

DELEGATURA DE PROPIEDAD INDUSTRIAL

SOLICITUD

PATENTE DE INVENCION

21. EXPEDIENTE No. _____

54. TÍTULO Composiciones para la
deterción, Granulación y re-
epitelización de heridas en humanos

51. CLASIFICACIÓN INTERNACIONAL _____

71. SOLICITANTE Victor Hugo Angulo Borja

DOMICILIO Esmeraldas, Ecuador

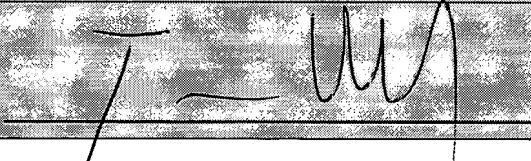
74. APODERADO Juan Carlos Uribe Restrepo

22. BOGOTÁ, D. C., Agosto 30 / 2013

 Industria y Comercio SUPERINTENDENCIA	SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO  No. 13-206064- -00000-0000 Fecha: 2013-08-30 14:51:56 Dep. 2020 DIR.NUEVASCR Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI Act. 411 PRESENTACION Folios: 137
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DIRECCIÓN
SOLICITUD FASE NACIONAL -PCT

1	TIPO DE SOLICITUD	☒ Patente de invención ☒ Capítulo I	☐ Patente de Modelo de Utilidad ☐ Capítulo II
2	DATOS SOLICITUD INTERNACIONAL PCT (86)		
Solicitud Internacional No.		PCT/ IB2012/000801	Fecha 31/01/2012
Publicación Internacional No.		WO 2012/104732 A1	Fecha 09/08/2012
3	TÍTULO DE LA INVENCIÓN (200 caracteres o espacios máximos)		
COMPOSICIONES PARA LA DETERSIÓN, GRANULACIÓN Y RE-EPITELIZACIÓN DE HERIDAS EN HUMANOS			
4	CLASIFICACIÓN INTERNACIONAL (CIP)		
A61K 35/64 (2006.01) A61K 36/81 (2006.01) A61K 36/80 (2006.01) A61K 36/41 (2006.01) A61K 36/68 (2006.01) A61P 17/02 (2006.01)			
5	SOLICITANTE (S) ☐ Esta persona también es inventor. Para datos adicionales utilizar hoja de información complementaria		
APELLIDOS O RAZÓN SOCIAL		NOMBRE	IDENTIFICACIÓN
ANGULO BORJA, VICTOR HUGO			
6	DATOS DEL SOLICITANTE		
DIRECCIÓN WILMER MOSQUERA y CARLOS ANIBAL, VICHE, ESMERALDAS, ECUADOR		No. TELÉFONO	
CIUDAD ESMERALDAS		CORREO ELECTRÓNICO	
DEPARTAMENTO/ESTADO		NACIONALIDAD O	
PAÍS DE RESIDENCIA ECUADOR		LUGAR DE CONSTITUCIÓN ECUADOR	
7	INVENTOR (ES) Para datos adicionales utilizar hoja de información complementaria		
APELLIDOS		NOMBRES	NACIONALIDAD
1. ANGULO CONFORME		NURIA SULAYNE	ECUATORIANO
2. ANGULO CONFORME		VICTOR GRACIEL	ECUATORIANO
3.			
4.			
5.			
DIRECCIÓN DE CORREO ELECTRÓNICO:			
8	DATOS INVENTOR (ES)		
PAÍS RESIDENCIA	DEPARTAMENTO/ESTADO	CIUDAD	DIRECCIÓN
1. ECUADOR		ESMERALDAS	WILMER MOSQUERA y CARLOS ANIBAL, VICHE, ESMERALDAS, ECUADOR
2. ECUADOR		ESMERALDAS	WILMER MOSQUERA y CARLOS ANIBAL, VICHE, ESMERALDAS, ECUADOR
3.			
4.			
5.			
OTRO(S) SOLICITANTE(S) Y/O (OTRO(S)) INVENTOR(ES)			
☐ Los demás solicitantes y/o (demás) inventores se indican en una hoja a continuación.			
9	☐ REPRESENTANTE LEGAL ☒ APODERADO		
APELLIDOS		NOMBRES	IDENTIFICACIÓN
URIBE RESTREPO		JUAN CARLOS	C.C. 79.159.313 T.P. 54.493
DIRECCIÓN CALLE 93B No. 12-48, Piso 4o. BOGOTÁ, D.C., COLOMBIA		No. TELÉFONO 6019660	
CIUDAD BOGOTÁ, D.C. COLOMBIA		CORREO ELECTRÓNICO tum@tumnet.com	
PAÍS COLOMBIA		No. RADICACIÓN DE PROTOCOLO DE PODER GENERAL	

10	DECLARACIONES DE PRIORIDAD ☒ SI ☐ NO			
(33) PAÍS DE ORIGEN		CÓDIGO PAÍS	(31) NÚMERO	(32) FECHA (AAAA/MM/DD)
1 ITALIA		IT	RM2011A000042	31/01/2011
2.				
3.				
11	DECLARACIÓN SOBRE USO DE RECURSOS GENÉTICOS O BIOLÓGICOS			
Declaro que el objeto de la presente solicitud de patente fue obtenido a partir de recursos genéticos o biológicos de los que cualquiera de los países miembros de la Comunidad Andina es país de origen.				
☐ SI ☒ NO				
Nota: En caso afirmativo deberá anexar copia del contrato de acceso de recursos genéticos o productos derivados, o certificado o número de registro, expedido por la Autoridad competente.				
12	DECLARACIÓN SOBRE USO DE CONOCIMIENTOS TRADICIONALES			
Declaro que el objeto de la presente solicitud de patente fue obtenido a partir de conocimientos tradicionales de comunidades indígenas, afroamericanas o locales de países miembros de la Comunidad Andina.				
☐ SI ☒ NO				
Nota: En caso afirmativo deberá anexar la licencia o autorización de uso de conocimiento tradicional, o certificado, o número de registro expedido por la Autoridad competente.				
13	REDUCCIÓN DE TASAS			
Declaro que carezco de medios económicos para presentar la solicitud de patente.				
☐ SI ☒ NO				
Nota: En caso de ser persona natural y carecer de medios económicos, y por lo tanto, aplique la reducción de tasas a que se refiere la resolución vigente en tarifas, debe firmar la presente solicitud bajo la gravedad de juramento.				
Micro, pequeñas y medianas empresas ☐				
Universidades públicas o privadas ☐				
Entidades sin ánimo de lucro ☐				
Debe aportar los documentos que se indican en el numeral 17 de anexos				
14	AUTORIZACIÓN DE NOTIFICACIÓN EN LÍNEA ☐ SI ☒ NO			
Manifiesto que he leído y entendido perfectamente los términos y condiciones de uso de medios electrónicos para las notificaciones en línea a través de Internet de los actos administrativos proferidos por la Superintendencia de Industria y Comercio que deben ser notificados personalmente y, en consecuencia, autorizo el servicio de notificación a través de internet.				
15	COMPROBANTE DE PAGO O PAGO ELECTRÓNICO	N°	Fecha	
16	FIRMA DEL SOLICITANTE, DEL APODERADO O DEL REPRESENTANTE LEGAL			
Junto a cada firma, indicar el nombre del firmante y su calidad (si tal calidad no es obvia al leer el petitorio).				
				
17	ANEXOS			
Documentación Técnica Solicitud Internacional en castellano		Documentación Jurídica		
1. ☒ Descripción N° de folios:		9. ☐ Poderes, si fuera el caso.		
2. ☒ Reivindicaciones N° Reivindicaciones: 19		10. ☐ Documento que legalmente pruebe la cesión del inventor al solicitante o a su causante.		
3. ☒ Dibujos y/o figuras N° folios:		11. ☐ Copia del contrato de acceso de recursos genéticos o productos derivados, certificado o número de registro, si fuera el caso.		
4. ☒ Resumen.		12. ☐ Copia de la licencia o autorización de Conocimientos Tradicionales, certificado o número de registro, si fuera el caso.		
5. ☐ Certificado de depósito de material biológico si fuera el caso.		13. Reducción de tasas		
6. ☐ Listado de secuencias de nucleótidos y/o aminoácidos en forma digital si fuera el caso.		Micro, pequeñas o medianas empresas		
7. ☒ Arte final 12 x 12.		☐ Copia simple de la declaración de renta del año inmediatamente anterior, o en su defecto prueba documental idónea.		
8. ☐ Anexo formato digital.		☐ Documento de constancia de cumplimiento con lo establecido en la ley 905 de 2004.		
9. ☐ TRADUCCIÓN DE ANEXOS DE REPORTE DE EXAMEN PRELIMINAR INTERNACIONAL.		Universidades públicas o privadas		
		☐ Copia acto de reconocimiento institucional emitido por el Ministerio de Educación		
		Entidades sin ánimo de lucro		
		☐ Copia de registro vigente en Cámara de comercio.		
		☐ Hoja de información complementaria.		
		☐ Otros, especificar		
		14. ☒ Comprobante de pago de la tasa de presentación de la solicitud.		
		15. ☐ Comprobante de pago por reivindicación de prioridad.		

- | | |
|--|---|
| | <p>16. ☐ Comprobante de pago de la tasa por concepto de excedente de palabras en la publicación.</p> <p>17. ☒ Comprobante de pago por reivindicación adicional a 10.</p> |
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
NIT : 800.176.089-2
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RECIBO DE CAJA

No. 13 - 0086646

Bogotá D.C., Agosto 29 de 2013 - 15:07:22

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*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR. PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	175302153	29/08/2013	770.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
9 50005-01-01	SOLICITUDES	1607 REIVINDICACION PATENTE UNITARIA ADICIONAL A LAS 10 INIC	30.000.00	270.000.00
				\$270.000.00

SON: **DOSCIENTOS SETENTA MIL PESOS MONEDA CORRIENTE***

Responsable: _____

Recibo de Caja Aplicado al Expediente No. _____

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Sede Centro: Carrera 13 No. 27 - 00 Pisos 3,4,5 y 10 Bogotá, D.C.- Colombia

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Agosto 29 de 2013 - 15:07:22

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
NIT : 800.176.089-2
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*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR.PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	175302153	29/08/2013	770.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE INVENCIÓN	500.000.00	500.000.00
				\$500.000.00

SON: **QUINIENTOS MIL PESOS MONEDA CORRIENTE**

Responsable: _____

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claims and to be republished in the event of receipt of
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(54) Title: COMPOSITIONS FOR THE DEBRIDEMENT, GRANULATION AND REEPITHELIALIZATION OF WOUNDS IN
MAN

(57) Abstract: Compositions for topical application based on natural products, specifically dried pulverized plants suspended in
bees honey, in which the ingredients are combined in proportions predetermined to provide three different types of preparations to
be applied at various stages of repair and regeneration of injured tissues. The application of the compositions shortens the stages of
healing in the treatment of acute and chronic injuries of any degree of depth and breadth, and of any etiology. The properties of the
preparations include an hemorheological and systemic vascular activity which extends for a certain period even after the end of top-
ical treatment.

WO 2012/104732 A1

**COMPOSITIONS FOR THE DEBRIDEMENT, GRANULATION AND
REEPITHELIALIZATION OF WOUNDS IN MAN**

DESCRIPTION

5

Field of the invention

The present invention concerns topical compositions for the debridement, granulation and reepithelialization of wounds in man. More particularly, this invention concerns compositions based on natural products, specifically plants and honey, combined in suitable proportions to form three different types of preparations for topical administration. Such three different types of preparations are suitable to shorten the phases of tissue regeneration in the treatment of acute and chronic wounds of any depth and extension, and of any etiology.

15

Background of the invention

As it is known, wound healing is a complex biological phenomenon aimed at filling the solution of continuity represented by the wound with a definitive structure of connective nature, the scar. Under normal conditions, the healing process is a series of events aimed to the new formation of a tissue having a function to replenish the loss of substance due to the wound. This process occurs through distinct phases, which partially overlap at different times. The methods of healing are partly different depending on whether the injuries were from a cut, such as those surgical, whose margins are sharp and which are sutured juxtaposing the edges of the wound with a minimum loss of substance, or wounds which are left open due to trauma with lacerations, or loss of tissue due to infection or burns, and that, in order to be remedied, they require the formation of a larger amount of tissue filler called "granulation", with longer times and higher risks of imperfections in the resulting scar. A third mode of healing is then the one that affects the wounds that have met post-operative complications, which require the re-opening of the wound and delicate treatments for cleansing, removing of damaged or

infected areas (which is indicated in Italian by the French term "debridement", i.e. removing necrotic matter in order to prepare the wound healing) and draining.

The process of wound repair typical of the first of the above mention
5 modes of healing, i.e. the case of injuries by cutting sutured and substantially without loss of substance, occurs first of all through an **hemostatic phase**, wherein coagulation tissue factors are activated and a clot is formed, consisting of a fibrin network in which the corpuscular elements of the blood located in the wound remain imprisoned. Then an **inflammatory phase** takes
10 place, being the typical response of the organism against pathogens, in which possible microbial agents, foreign bodies and necrotic cells are circumscribed and eliminated by neutrophil granulocytes and by macrophages, which together provide for the cleansing and debridement of wound. After the initial vasoconstriction which occurs in the hemostatic phase, the inflammatory
15 reaction is instead accompanied with a vasodilation, which makes the wound edematous and strongly reddened. As already noted in relation to the partial overlapping of the various phases of the process described here, the inflammatory reaction is also prolonged in part during the subsequent proliferative phase.

20 The **proliferative phase** is directed to replace the clot with a solid, final structure, and starts with cell proliferation of the epithelial structures, endothelial cells and connective tissue from the margins of the wound resulting in a tissue having a granular characteristic appearance, called granulation tissue. Neovascularization takes place through the formation of
25 cell outlines at the wound edges which, according to the scaffold formed by the fibrin network, proceed toward the center until joining with those from the other side and constituting a new vascular network (angiogenesis). At the same time the cells proliferation of the epithelium basal layer begins, again starting from the wound edges, and from the connective tissue the fibroblasts
30 proliferation starts. The latter are cell elements that, by secreting hyaluronic acid, give rise to the formation of collagen fibers that will serve to fill the wound.

In the healing processes of not sutured wounds, wherein a loss of substance occurred, the granulation tissue fills the wound starting from the deepest layers, and the lack of an adequate support at this stage not only prolongs the healing process, but also often provokes the irregular filling of the wound, with imperfections and hypertrophy of the resulting scar. The completion of the outer epithelial layer ends the proliferative phase.

In the later **step of maturation** and remodeling, the wound contraction continues, which began already in the previous step, and goes on even after the complete epithelialization. In the meantime the maturation takes place, as well as the rearrangement and crosslinking of collagen fibers, a process whose duration is extremely variable, and determines final consolidation of the wound area and a gradual normalization of the color of the scar. The remodeling phase can last for months or years, depending on the type of wound and on other factors that may influence the healing process.

Some local factors of the wound may indeed affect the course of wound healing, such as the intensity of the trauma, the presence of hematoma or serous collections, local infection or disease, the presence of foreign bodies or splinters, or alterations in the blood flow. Among the general or systemic factors that may affect the outcomes it is necessary to consider the age and general health of the subject, his nutritional status and possible vitamin deficiencies, the presence of some systemic diseases, especially diabetes, and the simultaneous application of certain therapies, especially the cytostatic therapies and those based on corticoids, which adversely affect the healing process.

The epithelial repair, on the other hand, appears to be influenced by other factors: it is slowed by hypothermia and accelerated by a moderate hyperthermia (up to 40°C). The significance of this fact is that an increase in the local temperature at the level of the scar, stimulates wound healing, probably by increasing of blood circulation.

It is now widely accepted that the best treatment for a normal surgical injury, is to let it evolve by itself. Only a cleaning is required, i.e., washing with physiological serum and rest, which means avoiding any kind of relaxation of

the wound and adjacent skin.

In the past, and to date, the plants have played an important role as remedies and aids in the treatment of human diseases, particularly in the treatment of wounds plants of all kinds and their derivatives have been part of the therapeutic arsenal, and among these: *Agrimonia eupatoria* (agrimony), *Arctium lappa* (burdock), *Capsella bursa-pastoris* (shepherd's purse), *Cupressus sempervivens* (mediterranean cypress), *Equisetum arvense* (puzzlegrass or horsetail), *Symphytum officinalis* (comfrey), *Echinacea spp.* (coneflower), *Rhamnus frangula* (frangula), *Fucus vesiculosus* (bladder wrack), *Arbutus uva-ursi* (bear grapes), *Gentiana lutea* (great yellow gentian), *Hedera helix* (ivy), *Citrus x limon* (lemon), *Plantago major* (plantain greater), *Zea mays* (mais), *Malva sylvestris* (mallow), *Matricaria chamomilla* (camomile), *Origanum majorana* (marjoram), *Melilotus officinalis* (melilot), *Melissa officinalis* (lemon balm), *Juglans regia* (walnut), *Carica papaya* (papaia), *Glycyrrhiza glabra* (liquorice), *Rosa gallica* (rose), *Salvia officinalis* (sage) e *Sambucus nigra* (elder). Among the currently most used medicinal plants are mentioned: *Aloe vera* o *Aloe barbadensis* (aloe), *Calendula officinalis* (calendula), *Uncaria tormentosa* (cat's claw) e *Hydrocotyle asiatica* (centella asiatica).

It is shown that many extracts topically applied exert a positive influence on wound healing, promoting increased levels of endogenous antioxidant enzymatic and non enzymatic, and promoting angiogenesis. An example worth mentioning is the extract of *Hippophae rhamnoides* L. *turkestanica* subspecies (sea buckthorn), a shrub native to Europe and Asia. The plant has been widely used in traditional oriental system of medicine for the treatment of asthma, skin diseases, gastric and lung disorders. All parts of the plant shall be deemed to a source of a large number of bioactive substances such as flavonoids (isorhamnetin, quercetin, myricetin, kaempferol and their glucosidic derivatives), carotenoids (beta-carotene, lycopene), vitamins (C, E, K), tannins, triterpenes, glycerides of palmitic, stearic and oleic acids and some essential amino acids. Thanks to the properties of the active compounds present in the plant, for example, experimental studies conducted on female rats with normal and streptozotocin-induced diabetes by means of

the extract of *Hippophae rhamnoides*, in mixtures in ratio 1:7:1 with *Aloe vera* extract and *Curcuma longa* (turmeric), showed efficacy in accelerating the healing of wounds, both acute and chronic (A. Gupta et al., *A poly-herbal formulation accelerates normal and impaired diabetic wound healing*, Department of Biochemical Pharmacology, Defence Institute of Physiology and Allied Sciences (DPAS), Delhi, India, asheesh_gupta2001@yahoo.co.in).

Among the most widely used medicinal plants worldwide, *Aloe vera* is widely used to treat many diseases, particularly of dermatology and of varying severity, including forms of diabetes. In several experiments on the treatment of wounds, about 90% of those treated with *aloe vera* gel are resolved with 72 hours earlier than those not treated with this active ingredient. In septic injury, however, recovery is much slower than with conventional treatment.

Another natural product, not directly from plant source, which is used to treat wounds since ancient times is the honey bee. Laboratory tests on animals and in vitro assays indicate that honey can accelerate wound repair due to its action on cell division, on the synthesis and maturation of collagen, the contraction and epithelialization of the wound and on improvement of nutritional. The honey has antibacterial properties, for its high content of hydrogen peroxide, as well as high levels of antioxidants that protect tissues from free radicals. Anti-inflammatory properties have been described, which reduce edema, exudate and local pain. Similarly, its acidity (pH below 4) favors the antibacterial action of macrophages, since an acid pH within the vacuoles facilitates the bacterial lysis, while it reduces the production of toxic ammonium.

It is known that in acute wounds the application of honey can reduce the healing time compared to conventional treatments; on the other hand, it has been also found that in chronic wounds honey, in addition to conventional compression bandage, does not significantly improve the healing varicose leg wound.

In order to successfully address the underlying causes of various chronic or incurable wounds of any kind, devices to restore or at least cover the surfaces of the lesions have been recently developed. Artificial substrates

dermal collagen-based are made, glycosaminoglycans, chitosan, or similar materials, in particular known by the name of "scaffold" consisting of porous three-dimensional structures to be used as matrices for the within tissue cells development to regenerate or rebuild. Such substrates promote the
5 regeneration of vascular and also nerve elements, and components of the structure of the sub-dermal connective tissue, to provide with skin grafts from autologous or artificially developed by *in vitro* culture, the environments that allow them an adequate insertion,

The skin substitutes were found to be a very useful alternative, and
10 sometimes essential in those cases in which the uncovered areas are very extensive, as happens in burns, or when for some particular conditions, autografts cannot be considered as a possibility, for example, when the area from which to obtain the skin is very painful or when there is a risk of developing scars or infection, or when there is a healing too slow. The long-
15 term studies on biopsies taken after years from the sites of application show the regeneration of the elastic fibers and partially of nerve cells, but also in this case, as in the physiological repair of tissues originally healthy, there is no regeneration of the skin attached, such as sebaceous and sweat glands and hair follicles.

20 Taking into account the persistent infection as a cause for delay or chronic wounds, medications and creams for topical application based on antibiotics were designed and built during the times, with the intention to treat or prevent infections. Among them, the silver-based creams have a global recognition. The use of silver as an antiseptic and disinfectant dates back to
25 ancient times, and was applied to the preparation of medicaments utility universally recognized as the sulfadiazine silver. In the treatment of second-degree burns the silver sulfadiazine is the preferred drug for its anti-inflammatory and stimulating of tissue regeneration action, and also for its analgesic properties.

30 Iodine is another agent commonly used in antiseptics preparations for the treatment of healing wounds, as well as certain antibiotics for topical use, generally in cream or gel, such as gentamicin, chloramphenicol, neomycin and

their combinations.

In addition, alginate based dressings (a chemokine of natural origin) have been proposed, to be used as a vehicle for active molecules to stimulate the regeneration of granulation tissue and accelerate the healing process of wounds. Some examples include alginate hydrogel patch as a vehicle for the factor-1 of stromal regeneration (SDF-1, stromal cell-derived factor-1), which is a factor stimulating tissue regeneration, or in combination with substances that increase the resistance to the infection, as in the ionic dressing alginate/silver carboxymethyl cellulose (SACMC) or also in combination with anti-inflammatory agents. In situations where it is important is to provide moisture, mainly in chronic wounds, the alginate is combined with hydrocolloids, hydrogels, foams or hydrofibres.

As is known, to prepare the wound bed of an acute or chronic wound, of traumatic or infective type, and especially of wounds in which the debris and necrotic material cover substantially the living tissue acting as a barrier which prevents or hinders the penetration and adherence of regenerative substances, a "debridement" of the lesion has to be made first. This consists in removing foreign materials or necrotic tissue, devitalized or infected in the area of the lesion, up to exposure of surrounding healthy tissue, in order to prepare the wound to regeneration. In medical practice use is made of surgical debridement, but in situations where this is hazardous because of the danger of bleeding or other complications, chemical enzymatic debridement, for example by means of collagenase, papain or papain-urea (with or without chlorophyllin) is most useful. In other circumstances a mixt debridement allows even better results.

There is also the alternative practice of using maggots for the debridement of wounds when conventional methods do not yield results, or when there is no contraindication. None of the techniques mentioned have sufficient scientific topic to be better than the others and to be recommend as a technique of choice for special cases.

Taking into account diabetic ulcers, as epidemiologically more common wounds that appear to be difficult to resolve, given the worldwide spread of

diabetes diseases, it is known that these lesions consist of the continuity of tissues that can affect, related to its importance and severity, the skin tissue, subcutaneous tissue and finally the bone tissue. The most common location is in the foot, where the lesion may involve the apical regions of the fingers, the joints between the phalanges joints, the heads of the metatarsals (plantar area), heel, the bony prominences of the ankle (tibio-peroneal-mortal talus), and leg. The involvement of the foot is very dangerous for the continuation of the disease, since it often comes to the interest of the subcutaneous tissues and bone, with infections and fistulas that can lead to amputation of the affected regions.

Clinical trial on patients with diabetes shows that in these patients all the metabolic processes are altered. In fact, one of the reasons because a person with diabetes develops serious injury, where a healthy person would have only light scratches, is in the fact that its metabolic control, despite the personal efforts and the medical one, is not the best. This situation is aggravated when the metabolic control is poor, and therefore there is a slowing of the regenerative processes and resistance to infections, and the body fluids of the patient are rather converted in excellent culture media. Under such conditions, saprophytic germs become harmful and opportunistic, fungi become invasive, facultative aerobic bacteria become anaerobic.

In studies that led to the present invention, with the aim of seeking a topical preparation that is effective to shorten the treatment of diabetic ulcers, it was found that some of the few commercially available products had a substantially debridement effect, others were only granulating and others were just re-epithelializing. Moreover, their positive effects in the beginning were reduced or suffer from some drawbacks, such as poor adhesion or poor absorption, and in some cases preparations acted as an occlusive material, in other producing excessive dehydration of the wound surface and of the wounds secretions, and further the remains of the precipitated product adhered to the wound resulting in scabs.

Specifically, the indicated preparations for the "debridement" of the wound (often improperly called, "healing", i.e. products generally proposed to

accelerate the healing of wounds, regardless of what stage of recovery process that we refer to) had beneficial effects in cleaning the beds of the wounds, but their use beyond this stage did not support the effort of the body to granulate and to fill the ulcer space with a granulation tissue. Some products marked as "granulating", that is active in stimulating the occurring and the growth of granulation tissue, strongly adhered to the tissues and acted as an occlusive material, and besides being difficult to remove, drying up the wound and produce scabs. Finally, essentially "re-epithelializing" preparations were particularly useful in the last stage of repair of a deep wound with tissue loss (or superficial wounds such as burns of first degree, even after the onset of the treatment), but if applied indiscriminately in the phase that does not match, they had the effect of hampering the processes of wound repair.

Summary of the invention

In the light of the foregoing, the object of the present invention is thus to provide for therapeutic means useful for the topical treatment of wounds having a difficult or slow healing, such as- specifically, open wounds with loss of tissue, and in particular the lacerated-contused wounds and ulcers, including diabetic ulcers, as well as burn wounds.

Starting from the concept of the utility and need to supply a moist medium to wounds, so that any living tissue can grow in the most propitious environment, compositions containing natural active principles have been designed from which, according to the invention, moist medicaments and dressings have been prepared. The latter have a contents of actives è partially different from one another, depending on the stage of development of the healing process in which they are applied.

According to the invention, the preparations had to meet the following requirements:

1. easily absorbed active components, in order to act by absorption and diffusion from the site of application in the wound bed to the surrounding tissues rather than by contact, with controllable systemic repercussions;

2. presence of nutrients which during absorption and assimilation by the neoformed tissues can ensure to the substrates carbohydrates and minerals, proteins, vitamins and fats required for the regenerative functions in the process;
- 5 3. arterial vasodilator effect, at least at the level of the lesion and around the same, with the purpose of improving the chaotic circulation which is common in diabetic patients;
4. stimulating effect for the generation of new arterial blood vessels (neoangiogenesis) which, in combination with the vasodilatory and
10 arterial effects, assures an excellent blood supply;
5. an hemorheologic effect that can result in a lower viscosity of the blood, in order to remove the occlusion of thrombosed veins and the subsequent disappearance from the lesion of the blackish lines corresponding to the above veins;
- 15 6. antiseptic and antibiotic properties, such as those that are already known in many medicinal plants currently in use.

Bearing in mind these requirements, a specific formulation has been found based on dried and pulverized medicinal plants, suspended in bees' honey, which in combination with each other in definite ratios can be applied
20 as a topical cream product on a wound, both acute and chronic, both superficial and deep, and having a considerable loss of substance, to stimulate and assist the healing process and recovery of injured tissue, and to accelerate the wound healing.

25 Detailed description of the invention

Therefore, the present invention specifically provides a topical composition the treatment of wounds consisting of a mixture of dried and powdered plants suspended in total proportions comprised between 5% and 80% by weight in bees' honey, wherein said plants comprise:

- 30 a) plants of the genus *Plantago*,
- b) plants of the genus *Solanum*, and
- c) plants of the genus *Kalanchoe*.

These three genera of plants, which are individually known in the field of medicinal plants and traditional herbal remedies, have necessarily to be present, all the three of them, in the formulations proposed according to the invention. To these, a fourth plant genus is added, the genus *Scoparia*, which is included in the formulation of two of the three specific types of preparations proposed according to the invention, namely the formulations having, respectively, activity in stimulating the granulation of the wound ("granulating" preparation), and activity in stimulating re-epithelialization of the same ("epithelializing" preparation). The fourth plant genus (*Scoparia*) is not included in the third type of preparation, having the activity of debridement ("debriding" preparation).

According to some specific embodiments of the invention, therefore, the plants of said mixture of plants also comprise

d) plants of the genus *Scoparia*.

The preparations proposed according to the invention, which have been called "**Hidy**", are characterized by being composed exclusively of plants naturally treated and honey, without any artificial additives or preservatives.

More specifically, the plant part of the topical compositions here proposed consists of dried plants of the species *Plantago* spp., *Solanum* spp., *Kalanchoe* spp. and *Scoparia* spp..

More specifically, the plants of the genus *Scoparia* are represented preferably by *Scoparia dulcis*, a species especially widespread in tropical South America, where it is traditionally used by local people for infusions and for external applications, with a variety of indications resulting from tribal or folk medicine, including pain relief, antiseptic and anti-inflammatory properties.

Plants of the genus *Plantago* (plantain) can be represented, in particular, by *Plantago lanceolata* or from *Plantago major*, also used since ancient times as herbal remedies, not only in tropical areas, but also in temperate areas, especially for their antimicrobial, antiseptic and anti-inflammatory properties.

The plants of the genus *Solanum* are a very wide family, which includes species cultivated for food production, such as tomato (*Solanum lycopers*-

18
sicum), potato (*S. tuberosum*) and eggplant (*S. melongena*), and numerous and wild species used as herbal remedies or herbal products. Specifically, the compositions according to the invention may contain plants of the species *Solanum dulcamara* (climbing nightshade), used as a topical herbal remedy
5 for abrasion and against some dermatoses, and *Solanum nigrum* (black nightshade) also known as *S. incertum*, also used as a herbal remedy against inflammations and skin diseases.

In the proposed composition according to the invention, plants of the genus *Kalanchoe* are represented preferably by *Kalanchoe pinnata*, tradi-
10 tionally used among the people of the Amazon and in many other areas of South America both for systemic use, in infusions, or for external use, even for treatment of wounds, burns, ulcers and insect bites.

The preparations obtained from the vegetable mixtures described, suspended in bees' honey and in which plants *Plantago spp.*, *Solanum spp.*
15 and *Kalanchoe spp.* are used, are particularly suitable for the first phase of therapy according to the invention, when an activity of debridement of the wound is specifically requested. In this case, the mixture of dried and pulverized plants contains *Plantago spp.*, *Solanum spp.* and *Kalanchoe spp.* preferably in weight ratios between 2:2:3 and 4:2:2. respectively.

20 In the case where the preparation proposed is to be used in the next phase of the healing process, when an action of stimulation of the wound granulation is primarily requested, the mixture of plants indicated according to the invention contains *Scoparia spp.*, *Plantago spp.*, *Solanum spp.* and *Kalanchoe spp.*, preferably in weight ratios between 1:1:3:1 and 1:2:4:1.

25 Finally, for a wound in which the tissue initially missing has been substantially replaced by granulation tissue, and that has to undergo the last part of the proliferative phase, i.e. that of re-epithelialization, the topical composition indicated according to the invention, having re-epithelializing activity, includes a mixture of *Scoparia spp.*, *Plantago spp.*, *Solanum spp.* and
30 *Kalanchoe spp.*, preferably in respective weight ratios of between 8:4:4:1 and 16:4:4:3.

According to another complementary aspect thereof, the present

invention relates to a medicinal preparation containing, as active ingredients, a mixture of dried and pulverized plants suspended in overall ratio between 5% and 80% by weight in bees' honey, which plants include::

- a) plants of the genus *Plantago*,
- 5 b) plants of the genus *Solanum*, and
- c) plants of the genus *Kalanchoe*.

for use as a topical medication. This definition includes the "debridant" version of the preparation of the invention, specifically designed for use in the process of debridement of wounds, wherein the mixture of *Plantago*, *Solanum* and
10 *Kalanchoe*, preferably *Plantago spp.*, *Solanum spp.* and *Kalanchoe spp.*, is used, preferably in weight ratios of between 2:2:3 and 4:2:2.

According to other embodiments, the invention relates to a preparation containing a mixture of dried and pulverized plants suspended in overall ratios between 5% and 80% in bees' honey, wherein said plants include:

- 15 a) plants of the genus *Plantago*,
- b) plants of the genus *Solanum*,
- c) plants of the genus *Kalanchoe*, and
- d) plants of the genus *Scoparia*

for use as a topical medication. This definition includes, in turn, the
20 "granulating" version of the preparation of the invention, specifically designed for use in the development phase of the granulation tissue, and the "re-epithelializing" version of the same preparation, specifically designed for use in the subsequent stage of re-epithelialization. In the first case the mixture of *Scoparia*, *Plantago*, *Solanum* and *Kalanchoe*, preferably *Scoparia spp.*,
25 *Plantago spp.*, *Solanum spp.* and *Kalanchoe spp.*, is used preferably in the weight ratios of between 2:2:3 and 4:2:2, while in the second case the mixture is preferably used in weight ratios of between 8:4:4:1 and 16: 4:4:3.

As already noted, the Hidyts creams have been developed and tested in diabetic patients suffering from severe injuries at the level of the lower limbs,
30 such as neuropathic, ischemic, infectious and traumatic type. These are often deep and large wounds, affecting the entire heel or instep, or all of the big toe or all toes, or the entire sole of the foot, and leave exposed the deep bone

structure, in many cases with plurimicrobial purulent infections, and with large areas of necrosis which involve the tissues up to the bone. They were also tested in diabetic wounds in different parts of the body as in parts of the buttock, pubic, abdominal and back areas, as well as the neck and hands. In
5 all these cases the results were excellent.

The compositions of the invention were also tested on patients not suffering from diabetes, but which, for some situation, had developed ulcers of different sizes and gravity. Were applied in varicose ulcers, traumatic wounds, pressure sores, burns and even in a case of longstanding facial chloasma.
10 The compositions have also been applied as an intravaginal cream in patients with ulcer of the cervix and in cases of hemorrhoids, and in all applications, the results were excellent.

With specific reference to the requirements 2 and 3 given above (the
15 effect of arterial vasodilation and stimulating neo-angiogenesis), these two properties have been successfully obtained in preparations of the invention, as shown by the deep red color of the lesion and particularly of the granulation tissue, and from the plethoric appearance (i.e. over-irradiated by blood) of all the treated area during therapy. Considering specifically the injuries to the
20 foot, it is noted that once the process of regeneration is ended and the wound is completely closed, the healthy foot is swollen. This phenomenon increases when the patient walks and the inflow of blood to the entire foot is such that the foot becomes swelled and warm and takes on a bluish color. For this reason it is recommended to the patient to stop and raise his/her foot, which is
25 deflated immediately, or alternatively to walk short distances.

The event described remits spontaneously over a period of between one and three months, at which time the newly formed vessels in the repaired wound close or degenerate, by virtue of the fact that it is not needed such a high amount of blood in the injured area. This contribution is very useful during
30 the period of active granulation and repair of tissues, but it must be reduced gradually in the later stages of healing.

Concerning the requirement no. 5 mentioned above (hemorheologic

effect that will result in a reduction of blood viscosity), results have been obtained from the use of the invention preparations Hidy, that can be attributed to an antiplatelet, or fibrinolytic, or antithrombotic or thrombolytic activity; or to the presence of any of these activities, the interaction of some of
5 them with one another, or even all.

During the initial preparation trial, the achievement of these results has been demonstrated in some cases with the presence of considerable hemorrhages, which were revealed by the stains on the sheets of the patient. To avoid undesired or excessive effects, the concentrations of the
10 components initially set were suitably reduced, but in any case possible bleeding effects of the proposed preparations are controlled with the intravenous administration of vitamin K, to stop the hemorrhage. In examined patients the value of the clotting time, represented by PT (prothrombin time) and PTT (partial thromboplastin time) are prolonged. At least this fact shows
15 that the components of the topical preparation proposed, as regards the activity hemorheologic, have a systemic action.

The cases cited allowed to establish, through experiments conducted on each of these plants taken separately, the effects attributable to each of them in terms of reducing the viscosity of the blood are not sufficient to justify
20 the effect achieved by the composition of the whole. Therefore it was deduced that in this case, as in the case of other properties, the fact of mixing the various active ingredients in certain proportions to each other produces a true synergism of reinforcement, which results in an unexpected healing effect.

With reference to the requirement no.6, the preparations of the
25 invention have antibiotic properties, both in consequence of the properties of the honey that forms the vehicle, or for the known antibiotic properties of some of the plants of the composition.

Purulent and short-changing infected wounds were treated with preparations of the invention, in septic patients and in a serious,
30 decompensated and anemic state, in which previously undertaken antibiotic therapy had failed; or long-standing wounds, clean and having in incomplete granulating, or completely granulated or in an incipient phase of re-

epithelialization. Finally, wounds have been treated in which for some reason the normal evolution of the healing was interrupted at any stage of the cure.

The preparations proposed and the treatment techniques thereof have been successfully tested on lesions evolving one, three, eight months, as well as lesions of long standing, who had also originated forty years before, which highlighted old tissues prepared in a disorderly manner, united with one another in different phases within the same wound, granulation tissue, edge regions in the incipient phase of re-epithelialization, areas with large amounts of necrotic tissue and debris, secretions. The interesting aspect is that in these wounds, already two or three days from the beginning of treatment with the preparations of the invention, the improvements were manifested in a surprising way, up to reach in a few weeks at a total cure. From this point, it follows that the proposed preparations have the ability to activate cell regeneration of blood vessels, granulation tissues and skin in an orderly and harmonious manner, regardless of environmental conditions of the lesion and of the reparative phase where the wound was maintained.

At least during the granulation stage the plants in the study underwent to experimental verification in an individual manner. In this way it has been found that the fact of mixing the plants between them in certain fixed ratios and, especially, of using different ratios depending on the reparative phase in which the healing process is, gives results surprisingly better than as might be expected based simply on an "addition" of their property.

PROPERTIES OF HIDYT PREPARATIONS

Anti-inflammatory – The topical preparations of the invention have potent anti-inflammatory action which is visible not only in the wound bed but also in the skin around the lesion, changing the erythema to normal, cyanosis and edema in the initial wound bed, the red wine of the traumatic and infected wounds gradually changes to bright red. For this reason, once the topical treatment begins to be applied, oral anti-inflammatory are not required. This fact is of great benefit, since it avoids the possible gastrointestinal, renal and other nature consequences, resulting from the indiscriminate use of anti-

inflammatory drugs (NSAIDs).

Stimulating the secretion - humectant - The main mechanism by which the preparations of the invention achieve the anti-inflammatory and deflation effects may be related to their wetting properties and stimulating the secretion. This property, properly regulated, softens the tissues and facilitates the removal of debris from the wound. This property is of particular importance because, while in other cases and with other techniques substances must be used such as to provide a humid environment to the wound by the application of dressings, in this case the wound itself, by induction of the preparation, is kept moist while it deflates, dehydrating the inflamed tissues up to useful limits. This property has been properly modulated, according to the invention, without having adverse effects on the benefits partial and final.

Stimulating the debridement - the properties of the preparations of the invention of stimulating debridement is the result of the chemical action of one or more of its components on the tendon and connective tissue, on the purulent material, the necrotic tissue and debris of the local wound.

The different plant components of the preparation were tested separately on bovine muscle and connective tissue for eight days, and the results were not very convincing. However, two of the plant components of the proposed preparation plant showed protease activity by approximately 33%. Mixing the products between them, instead, their effects have proved to be significant, probably because of a synergism between them, or between those and the enzymes or other products secreted from the wound itself.

As a result of this activity, we observe that day after day, the fibrous tissue that lies in the wound is losing grip and consistency, they can be removed easily from the wound, and in some cases remains adherent to the patch when you run the dressing at home, as is usually reported by patients themselves.

Thrombolytic - In the bed of varicose ulcers is common to see the tortuous routes of azure thrombosed veins in the wound bed and around the leg. For this reason the use of anticoagulant is indicated as part of treatment of these ulcers.

In this type of injury as early as the first week of applying the "debridant" cream thrombosed veins disappear completely without leaving the slightest trace of their existence; and this benefit is maintained through the successive application of other types of preparation according to the invention.

5 **Stimulating the granulation** - The appearance of the granulation tissue occurs regardless of the fact that the cleaning and the debridement of the wound are completed and it has the same origin as a substrate the same healthy connective tissue of the surface layers, the arteries and veins that remain exposed, the muscle fibers and bone marrow when it is exposed.

10 The stimulatory granulation activity fills all the gaps and recesses that can be left as a result of massive tissue destruction caused by infection, even those of the anatomy of body organs such as the foot and hand. This is a tissue of new formation, of exuberant red light, grainy, which bleeds easily, covering the whole extent of the wound and involving and surrounding
15 tendons, arteries, veins, bones and nerves, without cutting off functionality. After filling the deep voids, it grows toward the surface until above the level of the skin around the wound edges.

20 The granulating activity is the most important property of the preparations proposed according to the present invention. It is the result of all the desired properties and produced in the HidyT preparations, where are required properties of vasodilation and fluidizing in the blood, neoformation of blood mainly arterial vessels, additional nutrients, anti-inflammatory and moisturizing properties and the antibiotic effect.

25 The initial development of this granulation tissue is exuberant, with large granules that day by day grow excessively. However, at the beginning of the activity of re-epithelialization and of the change of the type of product according to the invention, the granulating activity is slowed and the tissue that was grainy becomes smooth, and the part that initially exceeded the level
30 of the skin surrounding the lesion planes at the same level of healthy skin in perfect harmony.

It has also been tried on several occasions that if the treatment with the

25
preparations of the invention is interrupted at this stage in favor of another epithelializing preparation, for example, commercial, the healing process slows down macroscopically and the granulation tissue is back smooth. After the restarting of the application of the preparations according to the invention
5 the same regenerating power of the large granules comes back clearly.

Reepithelializing - One of the most difficult challenges to achieve in a long-standing injury is undoubtedly the beginnings of a re-epithelialization.

According to some theories, this takes place through the proliferation of the epithelium of the edges of the wound and the subsequent slippage of new
10 epithelial cells from the edges, in the centered towards form within the wound bed.

In the application of the preparation according to the invention, in its "reepithelializing" form, it was found several times, unexpectedly, the presence of nuclei of re-epithelialization in the center of the lesion, or at some other
15 point in the wound bed, separated from the active edge. In some cases these nuclei of re-epithelialization appear prior to the re-epithelialization which starts from the edges.

The new skin is the same as the original skin, and gradually resumed normal color, so that practically no scar remains. The skin replenished, also
20 recovers normal sensitivity.

OTHER PROPERTIES '

It is common that the product of the normal secretion of wounds, over the granulation tissue and between the pores and the spaces which are among the granules, is deposited as a transparent gelatinous material, whose
25 consistency and adherence to the granulation tissue increases with time. This is the fibrin, which dries and gives rise to the crust that covers the aged wounds. In many cases between the surface of granulation tissue and this crust is formed a space occupied by pus.

With the use of preparations according to the invention the production
30 of fibrin is minimal, if not practically null, of little consistence and of little adherence to the granulation tissue.

This fact is particularly important, because if the wound must be

preserved free from fibrin the frequency of medical examinations required for her recovery-region and their total number is less.

METHOD OF APPLICATION

5 The use and application of the three topical preparations of the invention must be done in sequence: first, the product for the "debridant" action is applied, followed by granulating and finally the epithelializing preparation.

10 The "debridant" preparation must be applied after a control of the infection, and the application continues until all the fibrous tissue and debris were removed.

The preparation for granulating action is to be applied when the wound is completely clean, and its application continues until the granulation tissue has filled all the spaces, tunnels, caves and crevices formed by the infection, and has completely covered the bed of the wound so as to leave no difference
15 in level between the bed itself and the normal skin around the lesion.

The epithelializing preparation is applied from this moment, and since his aim is to cover all the uncovered area of skin, it is applied until it is necessary.

20 It was noted that during the re-epithelialization stage, in the skin around the new active edge very tight scabs are formed, which are better to remove. This fact persists until the wound has completely closed as a crust having color of coffee in the center of the scar, but eventually it disappears, and the skin takes the normal color and texture without signs of the former presence of a wound so bloody.

25 Not all of the wounds will require that the treatment is started with the preparation for the debridement: the type of preparation according to the invention which is the most appropriate to be applied at the beginning of the treatment will depend on the conditions of the lesion. For example, if at the first visit the wound to be treated is clean and without purulent or fibrous
30 material, or debris, it has to start with the granulating type. If it is a superficial wound, as in the case of a first-degree burn, or the wound has completely granulated and with good vascularization, in this case we may begin with the

re-epithelializing type.

In several cases the granulating preparation already operates the complete closure of the lesion, or the application period of the next re-epithelializing type is shorter than normal. This occurs because the three
5 varieties of the preparation according to the invention, each one being not versatile, as they perform their main functions, they also complete the previous phase, or prepare and promote the conditions for the preparation of the next step so as the latter may carry out its main task. Thus the granulating preparation has as its main function in stimulating the granulation to fill the
10 spaces of the connective tissue, but also has some debridement activity allowing the provision of a limited emollient properties to easily remove any debris or fibrin residue that may still occur. At the same time, has a mild stimulating effect of re-epithelialization, which is demonstrated by the color change of the edges, which begin to activate to revert to a rosy color, while
15 the granulating activity continues.

The indications with respect to the frequency of application of the preparations according to the invention are preferably the following: the debridement variety applies every day, once a day, up to achieve the softening and the elimination of all the devitalized material. Normally its use is
20 required for no longer than five days.

The variety stimulating the granulation is applied on alternate days once a day, and the epithelializing variety is applied once every two or three days. However, also these two varieties may be applied daily.

Overall, the results obtained with the clinical trial are surprisingly: a
25 maximum of three months cases were retrieved that were considered for lost, and where the diagnosis included the amputation.

Description of the Figures

The clinical results obtained with the application of the preparations
30 according to the invention are illustrated but not limited by the experimental cases reported in the following, as well as in the attached photographic documentation, which shows the evolution of an exemplary clinical case

28

treated with the compositions and the therapeutic procedure of the invention.

The attached figures show dated photographs in succession of the foot of a patient with a traumatic injury caused by an animal leg crush, with infection and amputation of the second and third toe.

5 **Figures 1a and 1b** show the situation after the initial amputation and the consequent severely inflamed status;

Figures 1c and 1d show the situation about a month later, when the the inflammation has been controlled and in its place a well demarcated area of necrosis is visible, which affects the big toe and fourth toe;

10 **Figure 1e** shows the surgical wound on the day of the amputation of the two necrotic fingers, the day when therapy begins with the topical preparations according to the invention;

Figures 1f and 1g show two following stages of the therapy according to the invention, in which are evident, respectively, the still bleeding ends of
15 the two recently amputated fingers and the formation of abundant granulation tissue;

Figures 1h and 1i show other two following stages of the healing in which the granulation tissue has become more compact and re-epithelialization is the main event.

20

Clinical trials on patients with wounds treated with typical Hidyt preparations

Firt case - Burn wound infection complicated by hot substance

25 Diabetic female patient since a long time, 48 years of age, which two years before has undergone the amputation of the external malleolus of the left foot showing fistulas up to the tibio-astragaline joint. Despite a conventional treatment by the same team of doctors who had performed the amputation, she did not respond satisfactorily. The wound sometimes secretes serous fluid and sometimes pus, or gets closed.

30 At the time of the first visit the patient had fever, the wound was in the process of secretion, surrounded by an erythematous bright halo; family members said that it should be due to a first degree burn produced by a warm

compress on the site. Incision is made, which drained a lot of yellow-blackish pus, foul-smelling.

The case was complicated by the fact that two superimposed layers of wounds had to be treated, the first deeper that reaches the articulation itself, and the other superficial, which widens the first. It has been defined the entire surface of the wounds, leaving exposed the subcutaneous connective tissue, tendons and ligaments of the joint. Once controlled the infection, we applied the topical preparation of the invention having debridement activity for three consecutive days.

After a month of treatment, the wound appeared in clear granulation. The subcutaneous connective tissue, tendons and ligaments remained viable despite the infection, but during the granulation process, obtained by the application of the granulating preparation of the invention, tended to be destroyed.

At nine weeks, the granulating activity filled the whole thickness, but the re-epithelialization was active, covering the front part of the wound. The subcutaneous connective tissue and fat were completely lost.

At the tenth week granulation and epithelialization were active. A small residue of the tendon remained, and a perilesional edema was noted, which is not synonymous with inflammation, but a sign of a great vascularization.

At the 14th week, the granulation was completed, and the granulation tissue that was crude became smooth. There remain residues of connective tissue or tendon, and the re-epithelialization covering the exposed surface continued. The appearance of the foot was pink, bloated.

Four months after, the new skin had nearly covered the whole bed of the wound, but the bottom over the new skin, near the center yet discovered the presence of a crust is noted, which came off easily leaving new pink skin. A week later the wound was totally re-epithelialized.

Despite the loss of the tendon, the patient could walk without any problem. We had to put a prosthetic to the amputated leg.

Several months later she returned to a medical examination and was

found in perfect condition. The skin had the same characteristics of normal surrounding skin.

Second case - Chronic wounds, diabetic male patient

5 Wound aged six months of development, which was treated with a drying powder, located at the root of the left foot toe nail. The wound appeared covered with fibrous connective yellowish tissue covered with white powder, with which he had been treated, the granulation tissue below appeared smooth and rosy.

10 A surgical debridement was performed to remove the macerated fibrous tissue and the treatments according to the invention were started with the preparation for granulating activity. After one week of treatment, the wound has been granulated turning the smooth granulation into a granulation with large granules and covering the entire wound bed of the alive tissue. The
15 new skin had covered about 40% of the wound surface.

 After two weeks, the granulation and epithelialization were active.

 After 26 days of treatment, the skin had covered 90% of the surface of the wound, and a week later the wound was completely closed.

 Six weeks later the patient returned for a medical examination, the
20 wound was covered with skin which persisted over the crust in the center of the original wound.

Third case - Varicose wound to the instep and external perimalleolar area

25 Non-diabetic female patient, suffering from varicose veins in the left leg, which spontaneously developed a wound that in a few weeks became very large.

 The patient was hospitalized for eight months in vascular surgery, and during this period various techniques and different types of creams of the best
30 internationally known were applied, without achieving the desired results.

 The patient showed a lot of pain, because of which she adopted analgesic positions walking. There were two related injuries, one on the instep

and the other at the top of the lateral malleolus. By the dark brown crusty appearance it was noted that the wounds were aged and crusted allowing to see in transparency the muscle plan and tendons in one case and the lower end of the tibia in the other case. The edges of the wounds were necrotic.

5 After just three days of application of preparation with debriding activity according the invention a change in the appearance of the tissues was noted: tissues initially necrotic dry and very adherent to the deep layers at the time to remove the gauze before cleaning, were moist and hydrated and softened, and the living tissue appeared red for the action of the debridant
10 preparation. Following the application of the product, that exerts a destructive action on tissues already necrotic and on those in the process of necrosis, a "isthmus" of skin that initially divided the wound into two parts, degenerates and is eliminated by the treatment . Once the cleaning of the wound was obtained the benefit of the preparation was clear.

15 After ten days of treatment and seven days of application of the granulating version of the preparation of the invention, the granulation was in full activity. The particular adhesion of the residues of plant material to the tendons was noted, and the latter began to appear devitalized and wearied. The wound was completely clean and full of granulation. The tibia was almost
20 all covered by a neoformation tissue.

 After At two weeks of application of the granulating preparation bleeding began to appear, which continued throughout the week, as was evidenced by the ecchymotic color of the fibrin impregnated by extravasated blood. At the time of removing the fibrin bleeding was widespread, tendons
25 continued to waste and the tibia appeared completely covered by granulation tissue.

 After three and a half weeks of treatment and three weeks after the application of the granulating preparation the granulation phase was completed and the re-epithelialization phase was in full development. The
30 activity of collagenase was such that it was sufficient to take the tendons humidified with the gripper to clean the wound, despite the fact that the main function of the applied preparation was the regeneration. The granulation

tissue appears thick, and the re-epithelialization was active since a bit of time, and the edges of the wound bed had been covered by the new skin.

Two and a half months after, the process of re-epithelialization progressed slowly because of the inconstancy of the patient and the bad
5 treatment of the wound, as a lack of rest and a too tight bandage. There remained very little portions of the tendons, the granulation tissue was smooth and the new skin covered it by the edges. The re-epithelialization was active, the texture and color of the skin tended to approach the normal skin color.

It is important to clarify that, in this patient, the results, though being
10 still exceptional, were not able to get the completion because the patient has not complied with the treatment program, and several times she gave it up, and then returned to follow it when the wound was getting worse. She also suffered a series of incidents during the period of treatment, including a burn with hot water and one with an acidic substance that, falling over the wound,
15 caused a regression so severe that it hurted all the results hitherto achieved.

Following each of these episodes it was possible to recover the injury-treating it with the topical preparations of the invention. The last time I visited the patient, the wound was regenerated up to 80%.

20 **Fourth case - Critical ischemia wound of lower limb, diabetic male patient**

Diabetic patient, 48 years of age, pale, anemic, fever, blood glucose 320 mg. Diagnosed with critical ischemia of the lower left limb, which is corroborated by arteriography showing the clogging of the deep femoral artery in the medial third and downward obstructions total and partial across the path
25 of the terminal branches of the same, below the popliteal branches, and a development of poor arterial collateral cycle.

The decision of the doctors in general and vascular surgery was to operate an amputation of the leg until the knee cap, secondary to the lack of response at the surgical transmetatarsian amputation of the big toe, despite
30 treatment with systemic anticoagulation and topical preparations in cream, and special care.

For the opposition of the patient to amputation, as a last tentative, for

33

15 days the patient was subjected to daily sessions of rectal ozone therapy. In the absence of evident signs of improvement in the wound that would give hope to have improved perfusion in order to ensure the tissue regeneration and healing of the wound, a treatment with the preparations according to the invention was initiated.

At the first consulting visit the foot appeared pale and emaciate, the wound base rosy, covered by abundant connective tissue devitalized. The second finger, necrotic and hardened, was amputee and the wound was debrided by surgery. The bleeding was moderate, and the granulating preparation Hidytt to 50% has been applied.

At the second consulting visit, three days after starting the treatment, the wound was already red, covered with blood clots, the bleeding persisted for two weeks, and this time it was significant and detectable by the sheet. The patient reported that the bleeding occurred mostly when he put the leg to the ground. The granulation tissue was red, with granules moderately thick, and the skin of the edges showed signs of reactivation. At one month of treatment, the foot was not inflamed but plethoric, with no pulse at the instep, or tibial rear. The wound was red and granulating showing active re-epithelialization from the top and from the outer edges.

In the following week the granulation tissue was thick and re-epithelialization was activated starting from the edges.

The therapy was continued every other day for seven months, without any gaps, and until the last day bleeding from the undiscovered persisted and the foot was still bloated, hot and pink, becoming dark red and more bloated when it was lowered.

Fifth case - Infected diabetic foot

The diabetic pathological event had affected the big toe finger, the area of the instep and went up over the outer ankle bone and under the anterior part of the plant. After a month of conventional treatment and without apparent cause it occurs a injury in the toe finger. Despite treatment evolution was chaotic.

At the first examination the patient had fever, he was cold, with all the left leg swollen and inflamed, with blisters and shiny skin, plump up to the medium third of the leg. The finger toe slightly cyanotic with plaques of necrotic skin in the dorsal side and more signs of necrosis of the finger that
5 made it no longer viable. From the rear, behind the hanging of the fingers a crusted lesion was present closed, which once engraved drained abundant blackish stinking pus, typical of an anaerobic infection. The skin was pale, flaccid with changes on the inside of the foot.

The day following the incision surgery to drain pus, skin color and
10 edema were improving, tendons and fascia remained exposed. At the fifth and sixth day of topical antibiotic treatment all the broken skin and the subcutaneous connective tissue devitalized were dried, the color of the skin around the lesion was tending to normal, and wrinkles showed that inflammation was under control. After controlling the primary infection
15 appeared an infection by *Pseudomonas*, characterized by the typical greenish color and smell of rotting vegetables. This situation forced to postpone the application of the preparations of the invention (Hidyt) to further eight days. The same infection appeared again 15 days after the starting of the application of the Hidyt debridement preparation.

20 Although it had not yet begun the application of the Hidyt granulating preparation, a granulation tissue below the fibrous tissue begun to be appreciate.

After three weeks of treatment, the big toe was amputee and the most distal surface of the finger metatarsal was cut to reach the trabecular bone of
25 the epiphysis, where is located the hematopoietic bone marrow. From this tissue, at the third day of treatment with the preparation of the invention, also begun the generation of a granulation tissue, which often grew with a rapidity never seen before. The granulation tissue is often exuberant, red and very bleeding.

30 Six weeks of treatment and three and a half weeks from the application of the granulating Hidyt preparation variety in studio, the wound presented a thick granulation tissue, as to be seen as an exuberant malignant

tumor excrescence. Between the grains a more intense red color was appreciated due to hemorrhage, which in this patient, as in other, appeared to be significant. The Incipient re-epithelialization appeared with pink edges.

After eighth weeks of treatment and at the fifth week of application of
5 the granulating preparation, the granulation phase was complete, and the top phase was the re-epithelialization one. At this time there is an interphase in which coexist the granulation phase and re-epithelialization phase and granulation tissue easily exceeds the level of normal skin.

As already noted, during the granulation process the tendons, fascia
10 and ligaments were lost and decomposed.

At the sixth week of application of the preparation the re-epithelialization was active, the granules of the granulation tissue were more smooth and the new skin covered the wound from the outer edges. Two weeks later the foot was totally healthy, as much the wound on the neck of the
15 foot and its extension towards the upper part of the lateral malleolus, as the plantar wound and the stump of the finger toe.

The present invention has been disclosed with particular reference to some specific embodiments thereof, but it should be understood that modifications and changes may be made by the persons skilled in the art without departing from the scope of the invention as defined in the appended claims.
20

CLAIMS

1. A topical composition for the treatment of wounds consisting of a mixture of dried and powdered plants suspended in total proportions comprised between 5% and 80% by weight in bees' honey, wherein said plants
5 comprise:
- a) plants of the genus *Plantago*,
 - b) plants of the genus *Solanum*, and
 - c) plants of the genus *Kalanchoe*.
- 10 2. A topical composition according to claim 1, wherein the said plants include, in addition
- d) plants of the genus *Scoparia*.
3. A topical composition according to claim 2, wherein the said plants a), b), c) and d) respectively consist of plants of the species *Plantago spp.*,
15 *Solanum spp.*, *Kalanchoe spp.* and *Scoparia spp.*.
4. A topical composition according to claim 3, wherein the said mixture of dried and powdered plants is suspended in total proportions comprised between 20% and 60% by weight in bees' honey.
5. A topical composition according to claim 3, wherein the said *Plantago* plants are *Plantago lanceolata* or *Plantago major*.
20
6. A topical composition according to claim 3, wherein the said *Solanum* plants are *Solanum nigrum* or *Solanum dulcamara*.
7. A topical composition according to claim 3, wherein the said *Kalanchoe* plants are *Kalanchoe pinnata*.
- 25 8. A topical composition according to claim 3, wherein the said *Scoparia* plants are *Scoparia dulcis*.
9. A topical composition for the treatment of wounds according to claim 1 having debridement activity, wherein said mixture of plants contains *Plantago spp.*, *Solanum spp.* and *Kalanchoe spp.* in weight ratios comprised between 2:2:3 and 4:2:2.
30
10. A topical composition for the treatment of wounds according to claim 2 having granulation stimulating activity, wherein said mixture of plants

contains *Scoparia spp.*, *Plantago spp.*, *Solanum spp.* and *Kalanchoe spp.*, in weight ratios comprised between 1:1:3:1 and 1:2:4:1.

11. A topical composition for the treatment of wounds according to claim 2 having reepithelialization stimulating activity, wherein said mixture of
5 plants contains *Scoparia spp.*, *Plantago spp.*, *Solanum spp.* and *Kalanchoe spp.* in weight ratios comprised between 8:4:4:1 and 16:4:4:3.

12. A medicinal preparation containing, as active ingredients, a mixture of dried and powdered plants suspended in bees' honey in total proportions comprised between 5% and 80% by weight, wherein the said plants comprise:

- 10 a) plants of the genus *Plantago*,
 b) plants of the genus *Solanum*, and
 c) plants of the genus *Kalanchoe*.

for use as a topical medicament.

13. A medicinal preparation according to claim 12, for use as a medi-
15 cament for the debridement in the treatment of wounds.

14. A medicinal preparation according to claim 13, wherein the said mixture of plants contains *Plantago spp.*, *Solanum spp.* and *Kalanchoe spp.*, in weight ratios comprised between 2:2:3 and 4:2:2.

15. A medicinal preparation containing, as active ingredients, a mixture
20 of dried and powdered plants suspended in bees' honey in total proportions comprised between 5% and 80% by weight, wherein the said plants comprise:

- a) plants of the genus *Plantago*,
 b) plants of the genus *Solanum*,
 c) plants of the genus *Kalanchoe*, and
25 d) plants of the genus *Scoparia*

for use as a topical medicament.

16. A medicinal preparation according to claim 15 for use as a medica-
ment stimulating the granulation in the treatment of wounds.

17. A medicinal preparation according to claim 16, wherein the said
30 mixture of plants contains *Scoparia spp.*, *Plantago spp.*, *Solanum spp.* and *Kalanchoe spp.*, in weight ratios comprised between 1:1:3:1 and 1:2:4:1.

18. A medicinal preparation according to claim 15, for use as a medi-

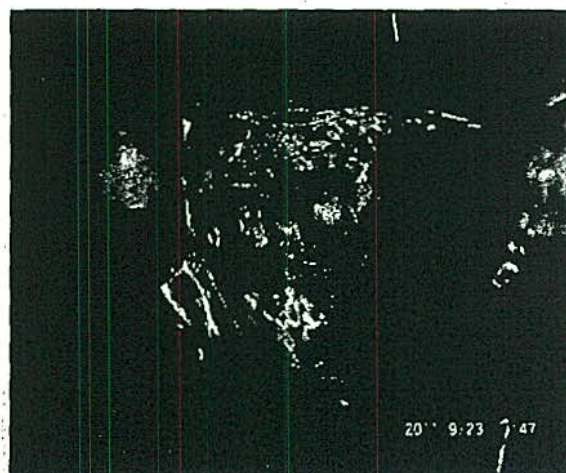
cament stimulating the reepithelialization in the treatment of wounds.

19. A medicinal preparation according to claim 18, wherein di the said mixture of plants contains *Scoparia spp.*, *Plantago spp.*, *Solanum spp.* and *Kalanchoe spp.* in weight ratios comprised between 8:4:4:1 and 16:4:4:3.



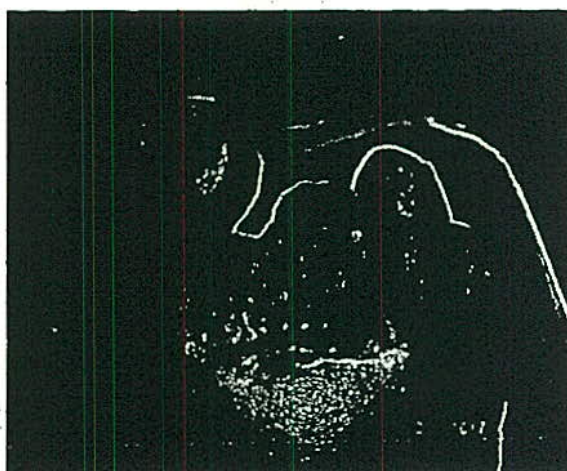
19/09/2011

FIG. 1a



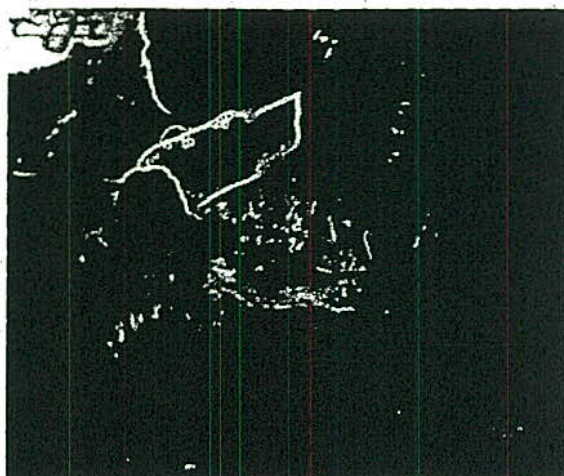
23/09/2011

FIG. 1b



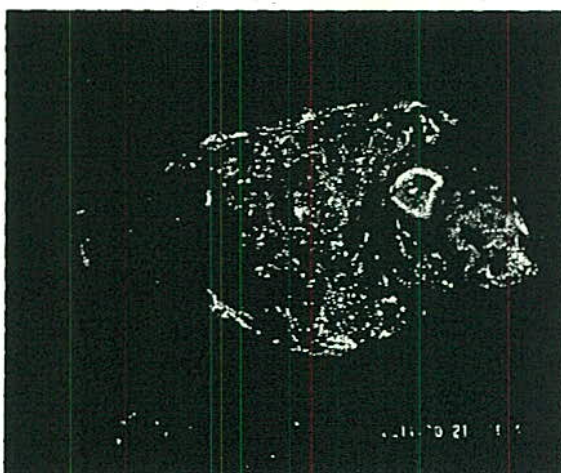
07/10/2011

FIG. 1c



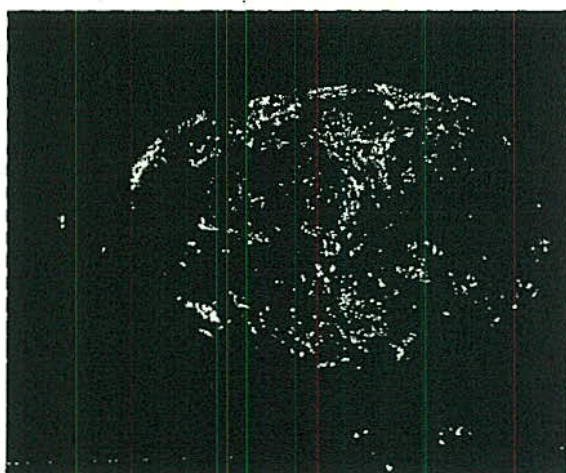
21/10/2011

FIG. 1d



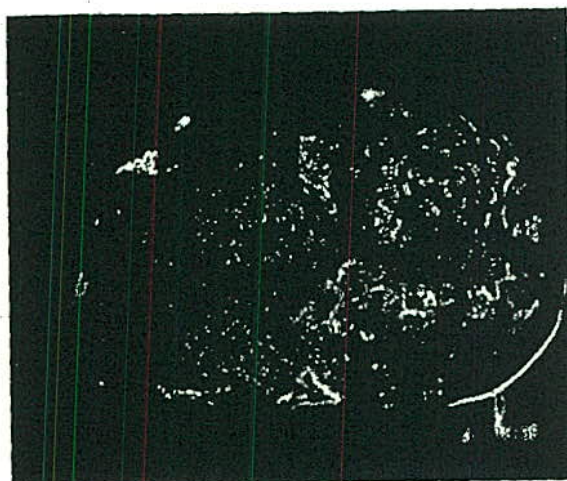
21/10/2011

FIG. 1e



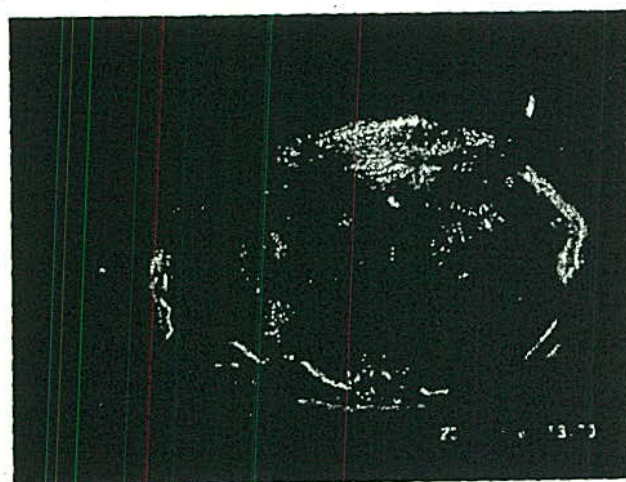
28/10/2011

FIG. 1f



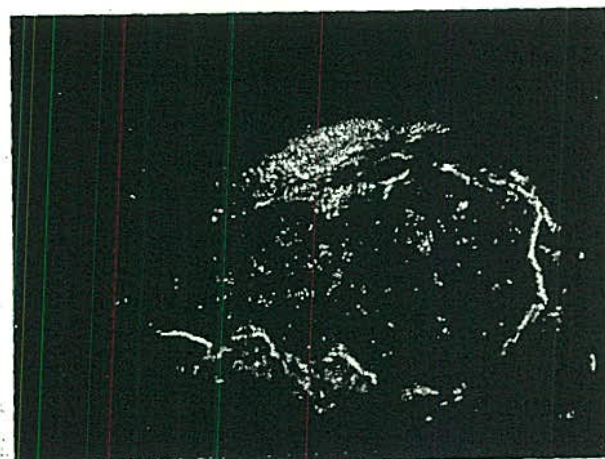
25/11/2011

FIG. 1g



8/12/2011

FIG. 1h



29/12/2011

FIG. 1i

INTERNATIONAL SEARCH REPORT

International application No
PCT/IT2012/000029

A. CLASSIFICATION OF SUBJECT MATTER INV. A61K35/64 A61K36/80 A61K36/68 A61K36/81 A61K36/41 A61P17/02 ADD. According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) A61K A61P Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) EPO-Internal, BIOSIS, EMBASE, WPI Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SAMUELSEN A B: "THE TRADITIONAL USES, CHEMICAL CONSTITUENTS AND BIOLOGICAL ACTIVITIES OF PLANTAGO MAJOR L. A REVIEW", JOURNAL OF ETHNOPHARMACOLOGY, ELSEVIER SCIENTIFIC PUBLISHERS LTD, IE, vol. 71, 1 January 2000 (2000-01-01), pages 1-21, XP002933658, ISSN: 0378-8741, DOI: 10.1016/S0378-8741(00)00212-9 abstract page 2, left-hand column, paragraph 3 - right-hand column, paragraph 3 page 1; table 1 page 12, right-hand column, paragraph 4 page 15, left-hand column, paragraph 1-3 page 16, right-hand column, paragraph 1-2 ----- -/--	1-19
☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.		
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search 5 June 2012		Date of mailing of the international search report 13/06/2012
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Camilleri, Alain

INTERNATIONAL SEARCH REPORT

International application No

PCT/IT2012/000029

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	WO 00/72860 A1 (LARSEN BJOERNAR [NO]) 7 December 2000 (2000-12-07) the whole document ----- -/--	1-19

INTERNATIONAL SEARCH REPORT

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PCT/IT2012/000029

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INTERNATIONAL SEARCH REPORT

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	----- S. E. E. EFEM: "Clinical observations on the wound healing properties of honey", BRITISH JOURNAL OF SURGERY, vol. 75, no. 7, 1 July 1988 (1988-07-01), pages 679-681, XP055005688, ISSN: 0007-1323, DOI: 10.1002/bjs.1800750718 the whole document -----	1-19

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No
PCT/IT2012/000029

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**COMPOSICIONES PARA LA DETERSIÓN, GRANULACIÓN Y RE-
EPITELIZACIÓN DE HERIDAS EN HUMANOS**

CAMPO DE LA INVENCION

5 La presente invención se refiere a composiciones tópicas para la deterción, granulación y re-epitelización de heridas en humanos. Más particularmente, esta invención se refiere a composiciones a base de productos naturales, específicamente plantas y miel, combinadas en proporciones adecuadas para
10 formar tres diferentes tipos de preparaciones para administración tópica. Tales tres diferentes tipos de preparaciones son adecuadas para acortar las fases de regeneración de tejido en el tratamiento de heridas agudas y crónicas de cualquier profundidad y extensión, y de cualquier
15 etiología.

ANTECEDENTES DE LA INVENCION

 Como se sabe, la sanación de heridas es un fenómeno biológico complejo dirigido a rellenar la solución de continuidad representada por la herida con una estructura
20 definitiva de naturaleza conectiva, la cicatriz. Bajo condiciones normales, el proceso de sanación es una serie de eventos dirigidos a la nueva formación de un tejido que tiene la función de reponer la pérdida de sustancia a causa de la herida. Este proceso ocurre a través de distintas fases, las
25 cuales parcialmente se superponen en diferentes momentos. Los

métodos de sanación son parcialmente diferentes dependiendo de si las lesiones fueron de una cortadura, tal como las quirúrgicas, cuyos márgenes son agudos y las cuales se suturan yuxtaponiendo los bordes de la herida con una pérdida mínima de sustancia, o heridas las cuales se dejan abiertas debido al trauma con laceraciones, o pérdida de tejido a causa de infección o quemaduras, y que, a fin de remediarse, requieren la formación de una gran cantidad de relleno de tejido llamado "granulación", con tiempos más prolongados y riesgos más altos de imperfecciones en la cicatriz resultante. Un tercer modo de sanación es después de que se afectan las heridas que han encontrado complicaciones post-operatorias, las cuales requieren la re-abertura de la herida y tratamientos delicados para la limpieza, remoción de áreas dañadas o infectadas (lo cual se indica en italiano con el término francés "detersión", es decir removiendo la materia necrótica a fin de preparar la sanación de la herida) y drenado.

El proceso de reparación de heridas típico del primero de los modos de sanación mencionados anteriormente, es decir el caso de lesiones por cortadura suturadas y sustancialmente sin pérdida de sustancia, ocurre primero que todo a través de una **fase hemostática**, en donde se activan los factores del tejido de coagulación y se forma un coágulo, que consiste de una red de fibrina en la cual los elementos corpusculares de la sangre ubicados en la herida permanecen encerrados.

Entonces tiene lugar una **fase inflamatoria**, que es la respuesta típica del organismo contra patógenos, en la cual los posibles agentes microbianos, cuerpos extraños y células necróticas se restringen y eliminan por los granulocitos neutrófilos y por los macrófagos, los cuales conjuntamente proveen la limpieza y detersión de la herida. Después de la vasoconstricción inicial la cual ocurre en la fase hemostática, la reacción inflamatoria en cambio es acompañada con una vasodilatación, que vuelve a la herida edematosa y fuertemente enrojecida. Como ya se observa en relación a la superposición parcial de las diversas fases del proceso descrito aquí, la reacción inflamatoria también es prolongada en parte durante la subsecuente fase proliferativa.

La **fase proliferativa** está dirigida a remplazar el coágulo con una estructura sólida final, y comienza con la proliferación celular de las estructuras epiteliales, células endoteliales y tejido conectivo de los márgenes de la herida que dan como resultado un tejido que tiene una apariencia característica granular, llamada tejido de granulación. La neovascularización tiene lugar a través de la formación de contornos celulares en los bordes de la herida los cuales, de acuerdo a la estructura de soporte formada por la red de fibrina, prosiguen al centro hasta unirse con las del otro lado y constituyen una nueva red vascular (angiogénesis). Al mismo tiempo comienza la proliferación de células de la capa

basal del epitelio, de nuevo desde los bordes de la herida, y desde el tejido conectivo comienza la proliferación de fibroblastos. Los últimos son elementos celulares que, al secretar ácido hialurónico, dan lugar a la formación de fibras de colágeno que servirán para rellenar la herida.

En los procesos de sanación de heridas no suturadas, en donde ocurrió una pérdida de sustancia, el tejido de granulación rellena la herida comenzando desde las capas más profundas, y la falta de un soporte adecuado en esta etapa no solamente prolonga el proceso de sanación, sino que también frecuentemente provoca el rellenado irregular de la herida, con imperfecciones y la hipertrofia de la cicatriz resultante. El completamiento de la capa epitelial externa termina la fase proliferativa.

En la última **etapa de maduración** y remodelación, la contracción de la herida continúa, lo cual comenzó ya en la etapa previa, y continúa incluso después de la completa epitelización. En tanto la maduración tiene lugar, así como el reacomodo y reticulación de fibras de colágeno, un proceso cuya duración es extremadamente variable, y determina la consolidación final del área de la herida y una normalización gradual del color de la cicatriz. La fase de remodelación puede durar meses o años, dependiendo del tipo de herida y otros factores que pueden influenciar el proceso de sanación.

Algunos factores locales de la herida de hecho pueden

afectar el curso de la sanación de la herida, tal como la intensidad del traumatismo, la presencia de hematoma o recolecciones de suero, infección o afección local, la presencia de cuerpos extraños o astillas, o alteraciones en el flujo sanguíneo. Entre los factores generales y sistémicos que pueden afectar los resultados es necesario considerar la edad y salud general del sujeto, su estado nutricional y posibles deficiencias de vitamina, la presencia de algunos padecimientos sistémicos, especialmente la diabetes, y la aplicación simultánea de ciertas terapias, especialmente las terapias citostáticas y aquéllas a base de corticoides, los cuales afectan adversamente el proceso de sanación.

La reparación epitelial, por otro lado, parece estar influenciada por otros factores: se retarda por la hipotermia y se acelera por una hipertermia moderada (hasta 40°C). La importancia de este hecho es que un incremento en la temperatura local al nivel de la cicatriz, estimula la sanación de la herida, probablemente por el incremento de la circulación sanguínea.

Ahora es ampliamente aceptado que el mejor tratamiento para una lesión quirúrgica normal, es dejar que la misma evolucione por sí misma. Solamente se requiere una limpieza, es decir, lavado con suero fisiológico y reposo, lo cual significa evitar cualquier tipo de relajación de la herida y piel adyacente.

En el pasado, y hasta la fecha, las plantas han jugado un papel importante como remedios y auxiliares en el tratamiento de padecimientos humanos, particularmente en el tratamiento de heridas las plantas de todo tipo y sus derivados han sido parte del arsenal terapéutico, y entre estos: *Agrimonia eupatoria* (agrimonia), *Arctium lappa* (bardana), *Capsella bursa-pastoris* (bolsa de pastor), *Cupressus sempervivens* (ciprés mediterráneo), *Equisetum arvense* (césped en segmentos o belcho), *Symphytum officinalis* (consuelda), *Echinacea spp.* (equinácea), *Rhamnus frangula* (frángula), *Fucus vesiculosus* (alga fucus), *Arbutus uva-ursi* (gayubas), *Gentiana lutea* (genciana amarilla grande), *Hedera helix* (yedra), *Citrus x limon* (limón), *Plantago major* (plantaina grande), *Zea mays* (maíz), *Malva sylvestris* (malva), *Matricaria chamomilla* (manzanilla), *Origanum majorana* (mejorana), *Melilotus officinalis* (meliloto), *Melissa officinalis* (bálsamo de limón), *Juglans regia* (nuez), *Carica papaya* (papaya), *Glycyrrhiza glabra* (regaliz), *Rosa gallica* (rosa), *Salvia officinalis* (salvia) y *Sambucus nigra* (saúco).

Entre las plantas medicinales más utilizadas actualmente se mencionan: *Aloe vera* o *Aloe barbadensis* (áloe), *Calendula officinalis* (caléndula), *Uncaria tormentosa* (uña de gato) e *Hydrocotyle asiatica* (centella asiática).

Se muestra que muchos extractos tópicamente aplicados ejercen una influencia positiva en la sanación de heridas,

propiciando niveles incrementados de angiogénesis endógena antioxidante enzimática y no enzimática y estimulante. Una hierba ejemplificante que se menciona es el extracto de *Hippophae rhamnoides* L. subespecie turkestanica (espino cervical de mar), un arbusto nativo de Europa y Asia. La planta ha sido ampliamente utilizada en el sistema oriental tradicional de medicina para el tratamiento del asma, padecimientos de la piel, enfermedades gástricas y pulmonares. Se estima que todas las partes de la planta son una fuente de un gran número de sustancias bioactivas tales como flavonoides (isorhamentina, cuarcetina, miricetina, kaempferol y sus derivados glucosídicos), carotenoides (beta-caroteno, licopeno), vitaminas (C, E, K), taninos, triterpenos, glicéridos de ácidos palmítico, esteárico y oleico y algunos aminoácidos esenciales. Gracias a las propiedades de los compuestos activos presentes en la planta, por ejemplo, estudios experimentales realizados en ratas hembra con diabetes normal e inducida con estreptozotocina por medio del extracto de *Hippophae rhamnoides*, en mezclas en relación de 1:7:1 con extracto de *Aloe vera* y *Curcuma longa* (cúrcuma), mostraron eficacia en la aceleración de la sanación de heridas, tanto agudas como crónicas (A. Gupta et al., *A poly-herbal formulation accelerates normal and impaired diabetic wound healing*, Department of Biochemical Pharmacology, Defence Insitute of Physiology and Allied Sciences (DPAS), Delhi,

India, asheesh_gupta2001@yahoo.co.in).

Entre las plantas medicinales más ampliamente utilizadas en todo el mundo, la sábila es ampliamente utilizada para tratar muchos padecimientos, particularmente de dermatología y de diversa severidad, incluyendo formas de diabetes. En varios experimentos en el tratamiento de heridas, aproximadamente el 90% de aquéllas tratadas con gel de sábila se resuelven 72 horas antes que aquéllas no tratadas con este ingrediente activo. En lesiones sépticas, sin embargo, la recuperación es mucho más lenta que con el tratamiento convencional.

Otro producto natural, no directamente de origen vegetal, el cual se utiliza para tratar heridas desde la antigüedad es la miel de abeja. Las pruebas de laboratorio en animales y en ensayos in vitro indican que la miel puede acelerar la reparación de heridas debido a su acción en la división celular, en la síntesis y maduración del colágeno, la contracción y epitelización de la herida y en la mejora de la nutrición. La miel tiene propiedades antibacterianas, por su alto contenido de peróxido de hidrógeno, así como altos niveles de antioxidantes que protegen a los tejidos de los radicales libres. Se han descrito propiedades anti-inflamatorias, las cuales reducen el edema, exudación y dolor local. De manera similar, su acidez (pH por debajo de 4) favorece la acción antibacterial de los macrófagos, puesto que un pH ácido dentro de las vacuolas facilita la lisis bacteriana, al mismo tiempo

que reduce la producción de amonio tóxico.

Se sabe que en heridas agudas la aplicación de miel puede reducir el tiempo de sanación en comparación con los tratamientos convencionales; por otro lado, también se ha
5 encontrado que en heridas crónicas la miel, además de un vendaje de compresión convencional, no mejora significativamente la sanación de heridas de piernas varicosas.

A fin de tratar exitosamente las causas subyacentes de varias heridas crónicas o incurables de cualquier tipo, se han
10 desarrollado recientemente dispositivos para restaurar o al menos cubrir las superficies de las lesiones. Se hacen substratos artificiales a base de colágeno dérmico, para regenerar o reconstruir glicosaminoglicanos, quitosán, o materiales similares, conocidos en particular por el nombre de
15 "estructuras de soporte" que consisten de estructuras tridimensionales porosas que se utilizan como matrices para el desarrollo de células de tejido internas. Tales sustratos promueven la regeneración de elementos vasculares y también elementos de nervios, y componentes de la estructura del
20 tejido conectivo sub-dérmico, para proveer injertos de piel autólogos o artificialmente desarrollados en cultivo *in vitro*, los entornos que permiten una inserción adecuada de los mismos.

Se encontró que los sustitutos de piel son una
25 alternativa muy útil, y algunas veces esencial en aquellos

casos en los cuales las áreas descubiertas son muy extensas, como ocurre en las quemaduras, o cuando para algunas condiciones particulares, los autoinjertos no se pueden considerar una como una posibilidad, por ejemplo, cuando el
5 área de la cual se obtiene la piel es muy dolorosa o cuando existe el riesgo de desarrollar cicatrices o infección, o cuando hay una sanación demasiado lenta. Los estudios de largo plazo en biopsias tomadas años después de los sitios de aplicación mostraron la regeneración de las fibras elásticas y
10 parcialmente de células nerviosas, aunque también en este caso, como en la reparación fisiológica de tejidos originalmente sanos, no hay regeneración de la piel anexada, tal como glándulas sebáceas y sudoríparas y folículos pilosos.

Tomando en cuenta la infección persistente como una
15 causa de las heridas demoradas o crónicas, se diseñaron medicaciones y cremas para aplicación tópica a base de antibióticos y se fabricaron con el tiempo, con la intención de tratar o prevenir infecciones. Entre los mismos, las cremas a base de plata tienen un reconocimiento global. El uso de
20 plata como un antiséptico y desinfectante se remonta a la antigüedad, y se aplicó a la preparación de medicamentos, utilidad universalmente reconocida como la sulfadiazina de plata. En el tratamiento de quemaduras de segundo grado la sulfadiazina de plata es el fármaco preferido por su acción
25 antiinflamatoria y estimulante de acción de regeneración de

tejidos, y también por sus propiedades analgésicas.

El yodo es otro agente comúnmente utilizado en preparaciones antisépticas para el tratamiento de sanación de heridas, así como ciertos antibióticos para uso tópico, generalmente en crema o gel, tal como la gentamicina, 5 cloranfenicol, neomicina y sus combinaciones.

Además, se han propuesto apósitos a base de alginato (una quimiocina de origen natural), que se utilizan como un vehículo para moléculas activas para estimular la regeneración 10 de tejido de granulación y aceleran el proceso de sanación de heridas. Algunos ejemplos incluyen parches de hidrogel de alginato como un vehículo para el factor-1 de regeneración de estromas (SDF-1, factor-1 derivado de células del estroma), que es un factor que estimula la regeneración de tejidos, o en 15 combinación con sustancias que incrementan la resistencia a la infección, como en el apósito iónico de alginato/carboximetil celulosa de plata para (SACMC) o también en combinación con agentes anti-inflamatorios. En situaciones donde es importante proveer humedad, principalmente en heridas crónicas, el 20 alginato se combina con hidrocoloides, hidrogeles, espumas o hidrofibras.

Como se sabe, para preparar el estrato de la herida de una herida aguda o crónica, de tipo traumático o infeccioso, y especialmente de heridas en las cuales los residuos y material 25 necrótico cubren sustancialmente el tejido vivo que actúa como

una barrera que previene o impide la penetración y adherencia de sustancias regenerativas, tiene que hacerse primero una "detersión" de la lesión. Esto consiste en remover materiales extraños o tejido necrótico, desvitalizado o infectado en el
5 área de la lesión, hasta la exposición del tejido sano circundante, a fin de preparar la herida para su regeneración. El uso práctico médico está hecho de detersión quirúrgica, aunque en situaciones donde esto es peligroso debido al riesgo de sangrado u otras complicaciones, es más útil la detersión
10 enzimática química, por ejemplo por medio de colagenasa, papaína o papaína-urea (con o sin clorofilina). En otras circunstancias una detersión mixta permite incluso mejores resultados.

También existe la práctica alternativa de utilizar
15 gusanos para la detersión de heridas cuando los métodos convencionales no dan resultados, o cuando no hay contraindicación. Ninguna de las técnicas mencionadas tiene suficientes antecedentes científicos que sean mejores que las otras y que sean recomendadas como una técnica preferida para
20 casos especiales.

Tomando en cuenta las úlceras diabéticas, como heridas epidemiológicamente más comunes que parecen ser difíciles de resolver, dada la propagación en todo el mundo de enfermedades de diabetes, es sabido que estas lesiones consisten de la
25 continuidad de tejidos que pueden afectar, en relación a su

importancia y severidad, el tejido de la piel, tejido subcutáneo y finalmente el tejido óseo. La ubicación más común es en el pie, donde la lesión puede involucrar las regiones apicales de los dedos, las articulaciones entre las articulaciones de las falanges, las cabezas de los huesos metatarsianos (área de la planta del pie), talón, las prominencias huesudas del tobillo (astrágalo de tibia-peroné-empalme), y pierna. La implicación del pie es muy peligrosa para la continuación del padecimiento, puesto que frecuentemente llega la complicación de los tejidos subcutáneos y huesos, con infecciones y fistulas que pueden llevar a la amputación de las regiones afectadas.

Un ensayo clínico en pacientes con diabetes muestra que en estos pacientes se alteran todos los procesos metabólicos. De hecho, una de las razones se debe a que una persona con diabetes desarrolla lesiones serias, donde una persona saludable podría tener solo ligeros rasguños, está en el hecho de que su control metabólico, a pesar de los esfuerzos personales y médicos, no es el mejor. Esta situación se agrava cuando el control metabólico es pobre, y por lo tanto hay una reducción de los procesos regenerativos y resistencia a infecciones, y los fluidos corporales del paciente se convierten más bien en excelentes medios de cultivo. Bajo tales condiciones, los gérmenes saprofitos se vuelven dañinos y oportunistas, los hongos se vuelven invasivos y las

bacterias aeróbicas facultativas se vuelven anaeróbicas.

En estudios que llevaron a la presente invención, con el propósito de buscar una preparación tópica que sea efectiva en acortar el tratamiento de úlceras diabéticas, se encontró que
5 algunos de los pocos productos comercialmente disponibles tenían un efecto de detersión sustancial, otros fueron solamente de granulación y otros fueron solo de re-epitelización. Además, sus efectos positivos en el comienzo se redujeron o padecieron algunas desventajas, tales como mala
10 adhesión o mala absorción, y en algunos casos las preparaciones actuaron como un material oclusivo, en otros produjeron la deshidratación excesiva de la superficie de la herida y de las secreciones de las heridas, y además el resto del producto precipitado se adhirió a la herida lo que causa costras.

15 Específicamente, las preparaciones indicadas para la "detersión" de la herida (con frecuencia denominada inapropiadamente "sanación", es decir productos generalmente propuestos para acelerar la sanación de heridas, independientemente de a qué etapa se refiere el proceso de
20 recuperación) tuvo efectos benéficos en la limpieza de los estratos de las heridas, aunque su uso más allá de esta etapa no ayuda en el esfuerzo del cuerpo de granular y rellenar el espacio de la úlcera con un tejido de granulación. Algunos productos señalados como "de granulación", que es activo en
25 estimular la aparición y el crecimiento del tejido de

granulación, fuertemente adherido a los tejidos y actuaron como un material oclusivo, y además es difícil de remover, secar la herida y producir costras. Finalmente, en esencia las preparaciones de "re-epitelización" fueron particularmente
5 útiles en la última etapa de reparación de una herida profunda con pérdida de tejido (o heridas superficiales tales como quemaduras de primer grado, incluso después del comienzo del tratamiento), aunque si se aplica indiscriminadamente en la fase en la que no corresponde, las mismas tuvieron el efecto
10 de obstaculizar los procesos de reparación de la herida.

BREVE DESCRIPCIÓN DE LA INVENCION

En vista de lo citado anteriormente, el objetivo de la presente invención es por consiguiente proporcionar medios terapéuticos útiles para el tratamiento tópico de heridas que
15 tienen una sanación difícil o lenta, tales como específicamente, heridas abiertas con pérdida de tejido, y en particular las heridas con laceraciones amoratadas y úlceras, incluyendo úlceras diabéticas, así como heridas por quemaduras.

Partiendo del concepto de la utilidad y necesidad de
20 suministrar un medio húmedo para heridas, de modo que cualquier tejido vivo pueda crecer en el ambiente más propicio, se han diseñado composiciones que contienen principios activos naturales a partir de los cuales, de acuerdo a la invención, se han preparado medicamentos y apósitos húmedos.
25 Los últimos tienen un contenido de activos parcialmente

diferentes entre sí, dependiendo de la etapa de desarrollo del proceso de sanación en la cual los mismos se aplican.

De acuerdo a la invención, las preparaciones han cumplido los siguientes requerimientos:

5 1. componentes activos fácilmente absorbidos, a fin de actuar por medio de absorción y difusión desde el sitio de aplicación en el estrato de la herida hasta los tejidos circundantes en vez de en contacto, con repercusiones sistémicas controlables;

10 2. presencia de nutrientes los cuales durante la absorción y asimilación por los tejidos neoformados pueden asegurar los substratos de carbohidratos y minerales, proteínas, vitaminas y grasas requeridos para las funciones regenerativas en el proceso;

15 3. efecto vasodilatador arterial, al menos al nivel de la lesión y alrededor de la misma, con el propósito de mejorar la circulación caótica la cual es común en pacientes diabéticos;

20 4. efecto estimulante para la generación de nuevos vasos sanguíneos arteriales (neoangiogénesis) que, en combinación con los efectos vasodilatadores y arteriales, asegura un excelente suministro de sangre;

25 5. un efecto hemorreológico que puede dar como resultado una viscosidad más baja de la sangre, a fin de remover la oclusión de venas con trombosis y la subsecuente desaparición de la lesión de las líneas negruzcas que corresponden a las

venas mencionadas anteriormente;

6. propiedades antisépticas y antibióticas, tales como las ya conocidas en muchas plantas medicinales actualmente en uso.

Teniendo en mente estos requerimientos, se ha encontrado
5 una formulación específica a base de plantas medicinales secas y pulverizadas, suspendidas en miel de abeja, la cual en combinación entre sí en relaciones definidas se puede aplicar como un producto de crema tópica en una herida, tanto aguda como crónica, tanto superficial como profunda, y que tiene una
10 considerable pérdida de sustancia, para estimular y ayudar al proceso de sanación y recuperación del tejido dañado, y para acelerar la sanación de la herida.

DESCRIPCIÓN DETALLADA DE LA INVENCION

Por lo tanto, la presente invención proporciona
15 específicamente una composición tópica para el tratamiento de heridas que consiste de una mezcla de plantas secas y pulverizadas suspendidas en proporciones totales comprendidas entre 5% y 80% en peso en miel de abeja, en donde dichas plantas comprenden:

- 20 a) plantas del género *Plantago*,
 b) plantas del género *Solanum*, y
 c) plantas del género *Kalanchoe*.

Estos tres géneros de plantas, los cuales son conocidos individualmente en el campo de las plantas medicinales y
25 remedios herbales tradicionales, que necesariamente tienen que

estar presentes, todos los tres, en las formulaciones propuestas de acuerdo a la invención. A estas, se agrega un cuarto género de planta, el género *Scoparia*, el cual se incluye en la formulación de dos de los tres tipos específicos de preparaciones propuestas de acuerdo a la invención, particularmente las formulaciones que tienen, respectivamente, actividad en la estimulación de la granulación de la herida (preparación para "granulación"), y actividad en la estimulación de la re-epitelización de la misma (preparación para "epitelización"). El cuarto género de planta (*Scoparia*) no se incluye en el tercer tipo de preparación, que tiene la actividad de detersión (preparación para "detersión").

De acuerdo a algunas modalidades específicas de la invención, por lo tanto, las dichas plantas de dicha mezcla también comprenden

d) plantas del género *Scoparia*.

Las preparaciones propuestas de acuerdo a la invención, las cuales han sido llamadas "**Hidyt**", se caracterizan por estar compuestas exclusivamente de plantas naturalmente tratadas y miel, sin ningún aditivo o conservador artificial.

Más específicamente, la parte de la planta de las composiciones tópicas aquí propuestas consiste de plantas secas de la especie *Plantago spp.*, *Solanum spp.*, *Kalanchoe spp.*, y *Scoparia spp.*

Más específicamente, las plantas del género *Scoparia*

están representadas preferiblemente por *Scoparia dulcis*, una especie especialmente endémica en la Sudamérica tropical, donde tradicionalmente se utiliza por las personas locales para infusiones y para aplicaciones externas, con una variedad de indicaciones que dan como resultado medicina tribal o tradicional, incluyendo alivio del dolor, propiedades antisépticas y anti-inflamatorias.

Las plantas del género *Plantago* (plantaina) se pueden representar, en particular, por *Plantago lanceolata* o de *Plantago major*, también se utilizan desde la antigüedad como remedios herbales, no solamente en áreas tropicales, sino también en áreas templadas, especialmente por sus propiedades antimicrobianas, antisépticas y anti-inflamatorias.

Las plantas del género *Solanum* son una familia muy amplia, que incluye especies cultivadas para la producción de alimentos, tales como tomate (*Solanum lycopersicum*), patata (*S. tuberosum*) y berenjena (*S. melongena*), y numerosas especies silvestres utilizadas como remedios herbales o productos herbales. Específicamente, las composiciones de acuerdo a la invención pueden contener plantas de la especie *Solanum dulcamara* (solano de montaña), utilizado como un remedio herbal tópico para abrasión y contra ciertas dermatosis, y *Solanum nigrum* (solano negro) también conocido como *S. incertum*, también utilizado como un remedio herbal contra inflamaciones y enfermedades de la piel.

En la composición propuesta de acuerdo a la invención, las plantas del género *Kalanchoe* están representadas preferiblemente por *Kalanchoe pinnata*, tradicionalmente utilizada entre la gente del Amazonas y en muchas otras áreas
5 de Sudamérica tanto para uso sistémico en infusiones, como para uso externo, incluso para el tratamiento de heridas, quemaduras, úlceras y picaduras de insectos.

Las preparaciones obtenidas de las mezclas vegetales descritas, suspendidas en miel de abeja en las cuales se
10 utilizan *Plantago spp.*, *Solanum spp.*, y *Kalanchoe spp.*, son particularmente adecuadas para la primera fase de terapia de acuerdo a la invención, cuando se requiere específicamente una actividad de detersión de la herida. En este caso, la mezcla de plantas secas y pulverizadas contiene *Plantago spp.*,
15 *Solanum spp.*, y *Kalanchoe spp.*, preferiblemente en relaciones en peso entre 2:2:3 y 4:2:2, respectivamente.

En el caso donde la preparación propuesta que se utiliza en la siguiente fase del proceso de sanación, cuando se requiere principalmente una acción de estimulación de la
20 granulación de la herida, la mezcla de plantas indicada de acuerdo a la invención contiene *Scoparia spp.*, *Plantago spp.*, *Solanum spp.*, y *Kalanchoe spp.*, preferiblemente en relaciones en peso entre 1:1:3:1 y 1:2:4:1.

Finalmente, para una herida en la cual el tejido que
25 inicialmente se pierde ha sido sustancialmente remplazado por

tejido de granulación, y que ha experimentado la última parte de la fase proliferativa, es decir la de la re-epitelización, la composición tópica indicada de acuerdo a la invención, que tiene actividad de re-epitelización, incluye una mezcla de

5 *Scoparia spp.*, *Plantago spp.*, *Solanum spp.*, y *Kalanchoe spp.*, preferiblemente en las respectivas relaciones en peso de entre 8:4:4:1 y 16:4:4:3.

De acuerdo a otro aspecto complementario de la misma, la presente invención se refiere a una preparación medicinal que

10 contiene, como ingredientes activos, una mezcla de plantas secas y pulverizadas suspendidas en una relación en conjunto de entre 5% y 80% en peso en miel de abeja, las cuales plantas incluyen:

- a) plantas del género *Plantago*,
- 15 b) plantas del género *Solanum*, y
- c) plantas del género *Kalanchoe*

para su uso como una medicación tópica. Esta definición incluye la versión de "detersión" de la preparación de la invención, específicamente diseñada para usarse en el proceso

20 de detersión de heridas, en donde la mezcla de *Plantago*, *Solanum* y *Kalanchoe*, preferiblemente *Plantago spp.*, *Solanum spp.*, y *Kalanchoe spp.*, se utiliza, preferiblemente en relaciones en peso de entre 2:2:3 y 4:2:2.

De acuerdo a otras modalidades, la invención se refiere

25 a una preparación que contiene una mezcla de plantas secas y

pulverizadas suspendidas en relaciones en conjunto entre 5% y 80% en miel de abeja, en donde dichas plantas incluyen:

- a) plantas del género *Plantago*,
- b) plantas del género *Solanum*,
- 5 c) plantas del género *Kalanchoe*, y
- d) plantas del género *Scoparia*

para usarse como una medicación tópica. Esta definición incluye, a su vez, la versión de "granulación" de la preparación de la invención, específicamente diseñada para
10 usarse en la fase de desarrollo del tejido de granulación, y la versión de "re-epitelización" de la misma preparación, específicamente diseñada para usarse en la subsecuente etapa de re-epitelización. En el primer caso la mezcla de *Scoparia*, *Plantago*, *Solanum* y *Kalanchoe*, preferiblemente *Scoparia* spp.,
15 *Plantago* spp., *Solanum* spp., y *Kalanchoe* spp., se utiliza preferiblemente en las relaciones en peso de entre 2:2:3 y 4:2:2, mientras que en el segundo caso la mezcla preferiblemente se utiliza en relaciones en peso de entre 8:4:4:1 y 16:4:4:3.

20 Como ya se indicó, las cremas Hidytt han sido desarrolladas y probadas en pacientes diabéticos que padecen heridas severas al nivel de las extremidades inferiores, tales como del tipo neuropático, isquémico, infeccioso y traumático. Estas son heridas frecuentemente profundas y grandes, que
25 afectan el talón o empeine entero, todo el dedo gordo del pie

o todos los dedos del pie, o la planta entera del pie, y dejan expuesta la estructura ósea profunda, en muchos casos con infecciones purulentas plurimicrobianas, y con grandes áreas de necrosis las cuales involucran los tejidos hasta el hueso.

5 Las mismas también se probaron en heridas diabéticas en diferentes partes del cuerpo como en partes de las áreas del glúteo, pubis, abdomen y espalda, así como el cuello y manos. En todos estos casos los resultados fueron excelentes.

Las composiciones de la invención también se probaron en
10 pacientes que no tienen diabetes, pero los cuales, por alguna situación, han desarrollado úlceras de diferentes tamaños y gravedad. Se aplicaron en úlceras varicosas, heridas traumáticas, llagas por presión, quemaduras e incluso en un caso de cloasma facial de muchos años. Las composiciones
15 también se han aplicado como una crema intravaginal en pacientes con úlcera de la cerviz y en casos de hemorroides, y en todas las aplicaciones, los resultados fueron excelentes.

Con referencia específica a los requerimientos 2 y 3 dados anteriormente (el efecto de vasodilatación arterial y
20 estimulación de neo-angiogénesis), estas dos propiedades se han obtenido exitosamente en preparaciones de la invención, como se muestra por el color rojo intenso de la lesión y particularmente del tejido de granulación, y de la apariencia pletórica (es decir sobre-cubierta de sangre) de toda el área
25 tratada durante la terapia. Considerando específicamente los

daños en el pie, se observa que una vez que se termina el proceso de regeneración y la herida está completamente cerrada, el pie sano se hincha. Este fenómeno se incrementa cuando el paciente camina y el flujo entrante de sangre al pie entero es tal que el pie se vuelve a hinchar y calentar y toma un color azulado. Por esta razón se recomienda al paciente detenerse y levantar su pie, el cual se deshinch a inmediatamente, o de manera alternativa caminar distancias cortas.

El caso descrito se remite espontáneamente durante un periodo de entre uno y tres meses, tiempo en el cual los vasos recién formados en la herida reparada se cierran o degeneran, en virtud del hecho de que no necesita tal alta cantidad de sangre en el área dañada. Esta contribución es muy útil durante el periodo de granulación activa y reparación de tejidos, aunque debe reducirse gradualmente en las etapas posteriores de sanación.

Refiriéndose al requerimiento no. 5 mencionado anteriormente (efecto hemorreológico que dará como resultado una reducción de la viscosidad sanguínea), se han obtenido resultados del uso de preparaciones Hidytt de la invención, que se pueden atribuir a una actividad anti-plaquetaria, o fibrinolítica, o antitrombótica o trombolítica; o a la presencia de cualquiera de estas actividades, la interacción de algunas de éstas con otras, o incluso todas.

Durante el ensayo de preparación inicial, el logro de

estos resultados se ha demostrado en algunos casos con la presencia de hemorragias considerables, las cuales se revelaron por las manchas en las láminas del paciente. Para evitar efectos indeseados o excesivos, las concentraciones de los componentes inicialmente establecidos se redujeron apropiadamente, aunque en cualquier caso los posibles efectos de sangrado de las preparaciones propuestas se controlan con la administración intravenosa de vitamina K, para detener la hemorragia. En paciente examinados el valor del tiempo de coagulación, representado por PT (tiempo de protrombina) y PTT (tiempo de tromboplastina parcial) se prolongan. Al menos este hecho muestra que los componentes de la preparación tópica propuesta, con respecto a la actividad hemorreológica, tiene una acción sistémica.

Los casos citados permitieron establecer, a través de experimentos realizados en cada una de estas plantas tomadas por separado, los efectos atribuibles a cada una de las mismas en términos de reducir la viscosidad de la sangre no son suficientes para justificar el efecto logrado por la composición en su totalidad. Por lo tanto se dedujo que en este caso, como en el caso de otras propiedades, el hecho de mezclar los diversos ingredientes activos en ciertas proporciones entre sí produce una verdadera sinergia de refuerzo, que da como resultado un efecto de sanación inesperado.

Con referencia al requerimiento no. 6, las preparaciones

de la invención tienen propiedades antibióticas, ambas en consecuencia de las propiedades de la miel que forma el vehículo, o por las propiedades antibióticas conocidas de algunas de las plantas de la composición.

5 Las heridas purulentas e infectadas con breves cambios se trataron con preparaciones de la invención, en pacientes sépticos y en un serio estado de descompensación y anemia, en el cual la terapia previamente realizada ha fallado; o heridas de muchos años, se limpian y tienen en granulación incompleta
10 o completamente granuladas o en una fase incipiente de re-epitelización. Finalmente, las heridas han sido tratadas en las cuales por alguna razón se interrumpió la evolución normal de la sanación en cualquier etapa de la cura.

Las preparaciones propuestas y las técnicas de
15 tratamiento de las mismas han sido probadas con éxito en lesiones que se desarrollan en uno, tres, ocho meses, así como lesiones de mucho tiempo, que también se han generado cuarenta años antes, cuyos viejos tejidos resaltados se prepararon de una manera desordenada, unidos entre sí en diferentes fases
20 dentro de la misma herida, el tejido de granulación, regiones del borde en la fase incipiente de re-epitelización, áreas con grandes cantidades de tejido necrótico y residuos, secreciones. El aspecto interesante es que en estas heridas, en sí dos o tres días a partir del comienzo del tratamiento
25 con las preparaciones de la invención, las mejoras se

manifestaron de una manera sorprendente, hasta alcanzar en unas cuantas semanas una cura total. Desde este punto, es de deducir que las preparaciones propuestas tienen la capacidad de activar la regeneración celular de vasos sanguíneos, tejidos
5 de granulación y piel de una manera ordenada y armoniosa, independientemente de las condiciones ambientales de la lesión y de la fase reparativa en la que se mantuvo la herida.

Al menos durante la etapa de granulación las plantas en el estudio sometido a verificación experimental de una manera
10 individual. De esta manera se ha encontrado que el hecho de mezclar las plantas entre las mismas en ciertas proporciones fijas y, especialmente, al utilizar diferentes relaciones dependiendo de la fase reparativa en la cual está el proceso de sanación, da resultados sorprendentes mejores a los que
15 podrían esperarse simplemente en base a una "adición" de su propiedad.

PROPIEDADES DE LAS PREPARACIONES HIDYT

Anti-inflamatoria - Las preparaciones tópicas de la invención tienen potente acción anti-inflamatoria la cual es
20 visible no solamente en el estrato de la herida sino también en la piel que rodea la lesión, cambiando el eritema a normal, cianosis y edema en el estrato de la herida inicial, el color vino tinto de las heridas traumáticas e infectadas gradualmente cambia a rojo subido. Por esta razón, una vez que el
25 tratamiento tópico comienza se a aplicarse, no se requiere un

anti-inflamatorio oral. Este hecho es de gran beneficio, puesto que se evitan las posibles consecuencias gastrointestinales, renales y de otra naturaleza, que dan como resultado el uso indiscriminado de fármacos anti-inflamatorios (NSAIDs).

5 **Estimulación de la secreción - humectante** - El principal mecanismo mediante el cual las preparaciones de la invención logran los efectos anti-inflamatorios y deflación puede relacionarse a sus propiedades humectantes y estimulación de la secreción. Esta propiedad, propiamente regulada, ablanda
10 los tejidos y facilita la remoción de residuos de la herida. Esta propiedad es de particular importancia debido a que, mientras que en otros casos y con otras técnicas las sustancias deben utilizarse tal como para proveer un ambiente húmedo a la herida mediante la aplicación de apósitos, en este
15 caso la herida la misma, mediante la inducción de la preparación, se mantiene húmeda mientras se deshinch, deshidratando los tejidos inflamados a límites útiles. Esta propiedad se ha modulado apropiadamente, de acuerdo a la invención, sin tener efectos adversos en los beneficios parciales y finales.

20 **Estimulación de la detersión** - las propiedades de las preparaciones de la invención de estimulación de detersión es el resultado de la acción química de uno o más de sus componentes en el tendón y tejido conectivo, en el material purulento, el tejido necrótico y residuos de la herida local.

25 Los diferentes componentes de la planta de la preparación

se probaron por separado en el tejido muscular y conectivo de bovino durante ocho días, y los resultados no fueron muy convincentes. Sin embargo, dos de los componentes de la planta de la planta de la preparación propuesta mostraron actividad de proteasa aproximadamente al 33%. El mezclado de los productos entre los mismos, en cambio, sus efectos han probado ser importantes, probablemente debido a una sinergia entre los mismos, o entre aquéllos y las enzimas u otros productos secretados de la herida misma.

10 Como resultado de esta actividad, se observa que día tras día, el tejido fibroso que yace en la herida pierde presión y consistencia, los mismos se pueden remover fácilmente de la herida, y en algunos casos permanece adherente al parche o área cuando se coloca el apósito en casa, tal como se reporta
15 usualmente por los pacientes mismos.

Trombolítico - En el estrato de las úlceras varicosas es común ver las rutas intrincadas de venas obstruidas azules en el estrato de la herida y alrededor de la pierna. Por esta razón el uso de anticoagulante es indicado como parte del
20 tratamiento de estas úlceras.

En este tipo de lesión ya en la primera semana de aplicación de la crema de "detersión" desaparecen completamente las venas obstruidas sin dejar el rastro más ligero de su existencia, y este beneficio se mantiene a través de la
25 sucesiva aplicación de otros tipos de preparación de acuerdo a

la invención.

Estimulación de la granulación - La aparición del tejido de granulación ocurre independientemente del hecho de que se complete la limpieza y la detersión de la herida y éste tiene
5 el mismo origen que un substrato, el mismo tejido conectivo sano de las capas superficiales, las arterias y venas que quedan expuestas, las fibras musculares y médula ósea cuando está expuesta.

La actividad de granulación estimulatoria llena todos
10 los espacios y cavidades que puede quedar como resultado de la destrucción del tejido masivo causado por infección, incluso aquéllos de la anatomía de los órganos corporales tales como el pie y la mano. Este es un tejido de nueva formación, de color rojo claro exuberante, granular, que sangra fácilmente,
15 cubriendo la totalidad de la herida y que involucra y rodea tendones, arterias, venas, huesos y nervios, sin interrumpir la funcionalidad. Después de rellenar los espacios vacíos profundos, crece hacia la superficie hasta más arriba del nivel de la piel alrededor de los bordes de la herida.

20 La actividad de granulación es la propiedad más importante de las preparaciones propuestas de acuerdo a la invención. Es el resultado de todas las propiedades deseadas y producidas en las preparaciones Hidytt, cuando se requieren propiedades de vasodilatación y fluidización en la sangre,
25 neoformación de vasos sanguíneos principalmente arteriales,

nutrientes adicionales, propiedades anti-inflamatorias y humectantes y el efecto antibiótico.

El desarrollo inicial de este tejido de granulación es exuberante, con grandes gránulos que día a día crecen
5 excesivamente. Sin embargo, al comienzo de la actividad de re-epitelización y del cambio del tipo de producto de acuerdo a la invención, la actividad de granulación se reduce y el tejido que era granuloso se vuelve liso, y la parte que inicialmente excedió el nivel de la piel que rodea la lesión
10 se alisa al mismo nivel de la piel sana en perfecta armonía.

También en varias ocasiones se ha intentado que en caso de que se interrumpa el tratamiento con las preparaciones de la invención en esta etapa en pro de otra preparación de epitelización, por ejemplo, comercial, el proceso de sanación
15 se reduce macroscópicamente y el tejido de granulación vuelve sea alisa de vuelta. Después de reanudar la aplicación de las preparaciones de acuerdo a la invención el mismo poder de regeneración de los gránulos grandes vuelve a ser claro.

Re-epitelización - Uno de los desafíos más difíciles a
20 alcanzar en una lesión de hace mucho tiempo es indudablemente el comienzo de una re-epitelización.

De acuerdo a algunas teorías, esto tiene lugar a través de la proliferación del epitelio de los bordes de la herida y la subsecuente demora de nuevas células epiteliales de los
25 bordes, en forma centrada dentro del estrato de la herida.

En la aplicación de la preparación de acuerdo a la invención, en su forma de "re-epitelización", se encontró varias veces, inesperadamente, la presencia de núcleos de re-epitelización en el centro de la lesión, o en algún otro punto en el estrato de la herida, se separa del borde activo. En algunos casos estos núcleos de re-epitelización aparecen antes de que comience la re-epitelización desde los bordes.

La piel nueva es igual a la piel original, y gradualmente vuelve a tomar un color normal, de modo que prácticamente no queda cicatriz. La piel rellena o repuesta, también recupera su sensibilidad normal.

OTRAS PROPIEDADES

Es común que el producto de la secreción normal de heridas, sobre el tejido de granulación y entre los poros y los espacios entre los cuales están los gránulos, se deposita como un material gelatinoso transparente, cuya consistencia y adherencia al tejido de granulación se incrementa con el tiempo. Esta es la fibrina, la cual se seca y da lugar a la costra que cubre las heridas viejas. En muchos casos entre la superficie del tejido de granulación y esta costra se forma un espacio ocupado por pus.

Con el uso de preparaciones de acuerdo a la invención la producción de fibrina es mínima, si no es que prácticamente nula, de poca consistencia y de poca adherencia al tejido de granulación.

Este hecho es particularmente importante, debido a que en este caso la herida debe conservarse libre de fibrina la frecuencia de exámenes médicos requeridos para su región de recuperación y su número total es menor.

5 **MÉTODO DE APLICACIÓN**

El uso y aplicación de las tres preparaciones tópicas de la invención debe hacerse en secuencia: primero, se aplica el producto para la acción de "detersión", seguido por el de granulación y finalmente la preparación de epitelización.

10 La preparación para "detersión" debe aplicarse después de un control de la infección, y la aplicación continúa hasta que se removi6 todo el tejido fibroso y residuos.

La preparación para la acción de granulación a aplicarse cuando la herida est6 completamente limpia, y su aplicaci6n
15 contin6a hasta que el tejido de granulaci6n ha llenado todos los espacios, t6neles, cavernosidades y hendiduras formas por la infecci6n, y ha cubierto completamente el estrato de la herida a fin de no dejar diferencia en el nivel entre el estrato mismo y la piel normal que rodea la lesi6n.

20 La preparaci6n de epitelizaci6n se aplica a partir de este momento, y puesto que su prop6sito es cubrir toda el 6rea descubierta de piel, la misma se aplica hasta que es necesario.

Se observ6 que durante la etapa de re-epitelizaci6n, en la piel que rodea el nuevo borde activo se forman costras muy
25 apretadas, que es mejor remover. Este hecho persiste hasta que

la herida se ha cerrado completamente como una costra que tiene color café en el centro de la cicatriz, aunque eventualmente el mismo desaparece, y la piel toma el color y textura normales sin signos de la anterior presencia de una
5 herida tan sangrante.

No todas las heridas requerirán que el tratamiento se comience con la preparación para la detersión: el tipo de preparación de acuerdo a la invención el cual es el más apropiado a aplicarse al comienzo del tratamiento dependerá de
10 las condiciones de la lesión. Por ejemplo, si en la primera visita la herida a tratar está limpia y sin material purulento o fibroso, o residuos, tiene que comenzarse con la preparación tipo granulación. Si la misma es una herida superficial, como en el caso de una quemadura de primer grado, o la herida se ha
15 granulado completamente y con buena vascularización, en este caso puede comenzarse con la preparación tipo re-epitelización.

En varios casos la preparación para granulación ya opera el cierre completo de la lesión, o el periodo de aplicación de
20 la siguiente preparación tipo re-epitelización es más corto de lo normal. Esto ocurre debido a las tres variedades de la preparación de acuerdo a la invención, cada una no es versátil, puesto que las mismas realizan sus principales funciones, las mismas también completan la fase previa, o
25 preparan y promueven las condiciones para la preparación de la

siguiente etapa de modo que la última puede llevar a cabo su principal tarea. Por consiguiente la preparación para granulación tiene como su principal función estimular la granulación para rellenar los espacios del tejido conectivo, aunque también tiene cierta actividad de detersión entre la provisión de una propiedad emoliente limitada para remover fácilmente cualquier desecho o residuo de fibrina que pueda presentarse todavía. Al mismo tiempo, tiene un leve efecto estimulante de re-epitelización, el cual se demuestra por el cambio de color de los bordes, los cuales comienzan a activarse para volver a un color rosado, mientras continúa la actividad de granulación.

Las indicaciones con respecto a la frecuencia de aplicación de las preparaciones de acuerdo a la invención preferiblemente son las siguientes: se aplica la variedad de detersión todos los días, una vez al día, para lograr el ablandamiento y la eliminación de todo el material desvitalizado. Normalmente se requiere su uso por no más de cinco días.

La variedad que estimula la granulación se aplica en días alternados una vez al día, y la variedad de epitelización se aplica una vez cada dos o tres días. Sin embargo, también estas dos variedades pueden aplicarse diariamente.

En general, los resultados obtenidos con el ensayo clínico son sorprendentes: se recuperó un máximo de casos de

tres meses que se consideraban perdidos, y donde el diagnostico incluía la amputación.

DESCRIPCIÓN DE LAS FIGURAS

Los resultados clínicos obtenidos con la aplicación de las preparaciones de acuerdo a la invención se ilustran pero no se limitan por los casos experimentales reportados a continuación, así como en la documentación fotográfica anexada, la cual muestra la evolución de un caso clínico de ejemplo tratado con las composiciones y el procedimiento terapéutico de la invención.

Las figuras anexadas muestran fotografías fechadas en secuencia del pie de un paciente con una lesión traumática causada por un aplastamiento con la pata de un animal, con infección y amputación del segundo y tercer dedos del pie.

Las Figuras 1a y 1b muestran la situación después la amputación inicial y el consecuente estado severamente inflamado;

Las Figuras 1c y 1d muestran la situación de aproximadamente un mes después, cuando la inflamación se había controlado y en su lugar es visible un área bien demarcada de necrosis, que afecta el dedo gordo del pie y cuarto dedo del pie;

La Figura 1e muestra la herida quirúrgica el día de la amputación de los dos dedos necróticos, el día en el que la terapia comienza con las preparaciones tópicas de acuerdo a la

invención;

Las Figuras 1f y 1g muestran las dos siguientes etapas de la terapia de acuerdo a la invención, en las cuales son evidentes, respectivamente, los extremos todavía sangrantes de los dos dedos recientemente amputados y la formación de abundante tejido de granulación;

Las Figuras 1h y 1i muestran otras dos siguientes etapas de la sanación en las cuales el tejido de granulación se ha vuelto más compacto y la re-epitelización es el evento principal.

Ensayos clínicos en pacientes con heridas tratadas con preparaciones Hidytt típicas

Primer caso - *Infección de herida por quemadura complicada por sustancias calientes*

Paciente mujer diabética desde hace tiempo, 48 años de edad, que dos años antes había padecido la amputación de los maléolos externos del pie izquierdo que muestra fistulas hasta la articulación de la tibia-astrágalo. A pesar de un tratamiento convencional del mismo equipo de doctores que había realizado la amputación, ella no respondió satisfactoriamente. La herida algunas veces secreta fluido seroso y algunas veces pus, o se cierra.

Al momento de la primer visita la paciente tenía fiebre, la herida estuvo en el proceso de secreción, rodeada por un halo eritematoso brillante; los miembros de la familia

indicaron que esto se debía a una quemadura de primer grado producida por una compresa caliente en el sitio. Se hice una incisión, la cual drenó una gran cantidad de pus de color amarillo-negrusco, que olía mal.

5 El caso se complicó por el hecho de que tenían que tratarse dos capas sobrepuestas de heridas, la primera más profunda que alcanza la articulación misma, y la otra superficial, la cual agranda la primera. Se había definido la superficie entera de las heridas, dejando expuesto el tejido
10 conectivo subcutáneo, tendones y ligamentos de la articulación. Una vez controlada la infección, se aplicó la preparación tópica de la invención que tiene actividad de detersión durante tres días consecutivos.

Después de un mes de tratamiento, la herida presentó
15 granulación clara. El tejido conectivo subcutáneo, tendones y ligamentos continúan siendo viables a pesar de la infección, aunque durante el proceso de granulación, obtenido por la aplicación de la preparación para granulación de la invención, tienden a destruirse.

20 En nueve semanas, la actividad de granulación rellenó el grosor total, aunque la re-epitelización siguió activa, cubriendo la parte frontal de la herida. El tejido conectivo subcutáneo y grasa se perdieron completamente.

En la décima semana la granulación y epitelización
25 seguían activas. Quedó un pequeño residuo del tendón, y se

observó un edema perilesional, el cual no es comparable con la inflamación, aunque si una señal de mayor vascularización.

En la 14a semana, la granulación se completó, y el tejido de granulación que era áspero se volvió liso. Quedaron
5 residuos de tejido conectivo o tendón, y continuó la re-epitelización que cubre la superficie expuesta. La apariencia del pie era rosa, hinchado.

Cuatro meses después, la nueva piel había cubierto casi el estrato completo de la herida, aunque en el fondo de la
10 nueva piel, cerca del centro aún descubierto se observa la presencia de una costra, que se desprende fácilmente dejando nueva piel rosada. Una semana después la herida se re-epitelizó totalmente.

A pesar de la pérdida del tendón, el paciente pudo
15 caminar sin ningún problema. Se tuvo que colocar una prótesis en la pierna amputada.

Varios meses después ella regreso para un examen médico y se encontró en perfectas condiciones. La piel tuvo las mismas características de la piel circundante normal.

20 **Segundo caso** - *Heridas crónicas, paciente varón diabético*

La herida con seis meses de desarrollo, que se trató con un polvo desecante, ubicado en la raíz de las uñas de los dedos del pie izquierdo. La herida se muestra cubierta con tejido amarillento conectivo fibroso cubierto con polvo
25 blanco, con el cual él se había tratado, el tejido de

granulación de abajo se muestra liso y rosado.

Se realizó una detersión quirúrgica para remover el tejido fibroso macerado y los tratamientos de acuerdo a la invención se comenzaron con la preparación para la actividad
5 de granulación. Después de una semana de tratamiento, la herida se había granulado cambiando la granulación lisa en una granulación con gránulos grandes y cubriendo el estrato de la herida entera del tejido vivo. La nueva piel había cubierto aproximadamente el 40% de la superficie de la herida.

10 Después de dos semanas, la granulación y epitelización seguían activas.

Después de 26 días de tratamiento, la piel había cubierto el 90% de la superficie de la herida, y una semana después la herida estaba completamente cerrada.

15 Seis semanas después la paciente volvió para un examen médico, la herida estaba cubierta con piel que persistió sobre la costra en el centro de la herida original.

Tercer caso - *Herida varicosa hasta el empeine y área perimaleolar externa*

20 Paciente mujer no diabética, que padece de venas varicosas en la pierna izquierda, que desarrolló espontáneamente una herida que en unas cuantas semanas se volvió muy grande.

La paciente se hospitalizó ocho meses en cirugía
25 vascular, y durante este periodo se aplicaron varias técnicas

y diferentes tipos de cremas de las mejores conocidas internacionalmente, sin lograr los resultados deseados.

La paciente mostraba mucho dolor, debido a lo cual ella adoptó posiciones analgésicas al caminar. Había dos lesiones
5 relacionadas, una en el empeine y la otra en la parte superior del maleolar lateral. Por la apariencia costrosa de color marrón oscuro se observó que las heridas eran viejas y con costras permitiendo ver con transparencia el trazo de los músculos y tendones en un caso y el extremo inferior de la
10 tibia en el otro caso. Los bordes de las heridas eran necróticos.

Después de apenas tres días de aplicación de la preparación con actividad de deterción de acuerdo a la invención se observó un cambio en la apariencia de los
15 tejidos: los tejidos inicialmente secos, necróticos y muy adherentes a las capas profundas al momento de remover la gasa antes de la limpieza, estaban húmedas e hidratadas y suaves, y el tejido vivo se muestra de color rojo por la acción de la preparación para deterción. Después de la aplicación del
20 producto, que ejerce una acción destructiva en los tejidos ya necróticos y en aquéllos en el proceso de necrosis, un "ismo" de piel que inicialmente dividió la herida en dos partes, se degenera y se elimina por el tratamiento. Una vez que se obtuvo la limpieza de la herida el beneficio de la preparación
25 fue claro.

Después de diez días de tratamiento y siete días de aplicación de la versión de granulación de la preparación de la invención, la granulación estuvo en completa actividad. La adhesión particular de los residuos del material de la planta se observó en los tendones, y éstos últimos comenzaron a mostrarse desvitalizados y extenuados. La herida estaba completamente limpia y llena de granulación. La tibia estaba casi totalmente cubierta por un tejido de neoformación.

Después de dos semanas de aplicación de la preparación para granulación comienza a aparecer el sangrado, que continúa a lo largo de la semana, como se evidencia por el color del coágulo de sangre debajo de la piel de la fibrina impregnada por sangre extravasada. Al momento de remover la fibrina el sangrado se dispersó, los tendones continuaron consumiéndose y la tibia se mostró completamente cubierta por tejido de granulación.

Después de tres y media semanas de tratamiento y tres semanas después de la aplicación de la preparación para granulación se completó la fase de granulación y la fase de re-epitelización estaba en completo desarrollo. La actividad de la collagenasa era tal que fue suficiente para tomar los tendones humidificados con las pinzas para limpiar la herida, a pesar del hecho de que la principal función de la preparación aplicada era la regeneración. El tejido de granulación se muestra grueso, y la re-epitelización siguió

activa poco tiempo, y los bordes del estrato de la herida habían sido cubiertos por la nueva piel.

Dos y medio meses después, el proceso de re-epitelización avanzó lentamente debido a la inconstancia de la
5 paciente y el mal tratamiento de la herida, como falta de reposo y un vendaje muy apretado. Quedaron porciones muy pequeñas de los tendones, el tejido de granulación era liso y la nueva piel cubrió la misma por los bordes. La re-epitelización siguió activa, la textura y color de la piel
10 tendieron a acercarse al color de piel normal.

Es importante aclarar que, en esta paciente, los resultados, si bien son todavía excepcionales, no fueron capaces de obtener la terminación debido a que el paciente no había cumplido con el programa de tratamiento, y varias veces
15 desistió, y luego volvió para seguir el mismo cuando la herida empeoraba. Ella también padeció una serie de incidentes durante el periodo de tratamiento, incluyendo una quemadura con agua caliente y una con una sustancia ácida que, cayó en la herida, causando un retroceso demasiado severo que
20 perjudicó todos los resultados hasta ahora logrados.

Después de cada uno de estos episodios fue posible recuperar la lesión tratando la misma con las preparaciones tópicas de la invención. La última vez que se visitó al paciente, la herida se regeneró hasta un 80%.

Cuarto caso - Herida con isquemia crítica de la extremidad inferior, paciente varón diabético

Paciente diabético, 48 años de edad, pálido, anémico, con fiebre, glucosa en sangre de 320 mg. Diagnosticado con isquemia crítica de la extremidad izquierda inferior, la cual que se corroboró mediante arteriografía que muestra la oclusión o la arteria femoral profunda en las obstrucciones tercera media y descendente totales y parciales a través de la trayectoria de las ramificaciones terminales de la misma, debajo de las ramificaciones poplíteas, y el desarrollo de un pobre ciclo colateral arterial.

La decisión de los doctores en general y la cirugía vascular fue operar una amputación de la pierna hasta la rótula, consecuencia de la falta de respuesta en la amputación quirúrgica del transmetatarso del dedo gordo del pie, a pesar del tratamiento con anticoagulación sistémica y preparaciones tópicas en crema, y cuidados especiales.

Por la oposición del paciente a la amputación, como una última tentativa, durante 15 días el paciente se sometió a sesiones diarias de terapia de ozono rectal. En la ausencia de evidentes signos de mejora en la herida que podrían dar la esperanza de tener una perfusión mejorada a fin de asegurar la regeneración del tejido y sanación de la herida, se inició un tratamiento con las preparaciones de acuerdo a la invención.

En la primera visita de consulta el pie se mostró pálido

y extenuado, la base rosada de la herida, fue cubierta por abundante tejido conectivo desvitalizado. El segundo dedo, necrótico y endurecido, se amputó y la herida se descombró mediante cirugía. El sangrado fue moderado, y la preparación para granulación Hidydt al 50% se había aplicado.

En la segunda vista de consulta, tres días después de comenzar el tratamiento, la herida ya era roja, cubierta con coágulos de sangre, el sangrado persistió durante dos semanas, y esta vez fue importante y detectable por la lámina. El paciente reportó que el sangrado ocurrió en mayor parte cuando él puso la pierna en el suelo. El tejido de granulación era rojo, con gránulos moderadamente gruesos, y la piel de los bordes mostró signos de reactivación. Al mes de tratamiento, el pie no se inflamó aunque estaba pletórico, sin pulso en el empeine, o parte trasera de la tibia. La herida era roja y granulaste que mostraba re-epitelización desde la parte superior y desde los bordes externos.

En la siguiente semana el tejido de granulación era grueso y la re-epitelización se activó comenzando desde los bordes.

La terapia se continuó cada segundo día durante siete meses, sin ningún espacio vacío, y hasta que el último día el sangrado de la parte descubierta persistió y el pie todavía estaba hinchado, caliente y rosa, volviéndose rojo oscuro y más hinchado cuando se redujo.

Quinto caso - Pie diabético infectado

El evento patológico diabético había afectado el dedo gordo del pie, el área del empeine y subió por encima del tobillo externo y debajo de la parte anterior de la planta.

5 Después de un mes de tratamiento convencional y sin aparente causa ocurrió una lesión en los dedos del pie. A pesar del tratamiento la evolución fue caótica.

En el primer examen el paciente tenía fiebre, estaba resfriado, con toda la pierna izquierda hinchada e inflamada,
10 con ampollas y piel brillante, regordeta hasta la tercera parte media de la pierna. Los dedos del pie ligeramente cianóticos con placas de piel necrótica en el lado dorsal y más signos de necrosis del dedo que lo volvieron ya no viable. Desde la parte trasera, detrás de la colgadura de los dedos se
15 presentó una lesión llena de costras cerrada, la cual una vez grabada drenó abundante pus fétida, negruzca típica de una infección anaeróbica. La piel estaba pálida, flácida con cambios en el interior del pie.

Al día siguiente de la cirugía de incisión para drenar
20 la pus, se mejoró el color de la piel y el edema, quedaron expuestos los tendones y la fascia. En el quinto y sexto día de tratamiento antibiótico tópico toda la piel rota y el tejido conectivo subcutáneo desvitalizado se secaron, el color de la piel que rodea la lesión tendió a ser normal, y las
25 arrugas mostraron que la inflamación estaba bajo control.

Después de controlar la infección primaria presentó una infección por Pseudomonas, caracterizado por el color verdoso típico y olor de verduras podridas. Esta situación forzó a posponer la aplicación de las preparaciones de la invención (Hidyt) más de ocho días. La misma infección apareció de nuevo 15 días después del comienzo de la aplicación de la preparación de deterción Hidyt.

Aunque aún no se ha comenzado la aplicación de la preparación para granulación Hidyt, comenzó a apreciarse un tejido de granulación debajo del tejido fibroso.

Después de tres semanas de tratamiento, el dedo gordo del pie se amputó y la superficie más distal del metatarso del dedo se cortó para alcanzar el hueso trabecular de la epífisis, donde está ubicada la médula ósea hematopoyética. Desde este tejido, al tercer día de tratamiento con la preparación de la invención, también comenzó la generación de un tejido de granulación, el cual frecuentemente creció con una rapidez nunca antes vista. El tejido de granulación frecuentemente es exuberante, rojo y muy sangrante.

Seis semanas de tratamiento y tres y media semanas desde la aplicación de la variedad de preparación para granulación Hidyt en estudio, la herida presentó un tejido de granulación grueso, que se veía como una excrecencia de tumor maligno exuberante. Entre los gránulos se apreció un color rojo más intenso debido a la hemorragia, que en este paciente, como en

otros, pareció ser importante. La re-epitelización incipiente se mostró con bordes rosas.

Después de ocho semanas de tratamiento y en la quinta semana de aplicación de la preparación para granulación, la fase de granulación se completó, y la fase superior fue la re-epitelización. En este momento hay una interfase en la cual coexiste la fase de granulación y la fase de re-epitelización y el tejido de granulación excede fácilmente el nivel de piel normal.

10 Como ya se indicó, durante el proceso de granulación los tendones, fascia y ligamentos se perdieron y descompusieron.

En la sexta semana de aplicación de la preparación para re-epitelización siguió activa, los gránulos del tejido de granulación fueron más lisos y la nueva piel cubrió la herida de los bordes externos. Dos semanas después el pie estaba totalmente sano, tanto como la herida en el gollete del pie y su extensión hacia la parte superior del maléolo lateral, como la herida plantar y el muñón de los dedos del pie.

La presente invención se ha descrito con referencia particular a algunas modalidades específicas de la misma, pero deberá entenderse que pueden hacerse modificaciones y cambios por las personas expertas en la técnica sin apartarse del alcance de la invención que se define en las reivindicaciones anexas.

REIVINDICACIONES

1.- Una composición tópica para el tratamiento de heridas que consiste de una mezcla de plantas secas y pulverizadas suspendidas en proporciones totales comprendidas entre 5% y 80% en peso en miel de abeja, caracterizada porque dichas plantas comprenden:

- a) plantas del género *Plantago*,
- b) plantas del género *Solanum*, y
- c) plantas del género *Kalanchoe*.

2.- Una composición tópica de conformidad con la reivindicación 1, caracterizada porque dichas plantas incluyen, además

- d) plantas del género *Scoparia*.

3.- Una composición tópica de conformidad con la reivindicación 2, caracterizada porque dichas plantas a), b), c) y d) respectivamente consisten de plantas de las especies *Plantago spp.*, *Solanum spp.*, *Kalanchoe spp.*, y *Scoparia spp.*

4.- Una composición tópica de conformidad con la reivindicación 3, caracterizada porque dicha mezcla de plantas secas y pulverizadas se suspende en proporciones totales comprendidas entre 20% y 60% en peso en miel de abeja.

5.- Una composición tópica de conformidad con la reivindicación 3, caracterizada porque dichas plantas de *Plantago* son *Plantago lanceolata* o *Plantago major*.

6.- Una composición tópica de conformidad con la

reivindicación 3, caracterizada porque dichas plantas de *Solanum* son *Solanum nigrum* o *Solanum dulcamara*.

7.- Una composición tópica de conformidad con la reivindicación 3, caracterizada porque dichas plantas de *Kalanchoe* son *Kalanchoe pinnata*.

8.- Una composición tópica de conformidad con la reivindicación 3, caracterizada porque dichas plantas de *Scoparia* son *Scoparia dulcis*.

9.- Una composición tópica para el tratamiento de heridas de conformidad con la reivindicación 1, que tiene actividad de deterción, caracterizada porque dicha mezcla de plantas contiene *Plantago spp.*, *Solanum spp.*, y *Kalanchoe spp.*, en relaciones en peso comprendidas entre 2:2:3 y 4:2:2.

10.- Una composición tópica para el tratamiento de heridas de conformidad con la reivindicación 2, que tiene actividad estimulante de granulación, caracterizada porque dicha mezcla de plantas contiene *Scoparia spp.*, *Plantago spp.*, *Solanum spp.*, y *Kalanchoe spp.*, en relaciones en peso comprendidas entre 1:1:3:1 y 1:2:4:1.

11.- Una composición tópica para el tratamiento de heridas de conformidad con la reivindicación 2, que tiene actividad estimulante de re-epitelización, caracterizada porque dicha mezcla de plantas contiene *Scoparia spp.*, *Plantago spp.*, *Solanum spp.*, y *Kalanchoe spp.*, en relaciones en peso comprendidas entre 8:4:4:1 y 16:4:4:3.

12.- Una preparación medicinal que contiene, como ingredientes activos, una mezcla de plantas secas y pulverizadas suspendidas en miel de abeja en proporciones totales comprendidas entre 5% y 80% en peso, caracterizada porque dichas plantas comprenden:

- a) plantas del género *Plantago*,
- b) plantas del género *Solanum*, y
- c) plantas del género *Kalanchoe*.

para usarse como un medicamento tópico.

13.- Una preparación medicinal de conformidad con la reivindicación 12, para usarse como un medicamento para la detersión en el tratamiento de heridas.

14.- Una preparación medicinal de conformidad con la reivindicación 13, caracterizada porque dicha mezcla de plantas contiene *Plantago spp.*, *Solanum spp.*, y *Kalanchoe spp.*, en relaciones en peso comprendidas entre 2:2:3 y 4:2:2.

15.- Una preparación medicinal que contiene, como ingredientes activos, una mezcla de plantas secas y pulverizadas suspendida en miel de abeja en proporciones totales comprendidas entre 5% y 80% en peso, caracterizada porque dichas plantas comprenden:

- a) plantas del género *Plantago*,
- b) plantas del género *Solanum*,
- c) plantas del género *Kalanchoe*, y
- d) plantas del género *Scoparia*

para usarse como un medicamento tópico.

16.- Una preparación medicinal de conformidad con la reivindicación 15, para usarse como un medicamento que estimula la granulación en el tratamiento de heridas.

5 17.- Una preparación medicinal de conformidad con la reivindicación 16, caracterizada porque dicha mezcla de plantas contiene *Scoparia spp.*, *Plantago spp.*, *Solanum spp.*, y *Kalanchoe spp.*, en relaciones en peso comprendidas entre 1:1:3:1 y 1:2:4:1.

10 18.- Una preparación medicinal de conformidad con la reivindicación 15, para usarse como un medicamento que estimula la re-epitelización en el tratamiento de heridas.

15 19.- Una preparación medicinal de conformidad con la reivindicación 18, caracterizada porque dicha mezcla de plantas contiene *Scoparia spp.*, *Plantago spp.*, *Solanum spp.*, y *Kalanchoe spp.*, en relaciones en peso comprendidas entre 8:4:4:1 y 16:4:4:3.

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RESUMEN DE LA INVENCION

Las composiciones para aplicación tópica a base de productos naturales, específicamente plantas pulverizadas secas suspendidas en miel de abeja, en la cual los
5 ingredientes se combinan en proporciones predeterminadas para proveer tres diferentes tipos de preparaciones a aplicarse en varias etapas de reparación y regeneración de tejidos dañados. La aplicación de las composiciones acorta las etapas de sanación en el tratamiento de lesiones agudas y crónicas de
10 cualquier grado de profundidad y anchura, y de cualquier etiología. Las propiedades de las preparaciones incluyen una actividad vascular hemorreológica y sistémica la cual se extiende durante un cierto periodo incluso después de la finalización del tratamiento tópico.

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(54) Title (EN): COMPOSITIONS FOR THE DEBRIDEMENT, GRANULATION AND REEPITHELIALIZATION OF WOUNDS IN MAN

(54) Title (FR): COMPOSITIONS PERMETTANT LE DÉBRIDEMENT, LA GRANULATION ET LA RÉÉPITHÉLISATION DE PLAIES CHEZ L'HOMME

(57) Abstract:

(EN): Compositions for topical application based on natural products, specifically dried pulverized plants suspended in bees honey, in which the ingredients are combined in proportions predetermined to provide three different types of preparations to be applied at various stages of repair and regeneration of injured tissues. The application of the compositions shortens the stages of healing in the treatment of acute and chronic injuries of any degree of depth and breadth, and of any etiology. The properties of the preparations include an hemorheological and systemic vascular activity which extends for a certain period even after the end of topical treatment.

(FR): Composition à application locale à base de produits naturels, en particulier de plantes séchées pulvérisées en suspension dans du miel d'abeilles, dans laquelle les ingrédients sont combinés dans des proportions prédéfinies pour fournir trois types différents de préparations destinées à être appliquées à divers stades de réparation et de régénération des tissus lésés. L'application de ces compositions raccourcit les stades de guérison lors du traitement de plaies aiguës et chroniques, quelles que soient leur profondeur, leur étendue et leur étiologie. Les propriétés de ces préparations comprennent une activité vasculaire hémorhéologique et systémique qui se prolonge pendant un certain temps, même après la fin du traitement local.

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COMPOSITIONS FOR THE DEBRIDEMENT, GRANULATION AND REEPITHELIALIZATION OF WOUNDS IN MAN

DESCRIPTION

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Field of the invention

The present invention concerns topical compositions for the debridement, granulation and reepithelialization of wounds in man. More particularly, this invention concerns compositions based on natural products, specifically plants and honey, combined in suitable proportions to form three different types of preparations for topical administration. Such three different types of preparations are suitable to shorten the phases of tissue regeneration in the treatment of acute and chronic wounds of any depth and extension, and of any etiology.

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Background of the invention

As it is known, wound healing is a complex biological phenomenon aimed at filling the solution of continuity represented by the wound with a definitive structure of connective nature, the scar. Under normal conditions, the healing process is a series of events aimed to the new formation of a tissue having a function to replenish the loss of substance due to the wound. This process occurs through distinct phases, which partially overlap at different times. The methods of healing are partly different depending on whether the injuries were from a cut, such as those surgical, whose margins are sharp and which are sutured juxtaposing the edges of the wound with a minimum loss of substance, or wounds which are left open due to trauma with lacerations, or loss of tissue due to infection or burns, and that, in order to be remedied, they require the formation of a larger amount of tissue filler called "granulation", with longer times and higher risks of imperfections in the resulting scar. A third mode of healing is then the one that affects the wounds that have met post-operative complications, which require the re-opening of the wound and delicate treatments for cleansing, removing of damaged or

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infected areas (which is indicated in Italian by the French term "debridement", i.e. removing necrotic matter in order to prepare the wound healing) and draining.

The process of wound repair typical of the first of the above mention
5 modes of healing, i.e. the case of injuries by cutting sutured and substantially without loss of substance, occurs first of all through an **hemostatic phase**, wherein coagulation tissue factors are activated and a clot is formed, consisting of a fibrin network in which the corpuscular elements of the blood located in the wound remain imprisoned. Then an **inflammatory phase** takes
10 place, being the typical response of the organism against pathogens, in which possible microbial agents, foreign bodies and necrotic cells are circumscribed and eliminated by neutrophil granulocytes and by macrophages, which together provide for the cleansing and debridement of wound. After the initial vasoconstriction which occurs in the hemostatic phase, the inflammatory
15 reaction is instead accompanied with a vasodilation, which makes the wound edematous and strongly reddened. As already noted in relation to the partial overlapping of the various phases of the process described here, the inflammatory reaction is also prolonged in part during the subsequent proliferative phase.

20 The **proliferative phase** is directed to replace the clot with a solid, final structure, and starts with cell proliferation of the epithelial structures, endothelial cells and connective tissue from the margins of the wound resulting in a tissue having a granular characteristic appearance, called granulation tissue. Neovascularization takes place through the formation of
25 cell outlines at the wound edges which, according to the scaffold formed by the fibrin network, proceed toward the center until joining with those from the other side and constituting a new vascular network (angiogenesis). At the same time the cells proliferation of the epithelium basal layer begins, again starting from the wound edges, and from the connective tissue the fibroblasts
30 proliferation starts. The latter are cell elements that, by secreting hyaluronic acid, give rise to the formation of collagen fibers that will serve to fill the wound.

In the healing processes of not sutured wounds, wherein a loss of substance occurred, the granulation tissue fills the wound starting from the deepest layers, and the lack of an adequate support at this stage not only prolongs the healing process, but also often provokes the irregular filling of the wound, with imperfections and hypertrophy of the resulting scar. The completion of the outer epithelial layer ends the proliferative phase.

In the later **step of maturation** and remodeling, the wound contraction continues, which began already in the previous step, and goes on even after the complete epithelialization. In the meantime the maturation takes place, as well as the rearrangement and crosslinking of collagen fibers, a process whose duration is extremely variable, and determines final consolidation of the wound area and a gradual normalization of the color of the scar. The remodeling phase can last for months or years, depending on the type of wound and on other factors that may influence the healing process.

Some local factors of the wound may indeed affect the course of wound healing, such as the intensity of the trauma, the presence of hematoma or serous collections, local infection or disease, the presence of foreign bodies or splinters, or alterations in the blood flow. Among the general or systemic factors that may affect the outcomes it is necessary to consider the age and general health of the subject, his nutritional status and possible vitamin deficiencies, the presence of some systemic diseases, especially diabetes, and the simultaneous application of certain therapies, especially the cytostatic therapies and those based on corticoids, which adversely affect the healing process.

The epithelial repair, on the other hand, appears to be influenced by other factors: it is slowed by hypothermia and accelerated by a moderate hyperthermia (up to 40°C). The significance of this fact is that an increase in the local temperature at the level of the scar, stimulates wound healing, probably by increasing of blood circulation.

It is now widely accepted that the best treatment for a normal surgical injury, is to let it evolve by itself. Only a cleaning is required, i.e., washing with physiological serum and rest, which means avoiding any kind of relaxation of

the wound and adjacent skin.

In the past, and to date, the plants have played an important role as remedies and aids in the treatment of human diseases, particularly in the treatment of wounds plants of all kinds and their derivatives have been part of the therapeutic arsenal, and among these: *Agrimonia eupatoria* (agrimony), *Arctium lappa* (burdock), *Capsella bursa-pastoris* (shepherd's purse), *Cupressus sempervivens* (mediterranean cypress), *Equisetum arvense* (puzzleglass or horsetail), *Symphytum officinalis* (comfrey), *Echinacea spp.* (coneflower), *Rhamnus frangula* (frangula), *Fucus vesiculosus* (bladder wrack), *Arbutus uva-ursi* (bear grapes), *Gentiana lutea* (great yellow gentian), *Hedera helix* (ivy), *Citrus x limon* (lemon), *Plantago major* (plantain greater), *Zea mays* (mais), *Malva sylvestris* (mallow), *Matricaria chamomilla* (chamomile), *Origanum majorana* (marjoram), *Melilotus officinalis* (melilot), *Melissa officinalis* (lemon balm), *Juglans regia* (walnut), *Carica papaya* (papaia), *Glycyrrhiza glabra* (liquorice), *Rosa gallica* (rose), *Salvia officinalis* (sage) e *Sambucus nigra* (elder). Among the currently most used medicinal plants are mentioned: *Aloe vera* o *Aloe barbadensis* (aloe), *Calendula officinalis* (calendula), *Uncaria tomentosa* (cat's claw) e *Hydrocotyle asiatica* (centella asiatica).

It is shown that many extracts topically applied exert a positive influence on wound healing, promoting increased levels of endogenous antioxidant enzymatic and non enzymatic, and promoting angiogenesis. An example worth mentioning is the extract of *Hippophae rhamnoides* L. *turkestanica* subspecies (sea buckthorn), a shrub native to Europe and Asia. The plant has been widely used in traditional oriental system of medicine for the treatment of asthma, skin diseases, gastric and lung disorders. All parts of the plant shall be deemed to a source of a large number of bioactive substances such as flavonoids (isorhamnetin, quercetin, myricetin, kaempferol and their glucosidic derivatives), carotenoids (beta-carotene, lycopene), vitamins (C, E, K), tannins, triterpenes, glycerides of palmitic, stearic and oleic acids and some essential amino acids. Thanks to the properties of the active compounds present in the plant, for example, experimental studies conducted

on female rats with normal and streptozotocin-induced diabetes by means of the extract of *Hippophae rhamnoides*, in mixtures in ratio 1:7:1 with *Aloe vera* extract and *Curcuma longa* (turmeric), showed efficacy in accelerating the healing of wounds, both acute and chronic (A. Gupta et al., *A poly-herbal*
5 *formulation accelerates normal and impaired diabetic wound healing*, Department of Biochemical Pharmacology, Defence Institute of Physiology and Allied Sciences (DPAS), Delhi, India, asheesh_gupta2001@yahoo.co.in).

Among the most widely used medicinal plants worldwide, *Aloe vera* is widely used to treat many diseases, particularly of dermatology and of varying
10 severity, including forms of diabetes. In several experiments on the treatment of wounds, about 90% of those treated with *aloe vera* gel are resolved with 72 hours earlier than those not treated with this active ingredient. In septic injury, however, recovery is much slower than with conventional treatment.

Another natural product, not directly from plant source, which is used to
15 treat wounds since ancient times is the honey bee. Laboratory tests on animals and in vitro assays indicate that honey can accelerate wound repair due to its action on cell division, on the synthesis and maturation of collagen, the contraction and epithelialization of the wound and on improvement of nutritional. The honey has antibacterial properties, for its high content of
20 hydrogen peroxide, as well as high levels of antioxidants that protect tissues from free radicals. Anti-inflammatory properties have been described, which reduce edema, exudate and local pain. Similarly, its acidity (pH below 4) favors the antibacterial action of macrophages, since an acid pH within the vacuoles facilitates the bacterial lysis, while it reduces the production of toxic
25 ammonium.

It is known that in acute wounds the application of honey can reduce the healing time compared to conventional treatments; on the other hand, it has been also found that in chronic wounds honey, in addition to conventional compression bandage, does not significantly improve the healing varicose leg
30 wound.

In order to successfully address the underlying causes of various chronic or incurable wounds of any kind, devices to restore or at least cover

the surfaces of the lesions have been recently developed. Artificial substrates dermal collagen-based are made, glycosaminoglycans, chitosan, or similar materials, in particular known by the name of "scaffold" consisting of porous three-dimensional structures to be used as matrices for the within tissue cells development to regenerate or rebuild. Such substrates promote the regeneration of vascular and also nerve elements, and components of the structure of the sub-dermal connective tissue, to provide with skin grafts from autologous or artificially developed by *in vitro* culture, the environments that allow them an adequate insertion,

10 The skin substitutes were found to be a very useful alternative, and sometimes essential in those cases in which the uncovered areas are very extensive, as happens in burns, or when for some particular conditions, autografts cannot be considered as a possibility, for example, when the area from which to obtain the skin is very painful or when there is a risk of developing scars or infection, or when there is a healing too slow. The long-term studies on biopsies taken after years from the sites of application show the regeneration of the elastic fibers and partially of nerve cells, but also in this case, as in the physiological repair of tissues originally healthy, there is no regeneration of the skin attached, such as sebaceous and sweat glands and hair follicles.

20 Taking into account the persistent infection as a cause for delay or chronic wounds, medications and creams for topical application based on antibiotics were designed and built during the times, with the intention to treat or prevent infections. Among them, the silver-based creams have a global recognition. The use of silver as an antiseptic and disinfectant dates back to ancient times, and was applied to the preparation of medicaments utility universally recognized as the sulfadiazine silver. In the treatment of second-degree burns the silver sulfadiazine is the preferred drug for its anti-inflammatory and stimulating of tissue regeneration action, and also for its analgesic properties.

30 Iodine is another agent commonly used in antiseptics preparations for the treatment of healing wounds, as well as certain antibiotics for topical use,

generally in cream or gel, such as gentamicin, chloramphenicol, neomycin and their combinations.

In addition, alginate based dressings (a chemokine of natural origin) have been proposed, to be used as a vehicle for active molecules to stimulate the regeneration of granulation tissue and accelerate the healing process of wounds. Some examples include alginate hydrogel patch as a vehicle for the factor-1 of stromal regeneration (SDF-1, stromal cell-derived factor-1), which is a factor stimulating tissue regeneration, or in combination with substances that increase the resistance to the infection, as in the ionic dressing alginate/silver carboxymethyl cellulose (SACMC) or also in combination with anti-inflammatory agents. In situations where it is important is to provide moisture, mainly in chronic wounds, the alginate is combined with hydrocolloids, hydrogels, foams or hydrofibres.

As is known, to prepare the wound bed of an acute or chronic wound, of traumatic or infective type, and especially of wounds in which the debris and necrotic material cover substantially the living tissue acting as a barrier which prevents or hinders the penetration and adherence of regenerative substances, a "debridement" of the lesion has to be made first. This consists in removing foreign materials or necrotic tissue, devitalized or infected in the area of the lesion, up to exposure of surrounding healthy tissue, in order to prepare the wound to regeneration. In medical practice use is made of surgical debridement, but in situations where this is hazardous because of the danger of bleeding or other complications, chemical enzymatic debridement, for example by means of collagenase, papain or papain-urea (with or without chlorophyllin) is most useful. In other circumstances a mixt debridement allows even better results.

There is also the alternative practice of using maggots for the debridement of wounds when conventional methods do not yield results, or when there is no contraindication. None of the techniques mentioned have sufficient scientific topic to be better than the others and to be recommend as a technique of choice for special cases.

Taking into account diabetic ulcers, as epidemiologically more common

wounds that appear to be difficult to resolve, given the worldwide spread of diabetes diseases, it is known that these lesions consist of the continuity of tissues that can affect, related to its importance and severity, the skin tissue, subcutaneous tissue and finally the bone tissue. The most common location is
5 in the foot, where the lesion may involve the apical regions of the fingers, the joints between the phalanges joints, the heads of the metatarsals (plantar area), heel, the bony prominences of the ankle (tibio-peroneal-mortal talus), and leg. The involvement of the foot is very dangerous for the continuation of the disease, since it often comes to the interest of the subcutaneous tissues
10 and bone, with infections and fistulas that can lead to amputation of the affected regions.

Clinical trial on patients with diabetes shows that in these patients all the metabolic processes are altered. In fact, one of the reasons because a person with diabetes develops serious injury, where a healthy person would
15 have only light scratches, is in the fact that its metabolic control, despite the personal efforts and the medical one, is not the best. This situation is aggravated when the metabolic control is poor, and therefore there is a slowing of the regenerative processes and resistance to infections, and the body fluids of the patient are rather converted in excellent culture media.
20 Under such conditions, saprophytic germs become harmful and opportunistic, fungi become invasive, facultative aerobic bacteria become anaerobic.

In studies that led to the present invention, with the aim of seeking a topical preparation that is effective to shorten the treatment of diabetic ulcers, it was found that some of the few commercially available products had a
25 substantially debridement effect, others were only granulating and others were just re-epithelializing. Moreover, their positive effects in the beginning were reduced or suffer from some drawbacks, such as poor adhesion or poor absorption, and in some cases preparations acted as an occlusive material, in other producing excessive dehydration of the wound surface and of the
30 wounds secretions, and further the remains of the precipitated product adhered to the wound resulting in scabs.

Specifically, the indicated preparations for the "debridement" of the

wound (often improperly called, "healing", i.e. products generally proposed to accelerate the healing of wounds, regardless of what stage of recovery process that we refer to) had beneficial effects in cleaning the beds of the wounds, but their use beyond this stage did not support the effort of the body to granulate and to fill the ulcer space with a granulation tissue. Some products marked as "granulating", that is active in stimulating the occurring and the growth of granulation tissue, strongly adhered to the tissues and acted as an occlusive material, and besides being difficult to remove, drying up the wound and produce scabs. Finally, essentially "re-epithelializing" preparations were particularly useful in the last stage of repair of a deep wound with tissue loss (or superficial wounds such as burns of first degree, even after the onset of the treatment), but if applied indiscriminately in the phase that does not match, they had the effect of hampering the processes of wound repair.

15 **Summary of the invention**

In the light of the foregoing, the object of the present invention is thus to provide for therapeutic means useful for the topical treatment of wounds having a difficult or slow healing, such as- specifically, open wounds with loss of tissue, and in particular the lacerated-contused wounds and ulcers, including diabetic ulcers, as well as burn wounds.

Starting from the concept of the utility and need to supply a moist medium to wounds, so that any living tissue can grow in the most propitious environment, compositions containing natural active principles have been designed from which, according to the invention, moist medicaments and dressings have been prepared. The latter have a contents of actives è partially different from one another, depending on the stage of development of the healing process in which they are applied.

According to the invention, the preparations had to meet the following requirements:

- 30 1. easily absorbed active components, in order to act by absorption and diffusion from the site of application in the wound bed to the surrounding tissues rather than by contact, with controllable systemic

repercussions;

2. presence of nutrients which during absorption and assimilation by the neoformed tissues can ensure to the substrates carbohydrates and minerals, proteins, vitamins and fats required for the regenerative functions in the process;
3. arterial vasodilator effect, at least at the level of the lesion and around the same, with the purpose of improving the chaotic circulation which is common in diabetic patients;
4. stimulating effect for the generation of new arterial blood vessels (neoangiogenesis) which, in combination with the vasodilatory and arterial effects, assures an excellent blood supply;
5. an hemorheologic effect that can result in a lower viscosity of the blood, in order to remove the occlusion of thrombosed veins and the subsequent disappearance from the lesion of the blackish lines corresponding to the above veins;
6. antiseptic and antibiotic properties, such as those that are already known in many medicinal plants currently in use.

Bearing in mind these requirements, a specific formulation has been found based on dried and pulverized medicinal plants, suspended in bees' honey, which in combination with each other in definite ratios can be applied as a topical cream product on a wound, both acute and chronic, both superficial and deep, and having a considerable loss of substance, to stimulate and assist the healing process and recovery of injured tissue, and to accelerate the wound healing.

Detailed description of the invention

Therefore, the present invention specifically provides a topical composition the treatment of wounds consisting of a mixture of dried and powdered plants suspended in total proportions comprised between 5% and 80% by weight in bees' honey, wherein said plants comprise:

- a) plants of the genus *Plantago*,
- b) plants of the genus *Solanum*, and

c) plants of the genus *Kalanchoe*.

These three genera of plants, which are individually known in the field of medicinal plants and traditional herbal remedies, have necessarily to be present, all the three of them, in the formulations proposed according to the invention. To these, a fourth plant genus is added, the genus *Scoparia*, which is included in the formulation of two of the three specific types of preparations proposed according to the invention, namely the formulations having, respectively, activity in stimulating the granulation of the wound ("granulating" preparation), and activity in stimulating re-epithelialization of the same ("epithelializing" preparation). The fourth plant genus (*Scoparia*) is not included in the third type of preparation, having the activity of debridement ("debriding" preparation).

According to some specific embodiments of the invention, therefore, the plants of said mixture of plants also comprise

15 d) plants of the genus *Scoparia*.

The preparations proposed according to the invention, which have been called "Hidyt", are characterized by being composed exclusively of plants naturally treated and honey, without any artificial additives or preservatives.

More specifically, the plant part of the topical compositions here proposed consists of dried plants of the species *Plantago spp.*, *Solanum spp.*, *Kalanchoe spp.* and *Scoparia spp.*

More specifically, the plants of the genus *Scoparia* are represented preferably by *Scoparia dulcis*, a species especially widespread in tropical South America, where it is traditionally used by local people for infusions and for external applications, with a variety of indications resulting from tribal or folk medicine, including pain relief, antiseptic and anti-inflammatory properties.

Plants of the genus *Plantago* (plantain) can be represented, in particular, by *Plantago lanceolata* or from *Plantago major*, also used since ancient times as herbal remedies, not only in tropical areas, but also in temperate areas, especially for their antimicrobial, antiseptic and anti-inflammatory properties.

The plants of the genus *Solanum* are a very wide family, which includes

species cultivated for food production, such as tomato (*Solanum lycopersicum*), potato (*S. tuberosum*) and eggplant (*S. melongena*), and numerous and wild species used as herbal remedies or herbal products. Specifically, the compositions according to the invention may contain plants of the species

5 *Solanum dulcamara* (climbing nightshade), used as a topical herbal remedy for abrasion and against some dermatoses, and *Solanum nigrum* (black nightshade) also known as *S. incertum*, also used as a herbal remedy against inflammations and skin diseases.

In the proposed composition according to the invention, plants of the

10 genus *Kalanchoe* are represented preferably by *Kalanchoe pinnata*, traditionally used among the people of the Amazon and in many other areas of South America both for systemic use, in infusions, or for external use, even for treatment of wounds, burns, ulcers and insect bites.

The preparations obtained from the vegetable mixtures described,

15 suspended in bees' honey and in which plants *Plantago spp.*, *Solanum spp.* and *Kalanchoe spp.* are used, are particularly suitable for the first phase of therapy according to the invention, when an activity of debridement of the wound is specifically requested. In this case, the mixture of dried and pulverized plants contains *Plantago spp.*, *Solanum spp.* and *Kalanchoe spp.*

20 preferably in weight ratios between 2:2:3 and 4:2:2. respectively.

In the case where the preparation proposed is to be used in the next phase of the healing process, when an action of stimulation of the wound granulation is primarily requested, the mixture of plants indicated according to the invention contains *Scoparia spp.*, *Plantago spp.*, *Solanum spp.* and *Kalan-*

25 *Choe spp.*, preferably in weight ratios between 1:1:3:1 and 1:2:4:1.

Finally, for a wound in which the tissue initially missing has been substantially replaced by granulation tissue, and that has to undergo the last part of the proliferative phase, i.e. that of re-epithelialization, the topical composition indicated according to the invention, having re-epithelializing

30 activity, includes a mixture of *Scoparia spp.*, *Plantago spp.*, *Solanum spp.* and *Kalanchoe spp.*, preferably in respective weight ratios of between 8:4:4:1 and 16:4:4:3.

According to another complementary aspect thereof, the present invention relates to a medicinal preparation containing, as active ingredients, a mixture of dried and pulverized plants suspended in overall ratio between 5% and 80% by weight in bees' honey, which plants include::

- 5 a) plants of the genus *Plantago*,
 b) plants of the genus *Solanum*, and
 c) plants of the genus *Kalanchoe*.

for use as a topical medication. This definition includes the "debridant" version of the preparation of the invention, specifically designed for use in the process
10 of debridement of wounds, wherein the mixture of *Plantago*, *Solanum* and *Kalanchoe*, preferably *Plantago spp.*, *Solanum spp.* and *Kalanchoe spp.*, is used, preferably in weight ratios of between 2:2:3 and 4:2:2.

According to other embodiments, the invention relates to a preparation containing a mixture of dried and pulverized plants suspended in overall ratios
15 between 5% and 80% in bees' honey, wherein said plants include:

- a) plants of the genus *Plantago*,
 b) plants of the genus *Solanum*,
 c) plants of the genus *Kalanchoe*, and
 d) plants of the genus *Scoparia*

20 for use as a topical medication. This definition includes, in turn, the "granulating" version of the preparation of the invention, specifically designed for use in the development phase of the granulation tissue, and the "re-epithelializing" version of the same preparation, specifically designed for use in the subsequent stage of re-epithelialization. In the first case the mixture of
25 *Scoparia*, *Plantago*, *Solanum* and *Kalanchoe*, preferably *Scoparia spp.*, *Plantago spp.*, *Solanum spp.* and *Kalanchoe spp.*, is used preferably in the weight ratios of between 2:2:3 and 4:2:2, while in the second case the mixture is preferably used in weight ratios of between 8:4:4:1 and 16: 4:4:3.

As already noted, the Hidyts creams have been developed and tested in
30 diabetic patients suffering from severe injuries at the level of the lower limbs, such as neuropathic, ischemic, infectious and traumatic type. These are often deep and large wounds, affecting the entire heel or instep, or all of the big toe

or all toes, or the entire sole of the foot, and leave exposed the deep bone structure, in many cases with plurimicrobial purulent infections, and with large areas of necrosis which involve the tissues up to the bone. They were also tested in diabetic wounds in different parts of the body as in parts of the
5 buttock, pubic, abdominal and back areas, as well as the neck and hands. In all these cases the results were excellent.

The compositions of the invention were also tested on patients not suffering from diabetes, but which, for some situation, had developed ulcers of different sizes and gravity. Were applied in varicose ulcers, traumatic wounds,
10 pressure sores, burns and even in a case of longstanding facial chloasma. The compositions have also been applied as an intravaginal cream in patients with ulcer of the cervix and in cases of hemorrhoids, and in all applications, the results were excellent.

15 With specific reference to the requirements 2 and 3 given above (the effect of arterial vasodilation and stimulating neo-angiogenesis), these two properties have been successfully obtained in preparations of the invention, as shown by the deep red color of the lesion and particularly of the granulation tissue, and from the plethoric appearance (i.e. over-irradiated by blood) of all
20 the treated area during therapy. Considering specifically the injuries to the foot, it is noted that once the process of regeneration is ended and the wound is completely closed, the healthy foot is swollen. This phenomenon increases when the patient walks and the inflow of blood to the entire foot is such that the foot becomes swelled and warm and takes on a bluish color. For this
25 reason it is recommended to the patient to stop and raise his/her foot, which is deflated immediately, or alternatively to walk short distances.

The event described remits spontaneously over a period of between one and three months, at which time the newly formed vessels in the repaired wound close or degenerate, by virtue of the fact that it is not needed such a
30 high amount of blood in the injured area. This contribution is very useful during the period of active granulation and repair of tissues, but it must be reduced gradually in the later stages of healing.

Concerning the requirement no. 5 mentioned above (hemorheologic effect that will result in a reduction of blood viscosity), results have been obtained from the use of the invention preparations Hidy, that can be attributed to an antiplatelet, or fibrinolytic, or antithrombotic or thrombolytic activity; or to the presence of any of these activities, the interaction of some of them with one another, or even all.

During the initial preparation trial, the achievement of these results has been demonstrated in some cases with the presence of considerable hemorrhages, which were revealed by the stains on the sheets of the patient. To avoid undesired or excessive effects, the concentrations of the components initially set were suitably reduced, but in any case possible bleeding effects of the proposed preparations are controlled with the intravenous administration of vitamin K, to stop the hemorrhage. In examined patients the value of the clotting time, represented by PT (prothrombin time) and PTT (partial thromboplastin time) are prolonged. At least this fact shows that the components of the topical preparation proposed, as regards the activity hemorheologic, have a systemic action.

The cases cited allowed to establish, through experiments conducted on each of these plants taken separately, the effects attributable to each of them in terms of reducing the viscosity of the blood are not sufficient to justify the effect achieved by the composition of the whole. Therefore it was deduced that in this case, as in the case of other properties, the fact of mixing the various active ingredients in certain proportions to each other produces a true synergism of reinforcement, which results in an unexpected healing effect.

With reference to the requirement no.6, the preparations of the invention have antibiotic properties, both in consequence of the properties of the honey that forms the vehicle, or for the known antibiotic properties of some of the plants of the composition.

Purulent and short-changing infected wounds were treated with preparations of the invention, in septic patients and in a serious, decompensated and anemic state, in which previously undertaken antibiotic therapy had failed; or long-standing wounds, clean and having in incomplete

granulating, or completely granulated or in an incipient phase of re-epithelialization. Finally, wounds have been treated in which for some reason the normal evolution of the healing was interrupted at any stage of the cure.

The preparations proposed and the treatment techniques thereof have
 5 been successfully tested on lesions evolving one, three, eight months, as well as lesions of long standing, who had also originated forty years before, which highlighted old tissues prepared in a disorderly manner, united with one another in different phases within the same wound, granulation tissue, edge regions in the incipient phase of re-epithelialization, areas with large amounts
 10 of necrotic tissue and debris, secretions. The interesting aspect is that in these wounds, already two or three days from the beginning of treatment with the preparations of the invention, the improvements were manifested in a surprising way, up to reach in a few weeks at a total cure. From this point, it follows that the proposed preparations have the ability to activate cell
 15 regeneration of blood vessels, granulation tissues and skin in an orderly and harmonious manner, regardless of environmental conditions of the lesion and of the reparative phase where the wound was maintained.

At least during the granulation stage the plants in the study underwent to experimental verification in an individual manner. In this way it has been found
 20 that the fact of mixing the plants between them in certain fixed ratios and, especially, of using different ratios depending on the reparative phase in which the healing process is, gives results surprisingly better than as might be expected based simply on an "addition" of their property.

25 PROPERTIES OF HIDYT PREPARATIONS

Anti-inflammatory – The topical preparations of the invention have potent anti-inflammatory action which is visible not only in the wound bed but also in the skin around the lesion, changing the erythema to normal, cyanosis and edema in the initial wound bed, the red wine of the traumatic and infected
 30 wounds gradually changes to bright red. For this reason, once the topical treatment begins to be applied, oral anti-inflammatory are not required. This fact is of great benefit, since it avoids the possible gastrointestinal, renal and

other nature consequences, resulting from the indiscriminate use of anti-inflammatory drugs (NSAIDs).

Stimulating the secretion - humectant - The main mechanism by which the preparations of the invention achieve the anti-inflammatory and deflation effects may be related to their wetting properties and stimulating the secretion. This property, properly regulated, softens the tissues and facilitates the removal of debris from the wound. This property is of particular importance because, while in other cases and with other techniques substances must be used such as to provide a humid environment to the wound by the application of dressings, in this case the wound itself, by induction of the preparation, is kept moist while it deflates, dehydrating the inflamed tissues up to useful limits. This property has been properly modulated, according to the invention, without having adverse effects on the benefits partial and final.

Stimulating the debridement – the properties of the preparations of the invention of stimulating debridement is the result of the chemical action of one or more of its components on the tendon and connective tissue, on the purulent material, the necrotic tissue and debris of the local wound.

The different plant components of the preparation were tested separately on bovine muscle and connective tissue for eight days, and the results were not very convincing. However, two of the plant components of the proposed preparation plant showed protease activity by approximately 33%. Mixing the products between them, instead, their effects have proved to be significant, probably because of a synergism between them, or between those and the enzymes or other products secreted from the wound itself.

As a result of this activity, we observe that day after day, the fibrous tissue that lies in the wound is losing grip and consistency, they can be removed easily from the wound, and in some cases remains adherent to the patch when you run the dressing at home, as is usually reported by patients themselves.

Thrombolytic - In the bed of varicose ulcers is common to see the tortuous routes of azure thrombosed veins in the wound bed and around the leg. For this reason the use of anticoagulant is indicated as part of treatment

of these ulcers.

In this type of injury as early as the first week of applying the "debridant" cream thrombosed veins disappear completely without leaving the slightest trace of their existence, and this benefit is maintained through the successive application of other types of preparation according to the invention.

Stimulating the granulation - The appearance of the granulation tissue occurs regardless of the fact that the cleaning and the debridement of the wound are completed and it has the same origin as a substrate the same healthy connective tissue of the surface layers, the arteries and veins that remain exposed, the muscle fibers and bone marrow when it is exposed.

The stimulatory granulation activity fills all the gaps and recesses that can be left as a result of massive tissue destruction caused by infection, even those of the anatomy of body organs such as the foot and hand. This is a tissue of new formation, of exuberant red light, grainy, which bleeds easily, covering the whole extent of the wound and involving and surrounding tendons, arteries, veins, bones and nerves, without cutting off functionality. After filling the deep voids, it grows toward the surface until above the level of the skin around the wound edges.

The granulating activity is the most important property of the preparations proposed according to the present invention. It is the result of all the desired properties and produced in the Hidydt preparations, where are required properties of vasodilation and fluidizing in the blood, neoformation of blood mainly arterial vessels, additional nutrients, anti-inflammatory and moisturizing properties and the antibiotic effect.

25

The initial development of this granulation tissue is exuberant, with large granules that day by day grow excessively. However, at the beginning of the activity of re-epithelialization and of the change of the type of product according to the invention, the granulating activity is slowed and the tissue that was grainy becomes smooth, and the part that initially exceeded the level of the skin surrounding the lesion planes at the same level of healthy skin in perfect harmony.

30

It has also been tried on several occasions that if the treatment with the preparations of the invention is interrupted at this stage in favor of another epithelializing preparation, for example, commercial, the healing process slows down macroscopically and the granulation tissue is back smooth. After
5 the restarting of the application of the preparations according to the invention the same regenerating power of the large granules comes back clearly.

Reepithelializing - One of the most difficult challenges to achieve in a long-standing injury is undoubtedly the beginnings of a re-epithelialization.

According to some theories, this takes place through the proliferation of
10 the epithelium of the edges of the wound and the subsequent slippage of new epithelial cells from the edges, in the centered towards form within the wound bed.

In the application of the preparation according to the invention, in its "reepithelializing" form, it was found several times, unexpectedly, the presence
15 of nuclei of re-epithelialization in the center of the lesion, or at some other point in the wound bed, separated from the active edge. In some cases these nuclei of re-epithelialization appear prior to the re-epithelialization which starts from the edges.

The new skin is the same as the original skin, and gradually resumed
20 normal color, so that practically no scar remains. The skin replenished, also recovers normal sensitivity.

OTHER PROPERTIES '

It is common that the product of the normal secretion of wounds, over the granulation tissue and between the pores and the spaces which are
25 among the granules, is deposited as a transparent gelatinous material, whose consistency and adherence to the granulation tissue increases with time. This is the fibrin, which dries and gives rise to the crust that covers the aged wounds. In many cases between the surface of granulation tissue and this crust is formed a space occupied by pus.

30 With the use of preparations according to the invention the production of fibrin is minimal, if not practically null, of little consistence and of little adherence to the granulation tissue.

This fact is particularly important, because if the wound must be preserved free from fibrin the frequency of medical examinations required for her recovery-region and their total number is less.

METHOD OF APPLICATION

5 The use and application of the three topical preparations of the invention must be done in sequence: first, the product for the "debridant" action is applied, followed by granulating and finally the epithelializing preparation.

10 The "debridant" preparation must be applied after a control of the infection, and the application continues until all the fibrous tissue and debris were removed.

15 The preparation for granulating action is to be applied when the wound is completely clean, and its application continues until the granulation tissue has filled all the spaces, tunnels, caves and crevices formed by the infection, and has completely covered the bed of the wound so as to leave no difference in level between the bed itself and the normal skin around the lesion.

 The epithelializing preparation is applied from this moment, and since his aim is to cover all the uncovered area of skin, it is applied until it is necessary.

20 It was noted that during the re-epithelialization stage, in the skin around the new active edge very tight scabs are formed, which are better to remove. This fact persists until the wound has completely closed as a crust having color of coffee in the center of the scar, but eventually it disappears, and the skin takes the normal color and texture without signs of the former presence of
25 a wound so bloody.

 Not all of the wounds will require that the treatment is started with the preparation for the debridement: the type of preparation according to the invention which is the most appropriate to be applied at the beginning of the treatment will depend on the conditions of the lesion. For example, if at the
30 first visit the wound to be treated is clean and without purulent or fibrous material, or debris, it has to start with the granulating type. If it is a superficial wound, as in the case of a first-degree burn, or the wound has completely

granulated and with good vascularization, in this case we may begin with the re-epithelializing type.

In several cases the granulating preparation already operates the complete closure of the lesion, or the application period of the next re-epithelializing type is shorter than normal. This occurs because the three varieties of the preparation according to the invention, each one being not versatile, as they perform their main functions, they also complete the previous phase, or prepare and promote the conditions for the preparation of the next step so as the latter may carry out its main task. Thus the granulating preparation has as its main function in stimulating the granulation to fill the spaces of the connective tissue, but also has some debridement activity allowing the provision of a limited emollient properties to easily remove any debris or fibrin residue that may still occur. At the same time, has a mild stimulating effect of re-epithelialization, which is demonstrated by the color change of the edges, which begin to activate to revert to a rosy color, while the granulating activity continues.

The indications with respect to the frequency of application of the preparations according to the invention are preferably the following: the debridement variety applies every day, once a day, up to achieve the softening and the elimination of all the devitalized material. Normally its use is required for no longer than five days.

The variety stimulating the granulation is applied on alternate days once a day, and the epithelializing variety is applied once every two or three days. However, also these two varieties may be applied daily.

Overall, the results obtained with the clinical trial are surprisingly: a maximum of three months cases were retrieved that were considered for lost, and where the diagnosis included the amputation.

Description of the Figures

The clinical results obtained with the application of the preparations according to the invention are illustrated but not limited by the experimental cases reported in the following, as well as in the attached photographic

documentation, which shows the evolution of an exemplary clinical case treated with the compositions and the therapeutic procedure of the invention.

The attached figures show dated photographs in succession of the foot of a patient with a traumatic injury caused by an animal leg crush, with
5 infection and amputation of the second and third toe.

Figures 1a and 1b show the situation after the initial amputation and the consequent severely inflamed status;

Figures 1c and 1d show the situation about a month later, when the the inflammation has been controlled and in its place a well demarcated area
10 of necrosis is visible, which affects the big toe and fourth toe;

Figure 1e shows the surgical wound on the day of the amputation of the two necrotic fingers, the day when therapy begins with the topical preparations according to the invention;

Figures 1f and 1g show two following stages of the therapy according
15 to the invention, in which are evident, respectively, the still bleeding ends of the two recently amputated fingers and the formation of abundant granulation tissue;

Figures 1h and 1i show other two following stages of the healing in which the granulation tissue has become more compact and re-
20 epithelialization is the main event.

Clinical trials on patients with wounds treated with typical Hidyt preparations

Firt case - Burn wound infection complicated by hot substance

25 Diabetic female patient since a long time, 48 years of age, which two years before has undergone the amputation of the external malleolus of the left foot showing fistulas up to the tibio-astragaline joint. Despite a conventional treatment by the same team of doctors who had performed the amputation, she did not respond satisfactorily. The wound sometimes
30 secretes serous fluid and sometimes pus, or gets closed.

At the time of the first visit the patient had fever, the wound was in the process of secretion, surrounded by an erythematous bright halo; family

members said that it should be due to a first degree burn produced by a warm compress on the site. Incision is made, which drained a lot of yellow-blackish pus, foul-smelling.

5 The case was complicated by the fact that two superimposed layers of wounds had to be treated, the first deeper that reaches the articulation itself, and the other superficial, which widens the first. It has been defined the entire surface of the wounds, leaving exposed the subcutaneous connective tissue, tendons and ligaments of the joint. Once controlled the infection, we applied the topical preparation of the invention having debridement activity for three
10 consecutive days.

After a month of treatment, the wound appeared in clear granulation. The subcutaneous connective tissue, tendons and ligaments remained viable despite the infection, but during the granulation process, obtained by the application of the granulating preparation of the invention, tended to be
15 destroyed.

At nine weeks, the granulating activity filled the whole thickness, but the re-epithelialization was active, covering the front part of the wound. The subcutaneous connective tissue and fat were completely lost.

At the tenth week granulation and epithelialization were active. A
20 small residue of the tendon remained, and a perilesional edema was noted, which is not synonymous with inflammation, but a sign of a great vascularization.

At the 14th week, the granulation was completed, and the granulation tissue that was crude became smooth. There remain residues of connective
25 tissue or tendon, and the re-epithelialization covering the exposed surface continued. The appearance of the foot was pink, bloated.

Four months after, the new skin had nearly covered the whole bed of the wound, but the bottom over the new skin, near the center yet discovered the presence of a crust is noted, which came off easily leaving new pink skin.
30 A week later the wound was totally re-epithelialized.

Despite the loss of the tendon, the patient could walk without any problem. We had to put a prosthetic to the amputated leg.

Several months later she returned to a medical examination and was found in perfect condition. The skin had the same characteristics of normal surrounding skin.

5 **Second case - Chronic wounds, diabetic male patient**

Wound aged six months of development, which was treated with a drying powder, located at the root of the left foot toe nail. The wound appeared covered with fibrous connective yellowish tissue covered with white powder, with which he had been treated, the granulation tissue below appeared
10 smooth and rosy.

A surgical debridement was performed to remove the macerated fibrous tissue and the treatments according to the invention were started with the preparation for granulating activity. After one week of treatment, the wound has been granulated turning the smooth granulation into a granulation
15 with large granules and covering the entire wound bed of the alive tissue. The new skin had covered about 40% of the wound surface.

After two weeks, the granulation and epithelialization were active.

After 26 days of treatment, the skin had covered 90% of the surface of the wound, and a week later the wound was completely closed.

20 Six weeks later the patient returned for a medical examination, the wound was covered with skin which persisted over the crust in the center of the original wound.

25 **Third case - Varicose wound to the instep and external perimalleolar area**

Non-diabetic female patient, suffering from varicose veins in the left leg, which spontaneously developed a wound that in a few weeks became very large.

The patient was hospitalized for eight months in vascular surgery, and
30 during this period various techniques and different types of creams of the best internationally known were applied, without achieving the desired results.

The patient showed a lot of pain, because of which she adopted

analgesic positions walking. There were two related injuries, one on the instep and the other at the top of the lateral malleolus. By the dark brown crusty appearance it was noted that the wounds were aged and crusted allowing to see in transparency the muscle plan and tendons in one case and the lower
5 end of the tibia in the other case. The edges of the wounds were necrotic.

After just three days of application of preparation with debriding activity according the invention a change in the appearance of the tissues was noted: tissues initially necrotic dry and very adherent to the deep layers at the time to remove the gauze before cleaning, were moist and hydrated and
10 softened, and the living tissue appeared red for the action of the debridant preparation. Following the application of the product, that exerts a destructive action on tissues already necrotic and on those in the process of necrosis, a "isthmus" of skin that initially divided the wound into two parts, degenerates and is eliminated by the treatment . Once the cleaning of the wound was
15 obtained the benefit of the preparation was clear.

After ten days of treatment and seven days of application of the granulating version of the preparation of the invention, the granulation was in full activity. The particular adhesion of the residues of plant material to the tendons was noted, and the latter began to appear devitalized and wearied.
20 The wound was completely clean and full of granulation. The tibia was almost all covered by a neoformation tissue.

After At two weeks of application of the granulating preparation bleeding began to appear, which continued throughout the week, as was evidenced by the ecchymotic color of the fibrin impregnated by extravasated
25 blood. At the time of removing the fibrin bleeding was widespread, tendons continued to waste and the tibia appeared completely covered by granulation tissue.

After three and a half weeks of treatment and three weeks after the application of the granulating preparation the granulation phase was
30 completed and the re-epithelialization phase was in full development. The activity of collagenase was such that it was sufficient to take the tendons humidified with the gripper to clean the wound, despite the fact that the main

function of the applied preparation was the regeneration. The granulation tissue appears thick, and the re-epithelialization was active since a bit of time, and the edges of the wound bed had been covered by the new skin.

Two and a half months after, the process of re-epithelialization
5 progressed slowly because of the inconstancy of the patient and the bad treatment of the wound, as a lack of rest and a too tight bandage. There remained very little portions of the tendons, the granulation tissue was smooth and the new skin covered it by the edges. The re-epithelialization was active, the texture and color of the skin tended to approach the normal skin color.

10 It is important to clarify that, in this patient, the results, though being still exceptional, were not able to get the completion because the patient has not complied with the treatment program, and several times she gave it up, and then returned to follow it when the wound was getting worse. She also suffered a series of incidents during the period of treatment, including a burn
15 with hot water and one with an acidic substance that, falling over the wound, caused a regression so severe that it hurted all the results hitherto achieved.

Following each of these episodes it was possible to recover the injury-treating it with the topical preparations of the invention. The last time I visited the patient, the wound was regenerated up to 80%.

20

Fourth case - Critical ischemia wound of lower limb, diabetic male patient

Diabetic patient, 48 years of age, pale, anemic, fever, blood glucose 320 mg. Diagnosed with critical ischemia of the lower left limb, which is corroborated by arteriography showing the clogging of the deep femoral artery
25 in the medial third and downward obstructions total and partial across the path of the terminal branches of the same, below the popliteal branches, and a development of poor arterial collateral cycle.

The decision of the doctors in general and vascular surgery was to operate an amputation of the leg until the knee cap, secondary to the lack of
30 response at the surgical transmetatarsian amputation of the big toe, despite treatment with systemic anticoagulation and topical preparations in cream, and special care.

For the opposition of the patient to amputation, as a last tentative, for 15 days the patient was subjected to daily sessions of rectal ozone therapy. In the absence of evident signs of improvement in the wound that would give hope to have improved perfusion in order to ensure the tissue regeneration and healing of the wound, a treatment with the preparations according to the invention was initiated.

At the first consulting visit the foot appeared pale and emaciate, the wound base rosy, covered by abundant connective tissue devitalized. The second finger, necrotic and hardened, was amputee and the wound was debrided by surgery. The bleeding was moderate, and the granulating preparation Hidyto 50% has been applied.

At the second consulting visit, three days after starting the treatment, the wound was already red, covered with blood clots, the bleeding persisted for two weeks, and this time it was significant and detectable by the sheet. The patient reported that the bleeding occurred mostly when he put the leg to the ground. The granulation tissue was red, with granules moderately thick, and the skin of the edges showed signs of reactivation. At one month of treatment, the foot was not inflamed but plethoric, with no pulse at the instep, or tibial rear. The wound was red and granulating showing active re-epithelialization from the top and from the outer edges.

In the following week the granulation tissue was thick and re-epithelialization was activated starting from the edges.

The therapy was continued every other day for seven months, without any gaps, and until the last day bleeding from the undiscovered persisted and the foot was still bloated, hot and pink, becoming dark red and more bloated when it was lowered.

Fifth case - Infected diabetic foot

The diabetic pathological event had affected the big toe finger, the area of the instep and went up over the outer ankle bone and under the anterior part of the plant. After a month of conventional treatment and without apparent cause it occurs a injury in the toe finger. Despite treatment evolution

was chaotic.

At the first examination the patient had fever, he was cold, with all the left leg swollen and inflamed, with blisters and shiny skin, plump up to the medium third of the leg. The finger toe slightly cyanotic with plaques of necrosic skin in the dorsal side and more signs of necrosis of the finger that made it no longer viable. From the rear, behind the hanging of the fingers a crusted lesion was present closed, which once engraved drained abundant blackish stinking pus, typical of an anaerobic infection. The skin was pale, flaccid with changes on the inside of the foot.

The day following the incision surgery to drain pus, skin color and edema were improving, tendons and fascia remained exposed. At the fifth and sixth day of topical antibiotic treatment all the broken skin and the subcutaneous connective tissue devitalized were dried, the color of the skin around the lesion was tending to normal, and wrinkles showed that inflammation was under control. After controlling the primary infection appeared an infection by Pseudomonas, characterized by the typical greenish color and smell of rotting vegetables. This situation forced to postpone the application of the preparations of the invention (Hidyt) to further eight days. The same infection appeared again 15 days after the starting of the application of the Hidyt debridement preparation.

Although it had not yet begun the application of the Hidyt granulating preparation, a granulation tissue below the fibrous tissue begun to be appreciate.

After three weeks of treatment, the big toe was amputee and the most distal surface of the finger metatarsal was cut to reach the trabecular bone of the epiphysis, where is located the hematopoietic bone marrow. From this tissue, at the third day of treatment with the preparation of the invention, also begun the generation of a granulation tissue, which often grew with a rapidity never seen before. The granulation tissue is often exuberant, red and very bleeding.

Six weeks of treatment and three and a half weeks from the application of the granulating Hidyt preparation variety in studio, the wound

presented a thick granulation tissue, as to be seen as an exuberant malignant tumor excrescence. Between the grains a more intense red color was appreciated due to hemorrhage, which in this patient, as in other, appeared to be significant. The Incipient re-epithelialization appeared with pink edges.

5 After eighth weeks of treatment and at the fifth week of application of the granulating preparation, the granulation phase was complete, and the top phase was the re-epithelialization one. At this time there is an interphase in which coexist the granulation phase and re-epithelialization phase and granulation tissue easily exceeds the level of normal skin.

10 As already noted, during the granulation process the tendons, fascia and ligaments were lost and decomposed.

 At the sixth week of application of the preparation the re-epithelialization was active, the granules of the granulation tissue were more smooth and the new skin covered the wound from the outer edges. Two
15 weeks later the foot was totally healthy, as much the wound on the neck of the foot and its extension towards the upper part of the lateral malleolus, as the plantar wound and the stump of the finger toe.

 The present invention has been disclosed with particular reference to some specific embodiments thereof, but it should be understood that modifica-
20 tions and changes may be made by the persons skilled in the art without departing from the scope of the invention as defined in the appended claims.

CLAIMS

1. A topical composition for the treatment of wounds consisting of a mixture of dried and powdered plants suspended in total proportions comprised between 5% and 80% by weight in bees' honey, wherein said plants
5 comprise:
- a) plants of the genus *Plantago*,
 - b) plants of the genus *Solanum*, and
 - c) plants of the genus *Kalanchoe*.
- 10 2. A topical composition according to claim 1, wherein the said plants include, in addition
- d) plants of the genus *Scoparia*.
3. A topical composition according to claim 2, wherein the said plants a), b), c) and d) respectively consist of plants of the species *Plantago spp.*,
15 *Solanum spp.*, *Kalanchoe spp.* and *Scoparia spp.*.
4. A topical composition according to claim 3, wherein the said mixture of dried and powdered plants is suspended in total proportions comprised between 20% and 60% by weight in bees' honey.
5. A topical composition according to claim 3, wherein the said
20 *Plantago* plants are *Plantago lanceolata* or *Plantago major*.
6. A topical composition according to claim 3, wherein the said *Solanum* plants are *Solanum nigrum* or *Solanum dulcamara*.
7. A topical composition according to claim 3, wherein the said
Kalanchoe plants are *Kalanchoe pinnata*.
- 25 8. A topical composition according to claim 3, wherein the said *Scoparia* plants are *Scoparia dulcis*.
9. A topical composition for the treatment of wounds according to claim 1 having debridement activity, wherein said mixture of plants contains *Plantago spp.*, *Solanum spp.* and *Kalanchoe spp.* in weight ratios comprised
30 between 2:2:3 and 4:2:2.
10. A topical composition for the treatment of wounds according to claim 2 having granulation stimulating activity, wherein said mixture of plants

contains *Scoparia spp.*, *Plantago spp.*, *Solanum spp.* and *Kalanchoe spp.*, in weight ratios comprised between 1:1:3:1 and 1:2:4:1.

11. A topical composition for the treatment of wounds according to claim 2 having reepithelialization stimulating activity, wherein said mixture of
5 plants contains *Scoparia spp.*, *Plantago spp.*, *Solanum spp.* and *Kalanchoe spp.* in weight ratios comprised between 8:4:4:1 and 16:4:4:3.

12. A medicinal preparation containing, as active ingredients, a mixture of dried and powdered plants suspended in bees' honey in total proportions comprised between 5% and 80% by weight, wherein the said plants comprise:

- 10 a) plants of the genus *Plantago*,
- b) plants of the genus *Solanum*, and
- c) plants of the genus *Kalanchoe*.

for use as a topical medicament.

13. A medicinal preparation according to claim 12, for use as a medic-
15 ament for the debridement in the treatment of wounds.

14. A medicinal preparation according to claim 13, wherein the said mixture of plants contains *Plantago spp.*, *Solanum spp.* and *Kalanchoe spp.*, in weight ratios comprised between 2:2:3 and 4:2:2.

15. A medicinal preparation containing, as active ingredients, a mixture
20 of dried and powdered plants suspended in bees' honey in total proportions comprised between 5% and 80% by weight, wherein the said plants comprise:

- a) plants of the genus *Plantago*,
- b) plants of the genus *Solanum*,
- c) plants of the genus *Kalanchoe*, and
- 25 d) plants of the genus *Scoparia*

for use as a topical medicament.

16. A medicinal preparation according to claim 15 for use as a medica-
ment stimulating the granulation in the treatment of wounds.

17. A medicinal preparation according to claim 16, wherein the said
30 mixture of plants contains *Scoparia spp.*, *Plantago spp.*, *Solanum spp.* and *Kalanchoe spp.*, in weight ratios comprised between 1:1:3:1 and 1:2:4:1.

18. A medicinal preparation according to claim 15, for use as a medic-

ament stimulating the reepithelialization in the treatment of wounds.

19. A medicinal preparation according to claim 18, wherein di the said mixture of plants contains *Scoparia spp.*, *Plantago spp.*, *Solanum spp.* and *Kalanchoe spp.* in weight ratios comprised between 8:4:4:1 and 16:4:4:3.

**COMPOSITIONS FOR THE DEBRIDEMENT, GRANULATION AND
REEPITHELIALIZATION OF WOUNDS IN MAN**

ABSTRACT

5

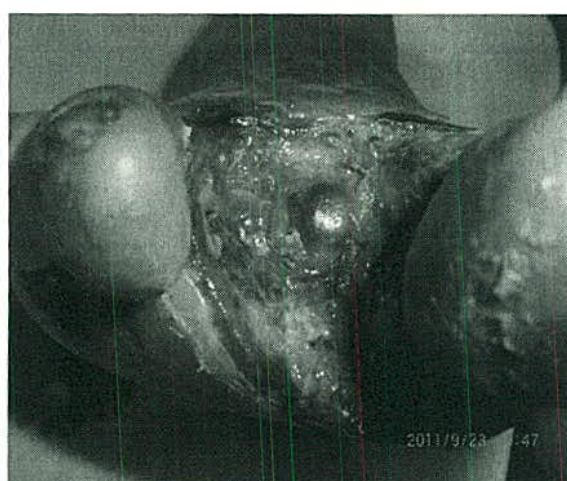
Compositions for topical application based on natural products, specifically dried pulverized plants suspended in bees honey, in which the ingredients are combined in proportions predetermined to provide three different types of preparations to be applied at various stages of repair and
10 regeneration of injured tissues. The application of the compositions shortens the stages of healing in the treatment of acute and chronic injuries of any degree of depth and breadth, and of any etiology.

The properties of the preparations include an hemorheological and systemic vascular activity which extends for a certain period even after the
15 end of topical treatment.



19/09/2011

FIG. 1a



23/09/2011

FIG. 1b

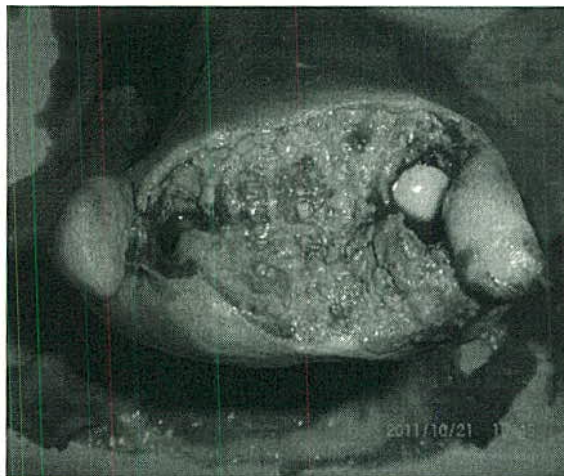


07/10/2011

FIG. 1c



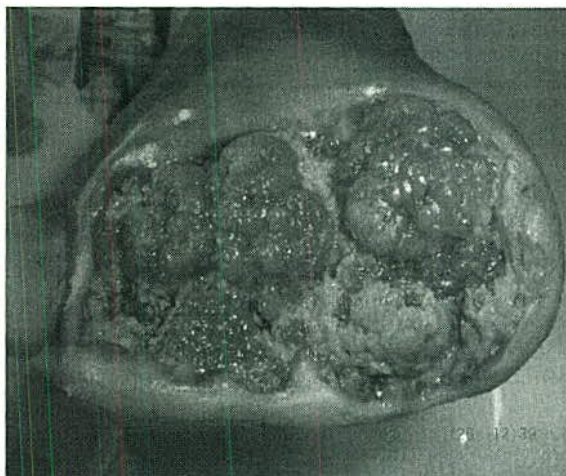
21/10/2011
FIG. 1d



21/10/2011
FIG. 1e



28/10/2011
FIG. 1f



25/11/2011
FIG. 1g



8/12/2011
FIG. 1h



29/12/2011
FIG. 1i



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Act. 411 PRESENTACION Folios: 137

PATENTE DE INVENCION ☐

MODELO DE

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Indicación que se solicita una patente.
Datos de identificación del solicitante o de la persona que presenta la solicitud
Descripción de la invención
Dibujos de ser estos pertinentes
Comprobante de pago de las tasas establecidas (De ser el caso formato de descuento)

Completa ☐ Incompleta ☐

PATENTE DE INVENCION PCT ☐

MODELO DE UTILIDAD PCT ☐

Art.33 Decisión 486/00, Circular Única

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Indicación que se solicita una PCT
Copia de la solicitud en español, tal como fue presentada inicialmente (capítulo descriptivo, reivindicatorio, resumen)
Dibujos de ser estos pertinentes
Comprobante de pago de las tasas establecidas (de ser el caso formato de descuento)

Completa ☐ Incompleta ☐

DISEÑO INDUSTRIAL ☐

(Art. 119 Decisión 486/00)

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Indicación que se solicita Diseño industrial
Datos de identificación del solicitante o de la persona que presenta la solicitud
Representación gráfica y fotográfica del Diseño industrial o muestra del material que incorpora el diseño
Comprobante de pago de las tasas establecidas

Completa ☐ Incompleta ☐

ESQUEMA DE TRAZADO ☐

(Art. 92 Decisión 486/00)

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Indicación que se solicita un esquema de trazado
Datos de identificación del solicitante o de la persona que presenta la solicitud
Representación gráfica de un esquema de trazado
Comprobante de pago de las tasas establecidas

Completa ☐ Incompleta ☐