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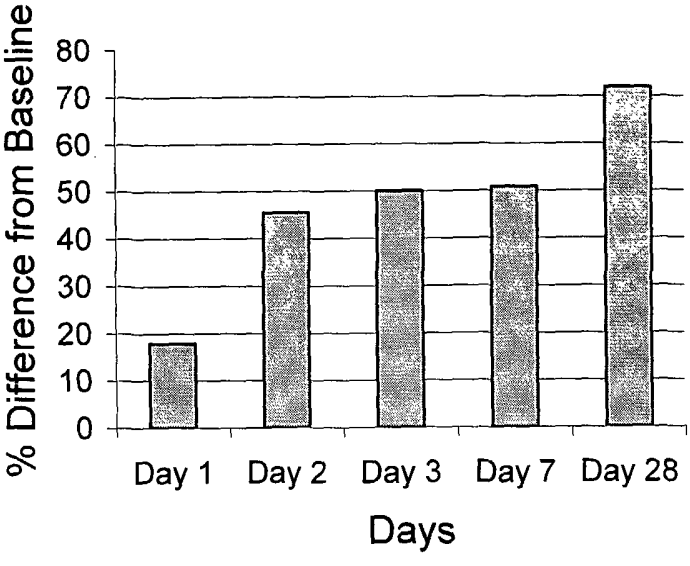

(57) Abstract: The present invention concerns an Inula viscosa extract for use in treating arthritis and for use an anti-inflammatory, anti-bacterial, anti-fungal, anti-oxidant, anti-yeast agent. The invention further concerns a method for cultivating Inula viscosa plants and an optimized efficient extraction process utilizing ethyl-acetate as the solvent for obtaining an extract characterized by the quantitative presence of carotanoids, flavanoids, tomentosin, sesquiterpene lactones, sterols, and saponins.

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NOVEL *INNULA VISCOSA* EXTRACTS AND THEIR USE FOR TREATMENT OF ARTHRITIS

FIELD OF THE INVENTION

This invention relates to *Inula viscosa* and its extracts and their use.

BACKGROUND OF THE INVENTION

The plant *Inula viscosa* (Aiton L.), defined by Aiton L. botanical guide "medicinal and Culinary" plant, synonyms: *Dittrichia viscosa*, (family Compositae). *Inula viscosa* is a perennial shrub that grows in the wild in the Mediterranean basin. Plants which are members of the *Inula viscosa* species are known to possess natural components which have biochemical activity. Antifungal activity of *Inula viscosa* extracts, especially against plant diseases were reported by Y. Cohen in US 6,423,352 and US 5,853,727. Debat, J. et al in US 4,254,112 disclose extracts of *Inula viscosa* for treatment of infectious diseases and as bacteriostatic and fungistatic agents. An active sesquiterpene isolated from *Inula viscosa* and its antifungal activity was disclosed by Neeman, I. and Maoz, M. in WO 99/20,109. WO 03/017768 discloses the use of an *Inula viscosa* formulation for controlling hematophagic insects, insects, mosquitoes and horseflies.

All of the above-mentioned extracts and their use were all done using *Inula viscosa* plants grown in the wild without standardization or optimization of the source of the *Inula viscosa* material and the extraction process in order to achieve sustainability, predictability, reproducibility and efficiency in extracting of the active components from the *Inula viscosa* plant which are essential in the production of a standardized, uniform, predictable and reproducible product.

Arthritis is an inflammation of the joints due to infectious, metabolic or constitutional causes. According to the USA arthritis foundation, it is the leading

cause of disability in the USA. The condition is not life threatening; however, it results in a medium to severe restriction in the range of motion, pain ,swelling and stiffness of the affected joints and the physical function of the individual suffering from such a condition. Presently it is treated by a combination of systemic and topical treatments and/or analgesics which are taken orally, parentally, or topically directed on (or injected into) the inflamed joints.

SUMMARY OF THE INVENTION

The present invention is based on the fact that it has been found that *Inula viscosa* extracts may be used for treating and alleviating the symptoms caused by arthritis. The extracts alleviate the symptoms of arthritis by, reduction of swelling, of the inflammation and of the pain associated with the condition. Furthermore, use of the extracts result in an increase in the range of motion of the affected joints and an increase in their strength. Unaffected and untreated joints are also positively affected. Re-occurrence incidence of these effects are lowered and/or prevented by the use of these extracts. In addition it has been found that the wild type *Inula viscosa* plant may be cultivated as a crop, grown commercially under careful and controlled conditions, extracted in standard commercial process resulting in optimized quantities of active material having a uniform and standardized quality which is reproducible, where the contents of the active components in the extract are characterized. The obtained extract showed excellent antifungal, antioxidant and antibacterial properties as well.

Thus the present invention is directed to an *Inula viscosa* extract for use in the treatment of arthritis. The arthritis may be osteoarthritis, rheumatoid arthritis, psoriatic arthritis, all which are degenerative joint diseases, nonarticular rheumatism and miscellaneous arthritis. The *Inula viscosa* extract may be used topically or preferably in a formulation comprising suitable excipients. The amount of the *Inula viscosa* extract in the formulation is about 0.1% to about

95% preferably between about 0.1% to about 50% and most preferably 5% to 30% (w/w).

The invention is further directed to a formulation comprising of an *Inula viscosa* extract for use as skin care and as an anti-inflammatory, anti-bacterial, anti-fungal, anti-oxidant, and anti-yeast and further as sun screen protection.

The invention is further directed to cultivation of *Inula viscosa* plants and optimized extraction to obtain a optimized quantities of *Inula viscosa* extract. The extract is obtained by harvesting the above-ground parts of cultivated *Inula viscosa* plants which are grown under controlled conditions at predetermined periods. The harvested parts are dried prior to extraction resulting in a moisture content of about 5% to 8% of the dry leaves biomass. The dried biomass is ground to yield a powder. Extraction is done by immersing the powder grain at least one time with ethyl-acetate, evaporating the ethyl-acetate at elevated temperatures and obtaining an extract characterized by its flavanoids, carotenoids, tomentosin, sesquiterpene lactones, saponins and sterol contents.

BRIEF DESCRIPTION OF THE DRAWINGS

In order to understand the invention and to see how it may be carried out in practice, a preferred embodiment will now be described, by way of non-limiting example only, with reference to the accompanying drawings, in which:

Fig. 1 shows the HPLC chromatogram of a combined extract of *Inula viscosa* extracted according to the present invention.

Fig. 2 shows the GC/MS chromatogram of the non-derivatized *Inula viscosa* extract showing the various sesquiterpenes (quantification given in Table 1).

Fig. 3 shows the anti-oxidant activity of the *Inula viscosa* of the present invention compared to commercial anti-oxidant agents such as BHT and quercetin.

Fig. 4 shows results of a clinical study demonstrating the pain reduction efficacy of a treatment with an *Inula viscosa* extract of the present invention (visual analog scale).

Fig. 5 shows results of a clinical study demonstrating the pain reduction efficacy of a treatment with an *Inula viscosa* extract of the present invention (Wong-Baker faces pain rating scale).

Fig. 6 shows results of a clinical study demonstrating the increase in range of motion of affected joint resulting from the treatment with an *Inula viscosa* extract of the present invention.

Fig. 7 shows results of a clinical study demonstrating the reduction of swelling (calculated as reduction of thumb gauge diameter) treated with the *Inula viscosa* extract of the present invention.

Fig. 8 shows results of a clinical study demonstrating the increase in joint strength (Palmer pinch) treated with the *Inula viscosa* extract of the present invention.

Fig. 9 shows results of a clinical study demonstrating the increase in joint strength (Tip pinch) treated with the *Inula viscosa* extract of the present invention.

Fig. 10 shows results of a clinical study demonstrating the increase in joint strength (Key pinch) treated with the *Inula viscosa* extract of the present invention.

Fig. 11 shows results of a clinical study demonstrating the increase in joint strength (Grip pinch) treated with the *Inula viscosa* extract of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

As mentioned the present invention deals with use of *Inula viscosa* preferably use of an extract of *Inula viscosa* for treating arthritis. Furthermore, *Inula viscosa* and extracts thereof according to the present invention may also be used as a natural skin care component for other uses. In particular, *Inula viscosa*

and its extracts may be used efficiently as an anti-inflammatory, anti-bacterial, anti-fungal, anti-oxidant, and anti-yeast and further as a sun screen protection for skin. Due to its anti-bacterial and anti-fungal properties it may further be used as a natural preservative material. *Inula viscosa* according to the present invention may be used in appropriate formulations comprising from about 0.1% to about 95% (w/w) of *Inula Viscosa*. The exact amount of *Inula viscosa* in a particular formulation depends on the intended use and on the mode of application. The *Inula viscosa* may be an aqueous based formulation or a non-aqueous based formulation. Depending on the nature of the intended formulation suitable exipients should be added. Non-limiting examples of such exipients may be C_2-C_5-alcohols, most preferably linear or branched C_2-C_4 alcohols, ethers, esters and emulsifiers. The non-aqueous formulations comprise vegetable oil, Aloe Vera, Vaseline or hydro gel, glycerin, vegetable oil, emulsifiers, water and their mixtures. Preferably, water borne formulations comprise of about 0.1% to 60%, more preferably between 4 to 30% and most preferably 6 to 12% (w/w) *Inula viscosa* extract dissolved in the appropriate formulation. An non-water formulation preferably comprises about 0.1% to 50% and most preferably 5% to 30%.

According to the present invention, the wild uncultivated *Inula viscosa* plant may be cultivated and extracted in a novel industrial process yielding optimized quantities of pure extract characterized by its distribution of chemical components. Thus according to another aspect, the present invention discloses a cultivated *Inula viscosa* plant grown under strict supervision in order to obtain optimized quantities of uniform and predictable quality of the extracted active material. The novel extraction is done using ethyl acetate as the extraction solvent. The obtained extract is characterized by its unique HPLC, I.R. GC-MS spectrum. Due to the fact that the extraction is carried out using ethyl acetate as the extracting medium, which is considered GRAS (**G**enerally **R**egarded **A**s **S**afe) the extract may be used as part of any conventional formulation in food, pharmaceutical or cosmetic formulations.

Introduction and cultivation of *Inula viscosa* as a crop included a selective collection of shoots and branches from plants growing in the wild in different regions as to encompass a diversify of ecotypes screening, cutting the shoots into sections, dipping the lower end of the said sections in liquid IBA rooting hormone in concentration of 4,000 PPM or powdered IBA T-8 rooting hormone, or equivalents, planting the sections in pots of 4 by 3.5 centimeters or similar planting pots, filled with a substrate of ground coconut and particles of polystyrene foam in equal volumetric parts, or an equivalent planting substrate. The planted pots were placed on a warm table that maintains a temperature range of 22° to 25°C, the warm table is located in a half shaded nursery greenhouse, having a roof made of shading net, the planted pots were irrigated by means of controlled fogging under which, water was sprayed in a form of fine mist during 1.5 seconds in 20 minutes intervals. The plants remained in the nursery for 3 to 4 weeks or until the roots overgrow the pot space. The plants were then transported from the nursery to a plowed field, where a dripping irrigation system is pre located. The plants were planted in standard distances of 30 to 60cm in a raw to maximize bio-mass per land unit, initial irrigation of 60 cubic meters of water per 1,000 square meters is applied to support rooting after transplantation. After 2 to 4 weeks in the field, tops of the young *Inula viscosa* plants were cut to stimulate branching out of the plant to enhance increased bio mass production of the plants. It is disclosed here that treatment of *Inula viscosa* cultivated as a crop includes irrigation by means of water dripping from holes along irrigation tubes placed on the ground or below ground, the fastest growth of bio mass takes place at irrigation to plant water evaporation of 1:1. in order to obtain a controlled irrigation rate, soil humidity indicators are placed in the field, readings of the soil wetness are transmitted from the indicators to a computer controlled irrigation system that commands the amount and frequency of irrigation through the dripping tubes system, it is further disclosed that irrigation rate lower than 1:1 *vs.* plant evaporation reduces the rate of bio mass growth, and causes early termination of further bio mass increase. It is further disclosed that fertilization

by nitrogen dissolved in the irrigation water, and served every 3 weeks at a rate of 15 Kilograms per 1,000 square meter, results in the fastest rate of growth and bio mass accumulation of the plants. These treatments and others not mentioned herein above, have been tested to cause average growth rate of 15.1 grams per day per plant of fertilized and irrigated plants, as compared to average of 1 to 2 grams a day of un fertilized and un irrigated plants. It is further disclosed that the dry leaves bio-mass of the treated plants is approximately double than that of untreated plants. It is further disclosed that treatment with herbicide GOL 150 or equivalent before planting has increased bio mass yield by 30% as compared to untreated plants.

Harvest time was determined by highest extract yield and its antioxidant activity. The general time frame of harvest is before the plants are preparing to bloom. It is further disclosed here that irrigation was stopped a week prior to harvesting as to increase the concentration of active ingredients in the leaves. It is yet further disclosed here that rain or irrigation applied to the leaves or aerial parts of the plants washes off water soluble ingredients of the protective resin that coats the leaves of *Inula viscosa*, where it should be understood that this particular resin constitutes a major part of the extract. Thus such washing off reduces overall extract yield and consequently the biological activity. Hence it is preferable to cultivate the *Inula viscosa* plant at a proper location where no rain falls during summer and early fall months June, July, August, September and October. Consequently, the cultivated *Inula viscosa* was harvested on three periods, namely June, August and October. Each harvest yielded about 1,300 Kg green biomass per 1,000m^2.

Harvesting the cultivated *Inula viscosa* entails chopping off *Inula viscosa* plants by a standard or customized spice harvesting combine, the plants are cut off at 10 to 25 centimeters above ground. The obtained green biomass comprising of leaves, cut branches or the entire plant was dried in an accelerated manner using a standard industrial spice drying facility. The biomass is placed on a moving perforated conveyer under hot air blast at 50°C to 65°C. Drying is

complete when the moisture content of the dried leaves is about 4% to 8%. At the end of the drying, leafs were separated from the stems by processing the entire dried mass through a system of rotating cylinders, stems were discarded and dry leafs were transported by air current to a vibrating sieve and a sizing apparatus where the dry leafs were broken and collected as small particles. The typical powder grain size is of 50 to 80 mesh, typical bulk density of powdered *Inula viscosa* leaves 0.37g/cm ^{3}.

Alternatively, slow dehydration of the harvested material can also be accomplished by open air drying where the cut branches and plants are placed on a well ventilated dry and shaded platform for 2 to 5 days depending on the ambient temperature, relative humidity and ventilation of the material. It should be noted that another route for dehydration was also employed. The cut branches were left in the field on top of the remaining stems for a period of initial dehydration of about 12 hours, followed by their collection using a standard combine designed to pick harvested plants.

The plants that remain in the field after harvesting are left to regenerate and grow during the next growth cycle, new shoots from the best yielding plants are cut off the new plants, and planted in new cultivation areas as described above. Leaves of the best extract yielding plants from the first year crop are cloned by method of tissue culture to further standardize the domesticated *Inula viscosa* species.

Quality control of the standardization process includes but not limited to the use of HPLC, GC MS and TLC methods to determine the content of marker groups of chemicals. The chemical groups which were found are Flavenoids, Sesquiterpenes including Tomentosin (Sesquiterpene Lactones) and Cartenoids. **Figure 1** displays the HPLC chromatogram of a combined extract of *Inula viscosa* extracted according to the present invention. The chromatogram (λ = 220nm) displays many peaks which were determined using derivitization (silylation reagent – BSTFA) and internal standard for each chemical group mentioned above. For quantification of the amount of the flavanoids, a quercetine

standard was used. Nootkatone was used as the internal standard for the sesquiterpenes and β-carotene standard was used for carotene determination. **Figure 2** shows a GC/MS chromatogram of the non-derivatized *Inula viscosa* extract showing the various sesquiterpenes where the quantification of the various sesquiterpenes is given in Table 1.

It was found out that the total content of flavonoids is directly dependent on harvest time whereas maximal content is found a month before the blooming phase of the plant. The analysis showed that the ethyl acetate extract comprises 34% sesquiterpenes, 12.0% flavenoids and about 0.53% carotenes. Table 1 lists the sesquiterpene components which were analyzed by GC/MS and their relative amounts.

Table 1: Characterization of Sesquiterpene fractions and contents of the *Inula viscosa* extract.

Rt (min)	Compound name	Synonym	Empirical formula and M.W.	% w/w
8.70	N.I.			0.128
9.16	***(I.S.) Nootkatone***		$C_{15}H_{22}O$ ***Mw=218***	
9.41	Sesquiterpene		$C_{15}H_{20}O_2$ **Mw=232**	1.23
9.60	Sesquiterpene		$C_{15}H_{22}O_2$ **Mw=234**	16.4
10.38	Sesquiterpene		$C_{15}H_{24}O_3$ **Mw=252**	6.20
10.49	Sesquiterpene		$C_{15}H_{22}O_3$ **Mw=250**	0.45
10.63	Sesquiterpene		$C_{15}H_{22}O_3$	0.51

			Mw=250	
10.71	Sesquiterpene		$C_{15}H_{22}O_3$ **Mw=250**	0.27
10.87	2H-Cyclohepta [b]furan-2-one, 3,3a,4,7,8,8a-hexahydro-7-methyl-3-methylene-6-(3-oxobutyl)-	Tomentosin Sesquiterpne lactone	$C_{15}H_{20}O_3$ **Mw=248**	6.56
10.92 (isomer)	2H-Cyclohepta [b]furan-2-one, 3,3a,4,7,8,8a-hexahydro-7-methyl-3-methylene-6-(3-oxobutyl)-	Tomentosin Sesquiterpene lactone	$C_{15}H_{20}O_3$ **Mw=248**	2.28
Total Amount (%)				34.0

To ensure product uniformity, *Inula viscosa* oleoresin extract standardized quality is determined by the content of the above-mentioned Sesquiterpene lactones, tomentosin, flvonoids, and carotens as well as quantitative analysis determining the relative amount of each of these natural components using the above-mentioned internal standards for each group (data not shown). The presence of these chemical groups and their relative amounts in each batch provide a fingerprint for the *Inula viscosa* extracts. Determination of the chemical markers is analyzed by High Performance Liquid Chromatograph (HPLC), Gas Chromatograph (GC MS), TLC, and FT-IR, and compared to

master files containing analysis data of a master *Inula viscosa* batch and other *Inula viscosa* plants whether or not domesticated or standardized.

The anti-oxidation properties of the *Inula viscosa* extract of the present invention is shown in **Fig. 3**. The anti-oxidation of the *Inula viscosa* was compared to that of commercial anti-oxidant agents such as BHT and quercetin in preventing β-carotene degradation. As demonstrated, the anti-oxidation activity of the *Inula viscosa* extract of the present invention is comparable to that of BHT and quercetin and has a long lasting effect.

It should further be added that high content of crotanoids and flavanoids in the extract make the *Inula viscosa* extract of the present invention useful as a sun screen.

Formulations prepared for treating arthritis according to the present invention are made by mixing 0.1% to 50% *Inula viscosa* extract in standard and commercially available carrier compounds, including but not limited to ethyl, propyl, isopropyl and butyl alcohol, Aloe-Vera gel, polymeric hydro gel petroleum Vaseline gel, glycerin gel, or in formulation with other commercially available carriers in common use for cosmetics and pharmaceuticals creams for topical application. Preparation of 0.1% to 95% of the said oleoresin dissolved in alcohol such as ethanol, propanol, iso-propanol, butanol or pentanol are useful for topical arthritis treatment. Liquid preparations of up to 15% *Inula viscosa* standardized extracts in a waterborne emulsion with standard food grade commercially available emulsifiers and oil-borne preparations in vegetable or mineral oils with emulsification support of standard food grade commercial emulsifiers. All preparations mentioned above are useful as topical applications on the arthritic joints areas. Waterborne emulsion of *Inula viscosa* oleoresin extracted by water or organic solvent are useful for arthritis and back pain treatment for people bathing in a bath tub or spa or a pool or a whirlpool containing waterborne *Inula viscosa* standardized extracts.

A topical application of a formulation containing the *Inula viscosa* of the present invention dissolved in alcohol (50% w/w) was used in a clinical test to

evaluate the efficacy in pain reduction, increase in range of motion of the affected joint(s), reduction in swelling and increase in strength of the affected and treated joints. The clinical trials lasted 28 consecutive days and included 6 randomly selected panelists (patients) who were physician diagnosed as suffering from osteoarthritis. None of the 6 patients was using any arthritis treatment drugs neither prior to, and during the clinical trials, nor any other medication (prescribed or over the counter medication). Each of the 6 randomly selected patients was suffering from pain, swelling and limited range of motion of the affected joint(s) for about 30 minutes for the majority of the days in the month immediately preceding the treatment. Each patient topically applied the alcoholic *Inula viscosa* extract formulation on the affected joint(s) twice a day for a period of 28 days. During this period the patients were evaluated at the beginning (0^{th} day), and on 1^{st}, 2^{nd}, 3^{rd}, 7^{th} and 28^{th} days. Reduction in pain was tested using two methods. The first is the visual analog scale (McCaffery & Pasero 1999) which allows the patient to determine his (or her) own pain using description or visual aids. A numeric scale ranging between 0 (no pain) and 10 (worst imaginable pain). The second method employed the Wong-baker "FACES" rating scale (Wong, D. Baker, C. 1995) uses drawings of faces in various levels of distress, where patients select the numerically weighted face representing their particular level of pain at examination time. The results of the two pain tests are shown in **Tables 2** and **3**, respectively.

Table 2:

	Day 0	1^{st} day	2^{nd} day	3^{rd} day	7^{th} day	28^{th} day
1^{st} patient	1.01	1.01	0.30	0.20	1.00	0.00
2^{nd} patient	9.40	4.70	3.50	1.20	0.20	0.00
3^{rd} patient	6.70	5.30	3.20	1.60	4.00	2.2
4^{th} patient	7.20	9.00	3.00	5.20	0.20	0.00
5^{th} patient	3.5	1.2	1.10	1.20	3.70	0.20
6^{th} patient	9.00	9.00	9.00	9.00	9.00	8.00
Mean	6.14	5.04	3.35	3.07	3.02	1.73

% Difference		-17.91% 0.55 0.29	-45.43% 1.52 0.07	-50.00% 1.59 0.07	-50.81% 1.62 0.06	-71.82% 22.35* 0.01*

Visual analog pain scale rating: 0=no pain – 10=worst pain; (*) – statistically significant.

Table 3:

	Day 0	1st day	2nd day	3rd day	7th day	28th day
1st patient	6.00	2.00	2.00	2.00	2.00	0.00
2nd patient	8.00	2.00	2.00	0.00	0.00	0.00
3rd patient	6.00	4.00	4.00	2.00	4.00	2.00
4th patient	8.00	10.00	4.00	6.00	9.00	0.00
5th patient	2.00	2.00	2.00	4.00	2.00	2.00
6th patient	8.00	8.00	8.00	4.00	8.00	4.00
Mean	6.33	4.67	3.67	3.00	2.67	1.33
% Difference		-26.22% 0.96 0.17	-21.41% 1.97 0.03	-52.60% 2.51 0.01	-57.81% 2.35 0.02	-78.98% 4.29* 0.00*

(*) – statistically significant;

Wong-Backer FACES pain scale rating

0-1-"does not hurt at all"; 2-3-"hurts just a little bit"; 4-5-"hurts a little more"; 6-7-"hurts even more"; 8-9-"hurts a hole lot"; 10-"hurts as much as you can imagine".

Figures 4 and **5** give a graphical representation of the results shown in Tables 2 and 3 demonstrating a statistically significant reduction in pain determined by the above-mentioned two tests.

Improvement in additional parameters characteristic to arthritis were further checked with the patients participating in the above-mentioned clinical test. Improvement in the range of motion of the affected joint as a result of the application of the topical *Inula viscosa* formulation was also observed. A finger goniometer was used to measure the active or passive joint range of motion. The apparatus measures joint flexion and hyperextension, where it is calibrated in degrees. **Fig. 6** demonstrates that the topical application of the *Inula viscosa*

extract formulation, results in an increase in the range of motion of the affected joint. The results are given in Table 4.

Table 4:

	Day 0	1st day	2nd day	3rd day	7th day	28th day	Differ. from 0 day (%)
1st patient	70°	80°	90°	90°	90°	90°	28.57
2nd patient	40°	30°	40°	60°	70°	75°	87.5
3rd patient	40°	40°	40°	40°	60°	90°	50.0
4th patient	45°	45°	60°	60°	60°	60°	33.33
5th patient	75°	90°	90°	90°	90°	90°	20.0
6th patient	60°	60°	60°	60°	60°	90°	50.0
Mean	54.00	58.00	63.00	67.00	68.00	78.00	
Differ. (%)	7.4	16.66	24.07	25.92	25.92	44.44	**Overall Mean**
t.p.	0.29 0.39	0.8 0.21	1.2 0.12	1.37 0.1	1.37 0.1	2.6* 0.01*	44.9

(*) statistically significant;

Another parameter characterizing arthritis is the inflammation causing the swelling of the affected joint. The effect of reduction in swelling (finger diameter) of the affected joint as a result of the application of the topical formulation of the *Inula viscosa* of the present invention is demonstrated in **Fig. 7**. The reduction of the swelling was determined by measuring the circumference gauge of the finger as a measure in the reduction of finger diameter. The circumference was measured in inches, where he numerical results are summarized in Table 5.

Table 5:

	Day 0	1st day	2nd day	3rd day	7th day	28th day	Differ. From 0 day (%)
1st patient	2.25	2.25	2.25	2.25	2.25	2.20	-2.22

2nd patient	2.75	2.75	2.70	2.55	2.5	2.5	-9.69
3rd patient	2.75	2.75	2.70	2.70	2.50	2.50	-9.09
4th patient	2.25	2.00	2.00	2.00	2.00	2.00	-11.11
5th patient	N.A.*	N.A.*	N.A.*	N.A.*	N.A.*	N.A.*°	N.A.*
6th patient	2.25	2.25	2.25	2.25	2.25	2.25	0
Mean	2.45	2.40	2.38	2.35	2.30	2.29	
Differ.(%)		-2.04	-5.71	0.00	-6.12	-6.53	**Overall Mean**
t.p.		0.25 0.40	0.37 0.35	0.57 0.29	0.97 0.17	1.03 0.16	-7.87

(*) Patient's finger joint not affected;

Figures 8, 9 and **10** demonstrate yet another parameter associated with arthritis, which is the finger pinch of the affected joint. Three pinches were measured, the palmer pinch, the tip pinch and the key pinch, where Tables 6, 7, and 8 display the data. In each measurement there were measured the pinch of both the affected (treated Tables 6A, 7A and 8A, respectively) and the unaffected (untreated Tables 6B, 7B and 8B, respectively) joint. All patients are right-handed. Pinch was measured by a pinch gauge calibrated in kilograms. The palmer pinch measures the thumb pad to pads of the index and middle fingers. The tip pinch measures thumb tip to index fingertip. The key pinch measures thumb pad to lateral aspect of middle phalanx of index finger. All three pinch measurements demonstrate that following the application of the *Inula viscosa* topical formulation of the present invention there is a significant improvement in all three pinches.

TABLE 6A: Palmer pinch measurements (affected/treated) joint

	Hand	**Day 0**	**Day 1**	**Day 2**	**Day 3**	**Day 7**	**Day 28**
		Kg	**Kg**	**Kg**	**Kg**	**Kg**	**Kg**
1st	R	4.33	3.83	5.00	4.96	3.83	5.33
2nd	L	3.83	8.00	7.33	5.50	4.83	5.66
3rd	L	1.83	2.16	1.83	2.00	2.50	2.66

4th	R	5.00	5.00	4.50	5.60	6.60	7.00
5th	R	4.13	5.00	5.20	6.00	5.83	5.60
6th	L	3.83	3.66	4.66	4.50	5.00	6.00
Mean		3.83	4.61	4.75	4.76	4.77	5.38
% Diff			2.36%	24.02%	24.54%	24.54%	**40.46%**
t			0.85	1.10	1.27	1.27	**2.10***
p			0.20	0.14	0.11	0.11	**0.03**

* Statistically Significant

TABLE 6B: Palmer pinch measurements (unaffected/untreated) joint

Panelist	Hand	Day 0	Day 1	Day 2	Day 3	Day 7	Day 28
		Kg	Kg	Kg	Kg	Kg	Kg
1st	L	4.00	3.33	4.56	4.33	4.00	4.33
2nd	R	5.00	5.50	5.83	6.33	6.16	7.33
3rd	R	1.60	2.80	2.00	2.00	8.50	2.66
4th	L	6.00	4.00	4.50	5.00	6.00	6.20
5th	L	6.16	5.60	6.00	6.30	6.30	6.00
6th	R	4.50	3.50	5.16	5.43	7.50	7.50
Mean		4.38	4.12	4.68	4.90	6.41	5.67
% Diff			-5.39%	6.84%	11.87%	45.34%	29.45%
t			0.32	0.34	0.57	2.31*	1.31
p			0.37	0.36	0.28	0.02*	0.10

- Statistically Significant; Dominant Right Hand – All Panelists

TABLE 7A: Tip pinch measurements (affected/treated) joint

Panelist	Hand	Day 0	Day 1	Day 2	Day 3	Day 7	Day 28
		Kg	Kg	Kg	Kg	Kg	Kg

1st	R	3.50	4.50	5.50	4.50	3.83	4.33
2nd	L	3.33	4.00	3.70	3.60	4.55	4.92
3rd	L	2.16	2.43	2.00	1.66	2.00	2.16
4th	R	4.00	4.60	4.70	5.00	6.00	6.10
5th	R	3.83	5.30	4.83	5.00	5.00	5.50
6th	L	3.50	3.66	3.86	4.50	5.33	5.16
Mean		3.39	4.08	4.09	4.04	4.45	4.70
% Diff			20.35%	24.49%	19.17%	31.26%	**38.64%**
t p			1.44 -0.08	1.24 0.12	1.12 0.14	1.68 0.04	**2.11*** **0.03**

* Statistically Significant

TABLE 7B: Tip pinch measurements (unaffected/untreated) joint

	Hand	**Day 0**	**Day 1**	**Day 2**	**Day 3**	**Day 7**	**Day 28**
		Kg	**Kg**	**Kg**	**Kg**	**Kg**	**Kg**
1st	R	3.33	3.16	4.16	4.26	5.50	4.33
2nd	L	4.83	4.83	5.16	5.66	5.66	5.83
3rd	L	3.66	2.60	2.60	2.00	3.00	2.33
4th	R	3.00	4.00	4.20	5.00	6.00	6.00
5th	R	4.20	5.50	5.20	5.50	5.30	6.00
6th	L	5.00	3.66	5.00	6.56	7.66	7.33
Mean		4.00	3.96	4.39	4.85	5.52	5.30
% Diff		-1.00%	9.75%	21.25%	38.00%	32.40%	**32.50%**
t p			0.08 .46	0.73 0.24	1.14 0.13	2.17* 0.12*	**1.65** **0.06**

• Statistically Significant

TABLE 8A: Key pinch measurements (affected/treated) joint

	Hand	**Day 0**	**Day 1**	**Day 2**	**Day 3**	**Day 7**	**Day 28**
		Kg	**Kg**	**Kg**	**Kg**	**Kg**	**Kg**

1st	R	4.00	4.50	5.33	4.83	5.00	6.00
2nd	L	6.00	5.60	5.00	7.00	6.83	6.83
3rd	L	2.60	2.00	2.00	2.30	2.60	2.83
4th	R	3.50	5.50	5.60	6.50	8.00	7.50
5th	R	4.50	4.60	5.00	5.00	5.20	5.30
6th	L	4.00	6.16	5.16	5.33	7.16	7.16
Mean		4.20	4.56	4.85	5.16	5.80	5.94
% Diff			8.57%	15.47%	22.85%	38.09%	**41.42%**
t			0.50	0.86	1.17	1.73	**2.05***
p			0.31	0.20	0.13	0.05	**0.03***

* Statistically Significant
Dominant Right Hand – All Panelists

TABLE 8B: Key pinch measurements (unaffected/untreated) joint

	Hand	**Day 0**	**Day 1**	**Day 2**	**Day 3**	**Day 7**	**Day 28**
		Kg	**Kg**	**Kg**	**Kg**	**Kg**	**Kg**
1st	L	3.50	3.50	3.80	3.50	4.50	5.16
2nd	R	6.50	7.60	7.40	8.16	6.30	8.00
3rd	R	3.60	3.16	6.00	7.00	7.00	7.00
4th	L	3.5	6	6	7	7	7
5th	L	5.50	5.30	5.00	5.60	5.60	6.00
6th	R	6.00	4.56	7.00	6.83	7.50	7.50
Mean		4.77	5.04	5.30	5.57	6.01	6.14
% Diff			5.66%	11.11%	16.77%	25.99%	28.72%
t			0.30	0.56	0.73	1.27	1.48
P			0.30	0.29	0.29	0.11	0.12

* Statistically Significant
Dominant Right Hand – All Panelists

Another parameter which was measured is the difference in the strength of grip of the affected joint. Grip measurements were done using an Hydraulic Hand Dynamometer calibrated in pounds or kilograms of force. Due to the fact that grip varies depending on the size of the object being grasped. Therefore the grip

handle is usually adjustable to accommodate various size hands. In order to further determine whether the person is indeed exerting maximum effort and to include only measurements where the person exerted maximum effort, each measurement consisted of three consecutive tests where breaks of 5 minutes were taken between each grip and there should be only a 10% variation between two sets of results. The results are given in **Figure 11** where the data is summarized in Tables 9A (grip pinch of the affected/treated hand) and 9B (grip pinch of the unaffected/untreated hand).

TABLE 9A: Grip pinch strength measurements (affected/treated) joint

	Hand	Day 0	Day 1	Day 2	Day 3	Day 7	Day 28
		Kg	Kg	Kg	Kg	Kg	Kg
1st	R	18.66	23.00	22.00	20.66	20.66	23.33
2nd	L	13.66	15.00	17.66	19.66	20.66	20.00
3rd	L	4.50	4.16	4.60	4.40	3.16	11.00
4th	R	16.50	15.50	23.00	17.50	22.50	19.50
5th	R	14.30	18.60	19.00	19.00	17.00	18.00
6th	L	8.33	11.33	10.66	18.66	15.66	16.75
Mean		12.66	14.60	16.15	16.65	16.61	18.10
% Diff			15.32	27.56%	31.51%	31.20%	**42.96%**
t			0.57	0.96	1.21	1.09	**1.98***
P			0.29	0.17	0.12	0.14	**0.03***

- Statistically Significant

Dominant Right Hand – All Panelists

TABLE 9B: Grip pinch strength measurements (unaffected/untreated) joint

	Hand	Day 0	Day 1	Day 2	Day 3		Day 28
		Kg	Kg	Kg	Kg	Kg	Kg

1st	L	18.66	19.00	19.33	16.00	20.00	20.00
2nd	R	25.66	23.33	24.00	2400	29.66	29.00
3rd	R	3.60	3.30	3.30	3.00	3.30	12.66
4th	L	17	15.5	18	19	16	20
5th	L	18.60	16.00	18.70	18.00	17.00	18.00
6th	R	12.00	14.00	10.00	12.60	20.00	22.00
Mean		15.92	16.19	15.56	15.43	17.66	20.28
% Diff			-4.58%	-2.26%	-3.07%	10.92%	27.38%
t			0.17	0.06	0.11	0.37	1.16
P			0.43	0.46	0.45	0.35	0.13

- Statistically Significant

Right Hand – All Panelists

It should however be understood that treatment of such patients is not limited to a topical formulation comprised of *Inula viscosa*. Arthritis patients may also be treated according to the present invention by bathing in a spa or whirlpool for certain periods of time where the spa or whirlpool contain an *Inula viscosa* extract of the present invention formulated for such an environment. Such bathing result in reduction of pain and effect positively morning stiffness.

Examples

Example 1: *Inula viscosa* oleoresin extraction

500 kilogram of dry minced and than milled leafs from mid summer harvest of domesticated Inula viscosa cultivated as a crop, under a standardized and controlled agro technical regime, having moisture content of 5.5 %, is fed into a standard extraction reactor vessel built of stainless steel or glass lined steel of 4,000 liters in volume or larger, 2500 liters of ethyl acetate is added into the reactor vessel, the mixture is agitated for a period of 2 hours at temperature of 25°C. The extracted pulp and miscella is discharged from the reactor into a filtering centrifuge. The miscella is directed from the centrifuge to holding tanks of 3000 liter capacity, where the miscella is left overnight to let the dust that stuck to the leaves sticky resin to separate and settle as a paste sediment on the

bottom of the holding tanks. The pulp from first extraction is placed in the reactor for a second extraction, where solvent to herbal material w/w ratio is 1:3.

Miscella from the two phase extraction, after having been separated from dust is placed in an evaporator reactor, where the miscella is agitated and recirculated, solvent is evaporated by warming the evaporator vessel to 50°C - 65°C under 40-70 milibar vacuum. Solvent vapor are directed to a cooling condenser, where liquefied solvent is recovered and collected in containers for reuse.

After solvent evaporation inside the reactor is complete, molten *Inula viscosa* oleoresin extract is pumped or drained out of the evaporator, total extract weight of the two phase extraction is 87 Kilogram.

Example 2: Preparation of *Inula viscosa* formulation based on gel for topical treatment.

Gel preparation: To 4 gram Amigel natural hydro gel powder (which may be substituted by Carbomer polymeric hydro gel) were added 94 gram de-ionized water slowly while stirring to give a uniform gel. To the gel there may be added 2gr of Aloe vera powder.

Example 3: Alcoholic tincture of *Inula viscosa* ethyl acetate extract for topical arthritis treatment.

Alcoholic tincture: 30gr *Inula viscosa* extract were melted at 50°C and consequently dissolved in 70 gram alcohol (technical alcohol 95%). Stirring gave in *Inula viscosa* extract in alcoholic tincture (30% mixture).

Example 4: Aloe vera gel mixture in *Inula viscosa* tincture

10 gram of the gel (Example 1) is added to 90 gram of *Inula viscosa* alcoholic tincture (Example 2) followed by stirring and shaking to form a uniform mixture (dispersion) of the tincture in the gel.

Example 5: Preparation of *Inula viscosa* extract 10% in petroleum Vaseline

Weigh 90 gram of petroleum Vaseline, add 10 gram of *Inula viscosa* extract paste, steer until even texture and color is obtained.

Example 6: Inula Olive oil (useful for skin softening, fungal treatment, for skin anti inflammatory, anti oxidant, anti fungus, anti bacteria and anti yeast treatment).

192 gram of olive oil were warmed to 55°C 4 gram of food grade emulsifier Span 80 or equivalent were added to the oil, steered until uniform blend was reached and kept warm at 55°C. *Inula viscosa* extract was warmed at 50°C, 4 gram of the molten extract were added slowly to the warm oil and steered until the emulsion is smooth and uniform

In a similar manner *Inula viscosa* may be mixed with any other vegetable oil.

Example 7: Inula soap (useful as antiseptic soap).

Dissolve 105 gram of soda caustic in 250 gram of distilled ice water and steer well. Add the lay water to 600 gram of vegetable oil, mix well for 20 minutes. When the mixture saponifies and becomes thick paste, add 10 gram of *Inula viscosa* extract, mix well until uniform. Cast to molds and leave the soap to cure over a week.

Example 8: Inula shampoo (useful as scalp inflammation treatment and for lice treatment)

Add 1 gram of *Inula viscosa* paste to 99 gram shampoo and mix until a uniform shampoo is reached.

Example 9: 7% *Inula viscosa* waterborne concentrate to be further diluted in a bath tab, pool or a whirlpool (useful for anti oxidant, anti inflammation, fungi, yeast and bacteria treatment).

70Gr of *Inula viscosa* extract in were warmed to 50°C. 20 gram of food grade emulsifier Span 80 were added to 100 gram of vegetable oil warmed to 50°C. The molten *Inula viscose* extract was added to the oil phase and steered well. In a separate container there were warmed 710 gram of tap water to 50°C. To the warmed water were added 100 gram of food grade emulsifier Tween 80 mixed well until the emulsifier blended with the water. The oil phase was added to the water phase while agitating. The emulsion was homogenized with a standard homogenizer. 1 Liter of the obtained 7% *Inula viscosa* waterborne emulsion may be added into a bath tab, pool or a whirlpool and mixed.

Example 10: Inula powder mud packing, useful for anti inflammatory, anti fungi, anti bacteria, anti yeast topical treatment.

One kilogram of dry *Inula viscosa* leafs is milled to fine powder. 4 kilogram of tap water is added to the fine powder and mixed well. The obtained mixture (mud) is spread on a person body and rap to retain moisture

Example 11: Sun screen lotion.

Mix 2 gram *Inula viscosa* extract paste in 48 gram of natural unpreserved Aloe Vera gel.

Example 12: *Inula viscosa* powder, useful for capsules and pills.

Mix 40 gram of *Inula viscosa* extract in alcoholic tincture 30% (described in Example 3:) in 60 gram of calcium carbonate powder and stir well, let the alcohol evaporate from the mixture under vacuum at ambient temperature, pulverize the dry calcium carbonate in a hammer mill and process the powder through a fine sieve to result in a 16.66% *Inula viscosa* extract embedded in calcium carbonate carrier. The same process may be employed using about 0.1% up to 30% *Inula viscosa* extract which may be incorporated in calcium carbonate and any other edible powder excipient.

CLAIMS:

1. An *Inula viscosa* extract for use in treating arthritis.

2. An *Inula viscosa* extract according to claim 1 wherein the arthritis is selected from inflammatory arthritis, inflammatory or degenerative joint condition, nonarticular rheumatism and miscellaneous arthritis.

3. A formulation for treating arthritis comprising an *Inula viscosa* extract.

4. An *Inula viscosa* extract according to claim 3 wherein said extract is an ethyl-acetate extract.

5. A formulation according to claim 3 wherein the amount of the *Inula viscosa* extract between about 0.1% to about 95% preferably between about 0.1% to about 50% and most preferably 5% to 30% (w/w) together with suitable excipients.

6. A formulation according to 3 being water borne formulation.

7. A formulation according to claim 3 together with suitable excipients, said excipients are selected from C_2-C_5 alcohol, most preferably C_2-C_4 alcohols, ethers, esters and emulsifiers, vegetable oil, Aloe Vera powder, Vaseline or hydro gel powders and their mixtures.

8. An *Inula viscosa* extract, said extract obtained by harvesting Inula viscosa plants, drying the harvested plants to obtain a moisture contents of about 5% to 10%, grinding the dry biomaterial to powder grain, contacting said powder grain at least one time with ethyl-acetate at elevated temperatures, evaporating the ethyl-acetate and obtaining an extract characterized by its carotanoids, flavanoids, tomentosin, sesquiterpene lactones, sterols, and saponins contents.

9. An *Inula viscosa* extract according to claim 8, wherein the harvested plants are dried at a temperature of about 45°C to about 70°C, the powder grain size is between 40 to 100 mesh and the ethyl-acetate:*Inula viscosa* ratio is between 8:1 to 3:1, preferably 6:1 and most preferably 5:1.

10. An *Inula viscosa* extract according to claim 9, wherein said *Inula viscosa* plants are cultivated plants.

11. An *Inula viscosa* extract according to any one of claims 7 to 10 useful as anti-inflammatory, anti-bacterial, anti-fungal, anti-oxidant, anti-yeast agent and for the treatment of arthritis.

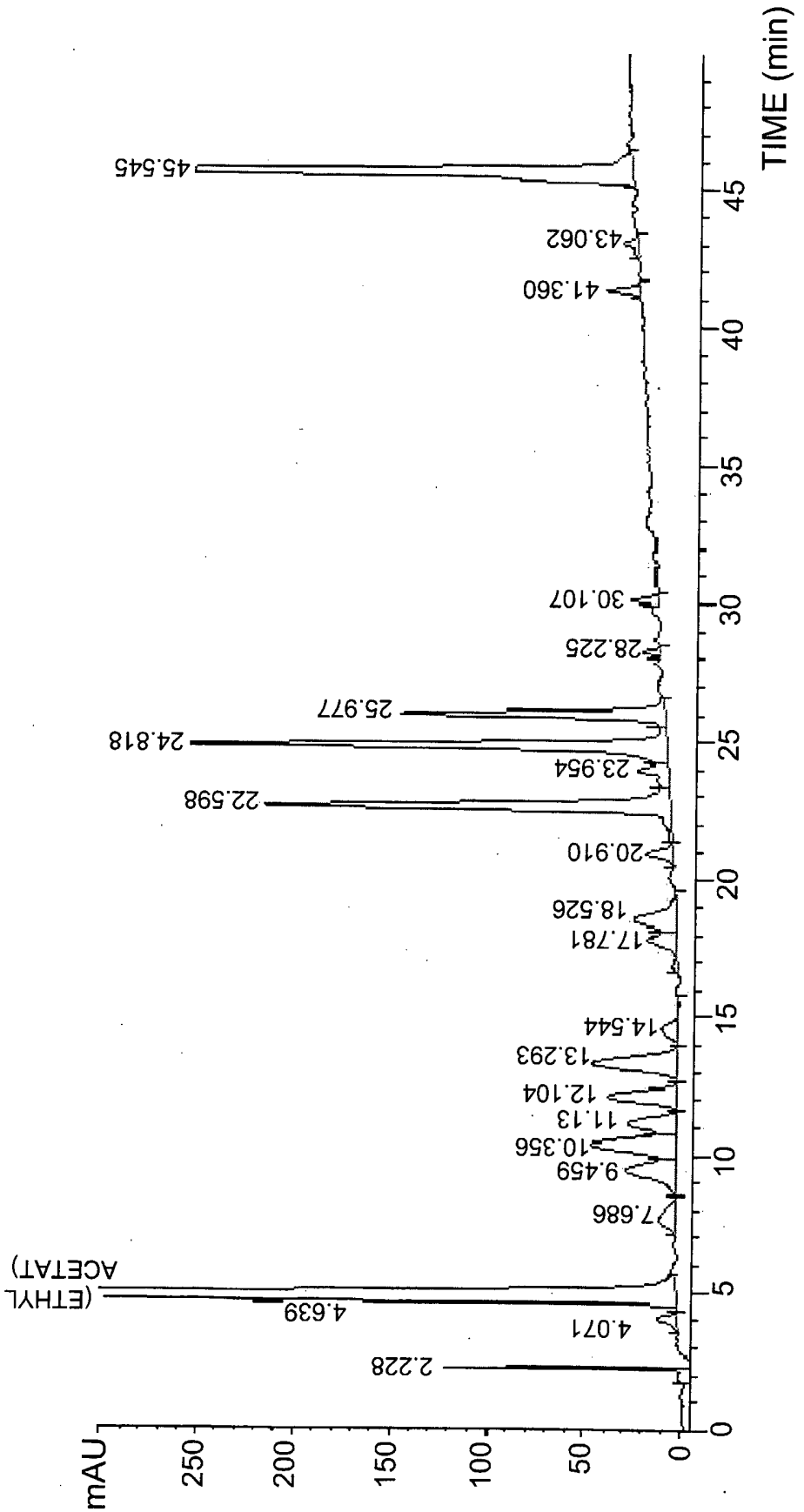
12. A waterborne *Inula viscosa* composition for the treatment of arthritis, said composition comprising 1 to 60%, preferably between 4 to 30% and most preferably 6 to 12% (w/w) *Inula viscosa* extract emulsified in water and emulsifiers.

13. A waterborne *Inula viscosa* composition useful as anti-inflammatory, anti-bacterial, anti-fungal, anti-oxidant, or anti-yeast agent, said composition comprising 1 to 60%, preferably between 4 to 30% and most preferably 6 to 12% (w/w) *Inula viscosa* extract dissolved in water and emulsifiers.

14. An alcoholic *Inula viscosa* composition for the treatment of arthritis, said composition comprising 1 to 60%, preferably between 4 to 30% and most preferably 6 to 20% (w/w) *Inula viscosa* extract, wherein the alcohol is chosen from the group consisting of ethanol, propanol, isopropanol, butanol, pentanol or neopentanol.

15. A process for extraction of cultivated *Inula viscosa*, said process comprising:

- harvesting *Inula viscosa* plants;
- drying the harvested plants to obtain a moisture contents of about 5% to 10%;
- milling the dry leaves to powder grain;
- contacting said powder grain at least one time with ethyl-acetate at elevated temperatures;
- evaporating and condensing the ethyl-acetate for reuse; and
- obtaining an extract in the form of a paste characterized by the quantitative presence of carotanoids, flavanoids, tomentosin, sesquiterpene lactones.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200
150
100
50
0
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0
5
10
15
20
25
30
35
40
45
2.228
4.071
4.639
(ETHYL ACETAT)
7.686
9.459
10.356
11.13
12.104
13.293
14.544
17.781
18.526
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25.977
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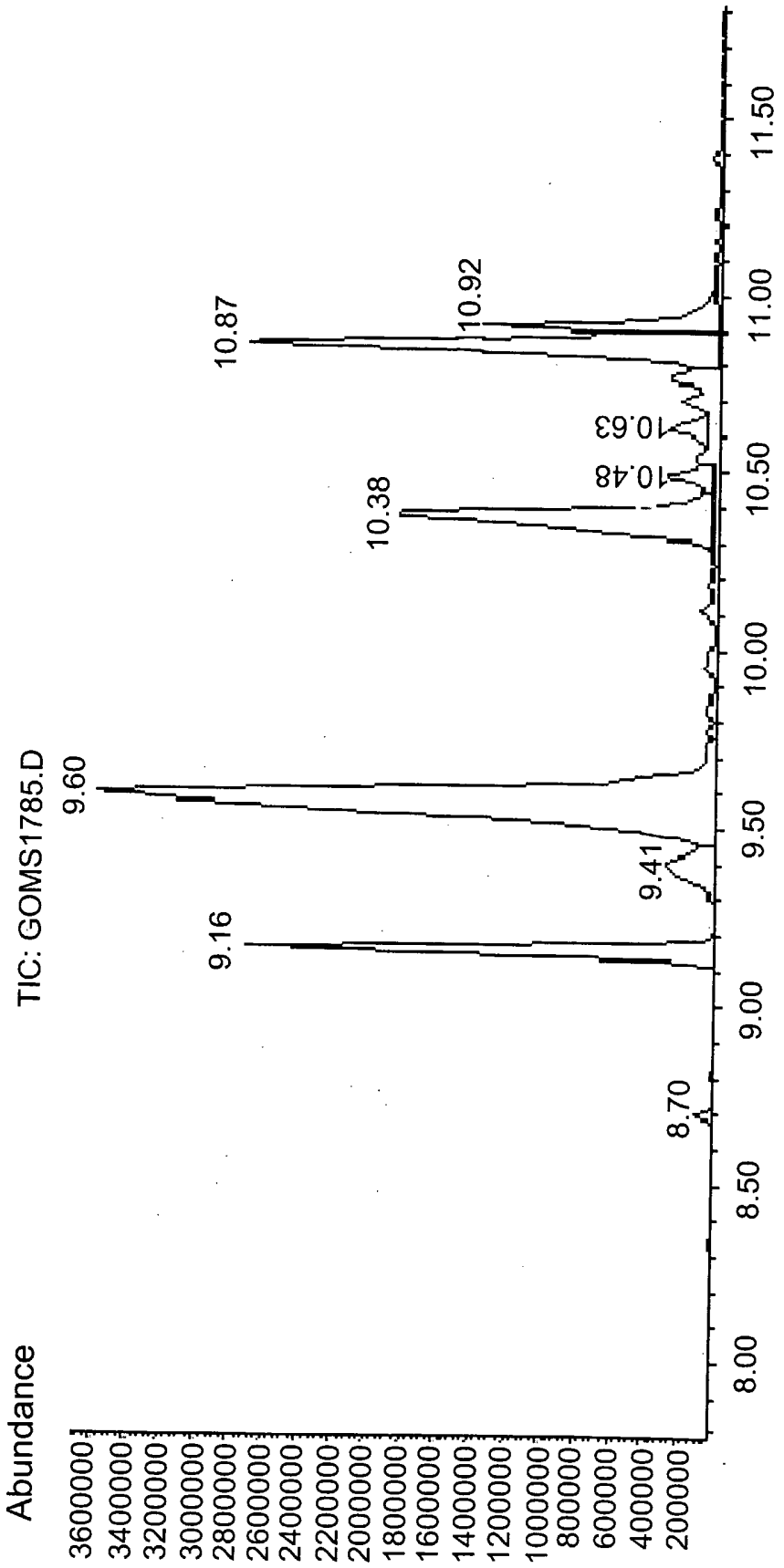
43.062
45.545

FIG. 1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10.87
10.92
10.38
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10.63
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3400000
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2800000
2600000
2400000
2200000
2000000
1800000
1600000
1400000
1200000
1000000
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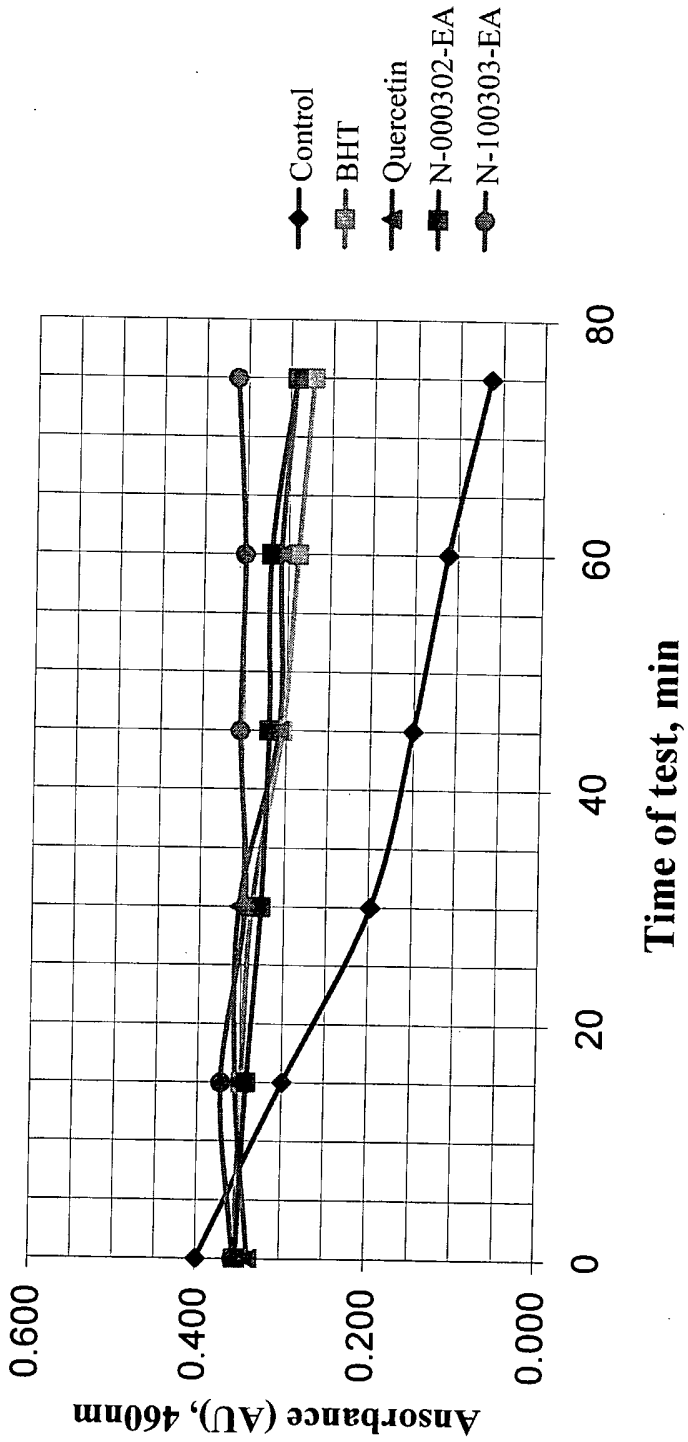
11.00
11.50

FIG. 2


Control
BHT
Quercetin
N-000302-EA
N-100303-EA
Ansorbance (AU), 460nm
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0.400
0.200
0.000
0
20
40
60
80
Time of test, min

FIG. 3

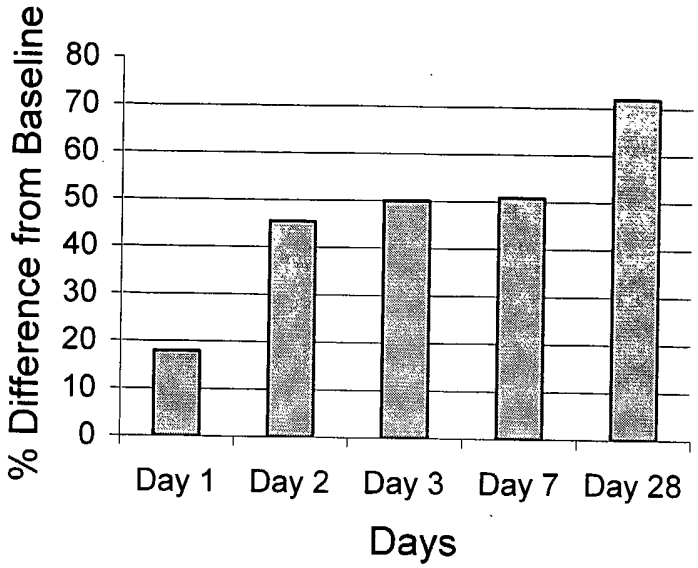

% Difference from Baseline
80
70
60
50
40
30
20
10
0
Day 1
Day 2
Day 3
Day 7
Day 28
Days

FIG. 4

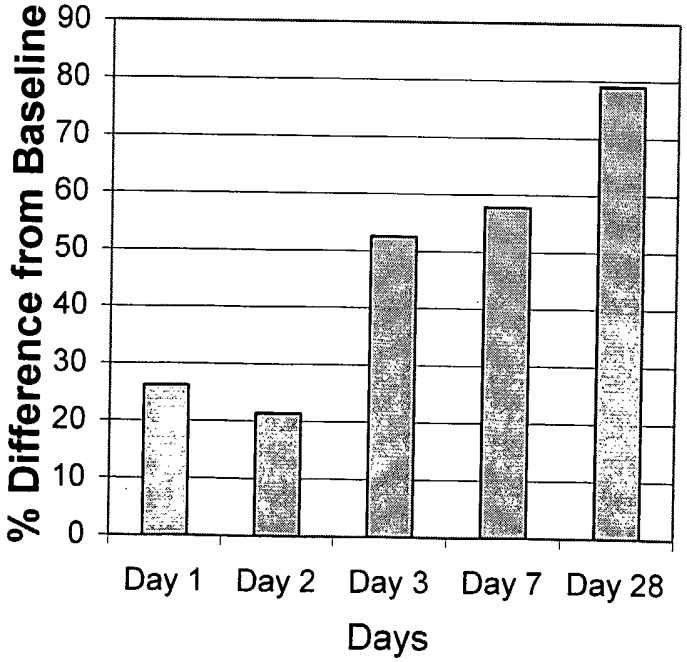
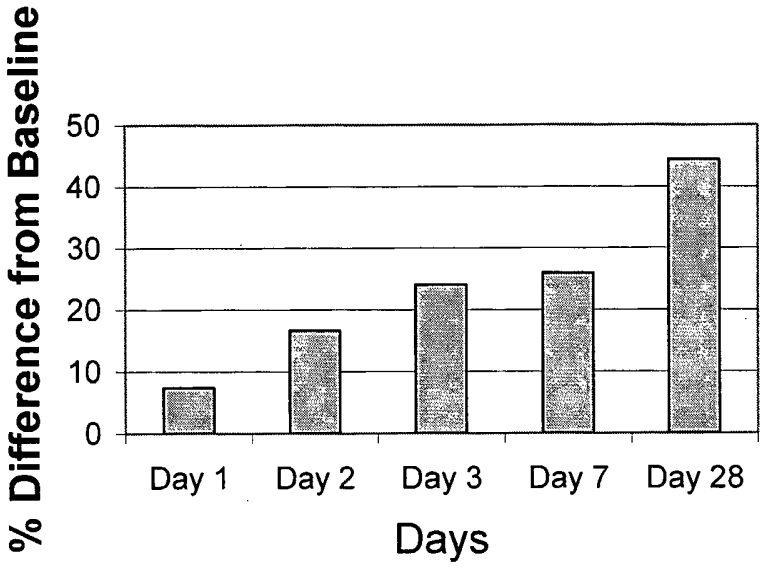

% Difference from Baseline
90
80
70
60
50
40
30
20
10
0
Day 1
Day 2
Day 3
Day 7
Day 28
Days

FIG. 5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30
20
10
0
Day 1
Day 2
Day 3
Day 7
Day 28
Days

FIG. 6

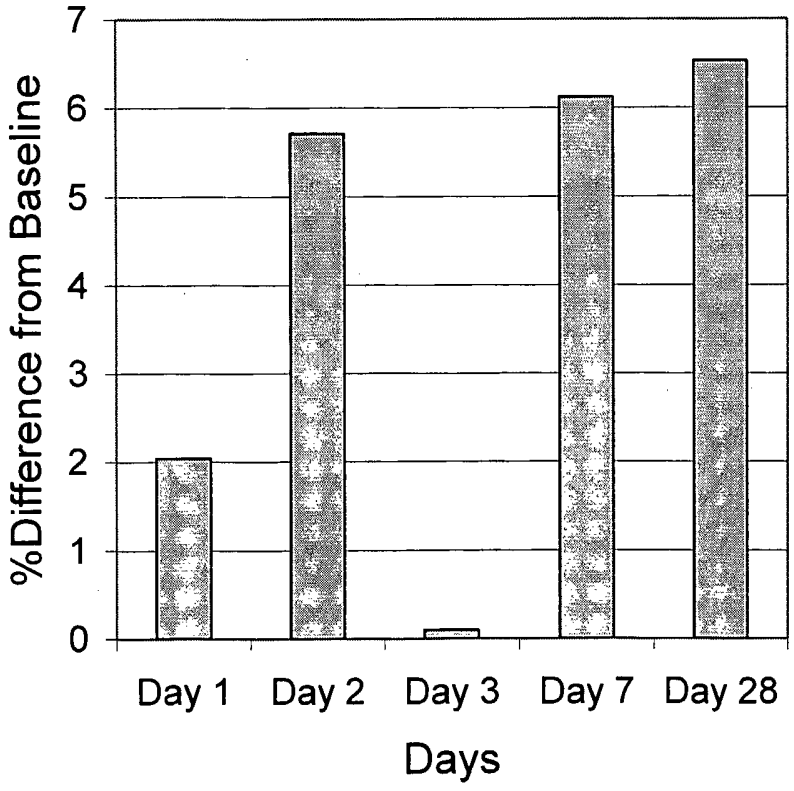
%Difference from Baseline
7
6
5
4
3
2
1
0
Day 1
Day 2
Day 3
Day 7
Day 28
Days

FIG. 7

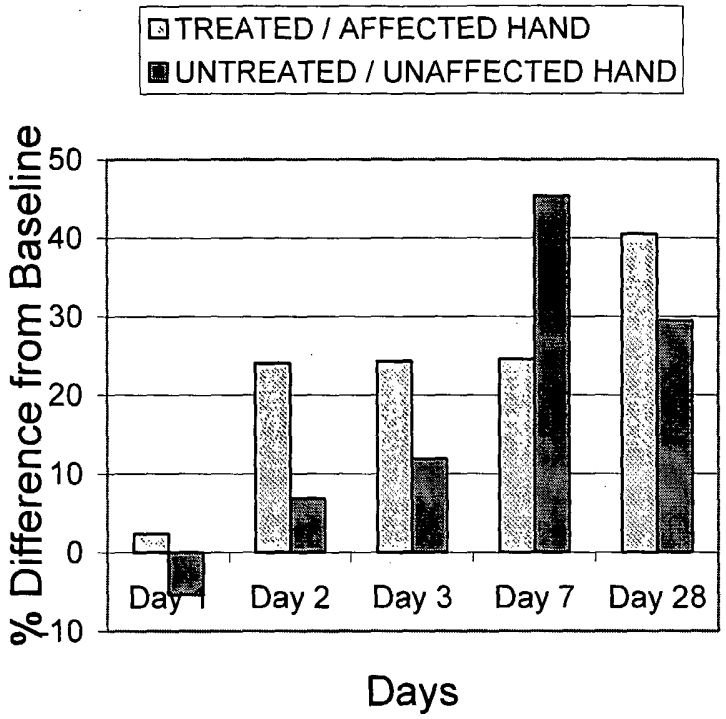
TREATED / AFFECTED HAND
UNTREATED / UNAFFECTED HAND
% Difference from Baseline
50
40
30
20
10
0
-10
Day 1
Day 2
Day 3
Day 7
Day 28
Days

FIG. 8

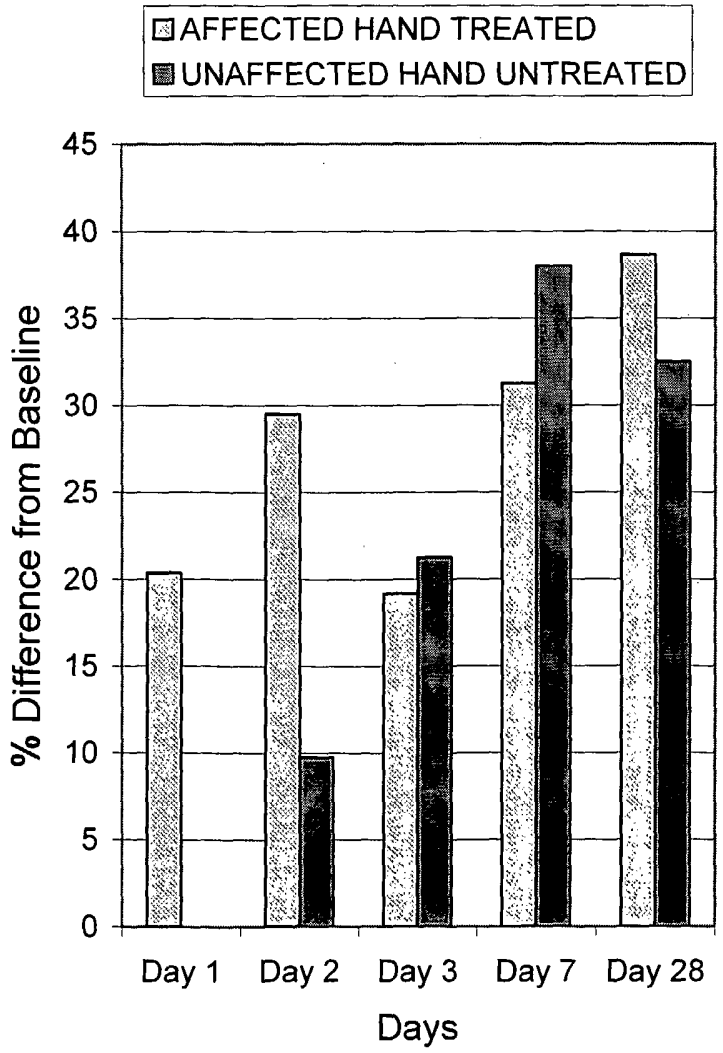
AFFECTED HAND TREATED
UNAFFECTED HAND UNTREATED
% Difference from Baseline
45
40
35
30
25
20
15
10
5
0
Day 1
Day 2
Day 3
Day 7
Day 28
Days

FIG. 9

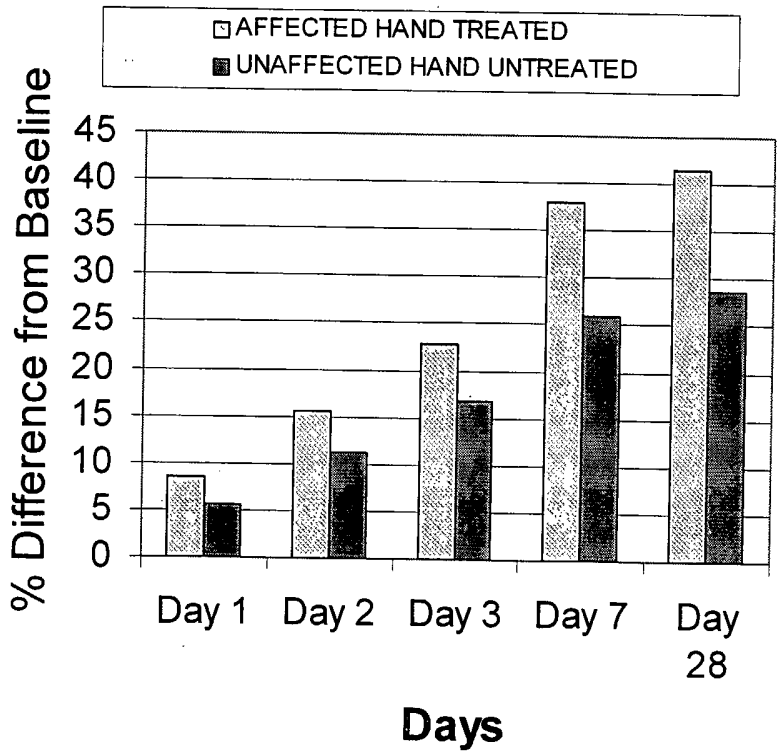
AFFECTED HAND TREATED
UNAFFECTED HAND UNTREATED
% Difference from Baseline
45
40
35
30
25
20
15
10
5
0
Day 1
Day 2
Day 3
Day 7
Day 28
Days

FIG. 10

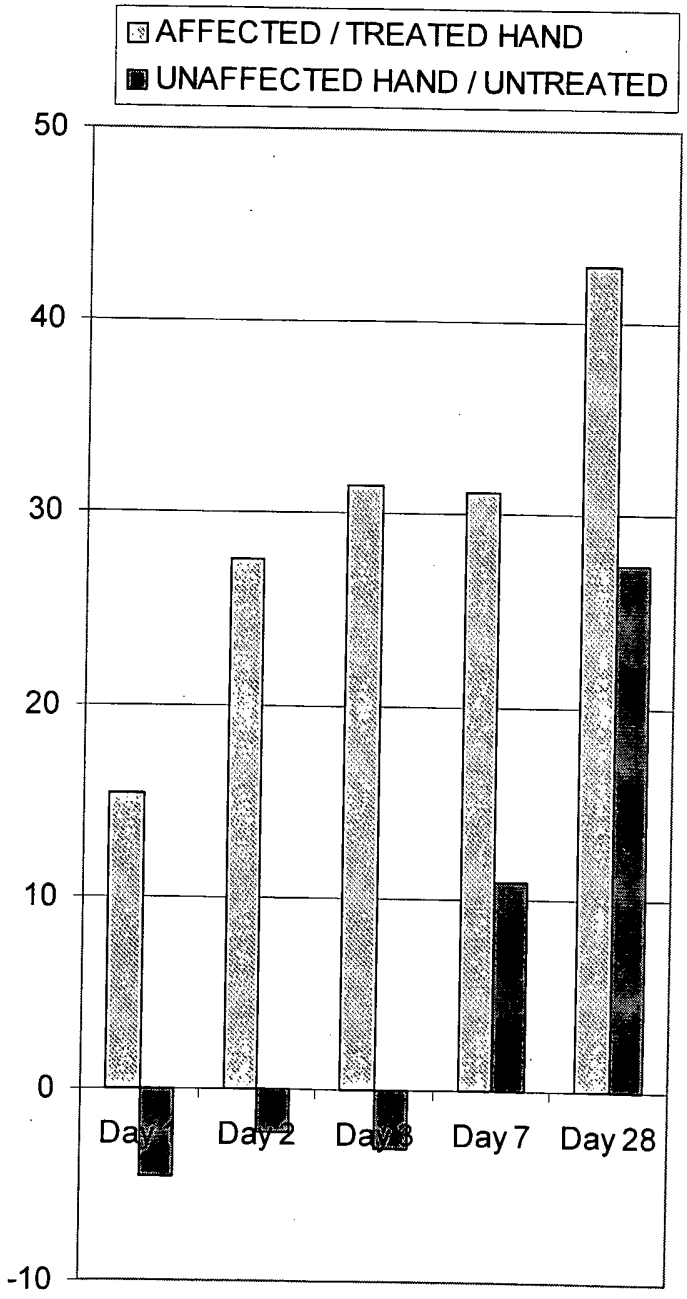
AFFECTED / TREATED HAND
UNAFFECTED HAND / UNTREATED
50
40
30
20
10
0
-10
Day 1
Day 2
Day 3
Day 7
Day 28

FIG. 11

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IL2005/000072

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K35/78

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)
IPC 7 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, PAJ, WPI Data, MEDLINE, BIOSIS, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 254 112 A (DEBAT ET AL) 3 March 1981 (1981-03-03) cited in the application example 7	1-4,6, 8-11
X	US 5 837 253 A (COHEN ET AL) 17 November 1998 (1998-11-17) column 6, line 7 - line 26; examples 11,12	1-14
X	KIVÇAK B ET AL: "Antimicrobial activity of Inula viscosa (L.) Ait" GAZI UNIVERSITESI ECZACILIK FAKULTESI DERGISI 2002 TURKEY, vol. 19, no. 2, 2002, pages 101-104, XP009046671 ISSN: 1015-9592 page 102, last paragraph	1,2,4, 8-11

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"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)

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"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.

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Date of the actual completion of the international search	Date of mailing of the international search report
21 April 2005	06/05/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Ganschow, S

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IL2005/000072

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BENAYACHE S ET AL: "The flavonoids of Inula viscosa L" PLANTES MEDICINALES ET PHYTOTHERAPIE, vol. 25, no. 4, 1991, pages 170-176, XP009046675 ISSN: 0032-0994 page 173, paragraph 1	1,2,4
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A	DATABASE MEDLINE 'Online! US NATIONAL LIBRARY OF MEDICINE (NLM), BETHESDA, MD, US; April 1999 (1999-04), MÁÑEZ S ET AL: "A glycosyl analogue of diacylglycerol and other antiinflammatory constituents from Inula viscosa." XP002325633 Database accession no. NLM10217718 abstract & JOURNAL OF NATURAL PRODUCTS. APR 1999, vol. 62, no. 4, April 1999 (1999-04), pages 601-604, ISSN: 0163-3864	1

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IL2005/000072

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