etc.); from a political point of view (15 megadiverse countries hold 75 per cent of the planet's biodiversity); from a social and cultural perspective (millions of people and indigenous and local communities around the world literally depend on biodiversity for their daily and immediate survival); and an ecological or environmental perspective (the environmental services supplied by elements of biodiversity and certain ecosystems are similarly vital for the "health" of the environment).

(iv) "Biopiracy"

17. Biopiracy should be understood as a political rather than a legal concept. Biopiracy refers to situations involving direct or indirect appropriation of biological or genetic resources or traditional knowledge by third parties. This appropriation may occur by means of physical control, the use of intellectual property rights over products incorporating these items (obtained unlawfully) or, in some cases, through the invocation of rights directly over such items.

18. There is a wealth of literature on different forms and cases of biopiracy throughout the world. In Peru and the Andean region in general, plants such as quinua, ayahuasca, grade blood, maca itself and color cotton are some of the traditional examples used in cases in which, sometimes involving the specific legal system in force, a legal situation (whereby a third party is considered the lawful owner or holder of a right) is made lawful, where this is lessunjust and questionable from the point of view of the principles and spirit of the CBD. Obviously, assuming that traditional materials or knowledge infringing the legislation in force are used, this form of biopiracy clearly becomes unlawful.

19. As already stated, the CBD aims to balance the situation between rich countries with biological diversity and those which, based on their technological progress, may benefit from and use this diversity in the pharmaceutical, biotechnology, agriculture industry and other sectors. This is particularly important for the megadiverse countries insofar as they hold a large share of this diversity and it is calculated that the annual global market for genetic resources reaches US$ 500 – 800,000 million (ten Kate and Laird, 2000). In addition to the accuracy of the figures, the magnitude thereof shows that we are dealing with a market to which, with complete security, the megadiverse countries make a substantial contribution but from which, in most cases, they do not benefit.

III. POLITICAL AND REGULATORY ADVANCES IN PERU AND THE ANDEAN REGION, AND THE INTERNATIONAL CONTEXT AS REGARDS ACCESS, TRADITIONAL KNOWLEDGE AND INTELLECTUAL PROPERTY

20. The CBD emerges not only as the agreement of States to preserve biological diversity which is deteriorating rapidly at the global level. The great bargain of the CBD was to respond in a precise manner to the problem of biopiracy and to the unfair way in which certain parties benefit from biological and genetic resources, without taking into account the rights and interests of others. A transition was therefore achieved from the paradigm of freely accessible resources, characterized as “the common heritage of humanity,” to a situation where the sovereign rights of countries over such resources were recognized. The States agreed that in order to gain access to these resources, the benefits arising from such access and utilization should be shared in a fair and equitable way (Article 15 of the CBD).

21. The discussions on the subject of access to genetic resources continue to be among the most intense and complex within the sphere of the CBD. In order to assist countries in their related internal policy and regulatory development processes, in 2002 the *Bonn Guidelines on Access to Genetic Resources and Fair and Equitable Sharing of the Benefits Arising out of their Utilization* (Decision VI/24 of the Conference of the Parties (COP), 2002) were adopted and provide guidelines and a (non-binding) reference to the legal factors which could be taken into account in devising policies and access rules and regulations.

22. Peru quickly ratified the CBD (Legislative Resolution 26181, 1993) and, at the time of its entry into force in 1993, one of the main aspects for implementation of Article 15 at the national level was to establish rules and standards governing access to genetic resources, the fair and equitable sharing of benefits, and the protection of knowledge, innovations and practices of indigenous communities.

23. The same concern in the national sphere also had repercussions at the regional level between the countries of the *Andean Community of Nations* (CAN), and in July 1996 CAN Decision 391 providing a Common Regime on Access to Genetic Resources was approved. This regulation – which is law in each of the member countries of CAN: Venezuela, Colombia, Ecuador, Peru and Bolivia – specifically determines the joint rules as to how, by whom and under what conditions access is possible to the genetic resources in the region.

24. The *Regional Biodiversity Strategy for the Tropical Andean Countries* (CAN Decision 523, 2002) and the *National Biodiversity Strategy* (Supreme Decree 102-2001-PCM) constitute, in their turn, biodiversity policy and planning instruments in which the genetic resources component (and the traditional knowledge of indigenous peoples) forms an essential part of the action plans and activities to be carried out both in the regional context and the national sphere.

25. The rules and regulations which refer or could be seen to relate to genetic resources are certainly not limited to Decision 391 or to the regional sphere. At the domestic level, *Law 27300 on Sustainable Development of Medicinal Plants* (2000) and *Law 27821 on Promotion of Nutritional Supplements for Alternative Development* (2002) are two recent examples of legal systems which affect the method of and existing conditions for the use of biological diversity components, in this specific case medicinal plants or those with nutritional properties respectively.

26. As regards traditional knowledge, the subject is also a matter of priority and strategy for the countries in the region. This is reflected, as already indicated in the action lines of the Regional Strategy. Mention is also made in the specific Decision 391 and in *CAN Decision 486 concerning a Common Intellectual Property Regime*. However, only Peru possesses a specific law – Law 27811, which establishes the *Regime for Protection of the Collective Knowledge of Indigenous Peoples Linked to Biodiversity* (2002) – designed to protect this knowledge and to establish the rules for its use and treatment.

27. In the specific context of patents, a novel landmark in the legislation on this subject, CAN Decision 486, has expressly established that: (a) individual biological components (which do not clearly involve an invention) are not patentable, and (b) in the case of inventions incorporating biological or genetic components, or traditional knowledge, the grant of the patent title is subject to the legal provenance of these materials and knowledge being demonstrated, and a patent may be refused or even revoked, where this requirement is not satisfied. In other words, the regime is dependent on compliance with other legal standards, including the CBD, Decision 391 and, in the case of Peru, Law 27811.

28. As indicated above, the *WTO Agreement on Trade-Related Aspects of Intellectual Property* (TRIPS) establishes certain minimum standards for the protection of intellectual property rights. It should be specified that although these requirements are not explicitly envisaged in the TRIPS Agreement, nothing prevents this type of measure being established, for the benefit of countries such as Peru (and other megadiverse countries).

IV. WHAT IS MACA?

29. In Peru, the Incas and their ancestors domesticated more than 180 cultivated species of plants over a period of several thousand years. This was feasible owing to the existence of great ecological and climatic diversity, availability of thousands of species of plants, and the Andean inhabitants who developed agriculture. One of the crops in the Andes is maca which, until a short time ago, was virtually unknown.

30. The plant, known in Quechua as maca, maka, maino, ayak chichita, ayak willku; in Spanish as maca; and in English as maca or Peruvian ginseng, comes from the Central highlands of the Peruvian Andes, where it has been cultivated for many centuries for its swollen roots which are edible. It is a magnificent example of a plant domesticated by the ancient Peruvians, which has helped to feed the inhabitants of Chinchaisuyo, in an environment with low temperatures and strong winds. In those areas, these climatic factors limit the cultivation of other species. For centuries maca was used to barter for other foodstuffs or to pay taxes.

(i) Historical precedents

31. Maca is briefly described in part 1 of the work by Pedro Cieza de León, in 1553, entitled "La Crónica general del Perú" (the General Chronicle of Peru). Vásquez de Espinoza, who visited Peru in 1598, also provides a short description of maca in his "Compendium and Description of the West Indies," and Father Bernabé Cobo, who visited Peru between 1603 and 1629, also includes it in his "History of the New World" (Ochoa & Ugent, 2001).

32. In Book 4, Chapter XV, Father Cobo (1956) says that "only in the province of Chinchaycocha was a small plant, known as maca, cultivated, which does not grow from the ground, and where no other plant, of those cultivated for human sustenance, grows owing to the frequent snows and frosts. This plant produces a root in the form of a chervil pear, white inside like a turnip, and which serves as bread, green and dry, which they keep for the whole year. It has a strange property, since, as they grow with this root, its natural features not only do not decrease in number, as in the other provinces in Peru, but increase daily, for which reason it is said that this root is virtuous." In view of the worth of this food, Spanish tax collectors demanded that the inhabitants of the province of Chinchaycocha should pay them with maca harvests.

33. In his account of his journey to the departments of Central Peru, in 1777 and 1778, the Spaniard Hipólito Ruiz states that the area where maca is produced and consumed were the villages of Carhuamayo, Pampa de los Reyes, Ninacaca and areas attached to these parishes, which currently belong to the districts of Carhuamayo and Ondores in the department of Junín. In his account, he says that they are "…potatoes or potato roots, the size of hazelnuts… very tasty but burning and an aphrodisiac, or which arouse Venus; for which reason, many people believe that they make men and women fertile…"

(ii) Taxonomy and biological characteristics

34. Maca is the only cultivated cruciferous species which produces starch. It is classified in the *Brassicaceae* Family, *Lepidieae* Tribe, *Monoploca* Section and *Lepidium* Genus, and *Lepidium meyenii* Species (Quirós & Aliaga, 1997).

35. The maca plant is herbaceous and is characterized by the formation of a rosette of short and decumbent stems with numerous leaves, and which grows almost stuck to the ground, thereby making it very tolerant to frosts. In the ground, the part of the stem which is below the cotyledons (hypocotyl) acquires a fleshy structure which comprises a radicle texture and ends with a swollen root and numerous absorbent lateral roots. This hypocotyl root is tuberous, succulent in the form of a turnip, and is the edible portion. The maca crops which currently exist are mainly distinguished by the color of the hypocotyls-roots which may be white, yellow, grey, purple, black, yellow and purple, and white and purple. The leaves exhibit a dimorphous structure, and are longer in the vegetative phase and more reduced in the reproductive phase. The flowers are not particularly noteworthy, with four sepals and four small white petals, as well as two or rarely three stamens. The ovary is oval and bicarpelar with a short style. The flowers are grouped in axillar bunches. The fruit is a siliqua with two seeds (Quirós & Aliaga, 1997).

36. Maca is autogamous, is reproduced predominantly by self-pollination, and produces fertile pollen trinuclear seeds. It has 2n=8x=64 chromosomes and is a disomic octoploid. It produces seeds which are rarely dormant and germinate in five days at 25°C (Quirós et al. 1996; Quirós & Aliaga, 1997).

(iii) Genetic diversity, related wild species and their conservation

37. Although little information exists regarding the *Lepidium* species endemic to the Andes, those which are known are classified in the *Dileptium*and *Monoplaca* sections. All these, including maca, grow in high altitude habitats, up to 4,500 meters above sea level. Brako and Zarucchi (1993) reported six other *Lepidium* species in Peru, distributed between the Departments of Ancash and Puno. However, some of those species are also to be found in Ecuador, Bolivia and Argentina.

38. Toledo et al. (1998) reported on a study with RAPD molecular markers of 29 entries of cultivated maca, which appear to represent approximately 80 per cent of known maca crops, and 27 entries of *Lepidium bipinnarifidum, L. kalenbornii* and *L. chichicara* wild species from Ecuador, Peru and Bolivia, which are morphologically different to maca and are classified in the *Dileptium* Section. All the entries of each species formed separate conglomerates and the authors concluded that none of the wild species studied is closely related to maca. They recommended a study of the *L. solomonii* (Bolivia), *L. jujuyanum* (Argentina) and *L. weddellii* (Peru) species, which are classified in the same *Monoplaca* Section as maca. In addition, *L. weddellii* appears to be the only species which produces swollen hypocotyls-roots. The RAPD markers also showed a low level of polymorphism between the samples of maca studied, which would indicate that maca has a very narrow genetic base. Similar results were reported by Kianian & Quirós (1991), using RFLPs and RAPDs with 30 crops and 21 wild species from Ecuador, Peru and Bolivia.

39. Chacón (2001) reported on wild forms of maca known by the common name of "shihua" and which are to be found, very rarely, in cultivated maca fields.

40. The largest *Lepidium* collection in Peru is kept in the La Molina National Agrarian University (UNALM), which contains 93 maca accessions, 41 wild *Lepidium* species, and 38 family lines of selections. The International Potato Center (CIP) holds 23 accessions, most of which duplicate the UNALM collection, and are conserved as seeds (> 2,000 per

accession) refrigerated at - 20°C. These seeds are obtained from 20 plants per accession and tests to monitor their viability are carried out every two years. All the accessions have been characterized using morphological descriptors.

41. CIP experts consider that the collections conserved *ex situ* do not represent the existing diversity *in situ*.

(iv) Origin and geographical distribution

42. Very little is known about the origin of maca and a wild species has not yet been identified, which might be considered its ancestor and from which it was domesticated. Maca appears to have been domesticated by human groups originating from the Peruvian forest, known as "Pumpush," who populated areas such as Cuncush Runa on the Bumbush or Bombón plateau, where the lagoon of Chinchaycocha or Junín is located. The Pumpush required salt which was produced in the Cerro de la Sal in Tarma, Catamarca or Cachipuquio, located in San Pedro de Cajas and San Blas. Ancestral maca plants appear to have been one of its sources of nutrition and the process of its domestication appears to have begun in 1,200 B.C. in the areas around San Blas (Rea, 1992, Obregón, 1998).

43. According to Javier Pulgar Vidal, the word maca comes from the words Ma, which means "high up" (which has been cultivated or is cultivated at altitude) and Ca "food which strengthens." In Quechua, it appears to mean "food with a strong taste" (Obregón, 1998).

44. It is believed that in the XVIth and XVIIth centuries maca was more broadly distributed in geographical terms. However, until a few years ago, the geographical distribution of maca was restricted to the areas surrounding the Junín lagoon, in the central highlands of Peru. Traditionally, the large areas under cultivation were to be found in the Department of Junín, in many communities in the districts of Ondores, Huayre, Carhuamayo, Tarma and Junín, in the Departments of Pasco en Ninacaca, Yanachachi and Vicco. Recently, its cultivation has been extended to other Departments such as Huancavelica, Ayacucho, Apurímac, Cusco and Puno. All these localities are situated in the agroecological areas Suni and Puna, at an altitude of between 3,500 and 4,500 meters.

(v) Nutritional and pharmacological properties of maca

45. The fresh hypocotyls-roots of maca contain 80 per cent water and, when they are dry, they have a nutritional value similar to that of maize, rice, and wheat. Its composition includes 55 to 60 per cent carbohydrates, ten to 12 per cent proteins, eight to nine per cent fiber and two to three per cent lipids. Maca contains large quantities of essential amino acids and high levels of iron and calcium. It also contains fatty acids, of which linolenicum, palmiticum and oleicum are the most important. It also contains esterols and alkaloids (Quiroz, et al., 1996).

46. The most important known property in the Andean tradition is its effect on fertility; this has been the main feature attributed to maca since the XVIth century and is considered to be one of the factors in increasing the population in the highest lying areas in Peru. It is also used to treat frigidity, sexual impotence and mental deficiency (León, 1964, 1986; Obregón, 1998; Johns, 1980).

47. The effects of maca on fertility have been verified in rats, in which an increase in spermatogenesis occurs, along with the maturing of follicles and an increase in offspring when they are supplied with a maca alkaloid extract (Chacón, 1961); in guinea pigs, which when fed with dry powdered maca increase their fertility (100 per cent) and their offspring (Alvarez, 1993; Jerį 1999); in sheep, which when fed with 80 grams of maca for two weeks increased the volume of semen, sperm concentration and the motility of spermatozoids; and in infertile cows which regain their fertility after being fed with maca (Pulgar, 1978). Reports also exist on the use of traditional recipes to treat infertility in men and women (García and Chirinos, 1999). The properties of maca in improving fertility could be due to the presence of biologically active isothiocyanates, derived from the hydrolysis of glucosinolates, specifically due to benzyl-isothiocyanate and p-metoxybenzyl isothiocyanate (Li, et al., 2001).

48. Maca is also known as an aphrodisiac which cures frigidity in women and is a remedy for impotence in men (Pulgar, 1978; Obregón, 1998; García y Chirinos, 1999). A great deal of evidence on successful treatment with maca for cases of frigidity, impotence and sterility is to be found in a Folkloric Clinic in Junín (León, 1986). This property of maca could be due to the presence of prostagladines and esterols in the hypocotyl-root, and of amides of polyunsaturated fatty acids (Li, et al., 2001).

49. Another medicinal property attributed to maca is its anticarcinogenic effect (Quiroz and Aliaga, 1997). However, a long list of scientific articles exists, which refer to the anticarcinogenic effect of glucosinolates and benzyl-isothiocyanate of various species of the *Brassicaceae* Family, to which maca also belongs (Wattenberg, 1977, 1983, 1990; Verhoeven et al., 1996). Since Johns (1980) isolated isothiocyanates from maca extracts, it is very possible that maca also has an anticarcinogenic effect.

50. Maca is also used traditionally to regulate changes in menstruation and the menopause, and alleviates insomnia and the loss of hearing and vision (Pulgar, 1978; Obregón, 1998). In addition, this plant has been used since time immemorial for its revitalization properties (Obregón, 1998), to treat malnutrition, aid convalescence, and restore physical and mental capacity (Quiroz and Aliaga, 1997).

V. MARKETING OF MACA

51. Maca is part of a rapidly expanding market and the characteristics of this natural and organic product, and properties which are scientifically verified, make maca a product with great potential. The current trend in Europe, the United States and Japan, where consumers are very concerned with healthcare, is toward the consumption of natural products, thereby allowing products such as maca, with high energy and nutraceutical value, to be in great demand.

52. According to information supplied by PROMPEX (Commission for the Promotion of Exports), exports of maca have grown from US$ 1,056,287.79 in 1998 to US$ 3,016,240.03 in 2002. This is equivalent to 293,548 metric tons exported per year (in different forms: powders, tablet extracts, caramels, etc.). The main destination markets are Japan (almost 50 per cent of the export market from Peru), United States, Venezuela and Hungary;

representing about 80 per cent of the FOB value exported in 2002. In 2002, 13,557 metric tons of maca were exported in dry fragment form for an amount of US$ 863,094 (FOB price), this being the second most important category that is exported immediately after meal, powder and microspray (174,642 tons, equivalent to US$ 1,244,066).

VI. RESPONSES OF PERU: FORMATION OF A WORKING GROUP FOR THE ANALYSIS OF PATENTS

53. Faced with this situation, INDECOPI called a meeting in July 2002 of a group of individuals and institutions to discuss these matters, as well as the strategy to be adopted in relation thereto.

54. The Group based itself on the idea that, prior to giving a value judgement on these patents, it was necessary to examine in technical terms whether they should be granted, from the point of view of patent laws, since, for this purpose, it was necessary to gather information in order to determine whether the examination of patentability of the inventions in question was duly carried out.

55. The Group has analyzed the patents and patent applications detailed in paragraph 7, and has compiled a significant amount of information relating to maca.

56. The Group has also analyzed whether causes other than patent laws exist (for example, non-compliance with regulations on access to genetic resources), which justify some kind of questioning of these patents[1], as well as the measures that could be adopted.

57. This working group has been coordinated by INDECOPI and has, as its members, individuals from different governmental institutions and non-governmental organizations (NGOs): the *Ministry of Foreign Affairs*, the *Ministry of Foreign Trade and Tourism*, the *National Environmental Council* (CONAM), the*National Agricultural Research Institute* (INIA), the *International Potato Center*, the *Peruvian Environmental Society*, PROBIOANDES, the *Peruvian Medicinal Plant Institute*, and the *Andes Association*.

58. The coordination of the Group was the responsibility of Begoña Venero (INDECOPI). The following individuals participated in it: Alejandro Riveros (Chancellery), Allan Angell (MINCETUR), María Luisa del Río (CONAM), Santiago Pastor (INIA), William Roca (International Potato Center), Alejandro Argumedo (Andes Association), José Luís Silva (Peruvian Medicinal Plant Institute), Manuel Ruiz (SPDA), Zósimo Huamán (Probioandes), Néstor Escobedo (INDECOPI) and Sylvia Bazán (INDECOPI).

59. In addition, the following people participated as guests:
Dr. Gloria Chacón de Popovici (maca researcher);
Dr. Fernando Cabieses (Rector of the Southern Scientific University);
Dr. Eric Cosio (researcher from the Catholic University);
Mr. Alfonso Higa (one of the main Peruvian exporters of maca);
Mr. Arturo Zevallos (representing PROMPEX);
Messrs. Marco Salazar and Fernando Ortega (representing CONCYTEC).

---

[1] See paragraph 9.

60. The Group enjoyed the continuous technical support of the pharmaceutical chemist María del Carmen Misol (INDECOPI), who was responsible for the technical analysis of the patents and patent applications detailed in paragraph 7. It also had the support of the biologist Catherine Espinoza (assistant to Dr. William Roca of the CIP).

61. Similarly, letters were sent to scientists and exporters of maca requesting their cooperation in compiling information on maca. Various scientists and exporters of maca sent information to us. It is important to highlight the opinion of Dr. Timothy Jones, a professor from McGill University in Canada, who, from an ethical and scientific point of view, questioned the validity of the patents granted.

62. The Group met on nine occasions: July 23, 2002; August 20, 2002; September 20, 2002; January 17, 2003; February 11, 2003; March 6, 2003; March 18, 2003; April 8, 2003; and April 29, 2003.

63. Specific activities were also entrusted to some of its members with a view to preparing this report.

64. At the request of the Group, the Embassy of Peru in the United States of America supplied us with copies of the official documents corresponding to patents nos. US 6,267,995 and 6,428,824, as well as to US application number 09/878,141 (published as US 2002/0042530 A1).

65. Finally, it should be mentioned that in November 2002 the Group sent a letter to Ms. Natalie I. Koether, President of Pure World Botanicals, Inc., the company holding patents numbers US 6,267,995 and 6,428,824, expressing to her our concern at the effects that these patents might have on Peruvians exporting maca to the United States of America, and requesting her to indicate to us the differences between the extract that her company has patented and the extracts exported by our nationals. However, no reply has been received to our letter.

VII. SUMMARY OF PATENTS REFERRING TO *LEPIDIUM MEYENII*

(i) International application (compositions and methods for preparation of Lepidium)

66. Application PCT/US00/05607 was filed on March 3, 2000, claiming priority on the basis of application no. US 09/261,806 of March 3, 1999, and was published on September 8, 2000 as WO 00/51548. It contains 54 claims referring to extracts, macamides, an extraction process and therapeutic methods:

Claims referring to extracts

Claim 1: This refers to an isolated composition derived from Lepidium, essentially free of cellulose material containing around 40 per cent or more of a polysaccharide Lepidium component.

In claims 2 to 7, other components such as amino acids, benzyl-isothiocyanate and macamide component are detailed.

Claim 8**:** This refers to an isolated composition derived from Lepidium, containing:

(a) around 0.3 per cent or more of benzyl-isothiocyanate;
(b) around 0.1 per cent or more of Lepidium esterols;
(c) around one per cent or more of Lepidium fatty acids;
(d) around 0.3 per cent or more of macamide component.

67. Claims 9 and 10 provide details of ranges of these components which, in claim 10, are five per cent to nine per cent for (a); one per cent to three per cent for (b); 20 per cent to 30 per cent for (c) and ten per cent or more for (d).

Claims referring to macamides

Claims 12 to 15: These define four specific compounds by chemical name, the structure of which corresponds to amides of fatty acids, referred to as macamides by the applicant.

Claims referring to an extraction process

Claim 16: This refers to a process for obtaining a composition from claim 2 which contains the steps of:

- placing Lepidium plant material in contact with an aqueous solvent, and
- separating the aqueous solvent in contact from the Lepidium plant material in order to obtain the composition of claim 2.

Claims 17 to 21 provide details of the type of solvent used, claims 22 to 28 of additional chromatography steps, and claim 29 states that the Lepidium to be used is Lepidium meyenii.

Claims referring to therapeutical methods-uses

Claims 33 to 46: These refer to a method for treating or preventing cancer in an animal, by administering a composition from claims 1 or 5 to 10.

Claims 47 to 54: These refer to a method for treating or preventing sexual dysfunction in an animal suffering from such a dysfunction, by administering a composition from claims 1 or 5 to 10. It is specified that the dysfunction in male animals is subnormal libido or impotence, and the dysfunction in female animals is subnormal fertility.

(ii) Patent US 6,297,995 (Extract of Lepidium meyenii roots for pharmaceutical applications)

68. Based on application no. 09/261,806, of March 3, 1999, a patent was granted for six claims, the aim of the main claim being an isolated COMPOSITION of *Lepidium meyenii* roots, which is substantially free of cellulose and contains:

(a) between around five per cent and nine per cent of benzyl-isothiocyanate;
(b) between around one per cent and three per cent of Lepidium esterols;
(c) between around 20 per cent and 30 per cent of Lepidium fatty acids;
(d) between around ten per cent or more of macamide component.

69. This composition is obtained by a process consisting in:
- placing in contact with *Lepidium meyenii* roots a first aqueous solvent comprising around 90 per cent by volume or more of water,
- separating the residual material from the first aqueous solvent,
- placing the residual material in contact with a second aqueous solvent, containing a mixture of alcohol and water which has around 90 per cent by volume of alcohol or more in order to form a strong alcohol, and
- making the strong alcohol concentrated so as to obtain the composition.

70. Claims 2 to 5 provide specifications concerning the macamide component and claim 6 specifies that the composition additionally contains a pharmaceutically acceptable excipient.

N.B.:

71. It is important to consider that original application no. 09/261,806 gave rise at the time to three divisional applications:

72. Application no. 09/878,141, of June 8, 2001; published as US 2002/0042530 A1, of April 11, 2002 and currently abandoned. Through its claims, it defines four amides of fatty acids using its chemical name, which are referred to by the applicant as macamides and are as follows:
- N-benzyl octanamide;
- N-benzyl-16(R,S)-hydroxy-9-oxo-10E,12E,14E-octadectrienamide;
- N-benzyl-16(S)-hydroxy-9-oxo-10E,12E,14E-octadectrienamide;
- N-benzyl-9,16-dioxo-10E,12E,14E-octadectrienamide.

73. Application no. 10/002,757 of October 19, 2001; granted as patent no. US 6,428,824.

74. Application no. 10/138,030 of May 2, 2002; published as US 2003/0068388 of April 10, 2003 where it is indicated that this a continuation of application no. 09/878,141, now abandoned. This application is limited to the amides of fatty acids or macamides 2 to 4.

(iii) Patent no. US 6,428,824 (treatment of sexual dysfunction with an extract of Lepidium meyenii roots)

75. Based on application no. 10/002,757 of October 19, 2001, this is a divisional application of application no. 09/261,806 of March 3, 1999.

76. This patent was granted for ten claims, the object of the main claim of which is a method for the treatment of SEXUAL DYSFUNCTION in an animal, which comprises the administration of an isolated composition derived from an aqueous extract of Lepidium meyenii roots to an animal in need of treatment for sexual dysfunction, where such a composition is free of cellulose and contains:

(a) between around five per cent and nine per cent of benzyl isothiocyanate;
(b) between around one per cent and three per cent of Lepidium esterols;
(c) between around 20 per cent and 30 per cent of Lepidium fatty acids;
(d) between around ten per cent or more of macamide component.

77. In claims 2 to 6, it is specified that the animal is a human and that the troubles referred to in a male animal are subnormal libido and impotence, and claims 7 to 10 provide specifications regarding the macamide component. In the description of the invention it is mentioned that the animal may be female and the sexual dysfunction may be infertility.

VIII. RESULTS OF THE ANALYSIS OF PATENTS

(i) Prior art considered by the offices responsible for examining the aforementioned patents and applications

78. The offices responsible for examining the aforementioned patents and applications carried out prior art searches and prepared the following reports:

(a) International Search Report drawn up by the United States Patent and Trademark Office (USPTO):

79. The international application was published as WO 00/51548 A2 and the international search report was published as document A3 on November 15, 2001, citing the following documents as particularly relevant in relation no novelty or inventive step ("X" or "Y" categories).

[X - Y] COMAS M. ET AL.: "Bromatological study of Maca or Paca"
FOOD CHEMISTRY, vol. 286, 1997, pages 85 – 90.

[X - Y] DINI A. ET AL.: "Chemical composition of Lepidium meyenii"
FOOD CHEMISTRY, vol. 49, no. 4, 1994, pages 347 – 349.

[Y] JP 408012565 A (KOMAZAKI et al)
January 16, 1996.

[Y] JOHNS T.: "The Anu and the Maca"
JOURNAL OF ETHNOBIOLOGY, vol. 1, no. 2, 1981, pages 208 – 212.

80. In the prior art it is mentioned that maca increases sexual potency and determines its centesimal composition in relation to lipids, proteins, fiber, mineral salts and water; the content of fatty acids, amino acids, sugars and cations (COMAS) is analyzed; the concentration of carbohydrates, lipids, proteins, fiber, amino acids, fatty acids and esterols is determined; and by means of thin-layer chromatography alkaloid-type compounds are detected, and mention is made of the use of the boiled or roasted plant as food or in medicine for its anti-depressant properties and in the healing of wounds (DINI); a composition is obtained for external use from an ethanol extract of stems and branches of maca (JP 408012565); and it is stated that the plant is known for its influence on fertility, while glycosinolates are identified, as well as therefrom benzyl-isothiocyanate as a main peak, for which reason paper chromatography and then High Performance Liquid Chromatography (HPLC) is used, with a sample of maca roots collected in 1973, preserved in p-dichlorobenzene and stored at room temperature until 1980 (JOHNS).

81. Since the cited prior art already describe, as components of the maca root, carbohydrates, amino acids, fatty acids and esterols, as well as their use in therapy, especially as regards their influence on fertility and sexual potency, claim 1 does not appear to meet the requirement of novelty, in the same way as claim 16 which describes the production of an aqueous extract and claim 47 referring to use in the treatment of sexual dysfunction, whereby this prior art also affects the novelty or inventive step of the remaining claims.

(b) Revision of the official document corresponding to patent no. US 6,267,995:

82. The procedure for this official document was launched on March 3, 1999 for 54 claims and the patent was finally granted on July 31, 2001 for six claims.

83. In the document with the PTO-1449 format, "Information Disclosure Statement by Applicant," prior art is cited, and the document also contains details of the strategies used by the examiner in the prior art search, aimed at relevant information on Lepidium. Similarly, communications from the patent examiner are noted, citing the documents by Comas et al, Dini et al and Komazaki et al as relevant to the novelty or inventive step of the subject matter of the application (already mentioned in the international application), to which the applicant responds with different arguments and with a statement in which an extract taken from the maca root is compared with an extract taken using stems and branches.

84. As a result of the relevance of the prior art, it is understood why protection has been limited to an extract containing four components in a specific range, characterized by the macamide component (amide of fatty acids), which is not mentioned in the prior art. Similarly, this extract is defined by its two-stage extraction process, which is not described either in the prior art, the two stages being somewhat limited to an extract using ethanol on the maca stems and branches rather than on the root.

(c) Revision of the official document corresponding to patent no. US 6,428,824:

85. The procedure for the official document was launched on October 19, 2001 for ten claims and the patent was finally granted on August 6, 2002 for a total of ten claims, a slight change suggested by the examiner being made as regards including in claim 1 the fact that the treatment is carried out in an animal in need of treatment for sexual dysfunction. This official document accompanies a copy of patent no. US 6,267,995.

(d) Revision of the official document corresponding to publication no. 2002/0042530, currently abandoned:

86. In this document a format is used known as "Notice of References Cited" in which the publication by Adamczyk et al. is cited, together with the strategies used in the search for prior art aimed at macamide-type compounds.

87. Similarly, a patent examiner's communication, dated December 28, 2001, is noted, in which the examiner concludes that claim 1 is anticipated by Adamczyk et al. ("Pseudomonas CEPACIA Lipase Mediated Amidation of Benzil esters" Tetrahedron Letters, vol. 37, no. 44, pp 7913-7916, 1996), which describes the compound N-benzil octanamide on page 7915, third compound.

88. On August 14, 2002, the applicant was informed that the application had been abandoned owing to the failure to respond to a communication issued by the USPTO on January 2, 2002.

89. Although this application has been abandoned, application no. 10/138,030, dated May 2, 2002 and published as US 2003/0068388 on April 10, 2003, retains claims in relation to three macamides.

(ii) Prior art compiled by the Group

90. Information was compiled regarding uses of the plant as medicine and as food, compositions or preparations containing it, and processes for extraction, identification and biological evaluation of the components; which in many cases has been provided by the authors or researchers into the subject. The following documents are worthy of special mention:

(1) Gloria Chacón Roldán (1961) "*Estudio fitoquímico de Lepidium meyenii Walp*" *(Phytochemical Study of Lepidium meyenii Walp).* Thesis for the degree of bachelor of biological sciences from the Higher National University of San Marcos (UNMSM), Lima.

On page 14, there are details of the process for extracting active ingredients, which uses 50 grams of the ground product corresponding to the grated root dried at a temperature heated to 70^{o}-75^{o} for 12 hours, and subjected via a Soxhlet apparatus to the successive action of solvents such as acetone, ether, alcohol and distilled water used here. The tests were carried out at the temperature at which the solvent boils, and a sheet is provided to illustrate the four extracts obtained and the compounds identified therein:

- Acetone extract: alkaloids, saponines, tannins;
- Ether extract: alkaloids, fatty acids, saponines, tannins;
- Alcohol extract: alkaloids, tanynes (negative identification);
- Aqueous extract: glucides, anthocyanines (negative identification).

The author concludes that "In the phytochemical observations of the root, a large concentration of alkaloids has been found and, in accordance with the chromatographic tests, there appear to be three such alkaloids. Also found were starches, glucides, fatty acids, tannins and a sparse concentration of saponines."

In the conclusions on pages 39 and 40, it is mentioned that the preliminary observations of the administration of the Lepidium meyenii alkaloid extract to rats and toads show the following effects:

- increase in procreation in albino rats;
- clear and marked stimulation of the maturing of follicles also in albino rats;
- no effect on the spermatogenesis induced in the toad.

(2) Suriaqui Condor, Anibal Dalmiro (1991) "*Influencia de la maca en el incremento de peso en la reproducción y descendencia de borregas en la cooperativa comunal San Ignacio de Junín*" *(Influence of maca on the weight increase in the reproduction and*

offspring of lambs in the San Ignacio de Junín community cooperative). Thesis for the title of animal industry engineer in the National University of Daniel Alcides Carrión, Cerro de Pasco.

A maca extract was used for the study with the proportion of 100 grams : 300 cc of water, previously boiled and liquefied, and administered orally to 50 second-delivery Corriedale race lambs for a period of 15 days prior to registration. It is concluded that maca has the property of making the signs of being in season more accentuated, avoiding or reducing the number of empty or aborted lambs, thereby also causing weight gain in the animal.

(3) G. Lama et al (1994) "*Estudio de la propiedad estrogénica del lepidium meyenii walp (maca) en ratas" (Study of the estrogenic property of Lepidium meyenii walp (maca) in rats),* summary of a paper given at the Second National Congress of Pharmaceutical and Biochemical Sciences.

The aim of this paper was to demonstrate the estrogenic effect of the hexane extract. The preliminary phytochemical study indicated the presence of steroidal triterpenes.

(4) Octavio Zolezzi (1997) "*Transformación de la uña de gato y la maca en el Perú*" *(Conversion of cat claw and maca in Peru)* in: Third Meeting of the Rural Agriculture Industry, Tarapoto, Peru.

This article states that the components identified in maca are proteins, carbohydrates, fatty acids, fiber, minerals, vitamins, steroidal saponines and amino acids, and that the substances contained therein participate in growth, fertility, virility, lactation and other physiological functions. On pages 37 and 38, different processes are described for the conversion of maca, for example by drying, burning, baking, cooking, grinding and hydroalcoholic extraction. In the cooking portion it is described how the maca is boiled in an equal amount of water and parboiled for 30 to 60 minutes. It can then be liquefied with the cooking water and the addition of other ingredients, or the maca may simply be consumed separately and the cooking water drunk.

In the hydroalcoholic extract section, it is mentioned that dry washed maca may be macerated into strong alcohols and/or rectified alcohol. The domestic maceration can be achieved with strong liquor, rum or cane liquor, by introducing 20 to 40 grams of maca per liter and leaving the mixture to macerate for a minimum of five days. However, owing to the characteristics of maca this is not recommended, since proteins, minerals and also certain carbohydrates are not soluble in the extract in question and would be lost, unless the filtered remnant is dried and reused. This process would extract the alkaloids and also a number of soluble glycosides.

(5) L. Obregón (1998) *"Maca: planta medicinal y nutritiva del Perú" (Maca: medicinal and nutritional plant of Peru),* a book published in Lima on January 18, 1998.

The book consists of a compilation of various works and includes the following chapters:
Part one: History and ethnomedicine
- Chapter I: maca in history
- Chapter II: maca: ethnomedicine and folklore

Part two: botanical, genetic and chemical studies, and the effect on cells, animals and humans

- Chapter I: botanical and genetic studies
- Chapter II: chemical studies of maca
- Chapter III: study of cells, animal and human
- Chapter IV: cultivation of maca and physiological studies.

In chapter II of part one, reference is made to properties of maca such as its fertilizing, aphrodisiac (frigidity and impotence), revitalizing and regulating action, as well as the ancestral use of fresh roasted maca roots, referred to as "Huatia" and the preparation of bread, based on cooked dry roots, known as "Atunca." Mention is also made of its current popular use in various preparations such as juices, strong alcohols, capsules and tablets. Chapter II of part two is devoted to chemical studies of maca and refers, in turn, to the following works:

- Garró et al (1993), "*Extracción, separación e identificación por cromatografía de alcaloides de lepidium meyenii walp (maka)" (Extraction, separation and identification by chromatography of Lepidium meyenii walp (maka) alkaloids).* Four fractions of alkaloids were separated from the dry and crushed roots of the plant.

- Yllescas (1994), Thesis for the title of pharmaceutical chemist entitled *"Estudio químico y fitoquímico comparativo de 3 ecotipos de Lepidium meyenii Walp "Maca"* procedente de Carhuamayo (Junín)" *(Comparative chemical and phytochemical study of three Lepidium meyenii Walp "Maca" ecotypes* originating from Carhuamayo (Junín)). Roots of stabilized and crushed maca were used, on which the phytochemical action was carried out to identify three alkaloids and a flavonoid, as well as observing the presence of steroids and triterpenes, phenol compounds, flavonoids and/or cumarins, tannins, glycosides, saponines, free amino acids, secondary aliphatic amines and tertiary amines.

- Garró, León, Fuertes and Carrasco (1995), "*Investigación química y biológica de Lepidium meyenii walp "maca" (Chemical and biological research into Lepidium meyenii walp "maca"*, published in the UNMSM review Theorema. Powder of maca roots and a methanol extract of dried and crushed roots were used, as well as fine layer analytical chromatography, finally reported as fruit-bearing components and alkaloids.

"*Estudio Botánico y químico de los ecotipos amarillo y morado de Lepidium peruvianum "Maca". Evaluación de su toxicidad aguda" (Botanical and chemical study of the yellow and purple ecotypes of Lepidium peruvianum in "Maca". Evaluation of its acute toxicity")* (1997), carried out by professionals from UNMSM and the American Phytotherapy Institute, including Dr. César Fuertes. Three alkaloids (in the ether extract), flavonoids, saponines and glycosinolates were reported.

Page 118 contains a general framework for ranges obtained in various analyses of dried "maca" from micronutrients, vitamins, minerals and calories, within which a value of carbohydrates is presented from 51.81 per cent up to 76.05 per cent; for proteins from 10.10 per cent to 18.25 per cent; and fats from 0.20 per cent up to 2.20 per cent.

(6) F. Retuerto et al, (1996), "*Efectos citostáticos del extracto etanólico de Lepidium meyenii W. En células meristemáticas de Allium cepa L.*" *(Cytostatic effects of the ethanol extract of Lepidium meyenii W. In meristematic cells of Allium cepa L).* Biological Science Research Institute "Antonio Raymondi" (ICBAR), March 13-15, 1996.

There is a strong belief that the consumption of Lepidium meyenii Walpers (Cruciferae), ie "maca," has aphrodisiac effects and causes an increase in human fertility. The composition of hydrolyzated carbohydrates is 59 per cent, most of which are thioglucosides. Bulbs of A. Cepa L., with roots of two to three centimeters in length, kept constantly at 20 +/- 0.5°C in aired water and darkness, are submerged in a solution of ethanol extract of L. Meyenii W., of six per cent for 2, 4, 6, 8, 10 and 12 hours respectively, whereby the mytotic index (MI) and the phase index (PI) of the meristematic population being treated are analyzed. Four thousand cells were analyzed.

The MI of the meristematic cells decreased from an MI=13 (control) to an MI of 7.45 after 12 hours' treatment. The roots treated with the ethanol extract demonstrate a cytostatic effect through the presence of C-mytosis; suggesting the results of the activity of the ethanol extract are due to the thioglycosides present in the extract.

(7) M. E. Valdivia et al (1998) *"Efecto de la soya y maca sobre la morfología y fisiología espermática en ratones"(Effect of soya and maca on the sperm morphology and physiology of mice),* Seventh Ibero-American Congress of Cellular Biology, October 26-30, 1998.

The weekly *in vivo* effect of natural products (soya and maca) in male mice is studied, using the alcoholic form of maca. It is concluded that maca may be used to stimulate fertility.

(8) Rodolfo Tello Saavedra and Mary Porras Osorio (1999) "*Estudio técnico para la elaboración de licor de maca (Lepidium meyenii Walp*) por maceración" *(Technical study for the preparation of maca strong alcohol (Lepidium meyenii Walp)* by maceration), a research work carried out in the National University of Central Peru, starting in July 1998 and ending in August 1999.

In the summary portion, it is mentioned that a flow of operations was as follows: selection and classification, weighing, washing, REHYDRATION, MACERATION, decanting, filtration, standardization, packaging and storage. It is specified that the soaking and/or rehydration are carried out with hot water at 40°C for a period of 24 hours, thereby eliminating the alkaloids and/or antinutrients which maca possesses. The optimum period for maceration of maca in extra fine alcohol of 96° gl was 13 days, in a proportion from one to three (maca-alcohol).

This document describes a process for preparing a strong alcohol with a rehydration step which amounts to an aqueous extraction, eliminating this aqueous extract and following with the ethanol maceration step, which amounts to a second consecutive extraction process.

(9) L. W. Wattenberg (1987), "Inhibitory effects of benzyl isothiocyanate administered shortly before diethylnitrosamine or benzo[a]pyrene on pulmonary and forestomach neoplasia A/J mice." Carcinogenesis 8 (12): 1971-1973. Summary only.

The inhibitive effects of benzyl isothiocyanate on carcinogenesis induced by the chemical carcinogens dimethylnitrosamine and benzopyrene were studied in mice. The results showed that the benzyl isothiocyanate compound, a natural derivative in cruciferous plants, completely inhibits formation of tumors both in the stomach and in the lungs.

(10) K. A. Steinmetz and J. D. Potter (1996), "Vegetables, fruit, and cancer prevention; a review." J Am Diet Assoc, October 1996 (10): 1027-1039. Summary only.

A revision of various studies relating to the consumption of fruit and vegetables and the risk of cancer was made. From 202 epidemiological studies in humans and 22 studies in animals, it is concluded that there is evidence of a preventive effect of various types of cancer: in the stomach, oesophagus, lungs, oral cavity, pharynx, endometry, pancreas and colon, through the consumption of certain vegetables, including cruciferous plants; among the substances or phytochemical compounds involved in this effect, isothyocyanates are some of the most frequently mentioned.

In the annex to this report reference is made to other texts which represent important precedents for studies carried out in relation to maca.

(iii) Analyses in relation to the international application

Claims referring to extracts (1 to 11)

91. From the revision of the cited documents, known aqueous extracts of Lepidium are considered (references 1, 4 and 5), together with the fact that a polysaccharide or carbohydrate component is a component normally present in the root in percentages which vary from 51.81 per cent to 76.05 per cent; for which reason, the composition defined in claim 1 does not meet the requirement of novelty, thereby also affecting its dependent claims, for example where they specify that additional components are amino acids, which have also been described as usual Lepidium components (reference 5), or in the case of benzyl isothiocyanates (derivative of a thioglycoside), esterols or fatty acids preferably present in extracts using alcohol (references 1, 4, 5 and 6), and it is concluded that claims 1 to 4, 6 and 7 do not meet the requirement of novelty.

92. Although claims 5 and 8 to 11 meet the requirement of novelty in that they refer to the macamide component, however, it is not clear from the description of the application that the macamide component is responsible for the activity.

93. It is noted that biological tests are generally carried out with extracts which comprise multiple components, including components with benzyl isothiocyanate and esterols to which the biological activity of maca is attributed (references 3, 4, 5 and 6). In this sense, it is OBVIOUS that an extract which contains these components with verified activity would maintain the desired activity, since claims 5 and 8 to 11 do not meet the requirement of inventive step, as explained in more detail in point (iv).

Claims referring to macamides (12 to 15)

94. Claim 12 for the compound N-benzyl octanamide, referred to by the applicant as macamide A or MA-3, does not meet the requirement of novelty, since this compound has already been described in the 1996 publication by Adamczyk et al., cited in the analyses of the American Publication US 2002/0042530: in the prior art, the compound is described as part of an example of synthesis of amides and not as an isolated maca component.

95. In the case of claims 13 to 15 which define three amides of fatty acids, it should be observed that although the compounds in question may be novel, as in the prior art only fatty acids and amines are described as a component of maca (reference 5), it is necessary to demonstrate that the compounds are biologically active, for which reason they may meet the requirement of industrial applicability. This information is not clear from the content of the application, since although in table 2 the activity of macamide A (MA-3) is tested, this corresponds to the compound N-benzyl octanamide which does not meet the requirement of novelty, and further information is not provided in relation to the biological activity of the three isolated compounds defined in claims 13 to 15 in comparison with the extracts comprising multiple components.

96. It is understood that a compound with unknown activity does not meet the requirement of industrial applicability, a fact which may apply to claims 13 to 15.

Claims referring to an extraction process (16 to 32)

97. The extraction process defined in claim 16 is anticipated by the extraction processes known as maceration in the case of an alcohol extract or infusion or cooking in the case of an aqueous extract (references 1, 4, 5 and 6), for which reason it does not meet the requirement of novelty, and this also affects its dependent claims, since although in claim 16 an aqueous solvent is mentioned, in the dependent claims it is specified that the solvent is water, alcohol or a mixture of both.

98. On the other hand, it should be pointed out that chromatography techniques are routinely used in processes for separating and identifying components.

Claims referring to therapeutic methods – uses (33 to 54)

99. Claims 33 to 54 as drafted define therapeutic methods which are not patentable, in accordance with a number of different legislative acts, including Decision 486 of the Commission of the Andean Community. In all cases, it should be considered that:

100. Use in the treatment of cancer appears to be anticipated by document 6 which describes the use as cytostatic for the ethanol extract, owing to the presence of thioglycosides: use as an anticarcinogenic agent is known in many members of the Brassicaceae family to which maca belongs.

101. This effect is attributed to the glucosinolate and isothiocyanate components which are found in the Brassicaceae family, mainly to benzyl isothiocyanate, which has been previously isolated and characterized in Lepidium meyenii by Johns (1980). In addition, this effect of the isothiocyanates has been studied in epidemiological terms both in animals and in humans with positive anticarcinogenic effects for different types of cancer (references 9 and 10).

102. The use in the treatment of sexual dysfunction, such as subnormal libido, impotence or subnormal fertility, appears to be anticipated by the traditional use as an aphrodisiac and fertilizing agent (reference 5), complemented by biological tests in animals (references 1, 2 and 3).

103. In conclusion, in light of the above and considering both the documents cited in the International Search Report and those obtained today by the working group: claims 1 to 4; 6; 7; 12; 16 to 32; and 33 to 54 do not meet the requirement of novelty. Although claims 5 and 8 to 11 meet the requirement of novelty, they do no meet the requirement of inventive step.

104. Since the biological activity of the isolated compounds 13 to 15 is not documented, it is possible that they do no meet the requirement of industrial applicability, despite the fact that the compounds in question are novel.

(iv) Analyses in relation to patents of the United States of America

105. Claim 1 of patent no. US 6,297,995 defines an extract which contains four main components, the extract also being defined by its production process.

106. Claim 1 of patent no. US 6,428,824 defines the use of this extract in a method for the treatment of sexual dysfunction.

107. Taking into account the fact that a Lepidium extract has not been described which contains the macamide component (d), nor is a process described with two extraction steps, using firstly 90 per cent water and subsequently 90 per cent alcohol, with a publication date prior to March 3, 1999, both claim 1 of patent no. US 6,297,995 and claim 1 of patent no. US 6,428,824 appear to meet the requirement of novelty, since only aqueous, alcohol or hydroalcohol extracts, or successive extractions, have been described, but with the use of four solvents (references 1, 4, 5 and 7).

108. Since the final composition obtained in claim 1 is a strong alcohol, as this relates to an alcohol extract, it is considered that the closest prior art is reference 4 which also describes an ethanol extract of maca and its production process, using alcohol rectified in a laboratory or a domestic maceration using strong alcohol, rum or cane alcohol, an extraction which contains between 20 and 40 g of the maca root per liter of alcohol.

109. In accordance with examples 2 and 3 of the patent description, it is clear that in:

- example 2 of the American patent 500 mg of maca root is used together with 14 liters of water, thereby obtaining an extract which evaporates completely until 20 g of a product is obtained, containing 0.01 per cent of esterols, 0.1 per cent of fatty acids, nine per cent of amino acids and 44 per cent of polysaccharides;
- example 3, the residue of example 2 is used, which is extracted with 15 liters of 100 per cent SDA alcohol, i.e. 33.3 g per liter of alcohol, thereby obtaining an extract which evaporates completely until 10 g of a product is obtained, containing 7.8 per cent benzyl isothiocyanate, 1.8 per cent esterols, 22 per cent fatty acids and 12 per cent macamide component.

110. Although reference 4 describes a single-step process using ethanol, the fact that it mentions that in this extraction process components such as proteins and carbohydrates would be lost, owing to the fact that they are not soluble in ethanol, this may suggest the need to find a process in which these components are not lost, which actually occurs in the claimed process that, by means of the first aqueous extraction, allows nine per cent of amino acid component and 44 per cent of polysaccharide component to be recovered, and it is therefore OBVIOUS in relation to reference 4, since the selection of water as a solvent in accordance with the solubility known for these components is predictable.

111. In relation to the components of the extract, the fact that the first three components are known as components of maca and are attributed mainly to the benzyl isothiocyanate components and esterols with biological activity, appear to make it necessary to demonstrate the advantages of an extract with macamide component over another extract which does not contain that component, for which reason the comparison made in examples 9 to 11 for examples 1 and 5 provides insufficient evidence, and since it deals with component mixtures of different concentrations does not allow a correct comparison to be made. Thus, although in example 5, 4.4 per cent of macamide is detected, a larger quantity of benzyl isothiocyanate (4.1 per cent) and esterols (0.4 per cent) than that detected in example 1 (0.89 and 0.079 per cent) is also observed, as may be noted in the following table:

Component	Example 1	Example 5
Benzyl isothiocyanate	0.89%	4.1%
Lepidium esterols	0.079%	0.4%
Lepidium fatty acids	1.46%	12%
Macamide components		4.4%
Amino acids	8.72%	
Polysaccharide	41.9%	
Total of solids	77%	

112. Since there is no proof to demonstrate the unexpected advantages of the claimed extract, in that it has ten per cent or more of macamides, this does not meet the requirement of inventive step.

113. Patent no. US 6,428,824 is a fractional application of patent no. US 6,267,995, and in claim 1 therein reference is made to the use of the extract defined by four components for the treatment of sexual dysfunction.

114. In the article by Johns, cited in the International Search Report, and in reference 3, details are given of the benzyl isothiocyanate component, derived from a glycoside, and of the esterols with biological activity. Reference 4 describes how the alkaloids and a number of glycosides will be found in an ethanol extract. In reference 7, it is noted that an ethanol extract of maca may favor fertility. Taking into account that the revised report does not provide a better demonstration of the beneficial effect of the macamide component, it may be concluded, in accordance with the description given by Johns and references 3 to 7, that it is OBVIOUS that an alcohol extract, in containing benzyl isothiocyanate and esterols among its components, will maintain the traditional use attributed to maca as an aphrodisiac and a fertilizing agent.

115. On the other hand, it should be highlighted that many references exist by various authors who, working both with maca extracts and the cooked and liquefied plant, have tested this beneficial effect on animals, as may be noted in reference 1 where an alkaloid extract is tested in rats and toads: reference 2 in lambs, reference 3 in rats and reference 7 in mice; the conclusion of all such authors is that maca possesses a beneficial effect on fertility.

116. In conclusion, the claims included in patents nos. US 6,267,995 and US 6,428,824 are suggested by the new prior art compiled by the working group, thereby affecting its inventive step.

IX. IN ADDITION TO PATENTS

(i) Access to genetic resources

117. The patents referring to *Lepidium meyenii* also bring to light problems connected with the method of access to these materials and whether compliance has been achieved with the basic principles of the CBD and with the relevant legislation in force in the Andean region and Peru (specifically with *Decision 391 concerning a Common Regime on Access to Genetic Resources*). Attention is drawn to the fact and concern expressed that the intellectual property regime (in this specific case that relating to patents) grants rights over materials and resources which could have been obtained unlawfully, contrary to the specific Decision 391 or even the rules in force for collecting and exporting biological materials.

(ii) Protection of knowledge

118. *Lepidium meyenii* has been known and used in various ways and for different purposes by indigenous populations in Peru since time immemorial. One question which arises as a result of the patents analyzed is the degree of indigenous knowledge which was used to generate the claimed inventions. In addition to whether or not rules exist for regulating or protecting indigenous knowledge, or whether it is possible to do so once this knowledge is disseminated outside the sphere of the communities in question, it is obvious that at any point in time during the scientific process of research and development (recent or past), which gave rise to these inventions, this knowledge must have been used directly or indirectly.

X. CONCLUSIONS AND FINAL REMARKS

(i) As regards the international patent application, some of the analyzed claims do not meet the requirement of *novelty*; although certain others do, they do not meet the requirement of *inventive step*; finally, since the biological activity of the isolated compounds of claims 13 to 15 has not been demonstrated, these claims do not appear to meet the requirement of *industrial applicability*. In sum, the claimed invention does not appear to be patentable in these terms.

On the other hand, as regards the inventions claimed in American patents, from the analysis made it is concluded that they do not meet the requirement of inventive step. In this regard, these patents are very questionable from a legal point of view.

(ii) Six of the seven inventors mentioned in the patents of the United States of America and international applications analyzed recognize that they obtained dry maca roots from Peru in 1998[2]. However, there is no evidence that: (i) these materials have been lawfully obtained from Peru or that they comply with the corresponding national legislation, and (ii) that provision has been made for the equitable sharing with the country of the benefits derived from the use of these patents.

(iii) A third conclusion which emerges from the work of this group is the enormous difficulty encountered by the country in its attempts to challenge or question, for administrative or legal reasons, in the United States or Europe, patents of this nature. Although the rules of the game are clear, the reality is that even where we wish to use them, the costs, time, and need for specialized advice make effective action in relation thereto and other similar patents very difficult. Any action taken after the event is prohibitively expensive.

(iv) The methodology used by the Working Group, combining local and international experience, complementing the scientific and legal capabilities, and acting in an open and participation-based manner, make it possible to conclude that as an area for evaluating and analyzing similar patents, this form of work is appropriate and it is to be hoped that the possibility arises to institutionalize the functioning and operation of a national group or committee which is directly responsible for cases such as that analyzed.

(v) This national group or committee should assess a monitoring or early-warning mechanism, providing familiarity with similar situations where, through the use of materials or components of national biological diversity (without following the corresponding procedures) or ancestral knowledge of our communities (without their consent), or through a mistaken interpretation of the specific rules or principles of intellectual property, attempts are made to invoke particular rights. In addition, the group must establish a channel of communication with patent and intellectual property offices in other countries so that they request information from it when applications on resources or materials of Peruvian origin are filed.

(vi) It has remained clear that, although much literature and information exists (a great deal of which is clearly documented and is in the public domain) on *Lepidium meyenii*, access to this information (and its general availability) is at times difficult. This explains why patent offices from third countries have not institutionalized the practice of revising documents and literature which could refer to ancestral uses of components of biological diversity by indigenous peoples or to different manifestations of traditional indigenous knowledge. These practical difficulties affect the possibilities for rigorous and comprehensive examinations of patent applications, giving rise, in many cases, to the granting of rights of doubtful legitimacy.

---

[2] See B. Zheng, K. He, C. Kim, L. Rogers, Y. Shao, Z. Huang, Y. Lu, S. Yan, L. Qien and Q. Zheng, 2000. Effect of a lipidic extract from *Lepidium meyenii* on sexual behavior in mice and rats. Urology 55 (4): 598-602.

(vii) The latter gives rise to the need to evaluate how it would be possible to organize and systematize much of this information and the role that could be played by a national database in that regard. In summary, how is it possible to articulate this database and information with the search procedures and examinations of the main patent offices throughout the world in order to avoid patents being granted on the basis of partial and limited examinations of novelty and inventive step.

(viii) Such principles and rules contained in the Andean Community Legislation (Decision 486 on the Common Industrial Property Regime), Costa Rica, Brazil and some other countries, in which supervision of the origin of biological materials and knowledge which could be part of an invention (especially in the biotechnology field) is required, and where it is even necessary to demonstrate the legal provenance of these materials as a requirement for the processing of patent applications, should be incorporated in international patent legislation and the domestic legislation of all countries. This is an alternative for avoiding cases of biopiracy in which attempts are made to invoke rights over products which incorporate materials unlegally or unlawfully obtained and used.

(ix) As the country of origin of a great variety of native crops with commercial and industrial potential, it is to be hoped that in the future in Peru cases similar to that of Lepidium meyenii continue to be presented. In that regard, there is an urgent need for the development of a standard for protection of native crops.

(x) As the country of origin, Peru should consider the possibility of participating much more actively in the research and development processes relating to plants and biological materials and, especially, being party to the benefits derived from the products resulting from such research and development. For that purpose, a national legal regime is required to generate appropriate incentives for cooperation in research and development.

(xi) As a final comment, it will be very difficult to generate appropriate incentives for the preservation of biological diversity and compliance with the CBD in general, not only where cases such as the subject of analyses in this report are presented but, for example, situations such as those imposed by the European regulations on *Novel Foods* arise (*European Communities* Regulation (EC) 258/97 of January 27, 1997) which have already led to restrictions on the export of maca from Peru to Europe.

These initiatives place at risk any possibility of exporting products prepared from the biodiversity existing in Peru, since as they are considered to be novel foodstuffs or medicinal plants, it should be verified that their use is not harmful to human beings, which would be very costly and complicated for our country. This specific point does not deal in a precise manner with the subject of patents, but there is a cumulative effect in the sense of biopiracy on the one hand, and trade restrictions on the other. In essence, it places at risk sustainable business which seeks precisely to give value to biodiversity and thereby provide an incentive for its preservation and better use. In the final analysis, it places at risk the political and regulatory agreements assumed as a party to the CBD, insofar as, in practice, the options of countries such as Peru are limited and it simply becomes impossible for the country to meet its obligations.

Lima, May 8, 2003.

References cited for the present report

1. Adamczyk, M. y Grote, J. 1996. *Pseudomonas cepacia Lipase Mediated Amidation of Benzyl Esters*. Tetrahedron Letters, Vol. 37, No. 44: 7913-7916.

2. Alvarez, C. 1993. *Utilización de diferentes niveles de maca en la fertilidad de cobayos . Tesis.* Universidad Nacional Daniel Alcides Carrión. Facultad de Ciencias Agrícolas, Cerro de Pasco, Perú.

3. Brako L. y J.L. Zarucchi. 1993. Catalogue of the flowering plants and gymnosperms of Perú. Monograph in Systematic Botany from the Missouri Botanic Garden 45: 1-1286.

4. Cobo, B: 1956. *Historia del Nuevo Mundo*. Biblioteca de Autores Españoles 81: 430.

5. Condor Suriaqui, Dalmiro Anibal. 1991. *Influencia de la maca en el incremento de peso en la reproducción y descendencia de borregas en la cooperativa comunal San Ignacio de Junín. Tesis para optar el título de ingeniero zootecnista en la Universidad Nacional Daniel Alcides Carrión, Cerro de Pasco.*

6. Chacón Roldán, G. 1961. *Estudio fitoquímico de Lepidium meyenii Walp*. Tesis, Universidad Nacional Mayor de San Marcos, Lima, Perú. 43 pp.

7. Chacón de Popovici, G. 2001. *Maca (Lepidium peruvianum Chacón). Planta milenaria del Perú, con propiedades altamente nutricional y medicinal*. Lima, Perú. 225 p.

8. García, A. y V. Chirinos (eds). 1999. *Manual Técnico de Producción de Maca. Recetas culinarias de la maca ¡Poderoso Reconstituyente!* Agronegocios No. 4, Lima, Perú pp 217-224.

9. *Instituto Geográfico Nacional.* 1989. Atlas del Perú, Lima, Perú. 400 p.

10. Jerí, H. 1999. *Evaluación nutricional. En: Manual técnico de producción de maca. Agronegocios No. 4, Lima, Perú.* pp 108-117.

11. Johns, T. 1980. Ethnobotany and phytochemistry of *Tropaeolum tuberosum* and *Lepidium meyenii* from Andean South-America. MSc. Thesis, Univ. of British Columbia, England, 113 p.

12. Kianian S.F. & C.F. Quirós. 1991. Genetic analysis of major multigene families of *Brassica oleracea* and related species. Genome 35: 516-527.

13. Lama, G., Quispe, G., Ramos, D., Ferreyra, C., Casas, H. and Apumayta, U. 1994. *Estudio de la propiedad estrogénica del Lepidium meyenii Walp (maca) en ratas. En: Resumenes de los trabajos, II Congreso Nacional de Ciencias Farmacéutica y Bioquímicas "Marco Antonio Garrido Malo", 17-21 octubre de 1994. Lima, Perú.* p. 73.

14. León, J. 1964. The "Maca" (*Lepidium meyenii*), a little known food plant of Peru. Economic Botany 18(2):122-127.

15. Li, G., U. Ammermann and C.F. Quirós. 2001. Glucosinolate contents of maca (*Lepidium peruvianum* Chacón) seeds, sprouts, mature plants and several derived commercial products. Economic Botany 55(2):255-262.

16. Obregón, L. 1998. *"Maca" Planta medicinal y nutritiva del Perú.* Instituto de Fitoterapia Americano, Lima, Perú.

17. Ochoa C. y D. Ugent. 2001. Maca (Lepidium meyenii Walp.: Brassicaceae): A nutritious root crop of the Central Andes", Economic Botany 55(3):344-345.

18. Ponce, D. 1999. *Avances logrados en el mejoramiento genético de la maca* (*Lepidium meyenii*, Walp.) *en Maca, Memoria del Primer Curso Nacional de Maca*. Grupo ECO, Lima, Perú p. 67-74.

19. Pulgar, J. 1978. *La Maca y el uso de la región Puna VIII*. Periódico "Expreso", 4 de julio de 1978. Lima, Perú. p. 18.

20. Quirós, C., Epperson, A., Hu, J. y Holle, M. 1996. Physiological studies and determination of chromosome number of maca, *Lepidium meyenii* (*Brassicaceae*). Economic Botany 50 (2): 216-223.

21. Quirós C. y Aliaga, R. 1997. Maca (*Lepidium meyenii* Walp.). Andean roots and tubers: Ahipa, arracacha, maca and yacon. Promoting the conservation and use of underutilized and neglected crops. 21. (M. Hermann and J. Heller, eds.). Institute of Plant Genetic and Crop Plant Research, Gatersleben / International Plant Genetic Resources Institute, Rome, Italy. pp. 173-197.

22. Rea, J. 1992. *Raíces andinas: Maca. Pp. 163-166 in Cultivos marginados, otra perspectiva de 1492* (J.E. Hernádez Bermejo y J.E. León, eds.) FAO, Roma.

23. Retuerto, F., De los Santos, M., Barreto, T. y Lezama, M. 1996. *Efectos citostáticos del extracto etanólico de Lepidium meyenii W. en células meristemáticas de Allium cepa L. En: Libro de resumenes, V Reunión Científica, Instituto de Investigación de Ciencias Biológicas "Antonio Raimondi" (ICBAR), 13-15 de marzo de 1996.* Lima, Perú.

24. Ruiz, H. 1952. *Relación histórica del viaje a los reinos del Perú y Chile, 1777-1778*, Madrid Acad. de Ciencias Exactas: Fis y Nat. 1: 526.

25. Steinmetz K.A. y Potter, J.D. 1996. Vegetables, fruit, and cancer prevention; a review. J Am Diet Assoc, Oct 96 (10): 1027-1039. Summary only.

26. Tello, R. y Porras, M. 1999. *Estudio técnico para la elaboración de licor de maca (Lepidium meyenii walp) por maceración. Trabajo de investigación.* Universidad Nacional del Centro del Perú. Instituto de Investigación de la Facultad de Ingeniería en industrias alimentarias. Huancayo, Perú.

27. Toledo J., P. Dehal, F. Jarrín, M. Hermann, I. Al-Shehbaz and C.F. Quiros. 1998. Genetic variability of *Lepidium meyenii* and other Andean *Lepidium* species (Brassicaceae) assessed by molecular markers. Annals of Botany 82: 523-530.

28. Valdivia, M.E., Del Valle, J.M., Ruiz, M.A., Maima, N.V. y Poma, J.G. 1998. *Efecto de la soya y maca sobre la morfología y fisiología espermática en ratones.* En: VII Congreso Iberoamericano de Biología celular, Sociedad Ibero-americana de Biología celular, 26-30 de octubre de 1998. Montevideo, Uruguay.

29. Verhoeven, D., R. Goldbohm, G. van Poppel, H. Verhagen y P. van den Brandt. 1996. Epidemiological studies on brassica vegetables and cancer risk. Cancer Epidemiology Biomarkers and Prevention. Vol. 5, Issue 9:733-748.

30. Wattenberg, L.W. 1977. Inhibition of carcinogenic effects of polycyclic hydrocarbons by benzyl isothiocyanate and related compounds. J. Natl. Cancer Inst., February 1, 1977; 58(2):395-398. Summary only.

31. Wattenberg, L.W. 1983. Inhibition of neoplasia by minor dietary constituents. Cancer Research 43(5):2448s-2453s. Summary only.

32. Wattenberg, LW. 1987. Inhibitory effects of benzyl isothiocyanate administered shortly before diethylnitrosamine or benzo[a]pyrene on pulmonary and forestomach neoplasia A/J mice. Carcinogenesis 8 (12): 1971-1973. Summary only.

33. Wattenberg, L.W. 1990. Inhibition of carcinogenesis by minor anutrient constituents of the diet. Proc. Nutr. Soc. July 1, 1990; 49(2):173-183.

34. Zolezzi, O. 1997. *Transformación de la uña de gato y la maca en el Perú. En: Tercer Encuentro de la Agroindustria Rural.* Tarapoto, Perú. pp 31-38.

35. Zúñiga, E. 1992. *El cultivo de la maca* (*Lepidium meyenii*, Walp.). Agronomía, XL (2): 54-56.

List of additional references relevant to*maca*

1. Aguila Calderón, J. y Chacón de Popovici, G. 1998. *El valor nutricional de la "maca" (Lepidium peruvianum Chacón) en niños anémicos por desnutrición. Trabajo presentado al II Curso nacional de maca. Huancayo, del 3 al 5 de diciembre de 1998.*

2. Aliaga, R. 1999. *Guía para el cultivo, aprovechamiento y conservación de la maca Lepidium meyenii Walpers.* Convenio Andrés Bello. Santa Fe, Colombia. 50 pp.

3. Arroyo Acevedo, J. y Sandoval de Arroyo, S. 1997. *Inocuidad de la maca (Lepidium peruvianum Chacón) con respecto a la DL50.* Sección Farmacología de la Facultad de Medicina Humana de la Universidad Nacional Mayor de San Marcos.

4. Bauer, R., Remiger, P. and Wagner, H. 1988. Alkamides from the roots of *Echinacea purpurea*. Phytochemistry, 27(7): 2339-2342. Summary only.

5. Bauer, R., Remiger, P. and Wagner, H. 1989. Alkamides from the roots of *Echinacea angustifolia.* Phytochemistry 28(2): 505-508. Summary only.

6. Cabieses, F. 1997. *La maca y la puna.* Universidad San Martín de Porres. Primera edición. Lima, Perú. pp. 65-94.

7. Capcha, R., Rojas, P., Aguilar, J. 2000. *Toxicidad Aguda (DL50) para dos extractos estandarizados de Uncaria tomentosa (Willd.) DC. y un extracto de Lepidium meyenii (maca) rico en glucosinatos.* Summary book of First International Congress FITO 2001. Lima, Perú. Pp. 159-160.

8. Castro de León, M. 1990. An Andean crop in extinction: Case of maca. Perú Indig. 12(28): 85-94.

9. Chacón de Popovici, G. 1990. *La maca (Lepidium peruvianum Chacón sp.nov.) y su habitat.* Revista Peruana de Biología 3(2) : 171-267.

10. Chacón de Popovici, G. 1997. *La importancia de Lepidium peruvianum Chacón (Maca) en la alimentación y salud del ser humano y animal, 2000 años antes y después de Cristo y en el siglo XXI.* Servicios Gráficos Romero. Lima, Perú. 137 pp.

11. Chacón de Popovici, G. 1998. *Análisis cuali-cuantitativo de los 31 elementos de la "Maca" (Lepidium peruvianum Chacón) y otros alimentos nativos del Perú. Trabajo presentado al II Curso nacional de maca.* Huancayo, del 3 al 5 de diciembre de 1998.

12. Chacón de Popovici, G. 1999a. *Estudio ecológico, fitoquímico y farmacológico de Lepidium peruvianum Chacon ("maca").* In Maca: Memories of First Course on Maca. ECO. Lima, Perú. pp. 23-42.

13. Chacón de Popovici, G. 1999b. *La maca: Alimentación y salud. INDOAGRO, FONDE. Agronegocios No. 4.* Lima, Perú. pp. 50-60.

14. Cicero, A., Bandieri, E., Arletti, R. 2001. *Lepidium meyenii* Walp. improves sexual behaviour in male rats independently from its action on spontaneous locomotor activity. Journal of Ethnopharmacology 75 (2001): 225-229.

15. Cicero, A., Piacente, S., Plaza, A., Sala, E., Arletti, R., Pizza, C. 2002. *Hexanic Maca* extract improves rat sexual performance more effectively than methanolic and chloroformic Maca extracts. Andrologia 34: 177-179.

16. Cole, R. 1976. Isothiocyanates, nitriles and thiocyanates as products of autolysis of glucosinolates in Cruciferae. Phytochemistry 15(5): 759-762.

17. Cóndor, D. 1994. *Efecto de diferentes niveles de maca en raciones de crecimiento para cuyes.* [Effect of diffeent maca (*Lepidium meyenii* WALP) levels on growth rations for guinea pigs]. In: Summary Book of research on guinea pigs. INIA. pp. 146.

18. Cuentas Jara, M.J., Domínguez Calderón, J.L., Mendoza Cabanillas, M.C., Mendoza Chávez, H., Montoya Henriquez, J.G., Mori Quispe, N. y Pérez Díaz, D.S. 2000. *Efectos del extracto alcaloideo de maca (Lepidium peruvianum G. Chacón) en la función testicular normal y la alterada por administración de decanoato y de nandrolona. Trabajo de investigación.* Universidad Nacional Mayor de San Marcos, Sección de Farmacología de la Facultad de Medicina Humana.

19. Dini A., Migliouolo G., Rastrelli L., Saturnino P. and Schettino O. 1994. Chemical composition of *Lepidium meyenii*. Food Chemistry 49: 347-349.

20. Ganzera, M., Zhao, J., Muhammad, I., and Khan, I. 2002. Chemical profiling and standardization of *Lepidium meyenii* (Maca) by Reversed Phase High Performance Liquid Chromatography. Chem. Pharm. Bull. 50(7): 988-991**.**

21. Garró, V., León, E. & Julca, B. 1993. *Extracción, separación e identificación por cromatografía de alcaloides de Lepidium meyenii WALP (maka).* Summary book VI Peruvian Meeting of Pharmacy and Biochemistry. Lima, Perú. pp 50.

22. Gómez, A. 1997. *Maca, Es alternativa nutricional para el año 2000. Report "Ojo con su Salud"* No. 58 August 15. Lima, Perú.

23. Gonzales, A. 1995. *La maca: cultivo y usos.* INIA. Lima, Perú. pp. 16.

24. Gonzales, W. 1995. *Cultivos andinos: La maka, alimento seleccionado con esfuerzo y sabiduría. Agroenfoque 47: 24-25.* Lima, Perú.

25. Gonzales, F., Villegas, L., Cordova, A., Ruiz, A., Gonzales, C., Rubio, A. 2001a. *Efecto del extracto acuoso de Lepidium meyenii (maca) sobre la espermatogénesis en ratas.* Summary book of First International Congress FITO 2001. Lima, Perú. pp. 153.

26. Gonzales, G., Cordova, A., Gonzales, C., Chung, A., Vega, K. & Villena, A. 2001b. *Lepidium meyenii* (Maca) improved semen parameters in adult men. Asian Journal of Andrology 2001 Dec; 3: 301-303.

27. Gonzales, G., Ruiz, A., Gonzales, C., Villegas, L., Cordova, A. 2001c. Effect of *Lepidium meyenii* (maca) roots on spermatogenesis of male rats. Asian journal of Andrology 2001 Sep; 3: 231-233.

28. He, X., Lin, L., Bernart, M. y Lian, L. 1998. Analysis of alkamides in roots and achenes of Echinacea purpurea by liquid chromatography–electrospray mass spectrometry. Journal of Chromatography vol. 815(2): 205-211. Summary only.

29. Illescas, Ma.G. 1994. *Estudio químico y fitoquímico comparativo de tres ecotipos de Lepidium meyenii Walp "maca" procedente de Carhuamayo (Junin). Trabajo de Aptitud Profesional para optar el título de Químico Farmacéutico,* Univ. Nac. Mayor de San Marcos, Lima, Perú.

30. Instituto Italo Latinoamericano (IILA). 1998. *La Maca 'Il ginseng delle ande' e alter radici e tuberi andini, contributo alla conoscenza e valorizzaziones delle risorse vegetali e animali dell'America Latina. IILA.* Serie Scienza no. 10. pp 24-25.

31. Jaramillo-Arango, J. 1952. *Relación histórica del viage, que hizo a los reynos del Perú y Chile el botanico D. Hipolito Ruiz en el año de 1777 hasta el de 1788, en cuya epoca regreso a Madrid.* Royal Academiy of Exacts, Physics and Natural Sciences of Madrid. Madrid, Spain. Pp. 78-79, 121-123.

32. Jerí, H. 1995. *Evaluación Químico-Farmacológico del Lepidium meyenii Walp (Maca-maca). Cultivos andinos*, special number Vol. 5, year 5, N°1. pp 74-75.

33. Johns, T. 1981. The añu and the maca. J. of Ethnobiology 1(2): 208-212.

34. Johns, T. 1986. Chemical selection in Andean domesticated tubers as a model for the acquisition of empirical plant knowledge. In: Plants in indigenous medicine and diet: Biobehavioural approaches. Edited by N.L. Etkin. Redgrave, New York, USA. Pp 268-288.

35. King, S.R. 1987. Four endemic tuber crops: Promising food resources for agricultural diversification. En: Mountain Research and Development, Vol. 7, No. 1: 43-52

36. King, S.R. 1988. Economic botany of the Andean tuber crop complex: *Lepidium meyenii, Oxalis tuberosa, Tropaeolum tuberosum* and *Ullucus tuberosus*. PhD Thesis. The City University of New York. USA.

37. Kjaer A and Wagnieres M; 1971. 3,4,5-trimetoxybenzylglucosinolat a constituents of Lepidium sordidum; Phytochemistry 10, 2195-2198.

38. Kjaer A: and Schuster A., 1968. Glucosinolats in Lepidium bonariense L.; Phytochemistry. 7, 1663-1666.

39. Lehninger A. 1987. *Bioquímica. Las bases moleculares de la estructura y función celular* [Biochemistry. Molecular basis of cellular structure and function]. Omega, S.A. Barcelona, Spain. pp 287-288.

40. León, C. 1986. *Un proyecto en marcha.* A project underway. AgroNoticias No. 83. September 1986. Lima, Perú. Pp 22-23.

41. Li, G., Ammermann, U. y Quirós, C. 2001. Glucosinolate contents in maca (*Lepidium peruvianum* Chacón) seeds, sprouts, mature plants and several derived commercial products. Economic Botany 55(2): 255-262.

42. Lobatón W. 1986. *Maca: Mejor que el famoso gingseng koreano. Un proyecto en marcha, Maca: Maná andino.* AgroNoticias No. 83. September 1986. Lima, Perú. pp 20-22.

43. Madrid Gironda, F. y Chacón de Popovici, G. 1998. *Acción fertilizante de la maca (Lepidium peruvianum Chacón) en perras sin celo. Trabajo presentado al II Curso nacional de maca. Huancayo, del 3 al 5 de diciembre de 1998.*

44. Marín Bravo, M. J. 2002 *Estudio morfohistológico y farmacológico de Lepidium meyenii Walpers (maca).* Tesis, Universidad Nacional Mayor de San Marcos, Escuela de Post Grado, Facultad de Farmacia y Bioquímica, Unidad de Post Grado. Lima, Perú.

45. Matos Tovar, T. 1995. *Efecto de la "maca" (Lepidium meyenii Walp.) en la presentación de celo en vaquillas Holstein en el establo "Chacra Valdivia" Matahuasi-Concepción.* Tesis. Facultad de Zootecnia. Universidad nacional del Centro del Perú. Huancayo, Perú. 78 pp.

46. Meza E. 1995. *Efectos de la maca (Lepidium meyenii Walp.) sobre los parámetros productivos y reproductivos de cuyes raza Wanka.* Tesis, Universidad Nacional del Centro del Perú. Facultad de Zootecnia. Huancayo, Perú.

47. Miura, T., Hayashi, M., Naito, Y., Suzuki, I. 1999. Antihypoglycemic effect of maca in fasted and insulin-induced hypoglycemic mice. Journal of Traditional Medicine 16, 93-96.

48. Molina-Torres, J., García-Chávez, A. and Ramírez-Chávez, E. 1999. Antimicrobial properties of alkamides present in flavouring plants traditionally used in Mesoamerica: affinin and capsaicin. Journal of Ethnopharmacology vol 64 (3): 241-248. Summary only.

49. Moreno, J. 1995. *Maca (Lepidium meyenii Walp): Recurso genético patrimonio del Perú para la humanidad. Agroindustriales de Productos Andinos. Lima, Perú. 79 pp.*

50. Muhammad, I., Zhao, J., Dunbar, D. and Khan, I. 2002. Constituents of *Lepidium meyenii* 'maca'. Phytochemistry 59: 105-110.

51. Obregón, L. 2001a. "Maca" (*Lepidium meyenii* WALP, *Lepidium peruvianum*). First International Symposium of Medicinal Plants and Phytotherapy FITO 2001. American Phytotherapy Institute. Lima, Perú. Pp 47-50.

52. Obregón, L. 2001b. Investigaciones en "Ajo" *Allium sativum* L. y "Maca". First National Course on Medicinal Plants and Phytotherapy. Conferences and Workshops. Lima, Perú. Pp 50-51.

53. Pulgar, J. 1978a. *La Maca y el uso agrícola de la puna IV. Periódico "Expreso", 29 de mayo de 1978. Lima, Perú. p. 12.*

54. Pulgar, J. 1978b. *La Maca y la región natural puna VI. Periódico "Expreso", 20 de junio de 1978. Lima, Perú. p. 10.*

55. Pulgar, J. 1978c. *La Maca y la región natural puna VII. Periódico "Expreso", 26 de junio de 1978. Lima, Perú. p. 12.*

56. Pulgar, J. 1978e. *La Maca y el uso agrícola de la puna IX. Periódico "Expreso", 15 de julio de 1978. Lima, Perú. p. 18.*

57. Química Suiza. 1998. *Monografía de Presentación: Maca Andina Naturalfa. Lima, Perú.*

58. Quiros, C. 1999. *Genética de la maca y especies relacionadas. Curso Taller Internacional de la maca. Universidad Nacional Agraria La Molina, del 14 al 18 de julio de 1999. Lima, Perú.*

59. Reyna, J., Gómez-Sáchez, I., Gagliuffi, A. and Ildefonso, C. 1995a. *Cultivos Andinos parte I: Evaluación químico-nutricional de la maca (Lepidium meyenii WALP). Agroenfoque 75: 44-46. Lima, Perú.*

60. Reyna, J., Gómez-Sáchez, I., Gagliuffi, A. y Ildefonso, C. 1995b. *Cultivos Andinos parte II: Evaluación químico-nutricional de la maca (Lepidium meyenii WALP). Agroenfoque 76: 51-52. Lima, Perú.*

61. Roberts J. and Caserio M. 1964. Basic principles of organic chemistry. W.A. Benjamin, Inc. New York. Pp. 528-536, 674-681.

62. Salas, A., Uriarte, O. 1997. *Investigación de los efectos de la Maca (Lepidium meyenii) en la nutricion y la actividad vigorizante en ratones.* Summary book of Peruvian Congress on Nutrition. Lima, Perú.

63. Solis, R**.** 1997. *Valor Nutricional, morfología, clasificación de las especies de maca cultivadas en la zona altoandina de Pasco, su uso y formas de cultivo por la comunidad.* Summary Book, IX International Congress of Andean crops. Cuzco, Perú. p. 63.

64. Sandoval, M**.** 1986. *Virtudes fecundantes de la maca* [Fertility virtues of maca]. *Revista Alimentaria No. 7 : 16-18.*

65. Tapia, A., López, C., Marcelo, A., Canales, M. & Aguilar, J. 2000. *La maca (Lepidium meyenii) y su efecto anti-estrés en un modelo animal en ratones* [Maca and its anti-stress effect on an animal model in mice. Acta andina (1999-2000) 8: 31-37.

66. Tello, J., Hermann, M., Calderon, A. 1992. *La maca (Lepidium meyenii WALP): cultivo alimenticio potencial para las zonas altoandinas.* Boletín de Lima No. 81: 59-66.

67. Torres, R. 1984. *Estudio nutricional de la maca (Lepidium meyenii Walp) y su aplicación en la elaboración de una bebida base. Tesis.* Universidad Nacional Agraria La Molina. Lima, Perú.

68. Torres, R., Lastarria, H., Scarpati, Z**.** 1986a. *Estudio de los componentes de la maca (Lepidium meyenii WALP). Anales Científicos UNALM XXVI: 249-259*

69. Torres, V., Lastarria, H. and Scarpati, Z. 1986b. *Elaboración de una bebida base a partir de maca (Lepidium meyenii Walp). Anales Científicos UNALM XXVI: 261-270.*

70. Valdivia, M. Stimulation of sperm function by a natural product derived from the peruvian herb *Lepidium meyenni Walp* "Maca". *Resumen presentado en: International Conference of Reproductive Biology, Slovak Academy of Sciences, 1-3 de setiembre del 2000.*

71. Vargas L. 1989. *La maca: Maravilloso afrodisiaco. Revista Globo 23-09-89. Lima, Perú. pag. 14-15.*

72. Vásquez de Espinosa, A. 1969. *Compendio y Descripción de las Indias Occidentales. Biblioteca de Autores Españoles. Madrid, España. Pp. 330-332, 355.*

73. Wattenberg, LW. 1981. Inhibition of carcinogenic-induced neoplasia by sodium cyanate, tert-butyl isocyanate, and benzyl isothiocyanate administered subsequent to carcinogen exposure. Cancer Research, August 1981, 41(2): 2991-2994. Summary only.

74. Yllescas, M[a].G. 1994. *Estudio químico, fitoquímico comparativo de tres ecotipos de Lepidium meyenii Walp "maca" procedente de Carhuamayo (Junin). Trabajo de Aptitud profesional para optar el titulo de Químico Farmacéutico*, Univ. Nac. Mayor de San Marcos, Lima, Perú.

75. Zheng, B., He, K., Kim, C., Rogers, L., Shao, Y., Huang, Z., Lu, Y., Yan, S., Qien, L. y Zheng, Q. 2000. Effect of a lipidic extract from *Lepidium meyenii* on sexual behavior in mice and rats. Urology 55 (4): 598-602.

76. Zheng, B., He, K., Hwang, Z., Lu, Y., Yan, S., Kim, C. y Zheng, Q. Effect of Aqueous Extract from *Lepidium meyenii* on Mouse Behavior in Forced Swimming Test. 2002. En: Quality Management of Nutraceuticals. American Chemical Society, Washington, DC. pp. 258-268.

[End of Annex and of document]