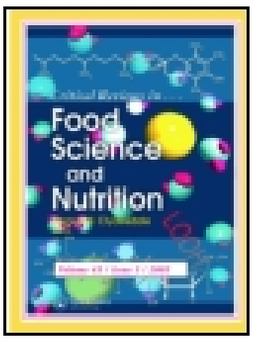

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REVIEW

Benefits of turmeric supplementation for skin health in chronic diseases: a systematic review

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ABSTRACT

The skin is a physical barrier that protects the body from the external environment. Through its immune system, it limits the attack of environmental threats. Unregulated immune reactions, however, can cause chronic inflammatory skin diseases, requiring that effective treatment routes be sought. Turmeric, a root originated from Southeast Asia, has a number of therapeutic benefits, including anti-inflammatory activity. The aim of this review was to evaluate the effects of turmeric oral supplementation in the treatment of chronic inflammatory skin diseases. Through PubMed, Scopus, and Web of Science databases, clinical studies examining the relationship between turmeric, curcumin, and skin health in humans until September 2019 were systematically searched. Evidence analysis were performed using robust tools to evaluate the risk of bias (RoB 2.0), (ROBINS-I) and methodological quality (GRADE) of the included studies. A total of eleven studies were included. The skin conditions examined include psoriasis, pruritus, oral lichen planus, facial redness, as well as types of skin cancers. Overall, therapeutic benefits for skin health have been observed through oral turmeric supplementation. The current published studies, nevertheless, are limited, requiring continuity and improvement in the intervention methodology employed.

KEYWORDS

Curcumin; curcuminoids; skin diseases; oral supplementation; humans; systematic review

Introduction

The skin is the largest organ in the human body. It plays an essential role protecting the body from the continued aggression caused by the hostile exogenous environment. Through its proper immune system, which consists of various resident and recruited cell types, it provides protective immunity. However, unregulated immune reactions can cause chronic inflammatory skin diseases (Nestle et al. 2009). Psoriasis, dermatitis, vitiligo are very common diseases with chronic evolution. They are conditioned by multifactorial aspects, such as genetic predisposition and environmental influences, which result in impaired epithelial function and altered immunity (Kowalska-Olędzka, Czarnecka, and Baran 2019; Reinholz, Ruzicka, and Schauber 2012). The Stress resulted from the chronicity and exacerbation of the physical symptoms of these diseases (skin lesions, blemishes, xerosis) can lead to reduced quality of life of the affected individuals, and, consequently, reflect on their social and emotional behavior (Magin et al. 2008; Evers et al. 2005).

The drugs available for treatment of chronic skin diseases, in addition to being limited and of varying effectiveness, can lead to adverse effects (Hengge et al. 2006). Chronic diseases are accompanied by long periods of treatment, increasing the risk of infections and malignancies. In addition, they increase the cost of therapy for the patient (Bilia et al. 2018). From this context, the need to seek new approaches with effective and safe natural therapeutic sources in order to provide a better quality of life for affected individuals is evident (Carrion-Gutierrez et al. 2015; Kocaadam and Şanlier 2017; Kurd et al. 2008). One spice that, due to its variable applicability, has shown increasing interest among studies in the functional clinical area is turmeric (Rathaur et al. 2012).

Turmeric, derived from *Curcuma longa* L. rhizomes, also known as sun root and yellow ginger, is a root that belongs to the ginger family, *Zingiberaceae*, and comes originally from India and other regions of Southeast Asia. Turmeric performs functions of great relevance to the human health, especially through its anti-inflammatory action, which is the main focus of this study, as they inhibit the production of inflammatory mediators through the negative regulation of cytokines and other proinflammatory agents (Ghandadi and Sahebkar 2017; Nedoszytko et al. 2014; Lantz et al. 2005; Ghiamati Yazdi et al. 2019). In addition, they demonstrate an important advantage over their safety and tolerability (Lao et al. 2006; Araújo and Leon 2001). Turmeric and

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curcumin safety assessments in clinical studies have suggested high tolerance and no toxic effects even at high doses (Chattopadhyay et al. 2004; Kunnumakkara et al. 2017). Turmeric consists of three curcuminoids (natural polyphenolics): curcumin (70–80%), demethoxycurcumin (18–20%) and bisdemetoxycurcumin (2–10%) (Aggarwal et al. 2013; Panahi et al. 2019). The best characterized of the compounds found in turmeric is curcumin, which is responsible for its biological actions (Jurenka 2009; Mantzorou et al. 2018). Nevertheless, other curcuminoids and bioactive components of turmeric have also been shown to have anti-inflammatory properties (Aggarwal et al. 2013).

To date, there are many review studies evaluating the efficacy and safety of tumeric. The main focus of the researches is especially on turmeric and its use in the treatment of various diseases, taking into account its various properties as antioxidant, anti-inflammatory, antimicrobial and, above all, antineoplastic agent. Neverteless, the objective of this systematic review was to evaluate clinical studies that analyzed the beneficial effects of turmeric and its curcuminoids on chronic inflammatory skin diseases by oral supplementation. Clinical evidence was sought through tools that robustly assessed the risks of bias in the studies and their methodological quality. Finally, the analyzes of the present study intend to contribute to the development of greater fundamentals in the decision making of functional therapeutic interventions for health professionals.

Methods

Protocol and registration

The systematic review protocol was reported in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA-P) protocol (Liberati et al. 2009). The protocol was registered at the international prospective register of systematic reviews (PROSPERO) database under the registration number CRD42019131424.

Search strategy and eligibility criteria

To identify potentially relevant studies to the present review, a systematic literature search of databases (PubMed, Scopus, and Web Of Science) was conducted through September 2019, following terms MeSH (1) *Curcumas; Tumeric(s); Turmeric(s); Curcuma zedoaria(s); "Zedoaria, Curcuma"; "Zedoary Zedoaria"; Zedoary; Zedoaria, Zedoary; "Curcuma longa(s)"; "Long Curcuma*", researched in combination with (2) "*Disease(s), Skin"; Skin Disease; Dermatoses; Dermatosis,* entertaining and synonyms. All terms were searched for in title, abstract and keyword. No restrictions were applied regarding language or publication date.

Our research only included articles with human clinical trials. Inclusion criteria were: (1) the terms turmeric, curcumin, curcuminoid, *Curcuma longa* were reported in the title or abstract or keyword; (2) the articles evaluated the effect of turmeric, curcumin or curcuminoid on skin of diseases or on blood biomarked in ill subjects; (3) the articles were published as full papers; (4) only considered supplementations orally. The exclusion criteria were as follows: (1) studies evaluating effects of topical use of turmeric or curcumin; (2) animal model; (3) Meta-analyzes, editorials, narrative reviews.

Study selection

The articles were screening in two phases. First, articles duplicates and triplicates articles were removed. In the first phase, two reviewers (I.R.M and L.S.F) independently analyzed titles and abstracts in the electronic database and selected articles to identify potentially eligible articles. In the second phase, three reviewers (I.R.M, L.S.F and R.C.R.M.) independently analyzed and performed the full reading of the articles selected in the first phase, excluding all the articles that did not meet the eligibility criteria. At all stages, a third reviewer (K.K.B.) was consulted in the case of any concerns or disagreements between the other investigators, being, all disputes, resolved by consensus.

Data extraction

Data extraction was completed independently by four authors. It was reconciled and recorded on a purpose-designed Microsoft Excel® spreadsheet and constant meetings were held to maintain the standard of analysis. The data from the articles were extracted: article title, study design, reference, sample size, mean or median age of participants, gender, year of publication, skin disease, intervention, placebo control or active drug, follow-up time, outcome and limitation of the included studies, conclusions of studies.

Risk of bias assessment

The Cochrane's bias risk assessment tool recommended were (RoB 2.0) and (ROBINS-I). The RoB 2.0 tool was used to assess risk of bias in randomized controlled trials (RCT) by examining the following domains: risk of bias arising from the randomization process; risk of bias due to deviations from the intended interventions (effect of assignment to intervention); missing outcome data; risk of bias in measurement of the outcome; risk of bias in selection of the reported result; and other bias risks (Sterne et al. 2019). For non-randomized trials (NCT) was used the risk of bias ROBINS-I tool, examining the following domains: confounding; selection of participants into the study; classification of interventions; deviations from intended interventions; missing data; measurement of outcomes; selection of reported result; and overall assessment of studies (Sterne et al. 2016). Due to the small number of heterogeneous studies and distinct results in this systematic review, meta-analysis or confidence assessment on the studies were not performed.

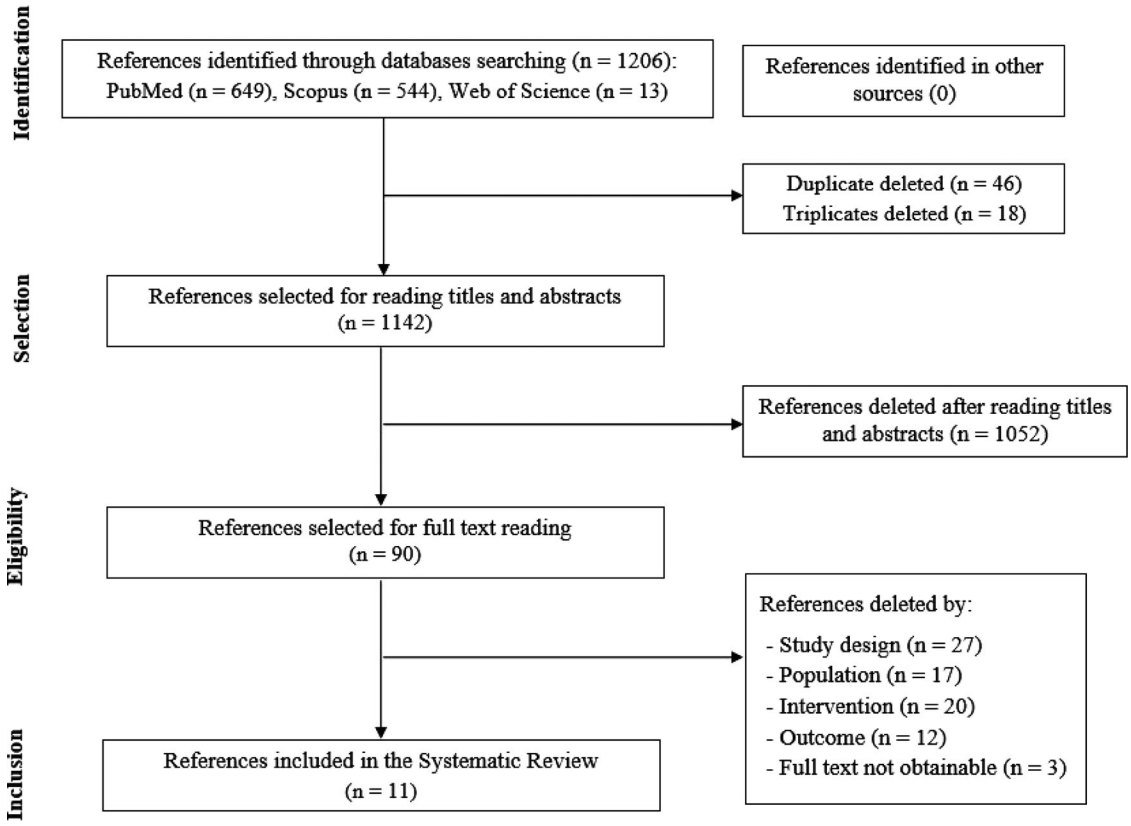

Figure 1. Flow diagram of systematic review.

Assessment of the quality of evidence

The Grading of Recommendations Assessment, Development and Evaluations (GRADE) tool was used to assess patient-important outcomes across studies to judge the quality as high, moderate, low, or very low (Guyatt et al. 2008). Three investigators (I.R.M, L.S.F and R.C.R.M.) scored each item and independently assessed the risk of bias in each included study. Disagreements between the three reviewers were resolved by a fourth investigator (K.K.B.).

Results

Study selection

There were identified 1206 potentially relevant studies from the results of the electronic searches (649 from PubMed, 544 from Scopus and 13 from Web of Science). After removing duplicates and triplicates, there were 1142 records for title and abstract screening. Of these, 90 full studies were read in their entirety. After excluding 79 articles that did not meet the inclusion criteria, 11 studies were included (Bilia et al. 2018; Carrion-Gutierrez et al. 2015; Chainani-Wu et al. 2007; Chainani-Wu et al. 2012; Cheng et al. 2001; Esposito et al. 2017; Kurd et al. 2008; Pakfetrat et al. 2014; Panahi, Sahebkar, Amiri, et al. 2012; Panahi, Sahebkar, Parvin, et al. 2012; Vaughn et al. 2019). A flow chart detailing the process of identification, screening, eligibility and inclusion of studies is presented in Figure 1.

Study characteristics

The main characteristics of the studies included in this systematic review are described in Table 1. Among the selected articles, eight are randomized controlled trials (Bilia et al. 2018; Carrion-Gutierrez et al. 2015; Chainani-Wu et al. 2007; Chainani-Wu et al. 2012; Pakfetrat et al. 2014; Panahi, Sahebkar, Amiri, et al. 2012; Panahi, Sahebkar, Parvin, et al. 2012; Vaughn et al. 2019) and three are non-randomized clinical trials (Kurd et al. 2008; Cheng et al. 2001; Esposito et al. 2017). The samples from the eleven selected studies totalized 378 individuals: 215 in the intervention group and 163 in the control group. The sample size ranged from 11 (Esposito et al. 2017) to 100 (Pakfetrat et al. 2014) patients affected by chronic inflammatory skin diseases, aged 18 (Esposito et al. 2017) to 77 years (Cheng et al. 2001), and with the prevalence of men ranging from 53.8% (Chainani-Wu et al. 2012) to 100% (Panahi, Sahebkar, Amiri, et al. 2012; Panahi, Sahebkar, Parvin, et al. 2012) of participants in the studies. The diseases evaluated were: pruritus (Pakfetrat et al. 2014; Panahi, Sahebkar, Amiri, et al. 2012; Panahi, Sahebkar, Parvin, et al. 2012); psoriasis (Bilia et al. 2018; Carrion-Gutierrez et al. 2015; Kurd et al. 2008); oral lichen planus, OLP (Chainani-Wu et al. 2007; Chainani-Wu et al. 2012); facial redness (Vaughn et al. 2019); Bowen's disease of the skin (Cheng et al. 2001); and neurofibromatosis 1, NF1 (Esposito et al. 2017). The mode of intervention was supplementation with turmeric and/or curcumin, isolated (Kurd et al. 2008; Chainani-Wu et al. 2012; Cheng et al. 2001; Esposito et al. 2017; Pakfetrat et al. 2014) or, concomitantly, with other substances, such as acitretin (Bilia et al.

Table 1. Human clinical trials of turmeric and curcumin for treatment of chronic skin diseases.

Author, reference, year, country	Study design	Disease assessed	Intervention	Dosage	Intervention duration	Sample	Control or placebo	Outcome
Bilia et al. (2018), Italy.	Randomized, double-blind, placebo-controlled, phase III clinical trial.	Psoriasis	Curcumin + Acitretin	3g/day oral curcumin + 0.4mg/kg per day Acitretin	12-weeks	30 patients, 16 males and 14 females (age 24–63 years).	Placebo (capsules with identical size, form and color) + Acitretin 0.4 mg/kg per day.	At 12-week, both groups achieved a significant reduction in PASI values (arm 1 = 3.4; arm 2/control group = 6.8) but much higher in arm 1 ($P < 0.0001$). Serum lipid profile: at 12-week, no changes could be observed in arm 1, but total cholesterol significantly increased in arm 2 (at T0 vs T12: $P = 0.0318$). Triglycerides levels and HDL cholesterol serum levels, after 12-week treatment, were almost unchanged in both arms. Also, oral curcumin nanoparticles has showed a good safety profile.
Carrion-Gutierrez et al. (2015), Spain.	Randomized, double-blind, phase IV, pilot clinical trial.	Plaque psoriasis	Curcuma longa plus Curcumin and UVA phototherapy + Visible Light Real Therapy (VLRT)	600 mg/day Curcuma longa plus 72 mg/day Curcumin (the total daily intake was 6 tablets)	8-weeks	21 patients, 13 males and 8 females (age 29–53 years).	Visible Light Simulated Therapy (VLST)	Regarding the PGA score, the end of the study, 81% of the patients in the VLRT group and 30% of the patients in the VLST group showed an evolution of their lesions in the selected area to at least "slight".
Chainani-Wu et al. (2007), EUA.	Randomized, double-blind, placebo-controlled, phase II clinical trial.	Oral lichen planus (OLP)	Curcumin C3 complex (70-80% of curcumin, 15-25% of demethoxycurcumin, and 2.5–6.5% of bisdemethoxycurcumin depending upon the batch) + Prednisone	60 mg/day of prednisone (for 7 days) + 2000 mg/day of curcuminoids (in 2 divided doses, for 7 weeks).	7-weeks	33 patients, 10 males and 23 females (age 51–70 years).	60 mg/day of prednisone (for 7 days) + Placebo tablets (Sunset Yellow FCF food color, rice powder, magnesium stearate) for 7 weeks.	The study didn't find a significant effect of using curcuminoids as an adjunct to short-course systemic corticosteroids on the symptoms and signs of OLP as compared with placebo at the time of the first interim analysis. However, in the third follow-up, the curcuminoid group showed a greater mean percentage reduction in all measures of symptoms and signs, although none of them reached statistical significance. Regarding adverse effects, curcuminoids were well tolerated and the frequencies of most side effects were similar between groups.
Chainani-Wu et al. (2012), EUA.	Randomized, double-blind, placebo-controlled, phase II clinical trial.	Oral lichen planus (OLP)	Curcumin C3 complex (70–80% of curcumin, 15–25% of demethoxycurcumin, and 2.5–6.5% of bisdemethoxycurcumin depending upon the batch).	6000 mg/day (in 3 divided doses)	12-days	20 patients, 7 males and 13 females (age 44–69 years).	Placebo tablets (microcrystalline cellulose, dicalcium phosphate, PVP-k30, sodium starch glycolate, magnesium stearate, OpaDry orange coating).	The curcuminoids group showed a greater reduction in clinical signs and symptoms as compared with the placebo group, measured by percentage change in erythema ($P = 0.05$) and total MOMI score ($P = 0.03$), and proportion showing improvement in NRS (0.8 vs 0.3, $P = 0.02$) and total MOMI score (0.9 vs 0.5, $P = 0.05$). Adverse effects were uncommon in both groups.

Table 1. Continued

Cheng et al. (2001), Taiwan.	Non-randomized, phase I clinical Trial	Bowen's disease of the skin	Curcumin	500, 1000, 2000, 4000, 8000 and 1200mg/day	12-weeks	25 patients, 13 men and 12 women (age 36–77 years).	NI*	Was observed histologic improvement in 7 out of 25 patients with various high-risk and premalignant lesions. A dose-dependent effect was not observed since histological improvement was seen at almost all dose levels. Also, this study demonstrated that curcumin is not toxic to humans up to 8,000mg/day when taken by mouth for 12 weeks.
Esposito et al. (2017), Italy.	Comparative study.	Neurofibromatosis 1 (NF1)	Mediterranean diet enriched with 1200 mg/day curcumin (MedDietCurcumin)	1200 mg/day	24-weeks	11 patients, 8 men and 3 women (age 18–59 years).	Mediterranean diet (MedDiet) and Western diet (WesDiet), without curcumin	Was observed a marked reduction in the number (ranging from 30 to 51%) and volume of neurofibromas after 24 weeks of MedDietCurcumin. Patients who followed the MedDietCurcumin exhibited a plasmatic increase in curcumin concentration, indicating an improvement of curcuminoid bioavailability. No patient reported any side effects of curcumin consumption.
Kurd et al. (2008), EUA.	Non-randomized, phase II, single-arm, single-dose, noncontrolled, open-label, modified Simon's two-stage clinical trial.	Psoriasis vulgaris	Curcuminoid C3 complex (capsules contained 95% curcuminoids)	4.5g/day (3 pills of 500 mg, 3 times daily)	12-weeks	12 patients, 9 males and 3 females (age 38–51 years).	–	The efficacy of the study drug was low with an intention-to-treat response rate of 16.7% (95% CI: 2%, 48%) and did not justify continuation of the study based on a priori termination rules. However, those who did respond achieved excellent responses of 83% and 88% improvement in PASI scores at week 12.
Pakfetrat et al. (2014), Iran.	Randomized, double-blind and placebo-controlled clinical trial.	Uremic pruritus	Turmeric and curcumina	500 mg oral turmeric, of which 22.1mg was the active ingredient curcumin, 3 caps/day	8-weeks	100 patientes, 60 males and 40 females (age 37–69 years).	Placebo (starch capsules).	The mean decrease in hs-CRP was significantly higher in the turmeric than the placebo group (- 0.8 ± 2.6 vs. 0.4 ± 8.7 mg/l, $p = 0.012$). Also reduction of pruritus scores was greater in the turmeric than the placebo group (13.6 ± 2.6 vs. 7.2 ± 2.6, $p = 0.001$).
Panahi, Sahebkar, Amiri, et al. (2012), Iran.	Randomized, double-blind and placebo-controlled clinical trial.	Chronic SM-induced pruritic skin lesions	Curcumin, administered in the form of C3 Complexw capsules (containing 500 mg curcuminoids plus 5 mg bioperine).	1g/day curcumin + 0.1g/day bioperine	4-weeks	96 male patients (age 37–59 years)	Placebo capsules used in the study were shape- and size-matched, and contained piperine (5mg).	The results of trial P, alleviates pruritic imply that curcumin effectively increases the activity of antioxidant enzymes, reduces serum substance symptoms and increases the QoL in SM-exposed patients who suffer from chronic pruritic skin lesions.

(*continued*)

Table 1. Continued

Panahi, Sahebkar, Amiri, et al. (2012), Iran.	Randomized, double-blind and placebo-controlled clinical trial.	Chronic SM-induced pruritic skin lesions	Curcumin, administered in the form of C3 Complexw capsules (containing 500mg curcuminoids plus 5mg bioperine).	1 g/day curcumin + 0.1 g/day bioperine	4-weeks	96 male patients (age 37–59 years).	Placebo capsules, contained piperine (5 mg).	Serum IL-8 and hs-CRP were significantly reduced in the curcumin group (P <0.001). Serum CGRP was reduced only in the curcumin group (P <0.001). No significant change in serum IL-6 was observed. Curcumin supplementation was associated with a marked decline in pruritus score. Effect of curcumin supplementation on QoL: the rate of reduction was greater in the curcumin vs placebo group.
Vaughn et al. (2019), EUA.	Randomized pilot study, double-blind, prospective	Facial redness	Turmeric polyherbal combination tablets (blend of organic herbs) or Turmeric tablets.	4000 mg/day (4 tablets of 500 mg, 2 times daily)	4-weeks	30 patients, 3 males and 27 females (age 25–59 years).	Placebo tablets.	The polyherbal combination tablet group showed a significant reduction in image analysis-based facial redness of 40% compared to baseline (P = 0.03). Furthermore, the clinical classification of the intensity and distribution of facial redness tended to decrease only in the polyherbal combination group (P = 0.1). The placebo and turmeric tablet groups showed no statistically significant change in facial redness after 4 weeks. There were no adverse events reported.

*__NI__: no information; __VLRT__: Visible Light Real Therapy; __VLST__: Visible Light Simulated Therapy; __PGA__: Physician Global Assessment (scoring system used to assess disease severity); __VAS__: Visual Analog Scale; __CSS__: change in symptoms scale; __PASI__: Psoriasis Area Severity Index values (range 0: no disease, to 72: maximal disease); __NRS__: Numerical Rating Scale (unidimensional measure of pain intensity in adults, 0 = no symptoms and 10 = maximal symptoms); __MOMI__: Modified Oral Mucositis Index (measuring the signs of oral lichen planus); __MedDiet__: Mediterranean diet; __WesDiet__: western diet; __MedDietCurcumin__: Mediterranean diet enriched with curcumin; __hs-CRP__: high-sensitivity C-reactive protein (higher levels in patients with uremic pruritus); __SM__: sulfur mustard; __CGRP__ (Calcitonin gene-related peptide) and __substance P__ (neuropeptides with potential to generate)

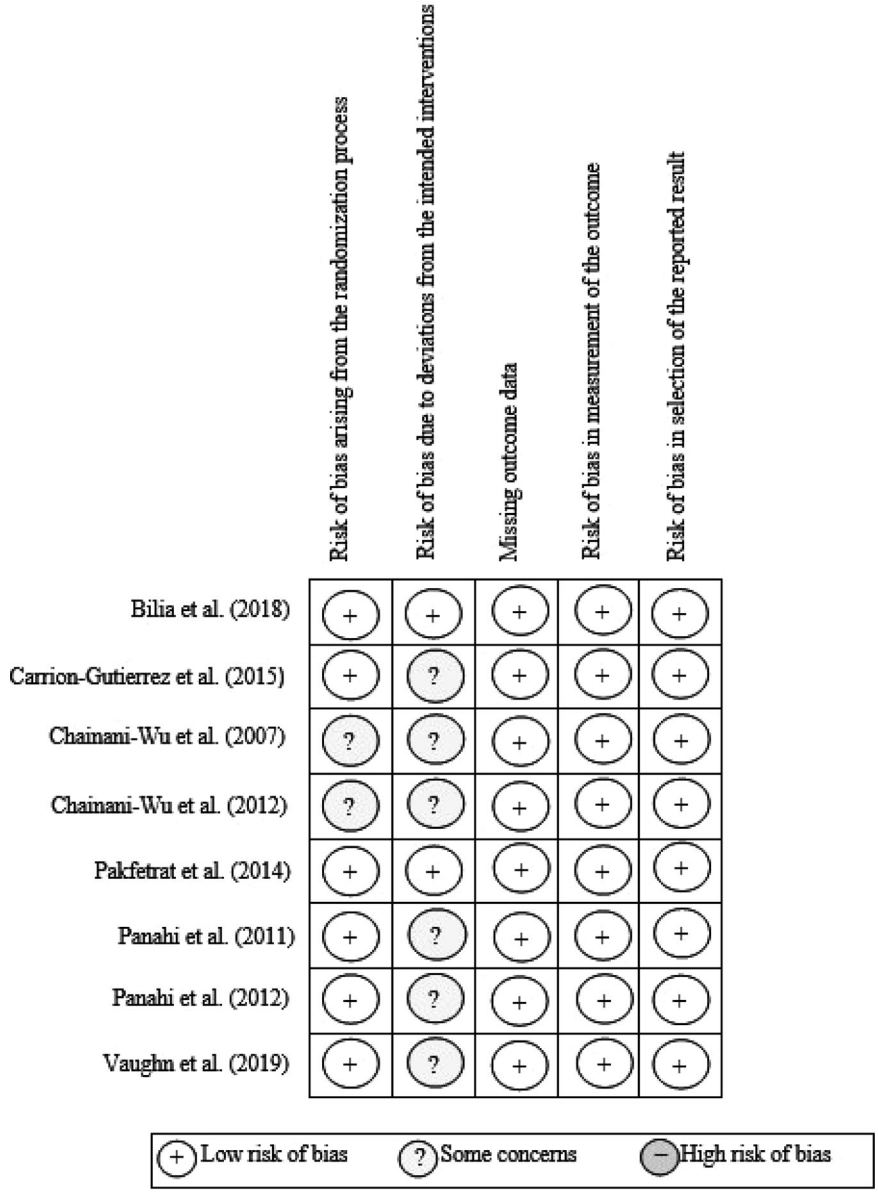

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

2018), bioperinew (Carrion-Gutierrez et al. 2015; Panahi, Sahebkar, Amiri, et al. 2012; Panahi, Sahebkar, Parvin, et al. 2012), prednisone (Chainani-Wu et al. 2007), and turmeric polyherbal combination (Vaughn et al. 2019). The eleven included studies were published between 2001 and 2019, all in english. The studies were conducted in the following countries: Iran (Pakfetrat et al. 2014; Panahi, Sahebkar, Amiri, et al. 2012; Panahi, Sahebkar, Parvin, et al. 2012), Italy (Bilia et al. 2018; Esposito et al. 2017), EUA (Chainani-Wu et al. 2007; Chainani-Wu et al. 2012; Kurd et al. 2008; Vaughn et al. 2019), Spain (Carrion-Gutierrez et al. 2015) and Taiwan (Cheng et al. 2001).

Assessment of risk of bias across studies

Randomized clinical trials showed low risk or some bias concerns for most items, as shown in Figure 2. Two studies presented low risk of bias (Bilia et al. 2018; Pakfetrat et al. 2014), while the others presented some concerns for risk of bias in one or more of the domains. Carrion-Gutierrez et al. (2015) demonstrated in their study potential bias for deviations from the intended interventions, due to the limited statistical significance caused by the small number of individuals in the sample. The studies by Chainani-Wu et al. (2007) and Chainani-Wu et al. (2012), showed baseline differences between their intervention groups, suggesting a problem with the randomization process, related to the occurrence of heterogeneous samples (in the author's first publication, the placebo group ($n = 17$), 35% of the sample was composed by male individuals, while in the curcuminoid group ($n = 16$), 25% were male; in the second study by the author, in the placebo group ($n = 10$), 50% were male, while in the curcuminoids group ($n = 10$), 20% were male) and both studies also presented a risk of bias for deviations in the intended interventions, which was caused by the limited statistical significance (due to the small number of individuals in the sample). Both RCTs published by Panahi, Sahebkar, Amiri, et al. (2012) and Panahi, Sahebkar, Parvin,

Table 2. Range of overall assessments by study and tool bias domains ROBINS-I.

	Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Domain 6	Domain 7	ROBINS-I overall
Cheng et al. (2001).	1–2	1	1	1	1	2–3	2–3	2–3[1] (Moderate–Serious)
Esposito et al. (2017).	1–2	1	1	1	1	1	1	1 (Low risk)
Kurd et al. (2008).	2–3	1	1	1	1	1	1	1–2[2] (Low–Moderate)

Domain 1: confounding; Domain 2: selection; Domain 3: classification of intervention; Domain 4: deviation from interventions; Domain 5: missing data; Domain 6: measurement of outcomes; Domain 7: selection of reported result.
Risk of bias assessment: 0 No information; 1 Low; 2 Moderate; 3 Serious; 4 Critical
[1] Cheng et al. (2001) presented potential for confounding bias on the effect of the intervention, caused by the small study sample; presented bias in the measurement and selection of reported results (methodology and results unclear or without information).
[2] Kurd et al. (2008) presented potential for confounding bias on the effect of the intervention, caused by the small sample of the study, and also by the interruption of the intervention, related to prognostic factors for the outcome (as the efficacy of the drug throughout the study was low, not justified its continuation).

et al. (2012) showed potential risk of bias for deviations from the intended interventions, caused by the abstention of 17% of the intended sample. Vaughn et al. (2019) presented in their study a risk of bias for deviations from the intended interventions due to the limited statistical significance caused by the short duration of the study and the small number of individuals in the sample.

The assessment of non-randomized trials can be observed in Table 2. Cheng et al. (2001) obtained a general classification of moderate-serious risk, as it has the potential for confounding bias about the effect of the intervention (caused by the small sample of the study), and bias in the measurement and selection of reported results (methodology and results unclear or without information). Kurd et al. (2008) obtained a general classification of low–moderate risk, also presenting potential for confounding bias about the effect of the intervention caused by the small sample, and for presenting interruption of the intervention, related to prognostic factors for the outcome (in the study, as the efficacy of the drug was low, did not justify its continuation). The study by Esposito et al. (2017) achieved overall rating on low risk tool, as it does not have potential for bias in the judged domains.

Assessment of the quality of evidences across studies

The quality evaluation of the eleven included studies was divided in summary of results and outcome quality assessment presented according to Table 3 and 4, respectively. The studies exhibited low or moderate level of evidence. The studies by Carrion-Gutierrez et al. (2015), Chainani-Wu et al. (2012), Cheng et al. (2001), Esposito et al. (2017), Kurd et al. (2008), Pakfetrat et al. (2014), Panahi, Sahebkar, Amiri, et al. (2012), Panahi, Sahebkar, Parvin, et al. (2012) and Vaughn et al. (2019) presented some type of methodological limitation (risk of bias, as shown in Table 3), compromising their level of evidence. Chainani-Wu et al. (2007) and Chainani-Wu et al. (2012) still presents some inconsistency due to heterogeneity in your sample.

Evidence of the effects of turmeric and curcuminoids in the treatment of chronic skin diseases

Psoriasis

Psoriasis is a chronic inflammatory skin disease that can have a major impact on quality of life, even in patients whose affected body surface area is relatively limited (Gelfand et al. 2005). Carrion-Gutierrez et al. (2015) conducted a study in Spain to investigate the efficacy and safety of oral curcumin along with local phototherapy in patients with plaque psoriasis. With a sample of 21 patients (8 women and 13 men, aged 29–53 years), the study lasted 8 weeks. During the duration of the study, the patients had a daily intake of 6 tablets containing, overall, 600 mg/day *Curcuma longa* plus 72 mg/day curcumin, concomitantly with ultraviolet A (UVA) phototherapy and visible light. At the end of the study, over 95% of patients exhibited a greater than 75% reduction in Psoriasis Area Severity Index Values (PASI), and over 80% of patients achieved a reduction in PASI values of over 90%. Thus, the results of this study suggested that moderate-to-severe plaque psoriasis demonstrated a therapeutic response to turmeric administered orally when activated with visible light phototherapy. However, the study was not managed by a control group (with curcumin and turmeric only). The research was also not carried out in the long-term, so further investigation is needed. The study conducted by Bilia et al. (2018) investigated the activity of orally administered curcumin nanoparticles in patients with moderate-to-severe psoriasis already treated with acitretin. Fifteen patients (7 men, 8 women, age range 24–63 years) were randomized to receive acitretin 0.4 mg/kg per day plus oral curcumin 3 g/day (arm 1) and fifteen patients (9 men, 6 women, 29–59) were randomized to receive acitretin 0.4 mg/kg per day plus placebo (capsules of identical size, shape and color) (arm 2). The treatment period was 12 weeks. Serum samples were collected during this period to investigate possible changes in the patient's lipid profile (not only common in psoriasis, but can also be worsen by treatment with acitretin). At 12 weeks, both groups achieved a significant reduction in PASI values (arm 1 = T0: 16.4 vs T12: 3.4; arm 2/control group = T0: 14.8 vs T12: 6.8), but of greater significance in arm 1 ($P < 0.0001$). Also in this study, serum lipid profile, after 12 weeks of intervention, no changes were observed in arm 1, but total cholesterol increased significantly in arm 2 (at T0 vs T12: $P = 0.0318$). Therefore, oral curcumin nanoparticles showed a good safety profile. In a third study (Kurd et al. 2008), the safety and efficacy of oral curcumin in psoriasis patients was evaluated. This was a 12-week NCT in which only 12 patients were treated with 4.5 g/day curcumin (3 tablets 500 mg 3 times daily). Only eight participants completed the study. The efficacy of the study drug was low, with an intention-to-treat response rate of 16.7% (95% CI: 2%, 48%) and did not justify further study based on a priori termination

Table 3. Summary of results for evidence presentation.

Author, reference, year	Outcomes	Sample	Quality of Evidence (GRADE)	Relative Effect (95% CI)
Bilia et al. (2018).	Psoriasis treatment and control serum cholesterol levels.	30	⨁⨁⨁◯	NI
Carrion-Gutierrez et al. (2015).	Psoriasis treatment.	21	⨁⨁⨁◯[1]	NI
Chainani-Wu et al. (2007).	Effect in symptoms and signs of OLP.	33	⨁⨁◯◯[2]	Mean of percentage changes in symptoms and signs observed at third follow-up visit in the curcuminoid and placebo group, for VAS had a difference between placebo and curcuminoids groups of 41.1 (95% CI: −74.1, 156.4), p= 0.42; NRS had a difference of 3.55 (95% CI: −30.1, 37.2), p= 0.83; MOMI (clinical signs total score) had a difference of 19.45 (95% CI: −22.2, 61.1), p= 0.34; MOMI (erythema only) had a difference of 13.8 (95% CI: −25.5, 53.2), p= 0.47; MOMI (ulceration only) had a difference of 25.1 (95% CI: −21.9, 72.2), p= 0.27.
Chainani-Wu et al. (2012).	Reduction in symptoms and signs of OLP.	20	⨁⨁◯◯[3]	In the placebo group, the percentage changes from baseline in NRS (median [IC] = 0.00 [−29 to 16.7], P [.99), erythema (0.00 [−10 to 16.7], P = .98), ulceration (0.00 [0.00 to 26.7], P = .63), and total MOMI scores (− 3.2 [−13 to 9.09], P = .95) were not statistically significant, whereas they were statistically significant in the curcuminoids group: NRS (−22 [−33 to −14], P = .0078); erythema (−17 [−29 to −8.3], P = .0078), ulceration (−14 [−60 to 0.00], P = .063), MOMI (−24 [−38 to −11], P = .0039).
Cheng et al. (2001).	Chemopreventive effect against human cancers (Bowen's disease of the skin).	25	⨁⨁◯◯[4]	NI
Esposito et al. (2017).	Chemopreventive effect against human cancers (NF1).	11	⨁⨁⨁◯[5]	NI
Kurd et al. (2008).	Psoriasis vulgaris treatment.	12	⨁⨁⨁◯[6]	Efficacy of the study drug was an intention-to-treat response rate of 16.7% (95% CI: 2%, 48%).
Pakfetrat et al. (2014).	Uremic pruritus treatment.	100	⨁⨁⨁◯	NI
Panahi, Sahebkar, Amiri, et al. (2012).	Serum inflammatory biomarkers, pruritus severity and QoL.	96	⨁⨁⨁◯[7]	Changes in serum IL-8 concentrations were found as the significant predictor of DLQI scores (B = 0.437; odds ratio [95% CI] = 0.351 [0.054–0.819]; p = 0.026)
Panahi, Sahebkar, Parvin, et al. (2012).	Pruritus treatment and QoL.	96	⨁⨁⨁◯[8]	In the curcumin group, the only significant correlation was between changes in pruritus score and serum SOD activity (r − 0.32, P = 0.041). In the placebo group, a significant correlation was only observed between changes in pruritus score and VAS score (r 0.40, P = 0.010). In addition, a borderline significant correlation was found in the placebo group between changes in serum SOD and GPx activities (r 0.31, P = 0.051). In the curcumin group, change in serum SOD activity was found as a significant predictor of pruritus score variations (b = −0.32, 95 % CI −2.78, 0.06, P = 0.04).
Vaughn et al. (2019).	Reduction in intensity and distribution in facial redness	30	⨁⨁◯◯[9]	NI

VAS: Visual Analogue Scale; **NRS**: Numerical Rating Scale; **MOMI**: Modified Oral Mucositis Index; **DLQI**: Dermatology Life Quality Index; **SOD** (Superoxide dismutase) and **GPx** (glutathione peroxidase): enzymes of antioxidant action.

[1]Study presents risk of bias to deviations from the intended interventions (limited statistical significance because of the small number of individuals in the sample).

[2]Study presents baseline differences between intervention groups suggest a problem with the randomization process (placebo (n = 17), 35% was male; while Curcuminoids group (n = 16), 25% was male) and presents risk of bias to deviations from the intended interventions (limited statistical significance because of the small number of individuals in the sample).

[3]Study presents baseline differences between intervention groups suggest a problem with the randomization process (placebo (n = 10), 50% was male; while Curcuminoids group (n = 10), 20% was male) and presents risk of bias to deviations from the intended interventions (limited statistical significance because of the small number of individuals in the sample).

[4]Study presents risk bias to domain confounding and bias in selection of the reported result (methodology and results not very clear or without information).

[5]Study with potential for confounding of the effect of intervention (limited statistical significance because of the small number of individuals in the sample and baseline differences between intervention groups).

[6] Study presents potential for confounding of the effect of intervention (single-arm, noncontrolled clinical trial)

[7,8]The study has a potential risk of bias for deviations from intended interventions (17% abstention from the sample).

[9]Study presents risk of bias to deviations from the intended interventions (limited statistical significance because of the short study duration and small number of individuals in the sample).

Table 4. Results and quality assessment.

Quality Assessment						Findings Summary				
						No. patients		Effect		
Study	Study design	Methodological limitations	Inconsistency	Indirect Evidence	Inaccuracy	Curcuma/Curcumin	Placebo	Relative (95% CI)	Quality (GRADE)	Importance
Reduction in symptoms and signs of Psoriasis (follow up 8 to 12 weeks)										
Bilia et al. (2018); Carrion-Gutierrez et al. (2015); Kurd et al. (2008)	RCTs (Bilia et al. 2018; Carrion-Gutierrez et al. 2015) NCT (Kurd et al. 2008)	With considerable limitations[1]	No serious inconsistency	No important indirect evidence	No serious inaccuracy	37	26	–	⨁⨁◯◯ Low	Critical
Reduction in symptoms of Pruritus (follow up 4 to 8 weeks)										
Pakfetrat et al. (2014); Panahi, Sahebkar, Amiri, et al. (2012); Panahi, Sahebkar, Parvin, et al. (2012)	RCTs	With considerable limitations[2]	No serious inconsistency	No important indirect evidence	No serious inaccuracy	96	100	–	⨁⨁⨁◯ Moderate	Critical
Reduction in symptoms and signs of Oral Lichen Planus (OLP) (follow up 7 to 12 weeks)										
Chainani-Wu et al. (2007) Chainani-Wu et al. (2012)	RCTs	With considerable limitations[3]	With some inconsistency[3]	No important indirect evidence	No serious inaccuracy	26	27	–	⨁⨁◯◯ Low	Critical
Reduction in intensity and distribution in facial redness (follow up 4 weeks)										
Vaughn et al. (2019)	RCTs	With considerable limitations[4]	No serious inconsistency	No important indirect evidence	No serious inaccuracy	20	10	–	⨁⨁◯◯ Low	Important
Effect chemopreventive against skin cancers (follow up 3 to 6 mouths)										
Cheng et al. (2001); Esposito et al. (2017)	NCTs	With considerable limitations[5]	No serious inconsistency	No important indirect evidence	No serious inaccuracy	36	–	–	⨁⨁◯◯ Low	Critical
Control serum cholesterol levels										
Bilia et al. (2018)	RCT	Not serious	No serious inconsistency	No important indirect evidence	No serious inaccuracy	15	15	–	⨁⨁⨁◯ Moderate	Important
Quality of life (QoL)										
Kurd et al. (2008), Panahi, Sahebkar, Amiri, et al. (2012); Panahi, Sahebkar, Parvin, et al. (2012)	RCTs (Panahi, Sahebkar, Amiri, et al. 2012; Panahi, Sahebkar, Parvin, et al. 2012) NCT (Kurd et al. 2008)	With considerable limitations[6]	No serious inconsistency	No important indirect evidence	No serious inaccuracy	58	50	–	⨁⨁⨁◯ Moderate	Critical

[1]Carrion-Gutierrez et al. (2015) demonstrated risk of bias to deviations from the intended interventions (limited statistical significance because of the small number of individuals in the sample). Kurd et al. (2008) demonstrated potential for confounding of the effect of intervention (single-arm, noncontrolled clinical trial).

[2]Panahi, Sahebkar, Amiri, et al. (2012) and Panahi, Sahebkar, Parvin, et al. (2012) demonstrated risk of bias to deviations from the intended interventions (effect of assignment to intervention)

[3]Chainani-Wu et al. (2007) and Chainani-Wu et al. (2012) demonstrated baseline differences between interventions groups (lack of heterogeneity in the sample) and demonstrated risk of bias to deviations from the intended interventions (limited statistical significance because of the small number of individuals in the sample).

[4]Vaughn et al. (2019) demonstrated risk of bias to deviations from the intended interventions (limited statistical significance because of the short study duration and small number of individuals in the sample).

[5]Cheng et al. (2001) demonstrated risk bias to domain confounding and bias in selection of the reported result (methodology and results not very clear or without information); and Esposito et al. (2017) demonstrated potential for confounding of the effect of intervention, with limited statistical significance because of the small number of individuals in the sample and baseline differences between intervention groups.

[6]Panahi, Sahebkar, Amiri, et al. (2012) and Panahi, Sahebkar, Parvin, et al. (2012), demonstrated risk of bias to deviations from the intended interventions (effect of assignment to intervention); and Kurd et al. (2008), demonstrated potential for confounding of the effect of intervention.

rules. However, those who responded had excellent responses: 83% and 88% improvement in PASI scores at week 12. Also in this study, the absence of agents that contribute to the absorption of turmeric and its curcuminoids by the body (such as formulations of black pepper or liposomal curcumin, for example, as indicated in several studies) was considered a limiting factor, causing a different result than expected (Hewlings and Kalman 2017; Kurd et al. 2008).

Pruritus

Pruritus is a common manifestation of dermatologic diseases, and is associated with a markedly reduced quality of life. A study of 100 hemodialysis patients with uremic pruritus (UP) was conducted to evaluate the effects of turmeric on patient treatment (Pakfetrat et al. 2014). With a lasting period of 8 weeks, patients (60 men, 40 women, age 37–69 years) were randomized into two groups: the experimental group ($n = 50$), which received a safe dose of turmeric (one capsule containing 500 mg turmeric, of which 22.1 mg was the active ingredient curcumin, 3 capsules/day), and controls ($n = 50$), who received placebo (starch capsules) for treatment. The pruritus score (proposed by Duo (1987), where score 1 = mild disease and score 10 = severe disease) and biochemical markers, including high-sensitivity C-reactive protein (hs-CRP, are reported to have higher levels in patients with UP) were compared at the beginning and end of the study between the two groups. In conclusion, a significantly greater reduction in pruritus scores and hs-CRP was observed in the tumeric group than in the placebo group. Two other studies conducted in Iran used a sample of 96 male subjects, aged 37–59 years, who suffer from chronic sulfur mustard (SM) induced pruritus. Participants were randomized to receive 1 g/day of curcumin ($n = 46$) or placebo ($n = 50$) for 4 weeks (Panahi, Sahebkar, Amiri, et al. 2012; Panahi, Sahebkar, Parvin, et al. 2012). The first published study aimed to investigate the efficacy of curcumin in relieving chronic pruritic symptoms induced by SM. In this study the concentrations of substance P (an important mediator of of pruritic), antioxidant enzymes, itching severity and quality of life were evaluated (Panahi, Sahebkar, Amiri, et al. 2012). The results suggested that curcumin effectively increases the activity of antioxidant enzymes, reduces serum levels of substance P, alleviates pruritic symptoms, and, consequently, increases the quality of life in SM-exposed patients suffering from chronic pruritic skin lesions. The second study by Panahi, Sahebkar, Amiri, et al. (2012) aimed to investigate the impact of curcumin on serum inflammatory biomarkers (IL-6 and IL-8, hs-CRP and CGRP) and their association with the severity of pruritus and quality of life. In the end, serum IL-8 and hs-CRP were significantly reduced in the curcumin group. Serum Calcitonin gene-related peptide (CGRP) was reduced only in the curcumin group. No significant change in serum IL-6 was observed. Curcumin supplementation was also associated with a marked decline in pruritus score. As a conclusion of the studies, curcumin can be considered as a safe, widely available and inexpensive natural treatment alternative for the treatment of chronic pruritic.

Facial redness

Facial redness is a common dermatological problem, multifactorial in nature and difficult to control. When in a permanent state, it can cause psychological, physical and esthetic concern for patients (Vaughn et al. 2019; Draelos and Donald 2018). The randomized pilot study by Vaughn et al. (2019) aimed to investigate the effects of turmeric tablets and turmeric-containing polyherbal combination tablets versus placebo, in the framework of facial redness, as well as to investigate changes in the intensity and distribution of facial redness in relation to the baseline. Thirty patients (3 men and 27 women, aged 25–59 years) were recruited from the University of California dermatology clinic and randomized into three groups: 10 subjects each in placebo, turmeric, and turmeric-containing polyherbal groups. The subjects were instructed to take 8 tablets a day (4000 mg) for 4 weeks. At the end of this period, 28 participants completed the study. As a result, it was observed that only the the polyherbal combination tablet group showed a significant decrease in facial redness (40%) compared to baseline ($P = 0.03$), while the turmeric tablet and placebo groups had no statistical significant change in facial redness. In addition, the intensity and distribution of facial redness also tended to decrease in the turmeric-containing polyherbal group, although the trend was not significant. There were no adverse events reported. At the end of the study, it was possible to conclude that the herbs of the turmeric-containing polyherbal combination formulation have potential benefits, such as antioxidant, anti-inflammatory properties and potential use for the treatment of different dermatological conditions.

Oral lichen planus

Oral lichen planus (OLP) is a common chronic inflammatory disorder of uncertain etiology that can affect oral mucosa, skin, nails and scalp (Gupta and Jawanda 2015). Two studies at the University of California (Chainani-Wu et al. 2007; Chainani-Wu et al. 2012), evaluated the efficacy, safety, and tolerability of high-dose curcuminoids in controlling OLP signs and symptoms. In the study by Chainani-Wu et al. (2007), 33 patients (10 men and 23 women, aged 51–70 years) who met the eligibility criteria were randomized to receive 2000 mg/day of curcuminoids (divided into two doses) or placebo, for a period 7 weeks. In addition, all individuals received 60 mg/day of prednisone (glucocorticoid medication) during the first week of intervention. After the intervention period, in the interim analysis, the proportion of patients who showed improvement in symptoms at the follow-up visit was 81.25% of patients in the placebo group and 83.33% of the curcuminoids group. Therefore, there were no significant differences in the reduction of symptoms or signs between the placebo and curcuminoids groups, so an analysis of futility was performed. Soon after these analyzes, the decision was made to terminate the study in advance for futility and the trial was interrupted. Still in this study, curcuminoids were well tolerated and the frequencies of most side effects were similar between both groups. In the second study by Chainani-Wu et al. (2012), 20 patients

(7 men and 13 women, aged 44–69 years) were randomized to receive Curcumin C3 complex ($n = 10$), 6000 mg/day curcumin (divided into 3 doses) or placebo tablets (cellulose microcrystalline, dicalcium phosphate, PVPK 30, sodium starch glycolate, magnesium stearate, orange coating). The study lasted 12 days. As a result, the curcuminoid group showed a greater reduction in clinical signs and symptoms compared to the placebo group, in addition to an improvement in the Modified Oral Mucositis Index score (MOMI, used to measure oral lichen planus signs). Adverse effects were uncommon in both groups.

Effect chemopreventive against skin cancers

Two studies were conducted to evaluate the chemopreventive effect of turmeric supplementation on skin cancers. The first was a phase I clinical trial conducted on patients who had, among other conditions, Bowen's skin disease, an endemic disease in southern Taiwan (Cheng et al. 2001). The study lasted 12 weeks and included a sample of 25 patients, of which 6 had Bowen's skin disease and the other patients had other risk conditions such as recently resected urinary bladder cancer, uterine cervical intraepithelial neoplasm (CIN), oral leucoplakia, and intestinal metaplasia of the stomach). The initial dose of curcumin was 500 mg/day, increasing to 1000, 2000, 4000, 8000 and 12,000 mg/day, according to the toxicity tolerance observed. Patients also received regular outpatient follow-up, routine physical examination and biochemical study. At the end of the study, no toxicity was observed until 8000 mg/day, but 12,000 mg/day was not acceptable to patients due to tablet size. Histological improvement of precancerous lesions was observed in patients. A dose-dependent effect was also observed at almost all dose levels. The second study, conducted by Esposito et al. (2017), compared the impact of the Mediterranean diet (MedDiet) and the western diet (WesDiet), with or without 1200 mg/day curcumin, on the health of 11 patients with type 1 neurofibromatosis (NF1). The sample was divided into four groups based on their diet: the first group ($n = 2$) was instructed to follow a Western diet (WesDiet); the second ($n = 3$) a traditional Mediterranean diet (MedDiet); the third ($n = 3$) a curcumin-enriched Western diet (WesDietCurcumin); and the fourth ($n = 3$) a traditional Mediterranean diet enriched with curcumin (MedDietCurcumin). After 24 weeks of follow-up, patients who adopted MedDietCurcumin showed a significant reduction in the number and volume of cutaneous neurofibromas. In this same group, a plasma increase in curcumin concentration was also observed, indicating an improvement in curcumin bioavailability. No patient reported side effects on curcumin consumption.

Discussion

The present systematic review included eleven articles that aimed to evaluate the effects of turmeric supplementation and its curcuminoids in the treatment of chronic skin diseases in patients undergoing randomized and nonrandomized clinical trial studies. Due to the heterogeneity of the data, this discussion will be divided into topics for a better content approach.

Protective mechanism of curcumin in chronic skin diseases

Chronic skin disease can cause lesions and inflammation is the standard initial response of the body to injury. The organism starts a dynamic repair process that consists of several steps in order to recover the integrity of the injured tissue. At the beginning of the damage, neutrophils and macrophages go to the wound site, as well as release cytokines, providing a route for fibroblasts to the site, which results in inflammation. The primary mechanism by which curcumin modulates inflammation occurs by reducing the expression of the two main cytokines responsible for the inflammatory response: interleukin 1 (IL-1) and tumor necrosis factor alpha (TNF-α), which are released by monocytes and macrophages. In addition, curcumin inhibits the activity of the pro-inflammatory transcriptional factor (NF-κB), a factor responsible for the regulation of several genes involved during the initial process of the inflammatory response. Suppression of NFκB activation causes negative regulation of cyclooxygenase-2 and inducible nitric oxide synthase, as well as prevents positive regulation of the vascular endothelial growth factor (VEGF) and microvascular angiogenesis messenger during inflammatory conditions (Panahi et al. 2019). The anti-inflammatory actions of curcumin can be used to control skin inflammation resulting from different skin diseases (Bilia et al. 2018; Carrion-Gutierrez et al. 2015; Chainani-Wu et al. 2007; Chainani-Wu et al. 2012; Cheng et al. 2001; Esposito et al. 2017; Kurd et al. 2008; Pakfetrat et al. 2014; Panahi, Sahebkar, Amiri, et al. 2012; Panahi, Sahebkar, Parvin, et al. 2012; Vaughn et al. 2019).

Dosage and bioavailability of curcuminoids

Turmeric and its curcuminoids are presented in the literature as safe and with low toxicity in humans, even at high doses (Lao et al. 2006; Chainani-Wu et al. 2012; Cheng et al. 2001). According to the Food and Drug Administration (FDA), curcumin should be used as an ingredient in addition levels of 0.5–100 mg/100 g, depending on the specific food category (FDA, 2018). And, according to the European Food Safety Authority (EFSA) reports, the value of curcumin acceptable daily intake (ADI) is 0–3 mg/kg (EFSA, 2014; FDA, 2013). However, to date, the maximum tolerated dose in humans has not been identified. In 2006, a study was conducted to determine the safety and tolerance of curcumin (Sabinsa Corporation C3 complex) at single oral doses of 500–12,000 mg. Twenty-four healthy volunteers (13 men and 11 women, aged 19–74 years) were included. Adverse events (diarrhea, headache, rash) were grade 1 (not significant). No toxicity appeared to be dose related (Lao et al. 2006). The study by Cheng et al. (2001), included in this review, also administered 500–12,000 mg/day of

curcumin, evolving according to the toxicity tolerance observed. At the end of the study, no toxicity was observed, nonetheless, the dose of 12,000 mg/day was not well tolerated by patients due to tablet size. Thus, successful administration may be affected by differences in drug formulation.

Notwithstanding the evidence on its efficacy and safety, curcumin has low bioavailability in the body, which may be justified by its low solubility and intestinal permeability. Many studies aim to find mechanisms that overcome this obstacle, intending to improve its absorption by the body. In this present review, we included studies that presented, in their interventions, absorptive aids which conditioned the improvement of curcumin bioavailability as secondary outcomes (Bilia et al. 2018; Carrion-Gutierrez et al. 2015; Chainani-Wu et al. 2007, Esposito et al. 2017; Panahi, Sahebkar, Amiri, et al. 2012; Panahi, Sahebkar, Amiri, et al. 2012; Vaughn et al. 2019). Among the reasons that led to this result are the use of curcumin nanoparticles (Bilia et al. 2018), bioperine (Panahi, Sahebkar, Amiri, et al. 2012; Panahi, Sahebkar, Parvin, et al. 2012), UVA phototherapy and visible light (Carrion-Gutierrez et al. 2015); prednisone (Chainani-Wu et al. 2007); foods rich in polyphenols, presented in the Mediterranean diet (Esposito et al. 2017); and turmeric polyherbal combination, ablend of organic herbs (Vaughn et al. 2019); all have shown potential to increase the action and absorption of curcumin by the human organism. Among the literary framework, Wang et al. (2019) conducted a study that aimed to verify whether piperine-coformed curcumin-free (PIP) solid dispersions (PIP) could increase curcumin bioavailability in vivo. Following administration of CUR-PIP, curcumin increased significantly by 2.16-fold, demonstrating better bioavailability, increased dissolution and easier membrane permeability. A second study, carried out by Antony et al. (2008), aimed to evaluate the bioavailability of curcuminoids through a simple and economical formulation, trademarked BCM-95®CG (BiocurcumaxTM), in humans. During the study, a comparison was made between the relative bioavailability of standard curcumin and BCM-95®CG, as well as a comparison between the bioavailability of BCM-95®CG with the formula of curcumin-lecithin-piperine. Eleven healthy volunteers, aged 28 to 50 years, were divided into 3 groups: group 1 ($n = 4$) consumed 4×500 mg capsules of BCM-95®CG, group 2 (control, $n = 4$) consumed standard curcumin, and group 3 (control, $n = 3$) consumed curcumin-lecithin-piperine formula, all received the same dose equivalent to the first group. After a wash out period of 2 weeks, individuals crossed over to the other medication (individuals in group 1 received curcumin control and groups 2 and 3 were consumed BCM-95®CG capsules), the same protocol being followed. At the end of the study, it was observed that the relative bioavailability of BCM-95®CG was about 6.93 times greater compared to standard curcumin and about 6.3 times greater compared to the curcumin-lecithin-piperine formula. In addition, the results of the present pilot study indicated a probable role for the non-curcuminoid components of turmeric (especially Ar-turmerone) in the absorbability of curcumin in vivo.

Benefits of the action of turmeric and its curcuminoids

To determine the effectiveness of using turmeric in the treatment of skin diseases, health-related parameters such as PASI scores and quality of life (QoL) are used. These important tools serve to assess the patient's health status, disease severity, and response to administered treatments (Mattei, Corey, and Kimball 2014). The present findings on the oral administration of turmeric and its curcuminoids in the treatment of chronic skin diseases have shown efficiency potential, as well as benefits for symptom relief and consequent improvement in the quality of life of these individuals. In studies by Bilia et al. (2018), by Carrion-Gutierrez et al. (2015), and by Kurd et al. (2008), a significant reduction in PASI values was observed in patients receiving oral turmeric and/or curcumin supplementation. Similarly, in the study conducted by Pakfetrat et al. (2014), a substantial reduction in pruritus scores was observed in the turmeric group compared to the placebo group. In two other randomized, placebo-controlled clinical trials conducted by Panahi, Sahebkar, Amiri, et al. (2012) and Panahi, Sahebkar, Parvin, et al. (2012), it was observed relief of pruritic symptoms. In addition, curcumin supplementation in these studies was also associated with a marked decline in pruritus score (Pretrial: 40.60 ± 3.43 vs. Post-trial 28.23 ± 4.95). Chainani-Wu et al. (2012) evaluated the efficacy and safety of curcuminoids in the control of signs and symptoms of OLP; after 12 days of intervention, it was possible to observe a greater reduction in clinical signs and symptoms, in addition to an improvement in the MOMI score. However, it is worth noting that studies such as those by Chainani-Wu et al. (2007) and Vaughn et al. (2019) showed a result more favorable to the benefits of the treatment of skin diseases in groups in which agents that aid in the absorption of curcuminoids were administered (such as prednisone and polyherbal combination).

In view of the promising results collected, the relevance of following up further investigations on oral supplementation of turmeric and its curcuminoids, along with other forms that enhance its efficacy and bioavailability in the human body, has been demonstrated, allowing its use as an instrument of substantial aid in the treatment of chronic skin diseases.

Study limitations

The findings of this review are limited by the small number of articles included. Among the selected studies, eight RCTs and three NCTs had sample size limitations (Bilia et al. 2018; Carrion-Gutierrez et al. 2015; Kurd et al. 2008; Chainani-Wu et al. 2007; Chainani-Wu et al. 2012; Cheng et al. 2001; Esposito et al. 2017; Vaughn et al. 2019), short follow-up treatment (Carrion-Gutierrez et al. 2015; Kurd et al. 2008; Chainani-Wu et al. 2012; Pakfetrat et al. 2014; Panahi, Sahebkar, Amiri, et al. 2012; Panahi, Sahebkar, Parvin, et al. 2012; Vaughn et al. 2019) and/or non-placebo controlled study (Kurd et al. 2008; Cheng et al. 2001). In addition, some studies have shown interventions using turmeric and curcumin concomitantly with other substances and therapeutic

mechanisms, such as: acitretin (Bilia et al. 2018), bioperine (Panahi, Sahebkar, Amiri, et al. 2012; Panahi, Sahebkar, Parvin, et al. 2012), prednisone (Chainani-Wu et al. 2007), polyherbal combination (Vaughn et al. 2019), UVA phototherapy and visible light (Carrion-Gutierrez et al. 2015). Joint application, however, makes it difficult to assess the benefits of turmeric in isolation. The use of turmeric and its curcuminoids as a dietary supplement is well characterized in the literature. However, the FDA does not support its therapeutic use because it requires proof of safety and effectiveness in clinical trials. Therefore, it is important to carry out new studies of high methodological quality to measure the legitimate effectiveness of turmeric and its curcuminoids in the treatment of skin diseases.

Conclusion

The qualitative analysis of the results obtained by the studies included in the present systematic review showed, although at a low or moderate level, due to its methodological limitations, evidence that the use of turmeric and its curcuminoids contributes beneficially to the treatment of chronic skin diseases. The selected studies have provided evidence that there is a positive association between oral turmeric administration and improvement of disease signs and symptoms without toxicity, which is even more important considering that the treatments are long term, which, consequently, allows the improvement of the quality of life of patients with those diseases.

Thus, given the favorable and promising results achieved by the use of turmeric as an auxiliary tool in the therapeutic route of chronic skin illness, studies with a larger number of participants, longer intervention period, as well as the use of other therapy devices that contribute to the increased efficacy and bioavailability of curcumin in the body has been becoming more important and should be encouraged. Finally, it is hoped that the results collected by this systematic review will contribute to the recognition of turmeric as an alternative and complementary therapy for chronic inflammatory skin diseases.

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The authors declare that they have no conflict of interest.

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