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Canadian Intellectual Property Office

CA 2708449 C 2020/11/24

(11)(21) 2 708 449

(12) BREVET CANADIEN
CANADIAN PATENT

(13) C

(86) Date de dépôt PCT/PCT Filing Date: 2008/12/19
(87) Date publication PCT/PCT Publication Date: 2009/07/02
(45) Date de délivrance/Issue Date: 2020/11/24
(85) Entrée phase nationale/National Entry: 2010/06/08
(86) N° demande PCT/PCT Application No.: ES 2008/000787
(87) N° publication PCT/PCT Publication No.: 2009/080850
(30) Priorités/Priorities: 2007/12/21 (ES PCT/ES2007/000753);
2008/02/22 (EP EP08003253);
2008/10/31 (EP EP08019146)

(51) Cl.Int./Int.Cl. *A61K 36/9066* (2006.01),
A61P 17/06 (2006.01), *A61P 35/00* (2006.01)

(72) Inventeurs/Inventors:
SANCHEZ-COVISA VILLA, ANGEL, ES;
DIAZ ALPERI, JOAQUIN, ES;
RAMIREZ BOSCA, ANA ADELA, ES;
BERND, AUGUST, DE

(73) Propriétaire/Owner:
ASAC COMPANIA DE BIOTECNOLOGIA E INVESTIGACION, S.A., ES

(74) Agent: NORTON ROSE FULBRIGHT CANADA LLP/S.E.N.C.R.L., S.R.L.

(54) Titre : METHODE POUR AUGMENTER L'EFFICACITE THERAPEUTIQUE DES CURCUMINOIDES ET ANALOGUES.

(54) Title: METHOD FOR IMPROVING THE THERAPEUTIC EFFICACY OF THE CURCUMINOIDS AND THEIR ANALOGUES.

(57) Abrégé/Abstract:
The invention relates to a method for increasing the therapeutic efficacy of curcuminoids and analogues. More specifically, the invention relates to a method for increasing the therapeutic efficacy of systemically administered formulations that contain curcuminoids and the equivalent therapeutics thereof. The method is characterised in that together with the administration of the formulation the patient is irradiated with visible-ultraviolet radiation. The invention also relates to phototherapy devices that emit visible radiation over a surface area greater than 0.2 m2 and irradiance of more than 2 mW/cm2, suitable for use in the treatment of proliferative diseases, particularly moderate-to-severe psoriasis or tumoral processes.

(12) SOLICITUD INTERNACIONAL PUBLICADA EN VIRTUD DEL TRATADO DE COOPERACIÓN EN MATERIA DE PATENTES (PCT)

(19) Organización Mundial de la Propiedad Intelectual
Oficina internacional

(43) Fecha de publicación internacional
2 de Julio de 2009 (02.07.2009)

PCT

(10) Número de Publicación Internacional
WO 2009/080850 A1

(51) Clasificación Internacional de Patentes:
A61K 36/9066 (2006.01) *A61P 35/00* (2006.01)
A61P 17/06 (2006.01)

(21) Número de la solicitud internacional:
PCT/ES2008/000787

(22) Fecha de presentación internacional:
19 de Diciembre de 2008 (19.12.2008)

(25) Idioma de presentación: español

(26) Idioma de publicación: español

(30) Datos relativos a la prioridad:
PCT/ES2007/000753 21 de Diciembre de 2007 (21.12.2007) ES
EP08003253 22 de Febrero de 2008 (22.02.2008) EP
EP08019146 31 de Octubre de 2008 (31.10.2008) EP

(71) Solicitante *(para todos los Estados designados salvo US)*: **ASAC COMPAÑIA DE BIOTECNOLOGIA E INVESTIGACION, S.A.** [ES/ES]; Calle Sagitario, 14, E-03006 Alicante (ES).

(72) Inventores: **DÍAZ ALPERI, Joaquín**; Calle Sagitario 14, E-03006 Alicante (ES). **RAMÍREZ BOSCÁ, Ana Adela**; Calle Sagitario 14, E-03006 Alicante (ES). **BERND, August**; Department of Dermatology, Johann Wolfgang Goethe University, Theodor-Stern-Kai 7, D-60590 Frankfurt/M (DE).

(72) Inventor; e
(75) Inventor/Solicitante *(para US solamente)*: **SANCHEZ-COVISA VILLA, Angel** [ES/ES]; Calle Sagitario 14, E-03006 Alicante (ES).

(74) Mandatario: **PARDO ZAPATA, José**; Calle Sagitario 14, E-03006 Alicante (ES).

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(84) Estados designados *(a menos que se indique otra cosa, para toda clase de protección regional admisible)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), euroasiática (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), europea (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Publicada:
— *con informe de búsqueda internacional*
— *antes de la expiración del plazo para modificar las reivindicaciones y para ser republicada si se reciben modificaciones*

(54) **Title:** METHOD FOR INCREASING THE THERAPEUTIC EFFICACY OF CURCUMINOIDS AND ANALOGUES

(54) **Título:** MÉTODO PARA AUMENTAR LA EFICACIA TERAPÉUTICA DE LOS CURCUMINOIDES Y ANÁLOGOS.

(57) **Abstract:** The invention relates to a method for increasing the therapeutic efficacy of curcuminoids and analogues. More specifically, the invention relates to a method for increasing the therapeutic efficacy of systemically administered formulations that contain curcuminoids and the equivalent therapeutics thereof. The method is characterised in that together with the administration of the formulation the patient is irradiated with visible-ultraviolet radiation. The invention also relates to phototherapy devices that emit visible radiation over a surface area greater than 0.2 m2 and irradiance of more than 2 mW/cm2, suitable for use in the treatment of proliferative diseases, particularly moderate-to-severe psoriasis or tumoral processes.

(57) **Resumen:** Método para aumentar la eficacia terapéutica de los curcuminoides y análogos. Se describe un método para aumentar la eficacia terapéutica de las formulaciones de administración sistémica que comprenden curcuminoides y sus equivalentes terapéuticos. El método se caracteriza porque concomitantemente con la administración de la formulación se irradia sobre el paciente una radiación visible-ultravioleta. También se describen equipos de fototerapia que emiten una radiación de luz visible sobre una superficie mayor de 0.20 m2 y una irradiancia mayor de 2 mW/cm2 de utilidad en el tratamiento de enfermedades proliferativas, especialmente, psoriasis moderada-grave o procesos tumorales

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Title of the invention

Method for improving the therapeutic efficacy of the Curcuminoids and their analogues.

Technical field of the invention

The present invention describes a method for improving the therapeutic efficacy of formulations comprising Curcuminoids and their analogues when they are systematically administered. The method is characterised in that a quantifiable visible-ultraviolet radiation is radiated on the patient concomitantly with the administration of the formulation.

The present invention also describes a phototherapy devices for emitting an visible light radiation over a surface greater than 0.20 m2 with an irradiance higher than 2 mW/cm2, and its use in dermatological and/or proliferative diseases.

State of the art

Curcumin and its therapeutic analogues: Curcuma rhizomes, extracts, Curcuminoids (desmethoxycurcumin, bisdesmethoxycurcumin, tetrahydrocurcumin), prodrugs and metabolites have been shown to exhibit various pharmacological activities such as anti-oxidant and antiproliferative properties, induction of apoptosis, etc. Based on *in vitro* results, Curcumin offers the potential to act as a drug for the treatment of pathologies described in the state of the art such as psoriasis, cancer, inflammatory processes, vitiligo, etc.

But Curcumin and its equivalents exhibit very low bioavailability. Br J Cancer. 2004 Mar 8;90(5):1011-5

describes that after administration, only trace levels of its metabolites were found in liver tissue and no curcumin. Therefore, Curcuminoids lack *in vivo* efficacy or efficacy is much reduced in comparison with that shown *in vitro*. J Am Acad Dermatol. 2008 Apr;58(4):625-31 corroborates this finding (published after priority date). The document reports that a phase II, uncontrolled trial in patients older than 18 years who were administered 4.5 g Curcuminoids/day had to be abandoned because only 17% of patients responded to treatment with a reduction of 75% of psoriatic plaque.

A subject matter expert, as cited in Amand et al Biochem Pharmacol. 2008 Aug 19. [Epub ahead of print](published after priority dated), was and is motivated to search for solutions for improving *in vivo* efficacy of Curcumin formulations and to discover "supercurcumin". Solutions that have been found were, for example, structural modifications for improving Curcumin absorption (EP1837030), new galenic formulations (WO/2008/030308) and the administration of high doses in combination of other active ingredients (US 5925376, WO03088986).

Phototherapy is a useful tool for treatment of various diseases such as proliferative and/or dermatological pathologies (psoriasis, cancer), acne and jaundice. Phototherapy activity is based on the structural changes induced by the radiation.

Phototherapy is used for the treatment of jaundice in newborn. The newborn, having a body surface area of 0.20 m2, is irradiated with visible light, preferably with an emission maximum at 550 nm, and an irradiance close to 40 W/m2 in order to degrade bilirubin.

Actinic light (maximum emission at 420 nm) is used for acne treatment based on its bactericide properties. The surface area irradiated by these lamps is less than 400 cm2.

Photochemotherapy, concomitant administration of psoralenes and irradiation with ultraviolet light is the treatment of choice for moderate to severe psoriasis, but the treatment has many secondary effects: hyperpigmentations, hepatotoxicity, hypersensitisation reactions and the irradiated dose must be carefully adjusted.

Aminolevulinic acid combined with blue light has been shown to be effective in the treatment of actinic queratosis. Thus, J Invest Dermatol. 2002 Jul; 119(1):77-83 describes its systemic administration (oral) in combination with 1-20 J/cm2 visible light (LED maximum emission at 417 nm) for the treatment of psoriasis, but the efficacy is limited and said treatment cannot be used in moderate to severe psoriasis. The results obtained showed that on 15 plaques of 1.5*1.5 cm (34 cm2) the severity of the plaques was only improved by 42% compared to baseline.

In *in vitro* trials and topical administration, photoradicals or artefacts generated *in situ* by irradiation are unstable and are those responsible for pharmacological activity. Photosensitization after the administration of a photosensitising agent administered by the systemic route cannot be produced immediately; the drug must first be metabolized and, later, must be photoactivated. In summary, effectiveness of phototherapy cannot be predicted *a priori*, because it depends on bioavailability of the drug administered and on

pharmacological activity of artefacts formed during the irradiation.

In the particular case of Curcumin, the state of the art shows that it has very low bioavailability and, further, it is known that Curcuminoids are degraded by visible-ultraviolet light, both in solution and solid state. The major degradation product is a cyclisation of Curcumin by loss of 2 hydrogen atoms.

Psoriasis is chronic disease and its aetiology is not fully understood. Clinically, psoriasis is characterized by presence patches or erythematosus plaques with a dark reddish colour, delimited borders and often covered with scales that are due to the changes in cellular proliferation marked by genetic and immunological mechanisms. Thus, psoriasis may be considered as a proliferative disease.

The severity of Psoriasis is determined by the PASI index (*Psoriasis Area Severity Index*), BSA (Body Surface Area) and PGA (Physican Global Assessment). According to PGA, psoriasis may be classified into:

- Mild or moderate psoriasis: lesions are under control with topical treatment; BSA<10%, PASI<10,

- Moderate psoriasis: it is still possible to control the disease with topical treatment; BSA>10%, PASI 10 or higher,

- Moderate to Severe psoriasis: topical treatment cannot control the disease; BSA>10%, PASI 10-20; very thick lesions in areas that are difficult to treat,

- Severe psoriasis: systemic treatment necessary to control the disease; BSA>20%, or PASI>20; important local lesions of high thickness with BSA>10%.

Currently, there is no animal model to assess the *in vivo* efficacy of pharmaceuticals in the treatment of psoriasis. Drug efficacy must be tested in people who suffer from psoriasis or in animal models by studying inhibition of tumour proliferation, for example, the cell proliferation of the A431 cell line (cells of epidermal carcinoma).

PASI, an objective index to assess psoriasis severity, is used to evaluate drug therapeutic efficacy. EMEA Guidelines criteria establish that a patients are considered responders when PASI reduction is at least 75% of the baseline.

Efalizumab, recently authorized for psoriasis treatment, has some efficacy. In 12 week studies, 22-35% of patients reached a score of PASI-75 (improvement of 75%).

Photochemotherapy with Aminolevulinic acid and visible light only showed 42% improvement in psoriatic plaques compared to baseline. According to EMEA guidelines, the treatment lacks effectiveness, in particular in the treatment of moderate to severe and severe psoriasis.

Psoriasis patients tend to hide their lesions and often abandon topical treatments, because these stain clothes. In accordance with an opinion poll conducted by European Federation of Psoriasis Associations, there is a high degree of dissatisfaction in psoriasis sufferers

regarding the efficacy of such treatments for this disease and they give up treatment.

EP1133992 described the photosensitising activity of visible-UV light on Curcuminoids, administered in the form of a topically applied extract, for the treatment of psoriasis. The cream described in EP1133992 must be applied before the radiation, but the treatment is abandoned by patients because the Curcuma extracts are coloured and stain clothes. Moderate to severe psoriasis that involves more than 10% of body surface area cannot be treated by the topical route because the patients do not respond to treatments administered via the topical route.

The results obtained in phototherapy by the topical administration route cannot be extrapolated to systemic administration as described for aminolevulinic acid.

Another type of phototherapy currently being used is photodynamic therapy. The drug is administered and the patients irradiated with a pulsed light having an high irradiance of approximately 300 mW/cm2. The light is administrated on a small surface for short time interval, irradiating 100 J/cm2, but the method causes pain to patients.

The phototherapy devices most similar to the invention are:

- UV-Cabins emitting an irradiance of 2-30 mW/cm2 of ultraviolet light over the whole body surface area of the patient, but without emitting visible light,
- devices emitting visible light irradiating a small surface area of approximately 500 cm2, but always less than 10% body surface area of an adult,
- Gas Discharge Lamps having an emission range of 400-550 nm and which may be fitted to UV-cabins, for example,

Phillips TLK 40 W/03 or TLK 140 W/03 but these lamps are used for photo printing and for aquarium lighting.

There are also filters for selectively absorbing certain wavelengths and transmitting radiations of 400-430 nm.

Given that to the date no drug has shown efficacy in phototherapy with visible light, the expert in the field would not combine the technical features of the equipment described above in order to manufacture a phototherapy device that emits visible light having a irradiance higher than 2 mW/cm2 over a surface greater than 0.2 m2.

Object of the invention

The problem solved by the invention is to improve the therapeutic efficacy of Curcuminoids and their therapeutic equivalents when they are administrated by a systemic route.

The solution found by the inventors is to combine systemic administration of Curcuminoids with a quantifiable visible-ultraviolet light radiation.

Using the solution found by the inventors, PASI reduction is higher than 75% and it is achieved in at least 80% of patients with a probability higher than 80% after light irradiation with 1-18 J/cm2, either ultraviolet light or visible light, thereby meeting the efficacy criteria of the EMEA.

In contrast to J Am Acad Dermatol. 2008 Apr;58(4):625-31, which reported that Curcuminoids administered at doses of 4.5 g/day lacked efficacy in the treatment of psoriasis, the combination of Curcuminoids with light, either ULTRAVIOLET or visible, is effective and all the patients achieved a PASI reduction of 75% and

no patient abandoned the therapy. In the middle of the trial, in week four (after 8 phototherapy sessions), 50% of patients reached a PASI reduction greater than 75% of baseline. In the middle of trial, the efficacy was higher than the therapy with Efalizumab after 12 weeks of treatment and without secondary effects.

In preferred embodiments for the treatment of psoriasis, the therapeutic equivalents of Curcumin are Curcuma extracts (hydroalcoholic extracts having a Curcuminoids concentration of 12% or alcoholic extracts having a concentration of Curcuminoids of 90%).

In another preferred embodiment, Curcumin is administered parenterally (intraperitoneally) to inhibit tumour growth in mice in combination with visible light, however Curcumin alone or light alone did not inhibit tumour growth.

The combination of visible and/or ultraviolet light with Curcuminoids gives a synergetic effect and may be used for the treatment of all pathologies in which Curcumin might have had potential activity. However visible light is preferred as the use of systemic Curcuminoids or their equivalents enables administration of the drug with the main meals and not two hours before radiation.

The administration of Curcumin, Curcuminoids, their metabolites or their prodrugs via the oral route with concomitant visible-ultraviolet light radiation avoids the problems commonly associated with photochemotherapy. By the systemic administration of curcumin or its analogues together with irradiation:

- therapeutic efficacy of curcumin is improved *in vivo* and efficacies higher than authorised treatments are achieved,

- the dose of Curcuminoids administered does not have to be adjusted, nor the radiation supplied when visible light is used,

- the patients' clothes are not stained,

- the emotional state of patients is improved and personal relations of treated patients are improved,

- if visible light and ultraviolet light are combined, patients are uniformly tanned without hyperpigmentations,

- it is possible to treat paediatric patients because no adverse reactions have been reported,

- after phototherapy, patients need not be protected from light,

- transaminases are normalised and the product in combination with radiation is not hepatotoxic,

- after radiation the use of corticoids and antihistamines is not required, or at least reduced,

- compliance with the treatment is improved and patients do not abandon their treatment,

- radiation doses may be increased per phototherapy session, reducing the number of phototherapy sessions and the time required for bleaching psoriatic lesions is reduced,

when visible light is used, secondary effects caused by the accumulation of ultraviolet light are avoided with the same therapeutic efficacy.

In another aspect, the problem resolved by the invention is to find a phototherapy device for the treatment of proliferative diseases, particularly for the treatment of moderate to severe or severe psoriasis. The solution found by the inventors is a phototherapy system characterised in that it emits visible light over a surface area greater than 0.2 m2 and with irradiance higher than 2 mW/cm2. In a preferred mode, the maximum wavelength is 420 nm and the light source is LEDs, and optionally the device may have an ultraviolet light source in order to promote a good pigmentation and a healthy tan.

The use of this phototherapy system together with the systemic administration of Curcumin or its therapeutic equivalents has higher efficacy than the UV-cabins currently used.

In accordance with a further aspect of the present invention there is a pharmaceutical composition comprising a curcuminoid and a carrier for treating psoriasis wherein the curcuminoid is formulated for an administration by oral route in combination with an ultraviolet (UVA)-visible radiation of a skin surface affected with psoriasis characterized in that an accumulative dose is 170-180 J/cm2.

In accordance with yet another aspect of the invention there is a kit for treating psoriasis comprising:

the composition as described herein and

a phototherapy device comprising a lamp for emitting an ultraviolet (UVA)-visible radiation having an irradiance higher than 2 mW/m2.

In accordance with yet a further aspect of the present invention there is a kit for treating epidermal carcinoma in mammals, comprising:

a pharmaceutical composition comprising Curcumin and suitable excipients for intraperitoneal administration wherein the Curcumin concentration is 2.5 mg/ml, and

a phototherapy device wherein the radiation is visible light from 400-550 nm, having a maximum emission at 420 nm, and the irradiance is 3 mW/cm^2 at a distance of 45 cm.

Detailed description of the invention

Curcuminoids, in the form of Curcumin, alcoholic Curcuma extracts (90% Curcuminoids) or hydroalcoholic Curcuma extracts (12% Curcuminoids), increase their therapeutic efficacy *in vivo* when they are systemically administered in combination with visible-ultraviolet light radiation (315-550 nm).

Alternatively, other therapeutic equivalents or analogues of Curcuminoids described in the state of art, for example those described in Anand et al Biochem Pharmacol. 2008 Aug 19. [Epub ahead of print], curcuma rhizomes or Curcumin cyclised by the action of irradiation increase their *in vivo* efficacy when concomitantly administered with visible-ultraviolet radiation.

rhizomes or Curcumin cyclised by the action of irradiation increase their *in vivo* efficacy when concomitantly administered with visible-ultraviolet radiation.

After oral administration of Curcuminoids, the combination of visible light/Curcuminoids exhibits the same efficacy in moderate to severe psoriasis as the combination with ultraviolet light.

In a mouse model, visible light irradiated on mice combined with intraperitoneal curcumin produced a 70% inhibition of the proliferation of human epidermal carcinoma cells (A431). The combination visible-ultraviolet light and systematically administered Curcuminoids would be effective for the treatment of any tumour type, for example, epidermal, esophageal, duodenum, colon, breast, liver, kidney or prostate. In the case of using visible light, any irradiance and any type of light can be used, for example incoherent, polarized, pulsed or laser due to the absence of secondary effects. In a preferred mode, irradiance of between 2-300 mW/cm2 and more preferably irradiances of 2-30mW/cm2 can be used to irradiate 1-18 J/cm2.

The combination of Curcuminoids/visible-ultraviolet light is effective therapeutically at doses lower than those described in the state of the art, for example 1 mg/kg/day in psoriasis by oral administration or 50 mg/kg/day in the inhibition of tumours in a mouse model by intraperitoneal administration.

In a study in vitiligo, the combination of Curcuminoids/ultraviolet light produced a pigmentation in the patients treated without causing burns. The combination of Curcuminoids/visible light plus ultraviolet light will allow homogenous pigmentation of

all patients who are treated with Curcuminoids/visible light.

Thus, formulations comprising at least a Curcuminoid or analogue together with excipients acceptable for systemic administration, and optionally other active principles, can be developed.

Once a drug has been discovered that is capable of increasing its efficacy when administered concomitantly with visible light, and expert in the field can develop any phototherapy system comprising the means to emit a visible wavelength (400-550 nm) with an irradiance greater than 2 mW/cm2 on a surface greater than 0.20 m2. Light sources that can be used include, for example, gas discharge lamps, LEDs, polarized light, a laser beam or filtered solar radiation.

Among gas discharge lamps emitting in the range of 400-550 nm with a maximum at 420 nm are the Phillips TLK 40W/03 and Phillips TLK 140W/03. Their dimensions are 60*4 cm and 140*4 cm respectively. Ten Phillips TLK 40W/03 lamps at a distance of 45 cm emit 5500 lx, that is a irradiance of 3 mW/cm2. Logically, if the distance between the source and the radiation surface is reduced, the irradiance would increase. A source having an irradiance of 3 mW/cm2 emitting for 20 minutes will give a dose of 3*20*60/1000 J/cm2 = 3.6 J/cm2. Such lamps can be connected without difficulty to the current phototherapy cabins that use ultraviolet light discharge tubes.

The development of LED technology allows obtaining radiations with a greater luminous efficiency and with a very narrow wavelength emission (± 5 nm) and can used in phototherapy. J Invest Dermatol. 2002 Jul;119(1):77-83 used LED panels to radiate over a surface of 30 cm2 with

an irradiance of 9-11 mW/cm2, but the distance between the source and the psoriatic plaque was not specified. If the distance between the source and surface irradiated is reduced then irradiance will be greater but irradiation surface area will be smaller. Irradiating at a distance of 5 cm, it is possible to achieve irradiances of 30 mW/cm2 with currently commercialised LEDs.

In the same way, increasing the number of panels of LEDs increases the radiated surface. 60 panels of 12*25 cm, similar to those described in J Invest Dermatol. 2002 Jul;119(1):77-83, would irradiate over the whole adult body surface with an irradiance of 30 mW/cm2 at a distance of 5 cm in order to treat the moderate to severe psoriasis.

It should noted that small spectral variations in radiation or incidence angles will modify the radiometric measurements.

Examples:

I. Effect of an orally administered hydroalcoholic extract of Curcuma longa in combination with ultraviolet light in moderate to severe psoriasis

A pilot clinical trial was designed for the treatment of patients diagnosed with chronic psoriasis with moderate to severe plaques in which other treatments such as cyclosporine, psoralenes/UVA or corticoids had previously failed. The study parameters were:

- number of patients: 22
- trial duration: 8 weeks // 16 ultraviolet radiation sessions
- Medication: 24 mg of Curcuminoids, in the form of hydroalcoholic Curcuma longa extract having a Curcuminoids concentration of 12%. The excipients used in the formulation were: cellulose, magnesium stearate, corn

starch, sodium starch glycolate, potassium hydrogen phosphate and silicon dioxide. The pH of one tablet dispersed in water (5% w/v) was 5.

The Curcuma extract was obtained according the following process: extraction of rhizomes of Curcuma longa with ethanol, evaporation of the solvent and quantification of the Curcuminoids content expressed as Curcumin; extraction of the rhizomes of the previous phase with water and evaporation of the solvent; the resultant extracts were mixed and an extract was obtained with a Curcuminoids concentration of 10-15%.

- Administration regime: 3 tablets/day before main meals (72 mg Curcuminoids/day).
- Radiation source: PUVA COMBI LIGHT cabin with 32 lamps of Philips UVA 100 W (315-400 nm maximum 365 nm).
- Irradiated surface: all the naked body surface except genitals, approximately 2 m2.
- Doses: 2 phototherapy sessions per week were administered. The initial dose was 2.5 J/cm2. The dose was increased by 0.5-1 J/cm2 until reaching a slight erythema and later increased by 2 J/cm2 per session until reaching 16 J/cm2. The radiation time to reach 16 J/cm2 was approximately 30 minutes.
- Rescue medication:
    - a emollient formulation containing vitamin B3 for the symptomatic relief of cutaneous manifestations.
    -Desloratadine, if itching occurred.

The phototypes of the patients were I, II, III, IV. The average weight was 70 kg.

PASI reduction is detailed in following table for the different visits V1-V16 (2 visits per week). The patients who achieved a PASI reduction of more than 90% left the study.

PASI Reduction

Patient																						
Visit No	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
v1	11	36	42	0	15	24	35	25	0	7	20	13	11	17	32	40	34	48	31	53	49	49
V2	31	51	63	21	43	65	53	35	6	45	17	25	32	21	47	60	61	52	49	54	58	69
v3	25	36	54	35	35	54	55	54	21	39	39	38	44	54	55	78	82	82	61	60	73	65
V4	47	41	63	33	44	69	55	26	30	36	36	47	59	45	40	80	83	84	63	75	79	67
V5	49	50	59	26	47	73	63	42	36	45	51	39	68	66	53	86	85	87	78	75	82	79
V6	26	56	52	40	47	78	70	42	38	37	72	54	73	73	52	82	89	**96**	80	78	85	85
V7	37	67	47	35	69	78	73	52	40	54	79	63	69	73	62	88	**93**		84	79	87	85
V8	45	67	59	69	69	78	80	67	48	42	77	37	69	77	62	89			85	85	**92**	88
V9	57	67	64	67	73	**92**	80	67	46	50	76	63	69	79	70	89			91	87		**93**
V10	76	73	71	68	66		**93**	83	44	67	78	67	82	82	70	90				88		
V11	80	77	74	80	69			81	47	57	86	69	82	85	76	**91**				**90**		
V12	79	77	77	74	80			80	59	69	82	82	89	84	80							
V13	79	81	84	77	87			80	70	70	82	86	**91**	87	80							
V14	79	87	82	75	89			83	70	66	89	87		86	81							
V15	81	81	82	77	89			87	75	78	86	85		88	82							
V16	**91**	89	87	88	**93**			**93**	76	86	**94**	87		88	82							

For example, the doses irradiated to patients, 1, 2, 3 and 9 were:

Patient	1	2	3	9	Patient	1	2	3	9
Phototype	III	II	I	IV	Phototype	III	II	I	IV
VISIT 1	2,5	2,5	2,5	2,5	VISIT 10	15,5	16	15,5	15
VISIT 2	3,5	3,5	3,5	3,5	VISIT 11	16	16	16	15,5
VISIT3	4,5	4,5	4,5	4	VISIT 12	16	16	16	16
VISIT 4	5,5	5,5	5,5	5	VISIT 13	16	16	16	16
VISIT 5	5,5	7,5	6,5	6	VISIT 14	16	16	16	16
VISIT 6	7,5	9,5	8,5	8	VISIT 15	16	16	16	16
VISIT 7	9,5	11,5	10,5	10	VISIT 16	16	16	16	16
VISIT 8	11,5	13,5	12,5	12					
VISIT 9	13,5	15,5	14,5	14					

The 22 patients reached the radiation of 16 J/cm2 and the accumulated dose were of the order of 170-180 J/cm2.

No patient abandoned the treatment and radiation was well tolerated without severe photo toxicity reactions. Only one patient received a 5 mg desloratadine tablet.

After the 7th phototherapy session, the patients showed a healthy tan without stains or hyperpigmentations. Hyperpigmentations did not appear in any patient.

Hepatic parameters were within the normal range and hepatotoxicity was not identified. An increase of the red series was observed.

At the end of trial, the patients was pleased with the therapy and the commented that their self-esteem and personal relations had improved.

The results show the potential use of Curcumin, Curcuminoids, metabolites or their prodrugs as sun filters against visible-ultraviolet radiation. That is, hyperpigmentations were not produced in patients with phototypes III and IV and erythema and freckles were avoided in patients with fair skin.

In the middle of the trial, after fourth weeks and only 8 phototherapy sessions, 50% of patients reached PASI reductions higher than 75%. The efficacy in the middle of trial, was similar to that of Efalizumab in 12 weeks and without secondary effects.

All the patients reached a PASI reductions of 80%.

II. Effect of orally administered hydroalcoholic extract of Curcuma longa in combination with visible light in moderate to severe psoriasis

The parameters were:

- Number of patients: 10
- Duration of trial: 8-weeks // 16 phototherapy sessions with visible light

- Medication: 24 mg of Curcuminoids in the form of a hydroalcoholic Curcuma longa extract with a Curcuminoids concentration of 12%. The excipients used in the formulation were: cellulose, magnesium stearate, corn starch, sodium starch glycolate, potassium hydrogen phosphate and silicon dioxide. The pH of 1 tablet dispersed in water (5% w/v) was 5. The Curcuma extract was obtained as in the above trial.
- Administration regime: 3 tablets/day before meals (72 mg Curcuminoids/day)
- Radiation source: Phillips TLK 40W/03 lamp giving 5500 lx visible light 100*40W, 400-550 nm maximum emission 420 nm
- Irradiated surface: 100*60*4 cm = 2.4 m2 over the naked body surface.
- Doses: 2 phototherapy sessions per week. The irradiated doses were 18J/cm2, irradiation time 1 hour 40 minutes.
- Rescue medication:
    - an emollient formulation containing vitamin B3 for the symptomatic relief of cutaneous manifestations.
    - Desloratadine if itching occurred.

The phototypes of the patients studied were skin types II and III. The average weight was 70 kg.

PASI reduction is detailed in following table for the different visits V1-V16 (2 visits per week). The patients who achieved a PASI reduction higher than 90% left the study.

PASI reduction

Patient										
VISIT	1	2	3	4	5	6	7	8	9	10
V1	23	17	48	30	40	42	37	25	0	30
V2	25	40	54	42	35	50	49	54	12	42
V3	31	38	63	61	44	57	65	46	25	57

V4	39	50	77	62	47	69	69	66	26	66
V5	47	70	80	70	47	75	81	72	39	73
V6	56	78	83	68	69	79	83	72	45	67
V7	45	78	85	69	69	78	86	77	48	67
V8	68	79	89	70	75	88	87	79	59	78
V9	65	86	**92**	78	79	**93**	**91**	83	65	83
V10	70	82		80	85			85	73	85
V11	79	85		84	85			80	76	86
V12	79	84		87	**91**			84	80	**95**
V13	79	87		85				87	84	
V14	82	81		86				88	84	
V15	85	89		88				88	86	
V16	85	90		89				88	87	

The results obtained show the same efficacy was achieved with visible light as with ultraviolet light. All the patients exhibited a PASI reduction of more than 80% before 8 weeks of treatment.

The treatment was well tolerated and antihistamines and corticoids were not administered.

III. Effect of orally administered alcoholic extract of Curcuma longa in combination with visible light in moderate to severe psoriasis

A clinical trial was conducted on 4 patients with average age of 48 years, average weight of 68 kg, diagnosed with moderate to severe psoriasis.

The diagnostic criteria were the PASI on psoriatic plaque on the back or gluteus with a surface area of 30-35 cm2.

The irradiation was carried out with a LED lamp, maximum emission 420 nm. The irradiation distance was 5 cm with an irradiance of 30 mW/cm2 over a surface of 40 cm2.

After the screening visit to carry out the electrocardiogram and analytical determinations on included patients, the most important plaque with a

surface area of between 30-35 cm2 was chosen for each patient.

The patients received one capsule/day containing 280 mg of Curcuminoids, as an alcoholic extract with 90% in Curcuminoids. The selected plaque was irradiated a week after the start of Curcuma extract treatment and irradiations continued with two phototherapy sessions per week. The initial radiation dose was 2 J/cm2 and was progressively increased to 16 J/cm2.

The four patients reached a PASI reduction of more than 90% of baseline after 8 weeks on the irradiated plaque.

IV. Effect of orally administered hydroalcoholic extract of Curcuma longa in combination with ultraviolet light in vitiligo

Six patients diagnosed with vitiligo were treated with 3 tablets/day of an hydroalcoholic extract of Curcuma (72 mg Curcuminoids/day) and irradiation in a UV-cabin (315-400 nm, maximum 365 nm). The initial dose was 1 J/cm2 and was increased by 2 J/cm2 until 7 J/cm2. The last irradiation sessions were at 8 J/cm2.

- Patient 1. Generalized vitiligo with a large facial patch. 8 phototherapy sessions. A quick tan was achieved without burns or erythema.
- Patient 2. Vitiligo with patches on hands, chin and legs. 8 phototherapy sessions on the hands of 12 J/cm2. Pigmentation foci appeared on the edges of some vitiligo patches.
- Patient 3. Extensive vitiligo associated with fibromyalgia and thyroid disorder. 8 phototherapy sessions. Good tanning. The re-pigmentation process was observed on the neck.

- Patient 4. Extensive vitiligo. 8 phototherapy sessions. Hypothyroidism. Rapid increase in tan without burns. Pigmentation appeared on the abdomen.

- Patient 5. Extensive vitiligo with large facial patches. 8 phototherapy sessions. Good tanning without burning. Appearance of pigmentation of face and neck.

- Patient 6. Extensive vitiligo with large facial patches. 8 phototherapy sessions. Good tanning. Vitiligo on the joints. Presence of pigmentation on the elbows.

V. Effect of Curcumin by intraperitoneal administration on inhibition of tumour growth in mice

$5*10^6$ A431 cells (human epidermal carcinoma) were injected subcutaneously into the left and right flanks of athymic nude mice (NMRI) (5-6 weeks old, 20-24 g). The mice were fed in pathogen-free conditions. The animals were fed *ad libitum* with sterilised food. The animals were sterilised with ketamine/xylazine. For the treatment, 5 mg Curcumin were dissolved first in 50 µl de ethanol and further diluted in 2 ml of 1% methylcellulose and sterilised. The mice were fed intraperitoneally twice a day with 200 µl of the solution or methylcellulose solution alone. 50 mg Curcuminoids/kg per day.

One group of mice (Curcumin and methylcellulose) after the injection were irradiated for 20 minutes with 5500 lx. The irradiation device was 10 Phillips TLK 40W/03 lamps (60 cm length * 4 cm diameter), at a distance of 45 cm. The emission range of the lamps was between 400-550 nm with a maximum at 420 nm.

The control, methylcellulose and Curcumin without irradiation groups were protected from light for 1 hour after infection. Tumour size was measured initially and after 10-12 days; afterwards tumour volumes and weights were determined twice a week. At the end of the

experiment 29 days, the animals were anesthetized and sacrificed.

The results showed that only the group treated with Curcumin/light showed a significant difference in inhibition of tumour growth compared with the control group. The average tumour volume at day 12 in Curcumin/light treated mice was reduced by 70% in comparison to control mice. The tumour volume of the Curcumin-treated but not irradiated group was not significantly reduced ($p=0.16$), that is visible light improved the efficacy of Curcuminoids *in vivo*.

CLAIMS

1. A pharmaceutical composition comprising a curcuminoid and a suitable excipients for treating psoriasis wherein the curcuminoid is formulated for an administration by oral route in combination with an ultraviolet (UVA)-visible radiation of a skin surface affected with psoriasis characterized in that an accumulative UVA radiation dose is 170-180 J/cm^2.

2. The composition of claim 1, wherein the UVA-visible radiation is between 315-550 nm.

3. The composition of claim 1 or 2, for treating moderate to severe psoriasis in a patient wherein :
    a. the psoriatic plaques, having a surface greater than 10% of body surface, and
    b. the composition comprising a dose of 1 mg/kg/day of curcuminoids.

4. A kit for treating psoriasis comprising:
    a. the composition of claim 1 and
    b. a phototherapy device comprising a lamp for emitting an ultraviolet (UVA)-visible radiation having an irradiance higher than 2 mW/m^2.

5. The kit of claim 4, for treating moderate to severe psoriasis, comprising:
    a. a pharmaceutical composition comprising 24 mg curcuminoids in form of an hydroalcoholic extract of *Curcuma longa* and suitable excipients for oral administration, and
    b. a phototherapy device wherein:
        i. the lamp emits a UVA radiation from 315-400 nm having a irradiance of 8.8 mW /cm^2 and
        ii. the phototherapy device irradiates over a surface of 2 m^2.

6. The kit of claim 4, for treating moderate to severe psoriasis, comprising:
    a. a pharmaceutical composition comprising 24 mg of curcuminoids in form of hydroalcoholic extract of *Curcuma longa* and suitable excipients for oral administration, and
    b. a phototherapy device wherein:

i. the radiation is visible light from 400-550 nm, having a maximum emission at 420 nm, and

ii. the irradiance is 3 mW/cm^2 over a distance of 2.4 m^2.

7. The kit of claim 4, for treating psoriasis, comprising:
    a. a pharmaceutical composition comprising 280 mg of curcuminoids in form of alcoholic extract of *Curcuma longa* and suitable excipients for oral administration, and
    b. a phototherapy device wherein:
        i. the radiation is visible light, having a maximum emission at 420 nm, and
        ii. the irradiance is 30 mW/cm^2 over a surface of 40 cm^2.

8. A kit for treating epidermal carcinoma in mammals, comprising:
    a. a pharmaceutical composition comprising Curcumin and suitable excipients for intraperitoneal administration wherein:
        i. the Curcumin concentration is 2.5 mg/ml, and
    b. a phototherapy device wherein:
        i. the radiation is visible light from 400-550 nm, having a maximum emission at 420 nm, and
        ii. the irradiance is 3 mW/cm^2 at a distance of 45 cm.