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(54) Title: TOPICAL OR INJECTABLE COMPOSITION COMPRISING HUMIC ACID SALTS AND POLYVINYLPIRROLIDONE FOR THE TREATMENT OF SKIN DISEASES

(57) Abstract: An agent containing the mixture of humic acid and its salts with polyvinylpyrrolidone and natural herbal oils provides a cure of pilonidal sinus or dermis/epidermis diseases by applying to skin in topical or injectable form without any need of surgical operation. This therapy method is a new technique in pilonidal sinus or skin diseases. The method guarantees patients to cure with the logic of "healing of an open wound" with low recurrence probability and without affecting the daily life standards. The result product is formed by humic acid -polyvinylpyrrolidone (HAP) about 10: 1 ratio, mixed by 150 d/d in a mixer, heated to max. 90°C, adjusted by pH 6.0 to 12.0 at 2-24 hours.



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**DESCRIPTION**

TOPICAL OR INJECTABLE COMPOSITION COMPRISING HUMIC ACID SALTS AND  
POLYVINYLPIRROLIDONE FOR THE TREATMENT OF SKIN DISEASES

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**FIELD OF THE INVENTION**

This invention relates to both topical and injectable application of an agent, which contains the mixture of humic acid and its salts with polyvinylpyrrolidone as a wound therapy in dermis and epidermis diseases. The aim of this invention is to produce a wound therapy agent more effective than the product previously patented in Turkish Patent Institute with registered number 2007 00973 in the treatment of pilonidal sinus by polyphenols. The invention provides a cure of pilonidal sinus or dermis/epidermis diseases by applying basically humic acid and sodium humate or potassium humate with polyvinylpyrrolidone to skin in topical or injectable form without any need of surgical operation. This therapy method is a new technique in pilonidal sinus or dermis/epidermis diseases. The method guarantees patient to cure with the logic of "healing of an open wound" with low recurrence probability and without affecting the daily life standards. There has been no invention related with curing of pilonidal sinus or dermis/epidermis diseases by using an agent formed by humic acid-polyvinylpyrrolidone (HAP) which can be injected into skin or applied topically.

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## BACKGROUND OF THE INVENTION

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There are several patents pointing out that humic acid and its salts named as humates are used for human being health. Kim et al. declared in USP 3,615,780 that suitable polyphenolic materials are obtained by extraction of Western hemlock, Douglas fir, White fir, Sitka spruce and Southern yellow pine, also quebracho, mimosa or other tannin containing trees or barks with aqueous solutions of sodium, ammonium and potassium hydroxides. The material obtained by this patent was used in the mixture of cement. Seubert et al. in USP 4,918,059 produced low molecular weight alkali metal huminates. The resulting alkali metal huminates of low molecular weight are useful as therapeutic agents in wound healing and for use in highly effective synthetic mud baths. Lown conceived the US patent number 5,626,881 "Humate Dietary Supplement" and USP 7,067,155 "Anti-inflammatory Humate Compositions And Methods Of Use Thereof". Laub studied the US patent number 5,945,446 "Process For Preparing Synthetic Soil-Extract Materials And Medicaments Based Thereon", USP 6,524,567 "Synthetic Soil-Extract Materials And Medicaments For Hemorrhagic Fever Viruses Based Thereon", USP 6,534,049 "Synthetic Soil-Extract Materials And Medicaments For Human Immunodeficiency Viruses Based Thereon", USP 6,576,229 "Synthetic Soil-Extract Materials And Medicaments For Influenza Viruses Based Thereon". Zanetti carried out "Treatment of HIV Infection With Humic Acid" in patent study of USP Application 20040137085. Herein is reported one such effort that suggests a safe alternative to existing therapeutic strategies. With this invention is demonstrated that humic acid, a natural, commercially available product extracted from soil, demonstrates potent anti-HIV activity in vitro. Also shown is the anti-viral activity of humic acid associated with an immunostimulatory effect mirrored by an enhanced production of interleukin-2 (IL-2) by human lymphocytes upon activation with mitogens like plant lectins.

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According to Achard in "Crelles Chem. Ann. 1786, 11, 391-403", humates have long been used as folk remedies for a wide variety of illnesses. Lotosh recounted this aspect in "Biol. Nauki 1991, 10, 99-103". Both Kuhnert et al. in "Arch. Exp. Veterinarmed. 1982, 36(2), 169-177" and Chen et al. "Ssu Chuan I Hsueh Yuan Hsueh Pao 1985, 16(2), 127-129" reported on the anti-inflammatory properties of humic

substances. Woyton et al. pointed out in "Arch. Immunol. Ther. Exp. (Warsz) 1993, 41(1), 99-103" that inflammatory states can be treated with humic preparations. Ansorg in "Arzneimittelforschung 1978, 28(12), 2195-2198", Nakamura in "Shika Kiso Igakkai Zasshi 1989, 31(3), 329-332" and Klocking in "Pharmazie 1981, 36(1), 50-53" indicated that humic substances exhibit anti-microbial properties.

Schultz in "Dtsch. Tierarztl. Wochenschr. 1962, 69, 613; 1965, 72(13), 294-297" and Klocking in "Experientia 1972, 28(5), 607-608; Pharmazie 1981, 36(1), 50-53; Acta Virol. 1983, 27(3), 200-208; " demonstrated that humic substances exhibit anti-viral properties in particular Coxsackie virus A9, herpes simplex virus type 1 and type 2. Cushman et al. studied in the paper "J. Med Chem. 1991, 34(1), 329-337" about human immunodeficiency virus (HIV). Schneider et al. carried out the influence of humic substances at influenza virus type A in "Virology 1996, 218(2), 389-395" and Mentel et al. worked on influenza virus type B in "Biomed. Biochim. Acta 1983, 42(10), 1353-1356"

Thiel et al. in "Zentralbl. Bakteriolog., 1977, 239(3), 304-321", Schols et al. in "J. Acquir. Immune Def. Syndr. 1991, 4(7), 677-685" and Schneider et al. in "Virology 1996, 218(2), 389-395" reported on the mechanism whereby humic substances inhibit the cytopathicity of a number of viruses in detail. They have thought that the materials prevent viral replicating by sorbing onto the viral envelope protein (gp120SU in the case of HIV) and thereby blocking the sorption of viral particles to cell surfaces.

Riede et al. in the paper "Arch. Orthop. Trauma Surg. 1992, 111(5), 259-264" reported on that there is extensive covalent as well as hydrogen bonding of humic substances to collagen fibers. Tendon strength is thereby increased by as much as 75 percent.

Vetvicka et al. in "J Med Food. 2010 Jun 16" have indicated that humic acids are biologically active immunomodulators affecting both the humoral and cellular branches of immune reactions. In addition, the two humic acids studied here are working in synergy in stimulation of the immune reaction, supporting further studies of these natural immunomodulators.

Riede et al. in the paper "Virchows Arch. B Cell Pathol. Incl. Mol. Pathol. 1991, 60(1), 27-34" and Kowalska et al. in "Acta Pol. Pharm. 1993, 50(4-5), 393-395" indicated that natural humic acids stimulate the phagocytic and bactericidal activity of granulocytes in humans at dose levels of 100-300 milligrams per day over a 14-day testing period. Klocking in "Arch. Toxicol. Suppl. 1991, 14, 166-169" studied on the

influence of natural as well as synthetic humic acids on haemostasis. It was found that humic acids in dose levels of 100-300 milligrams per kilogram body weight had no effect on bleeding time, clotting time, thrombin time, prothrombin time, kaolin-kephalin time, euglobulin lysis time, the concentration of fibrinogen, the platelet count, or ADP-induced platelet aggregation. van Rensburg in "Inflammation; 2009 Aug;32(4):270-6" investigated the effects of brown coal derived potassium humate on lymphocyte proliferation, cytokine production and complement activation.

Inglot et al. in "Arch Immunol Ther Exp (Warsz) 1993;41:73-80" studied on TTP (Tolpa Torf Preparation). A low molecular weight preparation of peat TTP induces tumor necrosis factor-alpha (TNF- $\alpha$ ) and interferon (IFN)- $\alpha$  and - $\gamma$  in human peripheral mononuclear blood cells in vitro. Immunoprotective activity has been suggested from a study of oral treatment of athletes with TTP.

Jooni et al. (Z Naturforsch [C] 2003;58:263-7) declared the effects of oxihumate on the proliferative response of lymphocytes in vitro and ex vivo. Oxihumate increased the proliferative response of phytohemagglutinin-stimulated human lymphocytes, from a concentration of 20  $\mu$ g/ml and upwards. This response was even more striking in the case of lymphocytes from HIV-infected patients and similar effects were observed ex vivo following administration of a non-toxic dosage of 4 g oxihumate per day to HIV-positive individuals for two weeks. Studies revealed that stimulation of the proliferative response of lymphocytes by oxihumate is associated with an increased production of IL-2, as well as expression of the IL-2 receptor in the setting of decreased production of IL-10. Oxihumate therefore holds promise for the treatment of immunocompromised patients.

Of particular interest is the UVB protection by peat substances. Humic acids were investigated in vitro using U937 culture cells. The cells were exposed to UVB and UV-induced cytotoxicity was assessed with the XTT reduction assay (EZ4U, Biozol). Ammonium humate and humic acids showed a protective activity by UVB absorption that is in the range of p-aminobenzoic acid (Kühn S, Klöcking H-P, Klöcking R; Akademie gemeinnütziger Wissenschaften zu Erfurt; Jahrbuch 2005; p. 63-4).

High-pressure liquid chromatography (HPLC) analysis revealed that aqueous peat extracts contain up to 18 fractions of water-soluble compounds of fulvic and humic acids. These compounds have been found to have a stimulatory response on the contractile activity of smooth muscles. In vitro diffusion studies showed that the permeability of these substances across human full-thickness skin (thickness: 200  $\mu$ m

1) is highly selective and the resulting stimulatory activity is dependent on the permeated fraction. Especially, the HPLC fractions 7-11 and 14 are able to permeate human skin. Fractions 7-11 show a moderate stimulatory effect on smooth muscles for more than 90 min whereas fraction 14 shows the strongest stimulatory effect which was, however, suppressed after 87 min. These results show that the cutaneous therapy with peat treatment results in transcutaneous permeation of biologically active fulvic and humic acid derivatives explaining the additional pharmacological effect of peat treatment in clinical practice (Beer AM, Juninger HE, Likanov J, Sagorchev P.; *Int J Pharm*; 2003;253:169-75.) In experimental rodent studies, therapeutic bathing in peat and humic acids extracted from peat resulted in significant reduction of intraabdominal gynecological adhesions (Mesroglu M, Maas DH, Mauss B, Plogmann S, Ziechmann W, Schneider J.; *Zentrabl Gynäk* 1991;113:583-90).

Wollina in paper "J. *Cutan Aesthet Surg*. 2009 Jan;2(1):17-20" has stated that humic substances are of potential interest in dermatology and cosmetology, especially in physiotherapy, rheumatology and sport medicine. Because of mild astringent and anti-inflammatory activity, humic substances are useful adjuncts in the topical therapy of inflammatory skin diseases like atopic dermatitis, cheiropodopompholyx, psoriasis and mild focal hyperhidrosis. Wollina observed benefit in patients suffering from chronic hand dermatitis and psoriasis palmaris as a result of an open trial with daily peat application. Peat from the Altteicher Moor (Germany) was used as an adjunct to standard therapy. Patients reported a more rapid relief from itch, inflammation was decreased and pustule formation was stopped earlier than usual. Astringent activity of humic substances may be responsible for such an effect. According to Wollina, peat applied topically may exert systemic effects by absorption of humic substances. Humic substances may be of potential interest in rosacea. Here, flushing and inflammation are mediated by neurogenic mediators. Serotonin uptake inhibitors and  $\alpha$ -adrenergic agonists have been shown to suppress erythema and flushing. Humic substances have a multimodal function in this disease, since UVB protection would inhibit a major trigger and  $\alpha$ 2-adrenergic receptor blockade might provoke a better  $\alpha$ 2-response.

Since humic acids have shown antiviral activity in vitro, their use in facial masks for prevention of viral reactivation after chemical or laser peeling would be of interest. Topical application in uncomplicated cases of cutaneous herpes simplex warrants clinical trials.

Ziechmann investigated the healing properties of humic acids found in moors, peat and colored clay or in humic matter containing water (Ziechmann, Therapiewoche 28 (1978), 1199-1211). Sea mud has been popularly used as an effective base in cosmetic preparations although its biologically-active materials and mechanisms on skin have not yet been fully determined. Kim et.al. (Nat Prod Commun; 2010 Mar;5(3):395-8.) isolated humic substances as the major organic substance of the sea mud from a tidal flat in Korea, and investigated their water-retentive properties. Among the three isolated humic substances, humic acid (HA) showed the highest water retentive property (approximately 50 % mass increase from water uptake).

Dizman has indicated in his study of "Treatment of Pilonidal Sinus By Polyphenol" in Turkish Patent Institute 2007 00973 that humic acid and its salts could cure the diseases of pilonidal sinus. Pilonidal sinus is a serious epidermic problem and a insidious disease being formed unwittingly in our body in our world where we have rapid life standards, heavy working conditions and densed tempo. Pilonidal sinus disease is an acquired condition, usually seen in young adults, manifest by midline pits in the natal cleft and associated with hair. The underlying pathophysiologic feature is enlarged hair follicles due to midline vacuum and pulling forces; when plugged with hair or keratin, the follicles rupture, leading to a foreign-body reaction within the presacral subcutaneous tissue and subsequent acute and chronic abscess. The seemingly simple nature of this entity has been overshadowed by the history of its treatment, focused on the surgical extirpation of "diseased tissue." The attendant morbidity of these treatments, in terms of chronic wounds, patient productivity lost to convalescence, and recurrence, has been impressive. The recent trend has been toward more conservative therapy, minimizing tissue loss. An extension of this thinking emphasizes perineal hygiene, including hair control, for management of the condition in general, with lateral incision and drainage reserved for acute abscess. In this scene the invention implies on a technique which has not been tried before that can be directly applied to dermis as an injectable form and to epidermis a topical form.

Humic acids are mixtures of organic, high molecular weight compounds having similar structures, the molecular weights of which are described in literature as being in a range of 200 Da to more than 200,000 Da. Humic acids are allomelanins found in soil, produced by the decomposition of organic matter, particularly plants (<http://ec.europa.eu/enterprise/cosmetics/cosing/index.cfm?fuseaction=search.details&id=56403>).

Polyvinylpyrrolidone (PVP) is a water-soluble polymer made from the monomer N-vinylpyrrolidone. The polymer PVP was used as a blood plasma expander for trauma victims after the first half of the 20th century. PVP added to iodine forms a complex called (Povidone-iodine) that possesses disinfectant properties. This complex is used in various products like solutions, ointment, pessaries, liquid soaps and surgical scrubs.

### **DESCRIPTION AND IMPORTANT TECHNICAL ASPECTS OF THE INVENTION**

10 It is therefore an object of the invention to provide novel humic acid-polyvinylpyrrolidone (HAP) mixture which is parenterally significantly nontoxic, the preparation of which has uniform pharmaceutical efficacy and which has long-term storability, and consequently can be safely used in human medicine. According to this, most probably, HAP eradicates wounds by two mechanisms: (1) HAP mixture removes  
15 the microorganisms located in the wound bed. HAP covers and fills wound related cavities. In this way HAP prevents atmospheric oxygen from reaching the microorganisms. HAP also prevents the microorganisms from using oxygen present in blood and neighboring tissues. The mixture produces these effects by its potent antioxidant actions (buffering effect). HAP increases the chemotaxis of phagocytes to  
20 the diseased area. Additionally, HAP enhances the capacity of granulocytes to engulf bacteria. HAP also increases the activities of lysosomal enzymes which are transferred into the phagolysosomes and lyse bacteria. (2) Promotion of wound healing is also achieved by the effects of humic acid-polyvinylpyrrolidone. HAP promotes cytokine, interferon and tumor necrosis factor alpha (TNF- $\alpha$ ) synthesis for faster healing. In  
25 other words, HAP exerts anti-inflammatory actions and causes the wound healing process to proceed better. Thus, healthy fibrin formation and collagen synthesis result in better wound healing and consequently in better healing of pilonidal sinus and of other skin diseases. So, the wound heals with the help of HAP in the same way as it heals erosive cervicitis. Below are the product samples of which are made of humic  
30 acid-polyvinylpyrrolidone quickens phagocytosis and strengthens collagen synthesis:

#### **SAMPLE 1**



The mixture is formed as below that humic acid (sodium humate) made by Turkish Patent of registered number 2007/00973 is mixed with polyvinylpyrrolidone and natural herbal oils in the liquid form.

5	Sodium humate	900-950 g
	Polyvinylpyrrolidone	50-100 g
	Nigella sativa oil	2-5 g
	Centaurium erythraea oil	1-3 g
	Carrot oil	1-5 g

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Sodium humate as 900-950 g and polyvinylpyrrolidone as 50-100 g with natural herbal oils are placed in a mixer containing 150 d/d motor, having a pH range of 6.0 to 12.0, in 20-90°C at 2-24 hours.

## 15 SAMPLE 2

The mixture is formed as below that humic acid (potassium humate) made by Turkish Patent of registered number 2007/00973 is mixed with polyvinylpyrrolidone and natural herbal oils in the liquid form.

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	Potassium humate	900-950 g
	Polyvinylpyrrolidone	50-100 g
	Nigella sativa oil	2-5 g
	Centaurium erythraea oil	1-3 g
25	Carrot oil	1-5 g

30

Potassium humate as 900-950 g and polyvinylpyrrolidone as 50-100 g with natural herbal oils are placed in a mixer containing 150 d/d motor, having a pH range of 6.0 to 12.0, at 20-90°C at 2-24 hours.

**CLAIMS**

I claim:

- 5 1. The method of treating skin diseases in both dermis and epidermis layers like acne, acanthosis nigricans, actinic keratosis, sun spots (age spots), allergic contact dermatitis, angioma, tinea pedis or athlete's foot, atypical mole, basal cell carcinoma, Bateman's purpura, boils (furuncle, carbuncle), candida or monilia, cyst, dandruff, Darier disease, dermatofibroma, diaper dermatitis, discoid lupus erythematosus, 10 dyshidrotic dermatitis (pompholyx), atopic eczema, folliculitis, Grover's disease, hidradenitis suppurativa, hyperhidrosis, hives, impetigo, irritant and allergic dermatitis, keloid, keratoacanthoma, keratosis, lichen planus, lyme disease, melanoma, pilonidal sinus, pityriasis, poison ivy and poison oak, pruritus ani, psoriasis, Schamberg's disease, scleroderma, sebaceous hyperplasia, shingles (herpes zoster), 15 skin aging, squamous cell carcinoma, stasis dermatitis, warts and xanthomas.
2. The method of claim 1 wherein said application is in both topical and injectable form.
3. The method of claim 2 wherein said product is the mixture of sodium or potassium salts of humic acid with polyvinylpyrrolidone and the natural herbal oils.
- 20 4. The method of claim 3 wherein said time is at 2-24 hours.
5. The method of claim 4 wherein said pH is ranging 6.0 to 12.0.
6. The method of claim 5 wherein said temperature is at 20-90°C.

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**INTERNATIONAL SEARCH REPORT**

International application No  
PCT/TR2011/000100

**A. CLASSIFICATION OF SUBJECT MATTER**  
 INV. A61K31/79      A61K35/10      A61K8/81      A61K8/97      A61Q19/08  
 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

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 practical, search terms used)  
 EPO-Internal, BIOSIS, CHEM ABS Data, 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.
Y	WO 2009/158667 A2 (COMGENRX INC [US]; ORONSKY BRYAN T [US]) 30 December 2009 (2009-12-30) the whole document, in particular the examples and paragraphs [0045], [0046] and [0047]	1-6
Y	----- JP 2006 273734 A (ENZYME KK) 12 October 2006 (2006-10-12) the whole document, in particular paragraph [0065]	1-6
Y	----- CN 1 372 926 A (XINJIANG INST CHEMISTRY CAS [CN]) 9 October 2002 (2002-10-09) the whole document	1-6
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Further documents are listed in the continuation of Box C.       See patent family annex.

\* Special categories of cited documents :

<p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"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)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p>	<p>"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</p> <p>"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</p> <p>"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.</p> <p>"&amp;" document member of the same patent family</p>
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Date of the actual completion of the international search	Date of mailing of the international search report
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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  Albrecht, Silke
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## INTERNATIONAL SEARCH REPORT

International application No  
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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.
Y	TR 2007 00973 A2 (DIZMAN MUEMIN [TR]) 22 October 2007 (2007-10-22) cited in the application the whole document -----	1-6
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# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No PCT/TR2011/000100
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