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Clinical Studies on Topical Curcumin

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Curcumin · Turmeric · *Curcuma longa* · Topical application · Skin diseases · Skin health · Dermatology · Cosmeceuticals · Nutricosmetics

Abstract
Background: Curcumin is a polyphenolic compound present in turmeric (*Curcuma longa*). Curcumin, turmeric powder, and extracts are widely used in traditional Indian medicine and are active ingredients of dietary supplements and cosmeceutical products. The pharmacological properties of curcumin/turmeric as well as the studies performed in vitro, in animal models, and in volunteers have been the objects of a vast literature. Most of the clinical studies report on the effects of curcumin/turmeric administered orally, while only a few describe its topical applications. ***Summary:*** This review focuses on clinical studies in which curcumin/turmeric was applied topically to treat various skin conditions based on its antioxidant, anti-inflammatory, and antimicrobial properties. ***Key Messages:*** The clinical studies employing curcumin/turmeric as the only active ingredient allow us to appreciate its therapeutic potential without confounding contributions coming from additional pharmacologically active substances present in the same formulation. Curcumin/turmeric was regarded as an attractive alternative to conventional drugs, such as corticosteroids and antibiotics, thanks to its characteristics of a safe and well-tolerated natural substance.

Introduction

Curcumin is one of the most frequently employed natural components of nutraceutical products. It is also increasingly being used in cosmeceutical formulations although its intense yellow-orange color is an unwelcome feature [1]. The recognized reputation of curcumin in these two markets can be mainly ascribed to its antioxidant, anti-inflammatory, and antimicrobial properties [2] combined with an excellent safety profile [3].

Oral usage of curcumin is complicated by poor bioavailability due to an extremely low water solubility, a high chemical reactivity with water and oxygen, and a first-pass effect [4]. To circumvent this problem, several technological approaches have been devised [5]. Efforts have likewise been made to optimize its topical delivery [6].

Curcumin can be used either as a single ingredient or as the main component of extracts obtained from the rhizome of *Curcuma longa* (turmeric). The complex pharmacology of curcumin encompasses at least the following activities: antioxidant, anti-inflammatory, antimicrobial, anticancer, neuroprotective, cardiovascular, and metabolic disease preventing [7]. Such a peculiar pharmacological profile results from a multitude of biochemical targets hit by curcumin, including transcription and growth factors, protein kinases, enzymes, cytokines, and others [8].

Most of the clinical studies concerning curcumin/turmeric refer to oral administration, while only a few

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Table 1. Clinical trials reporting efficacy assessment of curcumin or turmeric for topical treatment

No.	Intervention and dosage (w/w)	Skin condition	Trial design	Type of outcome	Statistical significance of results	Reference
1	1% curcumin	Psoriasis	OL, AC, NTC	Clinical, instrumental	Yes	Heng et al. [10] (2000)
2	Turmeric (ns)	Psoriasis	R, DB, PC	Clinical	Yes	Sarafian et al. [11] (2015)
3	Turmeric (ns)	Scalp psoriasis	R, DB, PC	Clinical	Yes	Bahraini et al. [12] (2018)
4	12% curcumin	Hypertrophic scarring	CR	Clinical	No	Heng et al. [13] (2011)
5	Turmeric (ns)	Vitiligo	R, DB, PC	Clinical	Yes	Jalalmanesh et al. [14] (2022)
6	200 mg curcumin per pump	Lactational mastitis	R, DB, PC	Clinical	Yes	Afshariani et al. [15] (2014)
7	0.5% curcumin	Skin and mucosae cancerous lesions	NC	Clinical	Yes	Kuttan et al. [16] (1987)
8	4% curcumin	Radiodermatitis	R, PB, PC, AC	Clinical	No	Ryan Wolf et al. [17] (2020)
9	5% *C. longa*	Androgenetic alopecia	R, DB, PC, AC	Clinical	No	Pumthong et al. [18] (2012)
10	Turmeric (ns), sandalwood oil (ns)	Radiodermatitis	R, OL, PC	Clinical	Yes	Palatti et al. [19] (2014)
11	0.1% curcumin, 0.1% piperine, 0.03% capsaicin	Alopecia areata	R, OL, AC	Clinical, instrumental	Yes	Mao et al. [20] (2022)
12	Turmeric (ns), neem (ns)	Scabies	NC	Clinical	No	Charles et al. [21] (1992)
13	Turmeric (ns), *A. indica* (ns), *C. tora* (ns)	Tinea corporis	R, SB, PC	Clinical, instrumental	Yes	R et al. [22] (2022)
14	0.5% turmeric, 10% henna	Capecitabine-related HFS	R, TB, PC	Clinical	No	Elyasi et al. [23] (2022)
15	Turmeric (ns), *C. gigantea* (ns), *P. glabra* (ns), *S. xanthocarpum* (ns), *C. camphora* (ns), *J. regia* (ns)	Eczema	NC	Clinical	Yes	Rawal et al. [24] (2009)
16	Turmeric (ns), *A. barbadensis* (ns), *A. indica* (ns), *H. indicus* (ns), *T. chebula* (ns), *T. arjuna* (ns), *W. somnifera* (ns)	Acne	R, DB, PC	Clinical	Yes	Lalla et al. [25] (2001)
17	16.0% turmeric, 0.1% turmeric oil, 8.0% *S. album*, 3.0% *L. inermis*, 3.0% *O. sanctum*, 0.5% *G. glabra*, 0.5% *V. zizanioides*, 0.5% surasar, 0.1% *A. moschatus*, 0.025% *C. sativus*, 0.00032% Swarna Bhasma	Pruritus	R, OL, AC	Clinical	No	Chatterjee et al. [26] (2005)
18	*C. zedoaria* (ns), *A. membranaceus* (ns), *S. pharbitidis* (ns), *cassia* twig (ns), *P. arecae* (ns), borneol (ns)	MPE	R, DB, PC	Clinical, instrumental	No	Freize et al. [27] (2017)
19	0.02% curcumin, 1.0% tocopheryl acetate, 1.0% acerola fruit, 0.5% selenomethionine (calcium phosphate)	Skin aging	R, DB, PC	Clinical, instrumental	Yes	Di Lorenzo et al. [28] (2022)

AC, active-controlled; CR, case report; DB, double-blind; NC, non-comparative; NTC, no-treatment-controlled; ns, not specified, OL, open label; PB, partially blind; PC, placebo-controlled; R, randomized; SB, single-blind; TB, triple-blind.

report its topical applications. After a brief recall of the chemical and physical properties of curcumin and curcuminoids, this review covers the most significant clinical studies in which curcumin (alone or as the principal component of turmeric extracts) was applied topically to relieve symptoms of skin diseases or to improve skin health care. Compared with a review by Vaughn et al. [9] discussing the effects of orally and topically administered curcumin/turmeric on skin health, this article represents an update as it includes additional works, most of which published after 2015.

A special attention has been given to investigations where curcumin/turmeric was employed as a single active ingredient. We have also summarized clinical studies employing curcumin/turmeric in combination with other active constituents in the same topical formulation although such studies do not permit to single out the specific effects exerted by curcumin/turmeric. The main features of the clinical studies discussed in the present paper are listed in Table 1.

Curcuminoids: Sources, Chemical, and Physical Properties

Turmeric is the common name of *C. longa*, a flowering plant belonging to the ginger family (*Zingiberaceae*) cultivated in India and Southeast Asia. The rhizomes of this plant are dried and ground to yield a yellow-orange powder used as a spice or a dye. Solid and liquid extracts of turmeric are the active ingredients of dietary supplements and topical products in the form of gels, creams, or ointments.

Turmeric contains several chemically related compounds, known as curcuminoids, in concentrations varying from 3% to 5% w/w [29]. The most abundant and biologically active curcuminoids are curcumin (1), demethoxycurcumin (2), and bisdemethoxycurcumin (3) (structures in Fig. 1) present in crude extracts in relative amounts (w/w) of 60–70%, 20–27%, and 10–15%, respectively [30]. Since curcuminoids display similar biological activities, curcumin, curcuminoids, and curcumin extracts are often employed as synonyms in literature.

Although curcumin can be synthesized [31], its industrial-scale production is based on extraction methods from turmeric. Good quality dry extracts of turmeric are commercially available which contain up to 95% w/w of curcuminoids.

Curcumin belongs to the chemical class of polyphenols. It is a symmetric molecule incorporating two feruloyl moieties separated by a methylene linker. It appears as a yellow-orange crystal powder. Its hydrophobic character (estimated logP = 3.2 [32, 33]) and high melting point (183°C [34]), this latter related to a high lattice energy, are consistent with an extremely low solubility in water (less than 10 mg dissolves in 1 mL [35, 36]).

Curcumin exists in the solid state as a keto-enol tautomer (4, Fig. 2) characterized by an intramolecular hydrogen bond, whereas in aqueous solutions it predominates as diketo form (1, Fig. 1) with intermolecular hydrogen bonds engaged between the two carbonyl oxygens and water [37]. In aqueous solutions, it behaves as a triprotic weak acid with pKa1, pKa2, and pKa3 values of 7.8, 8.5, and 9.0, the former related to the enol hydrogen of the keto-enol tautomer and the remaining ones to the two phenol hydroxyls [38]. Curcumin can be easily dissolved in acetone and is sparingly soluble in ethanol [39].

As mentioned, the clinical use of curcumin is hampered not only by low solubility in water but also by poor chemical stability [40, 41]. In fact, it rapidly degrades in aqueous solutions with a pH above 3 through hydrolysis [42] and autoxidation [43]. However, the speed of these reactions is much slower in non-aqueous solvents (e.g., ethanol, isopropanol) and reasonable stability can also be obtained in 10–20% w/v ethanol aqueous solutions [40]. The incorporation of curcumin into oil-in-water emulsions has been found to improve its water dispersibility and chemical stability [41].

Curcumin or Turmeric as a Single Ingredient

In this section, the discussion focuses on nine studies (#1–9 in Table 1) in which curcumin or turmeric was used as the only active ingredient in topical formulations used to treat various skin diseases.

Curcumin and Turmeric to Treat Psoriasis

Psoriasis, an inflammatory disease characterized by an abnormal proliferation of epidermal cells [44], has been associated with overactivity of phosphorylase kinase (PhK) [45]. PhK is a regulatory protein kinase that stimulates glycogen breakdown. It receives input from hormonal and neuronal signals transmitted through the second messengers Ca^{2+} and cAMP and responds by phosphorylating and thus activating glycogen phosphorylase [46].

The evidence that curcumin is a selective noncompetitive inhibitor of PhK [47] was the rationale of an open-label (OL) clinical study which tested the hypothesis that the anti-psoriatic property of curcumin is

linked to its capability of counteracting the PhK effects in the skin [10]. Thus, PhK activity was measured in the skin of 40 subjects (four groups of 10). The first 2 groups were psoriatic patients treated for 4 weeks with 1% curcumin (alcoholic gel) or 0.005% calcipotriol (a vitamin D_3 analogue); the third group of untreated patients with psoriasis was the control; the fourth group consisted of non-psoriatic subjects. Psoriasis was resolved by 90% in the curcumin-treated patients after 2–6 weeks (5 out 10 subjects) or by 50–85% after 3–8 weeks (the remaining 5 subjects). In the calcipotriol-treated group, 3 patients had 70–80% resolution after 4–6 months of treatment and 7 patients had 50–65% improvement after 6–18 months. As expected, no improvements of psoriasis occurred in the group of untreated patients.

The results of immunochemical measurements showed that the PhK levels in the groups treated with curcumin and calcipotriol decreased by a 5.8- and a 2.2-fold compared with the control group, respectively. The PhK activity in the skin of non-psoriatic subjects was 2-fold lower compared with the psoriatic skin treated with curcumin. Curcumin also reduced keratinocyte transferrin receptor expression, severity of parakeratosis, and density of epidermal CD8+ T cells.

A separate OL study was conducted on 6 patients to compare the effect of 1% curcumin alcoholic gel with the effect of the vehicle alone. This study confirmed that the observed reduction of the PhK levels in the curcumin-treated patients was not influenced by ethanol. The authors concluded that curcumin is an effective anti-psoriatic agent thanks to its capability of inhibiting PhK.

The therapeutic value of turmeric in the treatment of psoriatic lesions was assessed by Serafian et al. [11] in a randomized, intraindividual, right-left comparative, double-blind (DB), placebo-controlled (PC) trial involving 40 patients with mild-to-moderate psoriasis. The volunteers applied a hydro-alcoholic gel – containing a turmeric extract or the vehicle alone as the placebo – on the right or left lesions twice daily for 9 weeks. The amount of curcuminoids in the gel was determined according to a well-standardized method. However, the authors did not detail such a content. The turmeric gel and the placebo gel were identical in their presentation. The psoriasis area and severity index (PASI) [48] was assessed to evaluate the clinical efficacy of the treatment.

The study was completed by 34 patients. At the end of the treatment, the turmeric gel was found much more effective than the placebo gel. In fact, the former reduced the mean PASI score from 3.6 to 1.4 (−61%) whereas the latter reduced the same score from 3.7 to 3.3 (−11%). The authors hypothesized that the moisturizing property of the vehicle might have contributed to a small extent to the beneficial effects of the two gels.

Bahraini et al. [12] evaluated the clinical efficacy of turmeric in mitigating the symptoms of mild-to-moderate psoriasis. This randomized, DB, PC trial involved 30 volunteers. The patients were equally divided into two groups: one receiving a turmeric tonic (whose concentration was not specified) and the other one receiving a placebo tonic. The two formulations – having the same color – were applied on the scalp twice daily for 9 weeks. The effectiveness of the treatment was evaluated by means of PASI. After completion of the treatment, the mean PASI score in the turmeric-treated group decreased significantly – from 7 to 3 (−57%) – whereas in the placebo-treated group the PASI score increased from 4 to 7 (+43%). In the last two studies summarized above [11, 12], the anti-psoriatic activity of turmeric was related to the capability of curcumin not only to inhibit PhK but also to downregulate receptors of mediators of inflammation, such as 5-lipoxygenase, 5-cyclooxygenase, tumor necrosis factor-a, interleukin-1, interleukin-6, and interleukin-8.

Curcumin to Treat Hypertrophic Scarring

Hypertrophic scars result from an abnormal inflammatory response of injured skin characterized by an overproduction of collagen. They represent an undesirable process in wound healing [49].

Heng et al. [13] have reported six case studies in which a hydro-alcoholic gel of 12% curcumin reduced exceeding scarring of wounded skin of patients who underwent excision of a portion of skin affected by carcinoma. Curcumin was chosen as a wound-healing agent owing to its capability to inhibit PhK [45] and, consequently, interfere with NF-kB activation which is a key step in fibroblast proliferation and collagen synthesis [50]. Treatments consisted in topical application of the curcumin gel twice daily for periods ranging from 2 to 8 weeks.

Turmeric to Treat Vitiligo

Vitiligo is a skin disease characterized by loss of melanocytes and depigmentation. Although the exact etiology of vitiligo remains unknown, it is ascertained that it may be related to a chronic autoimmune disorder associated with an abnormal inflammatory response [51].

The well-known anti-inflammatory properties of curcumin prompted Jalalmanesh et al. [14] to carry out a randomized, DB, PC study in which turmeric was evaluated for its effects on skin pigmentation in patients suffering from mild-to-moderate vitiligo. Thirty patients were enrolled, and 24 completed the study. Two creams

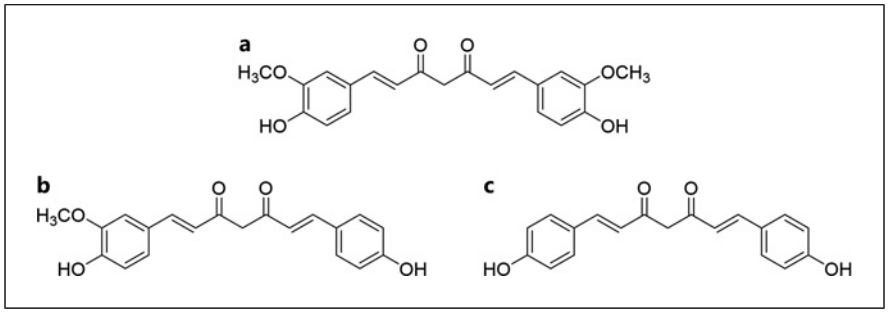

Fig. 1. Structures of curcuminoids: curcumin (**a**), demethoxycurcumin (**b**), and bisdemethoxycurcumin (**c**).

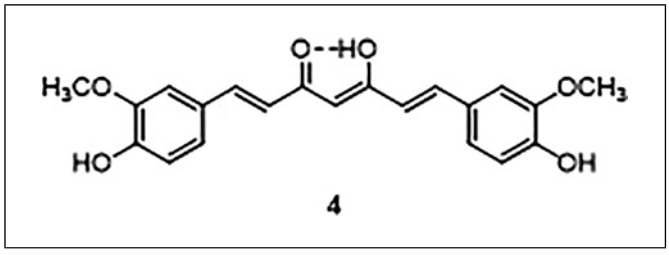

Fig. 2. Keto-enol tautomer of curcumin.

containing turmeric or placebo, identical in appearance, were given to patients who applied one of the two creams on the right or left side of depigmented skin areas according to a randomized procedure twice daily for 4 months. The content of turmeric in the cream was not detailed in the quoted article. Two clinical outcomes were assessed, namely, the vitiligo area scoring index [52] and the vitiligo noticeability scale (VNS) [53].

At the end of the treatment, the mean vitiligo area scoring index score of the turmeric-treated skin areas improved in 14 out of the 24 patients (from 10–25% to more than 50%) whereas treatment with the placebo in 20 subjects did not lead to any relevant change in this outcome. Regarding the VNS-based assessment, a greater number of patients reported more noticeable patches using the placebo cream while less noticeable patches and complete responses were recorded in the turmeric group. According to the authors, these results support the topical use of turmeric alone or as adjuvant therapy in patients suffering from vitiligo.

Curcumin to Treat Lactational Mastitis

Lactational mastitis is an inflammatory condition mainly caused by milk stasis in lactiferous ducts which is characterized by a hard, swollen, tense, and erythematous breast accompanied by pain (mastalgia) [54]. Sometimes, mastitis is associated with infection. Treatments for this condition are supportive (i.e., massage of the breast toward the nipple to improve breast emptying) and pharmacological if symptoms do not regress (i.e., analgesic, anti-inflammatory, and antibacterial drugs) [55].

The effectiveness of topical curcumin to treat lactational mastitis was investigated in a randomized, DB, PC clinical trial involving 63 breastfeeding women [15]. The patients were divided into two groups: 32 subjects were treated with a curcumin cream spray (Neurobiologix, TX, USA); 31 subjects received a topical moisturizer cream as the placebo. All patients were asked to apply one pump of the cream to the affected breast every 8 h. Although the authors did not provide information regarding the concentration of curcumin in the cream, they specified the content of curcumin released by each pump (200 mg). The clinical evaluation was based on a mastitis severity index made up of three different parameters: breast tension, erythema, and pain.

After 3 days, the mean values of the symptoms-related parameters in the curcumin-treated group exhibited significant favorable changes: tension, erythema, and pain decreased from 3.6, 2.5, and 5.2, respectively, to values below 0.5. In the placebo-treated group, the same parameters were reduced to a considerably less extent: from 3.5, 2.9, and 5.6 to 2.4, 2.3, and 3.1, respectively. The results of this study show that topical curcumin is a valuable anti-inflammatory and antimicrobial agent to manage lactational mastitis.

Curcumin to Treat Dermatitis Caused by Cancer or Radiotherapy

The anti-inflammatory and antioxidant properties of curcumin prompted some authors to test such a substance in relieving symptoms of dermatitis associated with cancer or caused by cancer radiotherapy. Curcumin has been employed topically to treat cancerous lesions of skin and mucosae (mouth and vulva) [16]. This noncomparative (NC) clinical trial was conducted on 62

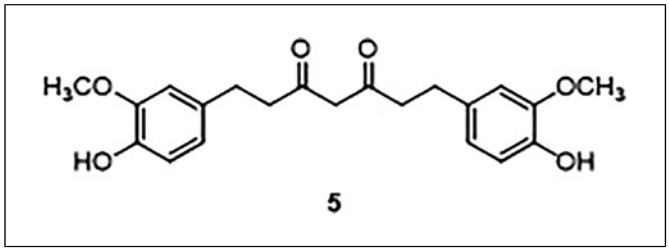

Fig. 3. Structure of tetrahydrocurcumin.

patients suffering from recurrent ulcerating tumors characterized by itching, exudates, foul smell, and pain. All the patients did not respond to standard treatments (surgery, chemotherapy, radiotherapy). They were treated 3 times daily with 0.5% curcumin in two formulations: (i) as an ointment applied on the skin or the vulva and (ii) as a hydro-alcoholic solution (water and ethanol 1:1) applied in the oral cavity. During the study, the patients did not receive any anticancer treatment; a few of them took analgesic drugs, and those hospitalized received sedative drugs to improve sleep. The skin conditions were evaluated weekly in terms of positive or negative response of a given symptom to the treatment continued not longer than 4 weeks.

The topical application of curcumin produced beneficial effects in most of patients. Particularly, in more than 90% of the cases the foul smell of the lesions was reduced considerably; in 70% of the patients the exudates decreased; the thickness of the lesions was reduced only in 10% of the patients. Although half of the patients reported a decrease in pain, this effect could not clearly be attributed to curcumin owing to the concomitant administration of analgesic and sedative drugs. Some patients complained of local irritations likely caused by the ethanol content in both topical formulations. Curcumin was not tolerated only in 1 patient due to an allergic reaction. Despite the limitations in the design of the quoted study, these results suggest that curcumin may play a beneficial role in relieving symptoms related to skin and mucosae cancers.

A common side effect of cancer radiotherapy is dermatitis whose severity is graded in a continuum, ranging from erythema and dry desquamation to the more severe desquamation and, eventually, ulceration [56, 57]. This condition is characterized by symptoms such as skin dryness, itching, discomfort, pain, warmth, and burning which may lead to the cessation of the treatment or persist up to a month after its completion [58].

A randomized, partially blind, PC and active-controlled (AC), clinical trial was conducted by Ryan Wolf et al. [17] on 169 females (those who completed the study) suffering from breast cancer to compare the effectiveness of three topical agents in reducing radiodermatitis: 4% curcumin gel, a commercially available gel containing tocopheryl acetate (concentration not given), and a placebo gel. Most of the skin damage produced by radiation is principally related to indirect mechanisms mediated by free radicals; this was the rationale of comparing curcumin versus tocopheryl acetate, both endowed with strong antioxidant properties. The blinding of the volunteers was partial because the placebo gel was the same color (yellow) and consistency as the curcumin gel, whereas the tocopheryl acetate gel was a white lotion. The patients applied the topical agent to their skin in the radiation area site 3 times daily starting the first day of radiation therapy until 1 week after its completion. Radiation-induced dermatitis was evaluated according to a radiation-induced dermatitis severity scale. The assessment of the clinical outcomes did not show a significant difference in radiation dermatitis severity among the groups of patients treated with the three topical gels.

Curcuma aeruginosa *to Treat Androgenic Alopecia*

Androgenetic alopecia is a common form of hair loss in both men and women. In men, this condition is also known as male-pattern baldness and has been associated with overactivity of dihydrotestosterone [59]. Therefore, inhibitors of steroid 5-alpha reductase type 2 – the enzyme converting testosterone in dihydrotestosterone in the epidermis and hair follicles – have been claimed as useful agents in the treatment of this condition [60]. Curcumin and related curcuminoids have been reported to behave as 5-alpha reductase type 2 inhibitors [61].

A randomized, DB, PC and AC trial evaluated the effectiveness of *C. aeruginosa* [62] (belonging to the same botanical family as *C. longa*) in the treatment of androgenetic alopecia [18]. The study was conducted on 87 men who were divided into four groups to receive twice daily for 6 months: (i) 5% *n*-hexane extract of *C. aeruginosa*; (ii) 5% minoxidil solution; (iii) *C. aeruginosa* plus minoxidil; and (iv) placebo consisting in a vehicle lacking active ingredients. The number of subjects was 21 in the first group or 22 in the remaining ones. All volunteers were instructed to apply three sprays onto the anterior and vertex areas twice daily. Additionally, they were required to use the same shampoo and maintain the same hairstyle, hair length, and hair color during the entire study and to refrain from cutting the scalp hair shorter than 1 inch.

A slight increase in hair count was found in the three groups treated with active ingredients that, however, did not reach a statistical significance level. The authors state that "*C. aeruginosa* extract used in the study was controlled for quality by assay for inhibitory activity against testosterone conversion by HPLC, as previously described" but they provide a reference [63] which does not describe such a procedure. Moreover, the amount of curcuminoids present in the *n*-hexane extract seems questionable as the maximum concentration of these substances in *n*-hexane does not exceed 0.04% [64].

Remarks about Studies Using Curcumin or Turmeric as a Single Ingredient

The clinical studies summarized in this section (#1–9 in Table 1) employed curcumin or turmeric (from here on curcumin) as the only active ingredient of topical formulations. They allow us to appreciate the real therapeutic potential of curcumin without confounding contributions coming from additional pharmacologically active substances present in the same formulation, such as herb extracts, vitamins, or drugs. In such cases, correlations between the clinical effects of curcumin and its pharmacological properties (antioxidant, anti-inflammatory, and antimicrobial) can be attempted.

These studies differ considerably from each other in their design, namely, case reports (#4), NC trial (#7), OL trial (#1), and randomized, PC trials (#2,3,5,6,8,9), listed in increasing order of internal validity. Two of them are also AC trials (#8,9). Except for two studies (#8,9), the remaining ones reached statistically significant results.

Studies #1–3 deal with use of curcumin to treat psoriasis and reinforce each other in terms of robustness of the results. Specifically, the first one (OL) demonstrates that the beneficial effect of curcumin is associated with measurable biochemical and histological changes in the skin of patients; the remaining two are randomized, DB, PC trials supporting the clinical efficacy of curcumin in terms of statistically significant differences between curcumin-treated and placebo-treated groups of patients.

A key methodological aspect of clinical studies aimed at evaluating curcumin as a topical agent should be establishing its exact concentration in the tested formulations. Among the nine studies considered in this section, studies #1,4,7–9 detail such data while studies #2,3,5 do not. In study #6, the authors do not specify the concentration of curcumin in the cream applied to treat lactational mastitis but, however, detail the total amount of curcumin released per pump (200 mg). The last study examined in this section (#9) evaluated the effect of a 5% *n*-hexane extract of *C. aeruginosa* to treat androgenetic alopecia. The results of this study did not reveal any significant improvement of such a formulation on hair growth. However, it may be relevant to such a finding that the amount of curcuminoids present in the *n*-hexane extract seems questionable as we have already observed while summarizing the quoted article.

The overall picture emerging from studies #1–7 is that curcumin might represent a valuable therapeutic option in several skin diseases differing in etiology, but all characterized by inflammation, such as psoriasis, hypertrophic scarring, vitiligo, lactational mastitis, cancerous lesions. Some of the above studies are well designed (#2,3,5,6) and therefore provide a stronger support to such a view. However, further studies remain to be undertaken to confirm the value of curcumin as a topical anti-inflammatory agent.

Curcumin or Turmeric Combined with Other Active Ingredients

The articles reviewed in this section refer to the use of curcumin or turmeric combined with other active ingredients mixed in the same formulation to treat various skin conditions.

Turmeric and Sandalwood Oil to Treat Radiodermatitis

A topical formulation containing a turmeric extract and sandalwood oil (Vicco® Turmeric Cream, Vicco Laboratories, Parel, India) was evaluated by Palatti et al. [19] as a skin-protecting agent in patients undergoing cancer radiotherapy. In this randomized, OL, PC study, a total of 50 patients with head and neck cancer were equally divided into two groups: the first one treated with 2 g of turmeric cream (concentration not specified) and the second one treated with 2 mL of a commercially available moisturizing baby oil as the placebo. The two formulations were applied on the irradiated skin region 5 times daily for 7 weeks of radiotherapy and 2 weeks after its conclusion. The skin condition of the volunteers was assessed twice weekly by a physician who did not mention the details of the trial. The outcome was a severity score made up of 4 grades of dermatitis [65].

The group using the turmeric cream had delayed appearance and reduced levels of dermatitis throughout the entire period of the trial (9 weeks). Particularly, grade 3 dermatitis was observed at weeks 6 and 7 in 4.3% and 13.6% of the turmeric cream-treated patients, respectively, compared with 12.5% and 29.2% of incidence, respectively, in the baby oil-treated patients. None of the patients developed

grade 4 dermatitis in each of the two cohorts. The turmeric cream treatment performed better than the baby oil also during the 2 weeks after completion of radiotherapy.

The results of this study using a combination of turmeric and sandalwood oil are somehow contrasting with those obtained from the study conducted by Ryan Wolf et al. [17] on a larger number of patients which found that 4% curcumin was not superior to placebo in treating radiodermatitis (see previous section). This suggests that the sandalwood oil might exert significant effects in relieving radiodermatitis under the experimental conditions of the study by Palatti et al. [19] (summarized above). Incidentally, sandalwood album oil has demonstrated beneficial effects in skin diseases such as acne, psoriasis, and eczema, owing to its anti-inflammatory, antimicrobial, and antiproliferative activities [66]. However, the two quoted studies cannot be compared in terms of design quality as the one by Ruan Wolf et al. was DB and PC whereas the one by Palatti et al. [19] was OL.

Curcumin with Piperine and Capsaicin to Treat Alopecia Areata

Alopecia areata is a transient, non-scarring hair loss with preservation of the hair follicle which is seemingly related to autoimmune, genetic, emotional stress, and endocrine factors [67]. Mao et al. [20] compared a mixed preparation of 0.1% curcumin, 0.1% piperine, and 0.03% capsaicin with a 5% minoxidil tincture for their effectiveness in promoting hair growth in patients suffering from alopecia areata. The rationale for combining curcumin with piperine and capsaicin was the following: curcumin has anti-inflammatory properties and increases blood circulation [68]; piperine has been reported to increase the bioavailability of curcumin [69]; capsaicin improves blood circulation and has shown beneficial effects in alopecia areata [70]. Sixty volunteers (23 males and 37 females) were enrolled in this randomized, OL, AC study. They were randomly assigned to apply on their scalp twice daily either the mixed preparation or the minoxidil tincture for 12 weeks. The degree of hair loss was assessed using the severity of the alopecia tool score [71] and by dermoscopy.

After completion of the treatment, statistically significant hair growth occurred in both groups as compared with the baseline at time 0. The mean severity of the alopecia tool score decreased from 4.4 to 2.2 (−56%) in the mixed preparation-treated group and from 3.9 to 2.0 (−57%) in the minoxidil-treated group. The count of hair follicles by dermoscopy increased by a 3.6-fold and a 3.8-fold in the mixed preparation- and minoxidil-treated groups, respectively. According to the authors, the clinical efficacy of curcumin combined with piperine and capsaicin in treating alopecia areata was comparable with that offered by minoxidil.

Turmeric and Azadirachta indica *to Treat Scabies*

Scabies is an infestation of the skin caused by a tiny mite called *Sarcoptes scabiei* var. hominis. It represents an endemic disease in many non-industrialized tropical regions of the world [72]. Typical symptoms of scabies are intense itching and skin rash. Scabies is spread by skin-to-skin contact among persons or by contact with infested clothes.

An NC study evaluated the use of turmeric and neem (*A. indica*) to treat scabies in 824 people living in a village located in an Indian district [21]. Neem is endowed with anti-inflammatory, wound healing, and antimicrobial activities [73]. Usage of the two plants to treat scabies represented a traditional medicine approach offering economical and practical advantages over synthetic drugs such as benzyl benzoate. Diagnosis of scabies was confirmed by a physician. The treatment consisted in the topical application of a paste containing turmeric powder and fresh neem leaves in the proportion of 1:4 by weight. Boiling the clothes and a scrub bath were carried out before the treatment. The paste was rubbed all over the body of the patient and left to dry. This procedure was repeated daily. If the lesions had healed within 15 days of treatment, the patient was considered cured.

The results of this study were remarkable as 97.9% of the 814 patients were cured. Treatment failure occurred in only 17 cases owing to scarce compliance in the application of the paste and/or the preliminary procedures (scrub bath and boiling clothes).

Turmeric with A. indica *and* Cassia tora *to Treat Tinea Corporis*

Tinea corporis is a fungal infection affecting the surface layer of the skin caused by dermatophytes, the most widespread types belonging to genera *Microspora*, *Trichophyton*, and *Epidermophyton*. The use of a soap containing extracts of *C. longa*, *A. indica*, and *C. tora* to treat tinea corporis was investigated in a randomized, single-blind, PC clinical trial [22]. The medical herbs employed in this study were selected owing to their proven antifungal activities [74–76]. The contents of the three active ingredients in the antimicrobial soap were not specified in the quoted article. Thirty patients affected by tinea corporis were included in the study. The diagnosis was confirmed by potassium hydroxide (KOH) preparation [77]. The volunteers were divided into two groups: 20 in the test group who used the multi-herbal soap and 10 in the placebo group who used a soap similar

in color and smell to the tested soap. Participants were blinded regarding the assigned group. Treatment consisted in applying the soap on the affected areas a minimum of twice daily and lasted 4 weeks. Two outcomes were assessed at baseline (time 0) and after completion of the treatment, namely, total symptom score and KOH test to reveal the presence or absence of fungi.

On completion of the study, a statistically significant reduction in mean total symptom score was observed in the test group (8.6–3.0), differently from the placebo group (8.8–8.1). Moreover, the percentage of patients who turned out negative for KOH preparation was 80% in the test group and 20% in the placebo group. These results suggest that the multi-herbal formulation of the tested soap can be effective against fungal infections of the skin.

Turmeric with Lawsonia inermis *to Treat Capecitabine-Induced Hand-Foot Syndrome*

Hand-foot syndrome (HFS) or palmar-plantar erythrodysesthesia is a side effect caused by some antineoplastic drugs, such as capecitabine (an oral prodrug of 5-fluorouracil), characterized by redness, swelling, and pain on the palms of the hands and/or the soles of the feet [78]. A randomized, triple-blind, PC study was conducted by Elyasi et al. [23] to evaluate whether a commercially available ointment containing 0.5% turmeric and 10% henna (*L. inermis*) could reduce HFS in patients taking oral capecitabine. The rationale of such a topical treatment relied on the anti-inflammatory properties of curcumin and the recognized beneficial effects of henna in HFS [79, 80].

For this study, 110 patients taking capecitabine were enrolled and randomly divided into two groups of 55 subjects each: one treated with the ointment containing curcumin and henna (Alpha®, Alpha Development Company, Tehran, Iran) and the other one treated with an ointment as the placebo which was similar in appearance to the one with active ingredients. The volunteers applied twice daily half a fingertip unit of the ointment on the soles and one fingertip unit on the palms. This treatment started from the first day of chemotherapy with capecitabine and continued consecutively for 4 courses of chemotherapy (each course consisted in oral capecitabine on days 1–15 every 3 weeks). Forty-six patients in the treatment group and 44 patients in the placebo group completed the study. The severity of HFS was clinically assessed at the end of each of the four chemotherapy courses based on a World Health Organization (WHO) scale.

The median score of HFS was not significantly different between the two groups at the end of all four assessed courses of chemotherapy. However, at the end of each of the first three courses, the rate of HFS grades 1–3 occurrence was slower in the curcumin plus henna-treated group than in the placebo-treated group. The authors concluded that the ointment containing curcumin and henna delays HFS manifestations in patients under treatment with oral capecitabine.

Turmeric with Herbal Extracts to Treat Eczema

A commercially available cream (Herbavate®, Troikaa Pharmaceuticals Ltd, Ahmedabad, India) – containing extracts of turmeric, *Calotropis gigantea*, *Pongamia glabra*, *Solanum xanthocarpum*, *Cinnamomum camphora*, and *Juglans regia* – was evaluated for its effectiveness in the treatment of atopic dermatitis (eczema) [24]. The concentrations of the herbal extracts in the cream were not specified by the authors. This NC study involved 150 patients. The volunteers were asked to apply the cream twice daily for 4 weeks. The primary outcome was a change in symptoms (erythema, scaling, thickening, and itching) assessed after 4 weeks according to a 4-point score scale as compared to the baseline scores before treatment. The secondary outcome was the weekly change in symptom scores as compared to the previous clinical evaluation.

The trial was completed by 131 patients. After 4 weeks, the reduction of each of the four symptoms ranged from 28% to 35%. The cream produced statistically significant improvements not only at the end of the trial but also after each week of treatment. The cream was well tolerated, with only 4 patients complaining of mild burning at the application site and only 1 patient reporting hyperpigmentation.

Turmeric with Herbal Extracts to Treat Acne

A mixture of turmeric with *Aloe barbadensis*, *A. indica*, *Hemidesmus indicus*, *Terminalia chebula*, *Terminalia arjuna*, and *Withania somnifera* was evaluated for its effectiveness in the treatment of acne vulgaris in a randomized, DB, PC trial [25]. No information regarding the amounts of the various constituents of topical and oral formulations was given in the quoted article. The polyherbal formulation was applied topically as a gel or a cream and administered orally as tablets (these latter contained *Piper longa* to improve the bioavailability of turmeric). This study lasted 4 weeks and involved 53 patients divided into four groups treated as follows: (i) topical active gel plus active tablets; (ii) topical active cream plus active tablets; (iii) topical placebo plus active

tablets; and (iv) topical placebo plus placebo tablets. All patients were asked to take two tablets twice daily and to apply the topical formulation twice daily on the affected area. The outcome was a clinical assessment based on a 4-point scale ranging from "excellent" to "poor" response.

The four treatments showed different performances according to the following order of efficacy: (ii) > (i) > (iii) > (iv). The superior beneficial effects of the two active combined therapies compared with the topical placebo plus active tablet therapy suggest that the topical treatment with herbal extracts gave a significant contribution to reduction of acne.

Turmeric with Herbal Extracts to Treat Pruritus

A commercially available cream ("itch cream") containing turmeric together with several additional active ingredients was evaluated for its effectiveness as symptomatic relief of pruritus in various dermatological disorders like atopic dermatitis, senile pruritus, and ichthyosis [26]. The composition of the cream was the following: 16.0% turmeric, 8.0% *Santalum album*, 3.0% *L. inermis*, 3.0% *Ocimum sanctum*, 0.5% *Glycyrrhiza glabra*, 0.5% *Vetiveria zizanioides*, 0.5% surasar, 0.1% *Abelmoschus moschatus*, 0.1% turmeric oil, 0.025% *Crocus sativus*, 0.00032% Swarna Bhasma. This randomized, OL, AC trial involved 64 subjects who were divided into two groups: those treated with the itch cream and those treated with a commercially available cream (Moisturex® Cream, Croslands) as active control containing the following constituents: 10% urea, 10% lactic acid, 10% propylene glycol, 10% light liquid paraffin. The patients were instructed to apply the cream (tested or control) topically twice daily as a thin film over the affected area without rubbing or massaging. No topical or systemic antihistaminic or corticosteroid drugs were allowed to use during the trial. The outcome was a clinical assessment of pruritus according to a 3-point score scale. The baseline scores were recorded after enrollment, and the volunteers were instructed to attend three weekly follow-up visits. The study was completed by 25 subjects in group A and 21 subjects in group B. The results showed that the cream containing polyherbal extracts was not superior to placebo in reducing pruritus.

Curcuma zedoaria *with Herbal Extracts to Treat Malignant Pleural Effusion*

Malignant pleural effusion (MPE) is a metastatic involvement of the pleura from primary malignancy at lung, breast, and other body sites [81]. Feize et al. [82] described the results of a randomized, DB, PC study aimed at investigating the effects of an ointment containing *Curcuma zedoaria* and other active ingredients on the thorax of patients suffering from MPE [27]. In addition to *C. zedoaria*, the ointment contained *Astragalus membranaceus*, *Semen pharbitidis*, *cassia* twig, *Pericarpium arecae*, borneol, and other substances. A total of 72 patients were enrolled and equally divided into two groups: one using the herbal ointment and the other one using an ointment devoid of active ingredients as the placebo. The patients applied the ointment on the thorax wall for 8 h daily. The treatment lasted 2 weeks. The outcomes consisted of measurement of the quantity of pleural effusion and clinical evaluations of MPE symptoms. The study was completed by 33 and 32 patients in the two groups, respectively.

Regarding the pleural effusion volume, no statistically significant differences were observed between the treatment group and the placebo group. However, the clinical evaluation of symptoms of MPE showed that the treatment with herbal extracts was superior to the treatment with the placebo. The authors did not provide pharmacological basis as a rationale to support their study.

Curcumin with Active Ingredients to Treat Skin Aging

Di Lorenzo et al. [28] evaluated a cream composed of 0.02% curcumin, 1.0% tocopheryl acetate, 1.0% *Acerola fruit extract*, and 0.5% selenomethionine calcium phosphate for its capability of reducing facial skin aging in 60 women aging between 45 and 60. The volunteers were divided into three groups each of 20 subjects: (i) a cream-treated group (cosmeceutical formulation); (ii) a group treated with the cream and a dietary supplement (nutricosmetic formulation) corresponding to a turmeric extract containing 70 mg of curcuminoids taken once daily; and (iii) a placebo group made up by subjects treated with a cream lacking active ingredients. The following skin parameters were assessed through instrumental measurements at the beginning of the treatment, after 2 weeks, and after completion of the trial (4 weeks): water loss, hydration, elasticity/firmness, dermal thickness, and wrinkles.

Both the cosmeceutical and nutricosmetic formulations were found effective in improving skin quality compared with the placebo. The nutricosmetic product performed generally better than the cosmeceutic one, except for the hydration test where they gave equivalent results.

Remarks about Studies Using Curcumin or Turmeric Combined with Other Active Ingredients

The ten clinical studies summarized in this section (#10–19 in Table 1) deal with curcumin or turmeric (from here on curcumin) combined with pharmacologically

active substances – especially herbal extracts – mixed in the same topical formulation to treat various skin conditions. For all of them, the use of curcumin was justified by its recognized reputation of anti-inflammatory, antioxidant, and antimicrobial agent.

The considered clinical trials differ in the quality of design (e.g., NC, OL comparative, DB comparative). An important caveat of these studies is that they do not allow to single out the potential beneficial effect of curcumin. In other words, any trial making use of a mixture of active ingredients, all employed at fixed concentrations, provides information on the clinical efficacy of that specific mixture without enabling any inference regarding the efficacy of each single ingredient. This implies that the combination of curcumin with active substances in these studies, regardless to their design, represents the unavoidable bottleneck of the information concerning the potential beneficial effects of curcumin. Therefore, it is impossible to reach sound conclusions about the utility of curcumin as a single ingredient by looking at the statistically significance of the results. However, the studies presented in this section, especially those in which curcumin was combined with no more than three active ingredients, may prompt researchers to undertake novel clinical trials using curcumin alone to gain a deeper insight on the real therapeutic value of this substance.

Tetrahydrocurcumin as an Alternative to Curcumin

Tetrahydrocurcumin (5) (Fig. 3) is one of the chemically related compounds of curcumin present in turmeric in small amounts and is also a metabolite of curcumin. It is derived by the reduction of the two olefinic bonds of curcumin. Tetrahydrocurcuminoids include tetrahydrocurcumin and its derivatives. These are colorless substances differing from each other in the substituents attached to the phenyl rings.

Tetrahydrocurcuminoids Combined with UVB Radiations to Treat Vitiligo

Tetrahydrocurcuminoids were evaluated in an OL, comparative study for their capability to induce repigmentation in 10 patients suffering from vitiligo in combination with narrowband UVB phototherapy [83]. These substances were the constituents of a commercially available curcuminoid cream (GPO Curmin, Government Pharmaceutical Organization, Bangkok, Thailand). Their content in the cream was not given. For each subject, two target lesions within the same anatomical area were chosen. One patch was randomly assigned to be treated with combination therapy (group A) and the other with a targeted narrowband UVB alone (group B). The UVB treatments were carried out twice weekly for 12 weeks. The degree of repigmentation, documented by monthly digital photography, was assessed by a blinded dermatologist using a 9-point score scale.

The repigmentation acquired at the end of the study improved in groups A and B with increased scores of 1.9 and 1.7 compared with the baseline score of 0, respectively. The authors affirmed that the combination treatment of tetrahydrocurcuminoids plus UVB therapy was more effective than UVB monotherapy in reducing vitiligo although, due to the relatively small sample size, the results did not reach statistically significant levels.

Tetrahydrocurcumin with Herbal Extracts to Treat Photoaging

A gel containing tetrahydrocurcumin and other active ingredients (Tricutan®, Adderma AB, Stockholm, Sweden) was tested in 28 women to evaluate its effectiveness in improving skin firmness and elasticity in photoaged facial skin [84]. This randomized, DB, PC trial lasted 4 weeks and was based on self-assessment, clinical examination, and a quantitative endpoint of cutaneous elasticity and firmness. This latter was carried out by using a Reviscometer measuring shear wave propagation in the skin [85]. The active components of the gel were 0.1% tetrahydrocurcumin, 0.3% *Rosmarinus officinalis* water extract, 0.3% dimethylaminoethanol, 0.1% *Centella asiatica* butylene glycol extract. The placebo was a gel identical in color, smell, and consistency to the Tricutan gel. Each woman applied both gel formulations (active or placebo) on the left or right part of her face according to a random coded list. The gel was applied twice daily for 4 weeks. Three women out of the 28 included did not complete the study. The reason for discontinuing was mild irritative contact dermatitis. Three further women did not fill out the self-assessment form.

The instrumental measurements showed a statistically significant improvement in skin firmness in the Tricutan-treated half-face with respect to the placebo-treated half-face. The clinical evaluations and the self-assessments also showed Tricutan to give more beneficial effects on skin quality compared with the placebo.

Remarks about Studies on Tetrahydrocurcumin

Tetrahydrocurcumin offers a considerable advantage over curcumin as consumers do not like products that dye their skin. However, the results of clinical trials performed using tetrahydrocurcumin should be considered bearing in mind that this substance, as outlined by Aggarwal et al. [86], does not exhibit the same

pharmacological profile of curcumin. The quoted review provides examples of biological activities in which curcumin was found more active than tetrahydrocurcumin together with others in which, on the opposite, tetrahydrocurcumin performed better than curcumin.

Conclusions

To date, the number of articles reporting on the evaluation of topical curcumin or turmeric (from here on curcumin) in humans is relatively low compared with the vast literature describing their pharmacological properties at the molecular level, in cells, tissues, and animal models as well as the effects of their oral administration [87]. In the present article, we have reviewed 19 clinical studies in which curcumin was tested alone or combined with additional active ingredients in the same topical formulation to treat various skin conditions. The studies based on the use of curcumin alone offer a clear advantage in terms of information concerning the real therapeutic efficacy of curcumin as an anti-inflammatory, antioxidant, and antimicrobial topical agent.

Curcumin is practically insoluble and highly unstable in aqueous solutions with neutral-to-alkaline pH values where hydrolysis, oxidation, and photodegradation reactions take place [40, 41]. Such unfavorable chemical properties hamper the topical use of curcumin, although higher solubility and stability can be achieved by dissolving it in alcoholic solutions, oil-in-water emulsions, and ointments. Therefore, technological approaches to optimize the topical delivery of curcumin have been devised [5, 6]. The works of Lademann' group occupy a prominent position in this field of research [88–90].

The intense yellow color of curcumin is undoubtedly an organoleptic undesirable factor for a daily topical usage [1]. This also represents a key issue in PC trials that should be properly managed by researchers and addressed in their articles (i.e., by detailing the color and the composition of the placebo). In this regard, tetrahydrocurcumin, a colorless derivative of curcumin, has been employed to surrogate curcumin in the treatment of some skin diseases, such as vitiligo, or to improve skin firmness although these substances display non-identical pharmacological properties. Further research is probably needed to compare the effectiveness of curcumin and tetrahydrocurcumin in dermatology.

To sum up, in most of the clinical studies discussed in this review curcumin has been regarded as an attractive alternative to conventional drugs, such as corticosteroids and antibiotics, thanks to its characteristics of a safe and well-tolerated natural substance. Literature offers some examples of how curcumin can be useful as a topical agent in skin diseases and health care, thus paving a way to new clinical studies aimed to explore its full therapeutic potential.

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

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