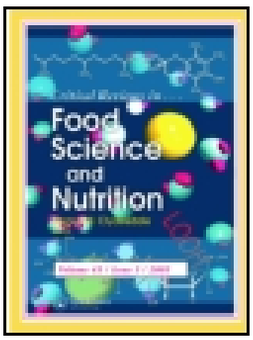

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REVIEW

Curcumin, autoimmune and inflammatory diseases: going beyond conventional therapy – a systematic review

Ledyane Taynara Marton[a], Sandra Maria Barbalho[a,b,c], Kátia Portero Sloan[d], Lance Alan Sloan[d,e], Ricardo de Alvares Goulart[c], Adriano Cressoni Araújo[a,c], and Marcelo Dib Bechara[a]

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ABSTRACT

Autoimmune and inflammatory diseases affect innumerous people and are considered a significant cause of morbidity and mortality worldwide and *Curcuma* sp can work as important therapies in the approach of these diseases. For this reason the aim of this review is to evaluate the effects of *Curcuma* or curcumin in five autoimmune and/or inflammatory diseases for instance, Inflammatory Bowel Disease, Osteoarthritis, Systemic Lupus Erythematous, Psoriasis, and Sclerosis. MEDLINE, EMBASE, and Cochrane Library were searched and PRISMA guidelines were used to build this systematic review. *Curcuma* sp or curcumin have been gaining ground in the treatment of autoimmune and inflammatory diseases due to the wide range of bioactive compounds capable of exerting substantial anti-inflammatory and antioxidant actions. The effects can be associated with improvement of symptoms and induction of remission in Inflammatory Bowel Disease patients; reduction of erythema and induration of lesions in psoriasis; and slow down the disease progression in patients with sclerosis. Furthermore, curcumin shows effects equivalent to ibuprofen and diclofenac, without the adverse effects generally reported by patients. *Curcuma* or its derivatives can be used safely and efficiently as adjuvants or as a main therapy for these diseases that increase year by year in the world population.

KEYWORDS

Curcuma longa; curcumin; psoriasis; lupus erythematosus; osteoarthritis; inflammatory bowel diseases

Introduction

Autoimmune diseases affect innumerous people and are considered a significant cause of morbidity and mortality worldwide. The incidence of autoimmune diseases is usually higher in industrial centers with triggering factors such as genetics, diet, alcohol consumption, and environmental factors (latitudinal gradients that are correlated with sunlight-ultraviolet radiation exposure and vitamin-D levels, regions susceptible to infections, and dietary iodine intake) (Piquet and Clardy 2018; Shapira, Agmon-Levin, and Shoenfeld 2010; Mansoori et al. 2020).

Inflammatory diseases, such as Inflammatory Bowel Disease (IBD), Osteoarthritis (OA), Systemic Lupus Erythematosus (SLE), Psoriasis, and Multiple Sclerosis (MS) also affect millions of people worldwide.

Inflammatory Bowel Disease mainly represented by Chrohn's Disease (CD) and Ulcerative Colitis (UC) exhibit increasing rates every year especially in Western and Eastern countries (Park et al. 2019). Their occurrence has been associated with higher socioeconomic status and living in urban areas. Moreover, different risk factors may be associated with IBD, such as genetics, lifestyle, smoking, indoor occupations, and environmental factors (Altaf-Ul-Amin et al. 2020; Barbalho et al. 2019).

Osteoarthritis is a chronic inflammatory degenerative condition that affects approximately 250 million of individuals. This chronic musculoskeletical disease affects the movable joints, including knees leading to inflammation and pain (Akuri et al. 2017; Gallotti, Serafini, and Thomazzi 2020). Besides aging, biomechanical, biochemical, and environmental factors can contribute to the initiation of the disease (Araya-Quintanilla et al. 2020; Bruce et al. 2020).

The Systemic Lupus Erythematosus is considered as an inflammatory, chronic multisystem autoimmune condition that can affect almost all organs including kidneys, brain, heart, skin, joints, and the central nervous system (Momtazi-Borojeni et al. 2018; Maria and Davidson 2020). This disease disproportionally affects more women than men (9:1), and has shown an increased incidence in patients of African ancestry (Lever, Alves, and Isenberg 2020).

Psoriasis is an immune-mediated chronic skin disease characterized by the presence of papules and plaques due to the hyperproliferation and accumulation of neutrophils. The inflammatory process shows dermal inflammatory cell infiltrates of T and dendritic cells. Its prevalence is around 2–4% in the globe and men are twice as likely as women to

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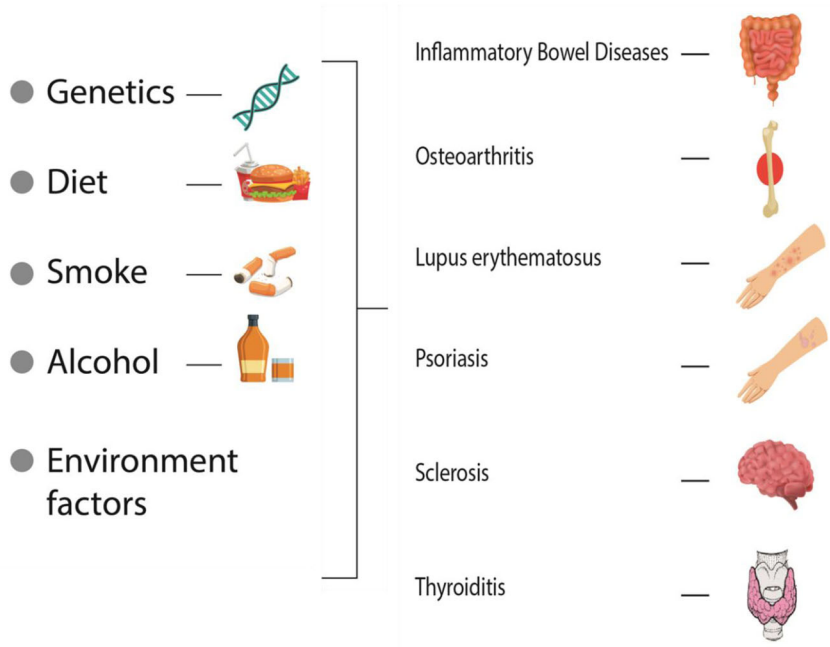

Figure 1. Factors related to the development of some inflammatory diseases (Inflammatory bowel disease, osteoarthritis, lupus erythematosus, psoriasis, sclerosis and thyroiditis).

be affected (Rajguru et al. 2020; Barbieri et al. 2020). While it can begin at any age, psoriasis has two peaks of onset; the first one occurs at the age of 20–30 years and the second one at 50–60 years. Men and women are equally affected, but it is more common in non-Hispanic white people. Patients can be more prone to developing psoriasis, especially if there is a family member with the condition. Some factors such as smoking, infection, and certain medications can the disease activity worse in some patients (Armstrong 2017; Castaldo et al. 2020).

Finally, Multiple sclerosis is a neuroinflammatory, demyelinating condition of the central nervous system and with an autoimmune attack on the components of the myelin axons and sheath. The etiology of the disease remains largely unknown, but it is commonly acknowledged that the development probably results from the interaction of environmental factors in conjunction with a genetic predisposition (Reich, Lucchinetti, and Calabresi 2018; Li et al. 2020; Cheng et al. 2017).

Figure 1 shows the possible causes of inflammatory diseases.

Since autoimmune and inflammatory diseases are a significant cause of death and account for a substantial burden for healthcare systems (Cooper, Bynum, and Somers 2009; Alzughayyar et al. 2020; Pham-Dobor et al. 2020), the use of unconventional therapies brings to light a new possibility of prevention or treatment at lower costs and with fewer side effects.

Lately, the use of natural products has been gaining ground in the treatment of autoimmune and inflammatory diseases. These products have a wide range of bioactive compounds capable of exerting substantial anti-inflammatory effects. One of these products is curcumin, which is extracted from *Curcuma longa* (Li et al. 2019; Alvarenga et al. 2020).

Curcuma species have been used since ancient times in the treatment of various diseases. Popularly it is used as antibacterial, expectorant, anti-diabetic, anti-inflammatory, and anticancer (Kocaadam and Şanlier 2017; Mansourizadeh et al. 2020; Jamilian et al. 2020). Figure 2 shows the bioactive compounds of *Curcuma longa* and their possible effects.

In this review we gathered and discuss data on the effects of the use of curcumin relevant to five autoimmune and/or inflammatory diseases for instance, Inflammatory Bowel Disease, Osteoarthritis, Systemic Lupus Erythematous, Psoriasis, and Sclerosis.

Methods

Data sources

For this review, the authors searched the MEDLINE-PubMed and EMBASE databases following the PRISMA guidelines (Preferred Reporting Items for a Systematic Review and Meta-analysis) (Moher et al. 2009). This survey was conducted to answer the following question: *Is curcumin effective in the treatment of Autoimmune and Inflammatory Diseases?*

Research

The research included Randomized Clinical Trials, and the combination of terms and mesh-terms used for this search was *Inflammatory Bowel Disease* or *Osteoarthritis* or *Lupus erythematosus* or *Psoriasis* or *Sclerosis* and *Curcuma* or *curcumin* or *bisdemethoxycurcumin* or *demethoxycurcumin*. There was no restriction on the search period. The consultation of the databases was completed until March 2020.

Based on the references resulted from the combination of these keywords, we built the flow diagram (Figure 3) that shows the selection of articles and inclusion and exclusion of studies. Other studies on Curcumin and autoimmune inflammatory diseases were used to build the discussion.

Eligible criteria and study selection

Our research included Randomized Clinical Trials that discussed the use of curcumin and its effects on autoimmune and inflammatory diseases. Only articles written and published in English from the last ten years that showed correspondence with the keywords were selected.

Inclusion criteria were studies that used Randomized Clinical Trials (RCT). The exclusion criteria were articles not in English, cross-sectional studies, cohort studies, case reports, poster presentations, and letters to the editor.

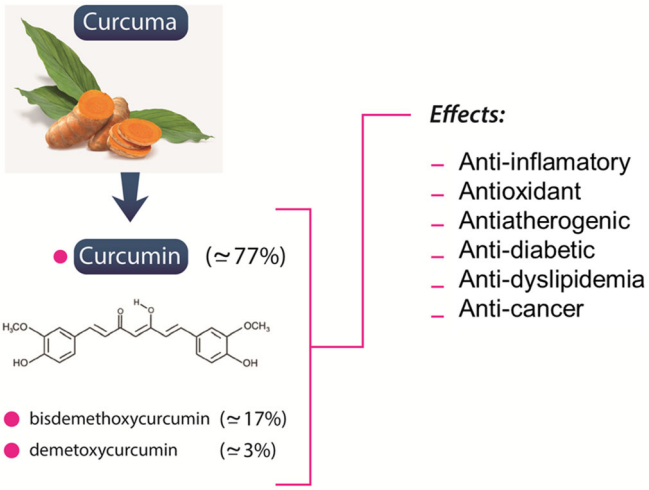

Figure 2. Bioactive compounds of *Curcuma longa* and physiological actions.

Extraction of data

The extraction of the data was carried out independently by two authors who used the predefined inclusion and exclusion criteria, as well as the descriptors presented above. Data were extracted from eligible articles that included the author, date, sample size, study design, information related to the use of curcumin, and its relationship with autoimmune inflammatory diseases. Only original articles were selected for the construction of Table 1.

Results

Figure 3 shows the selection of the included studies, and Tables 1–5 show thirty-six studies (Randomized Clinical Trials) in the final selection of the survey. These studies included 2,750 patients; 417 with UC, 1,700 with osteoarthritis, 63 with Lupus erythematosus, 202 with Psoriasis, 288 with Sclerosis, and 35 controls. From these patients, 1,557 were women, and 799 were men.

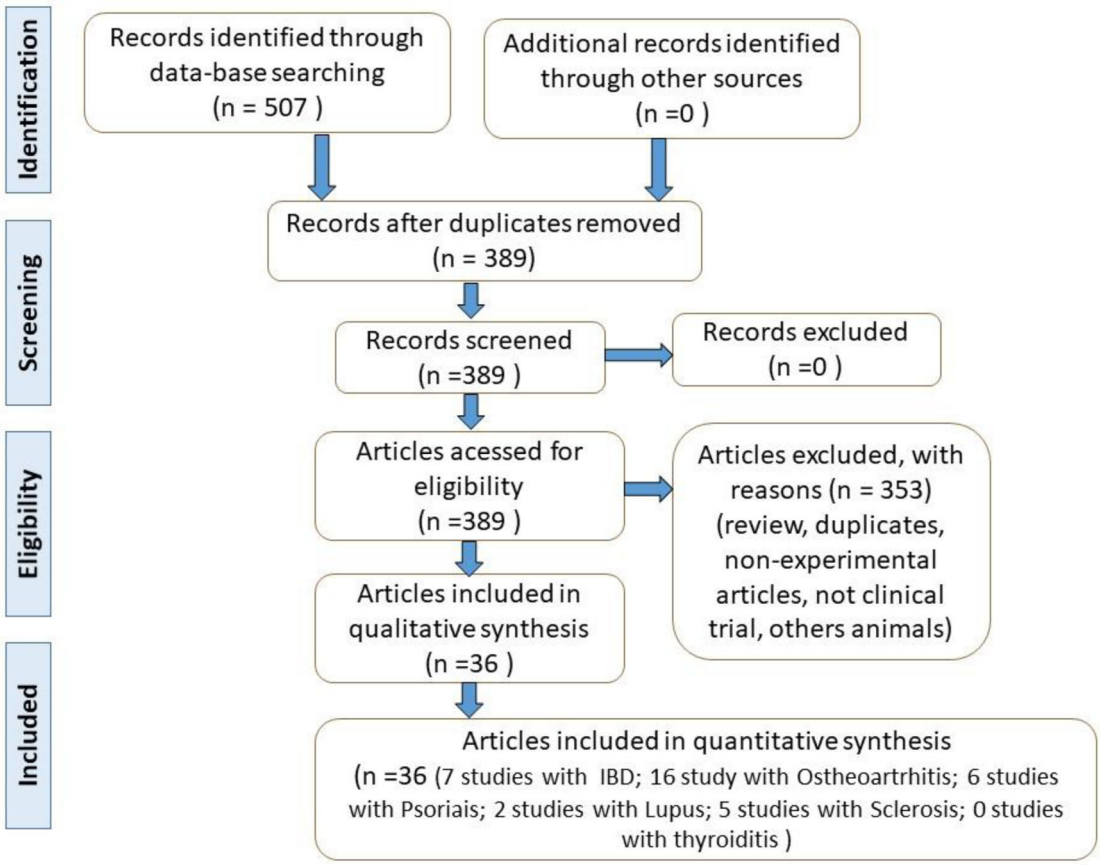

Figure 3. Flow diagram showing the results of the search according to PRISMA guidelines (Moher et al. 2009).

Table 1. Randomized clinical trials showing the effects of curcumin in inflammatory bowel disease.

Reference	Local	Model and patients	Intervention	Outcomes	Conclusion
Hanai et al. 2006 (Hanai and Sugimoto 2009)	Japan.	Randomized, Multicenter double-blind, and a placebo-controlled clinical trial with 89 patients with quiescent UC, 13–65 y, 49 ♂, 40 ♀)	Patient showed a CAI $\leq$ 4, stable for the previous 4 weeks, were given SZ (1–3 g/d; median, 2 g/d) or mesalamine (1.5–3 g/d; median, 2.25 g/d) plus 2 g curcumin, or placebo for 6 m.	From the patients who received curcumin, 4.55% relapsed during 6 m, and 20.51% in the placebo group relapsed. The mean CAI in the curcumin group was an improvement from 1.3 ± 1.1 at the beginning to 1.0 ± 2.0 at 6 months. In contrast, CAI in the placebo group showed significant deterioration; mean CAI increased from 1.0 ± 1.1 to 2.2 ± 2.3.	Curcumin seems to be efficient and safe for maintaining remission in patients with quiescent UC.
Ahuja et al. 2011 (Ahuja et al. 2011)	India.	Randomized, double-blind, single-center pilot trial studied with 43 UC patients with mild/moderate proctitis; 18♂and 25 ♀ (mean age was 32.8 y).	Of 43 randomized patients, 22 received curcumin enema and 5 ASA, 21 received placebo and 5ASA, for 8 weeks. The baseline UCDAI score was 6.05 and 6.1 in curcumin and placebo group, respectively.	The primary endpoint was a reduction in the UCDAI score >3 points. Both the treatments were well tolerated, 5 patients were lost to follow up (3 in curcumin group and 2 in placebo group), and treatment was stopped in 9 patients because of failure of therapy. The clinical response rates at 4 weeks were 71.3% vs 46.6%, at 8 weeks were 92.8% vs 53.3%; remission rates at 4 weeks were 64.2% vs 20%, and at 8 weeks was 78.5% vs 40%.	Curcumin enemas with oral 5ASA are significantly better than oral 5ASA and placebo in achieving better clinical response and remission rates.
Lang et al. 2015 (Lang et al. 2015)	Israel, Hong Kong, and Cyprus.	Multicenter randomized, placebo-controlled double-blind study with 50 patients (33♂, 17♀; 18 − 70 y) with a confirmed endoscopic and histologic diagnosis of UC were included	Patients with active mild/moderate UC, SCCAI score of $\geq$5, and <12 despite maximal 5-ASA treatment (oral 4 gr/day mesalamine + topical enema /suppository) were enrolled. Placebo and treated group received optimized oral and topical 5ASA; 26 patients underwent a run-in period of 2w receiving optimized treatment (4 g/d of oral 5-ASA + topical 5ASA at 1 g/4g enema or 1 g suppository/d). Patients who still had symptoms of active mild/moderate UC despite 2 w of optimized oral and topical 5-ASA, were entered into the trial. The intervention group received curcumin 3 g/d.	53.8% of the patients receiving curcumin achieved clinical remission at week 4 compared to none of the patients receiving a placebo. Clinical response was achieved by 65.3% in the curcumin group vs 12.5% in the placebo group. Endoscopic remission was observed in 38% in the treated group, compared with none of the placebo group. Adverse effects were similar between the groups	Curcumin and 5ASA is superior to placebo + 5ASA in inducing clinical and endoscopic remission in UC patients

(*continued*)

Table 1. Continued.

Reference	Local	Model and patients	Intervention	Outcomes	Conclusion
Benerjee et al. 2017 (Banerjee et al. 2017)	India.	Randomized, placebo-controlled study with 47 patients with active mild to moderate UC	Patients with active mild/moderate UC were divided to received 50 mg BID SMEDDS Curcumin capsules or placebo. Oral and rectal mesalamine was continued. Clinical response (reduction of ≥3 points of partial Mayo score) and endoscopic remission was made at 6w and 3 m	Clinical response after 6 w was achieved by 42.1% in the SMEDDS Curcumin group vs 13.04% in placebo. After 3 m, 5 of 19 patients (26.3%) receiving curcumin and 0 of 23 patients receiving placebo showed endoscopic remission	Novel bio-enhanced curcumin with mesalamine is effective in inducing remission in active mild to moderate UC
Kedia et al. 2017 (Kedia et al. 2017)	India	Prospective randomized, double-blind placebo-controlled trial with 62 patients (21♀, 41♂; ≥18 y) with mild-to moderately active UC	The patients were divided to receive 1 capsule 3xd of placebo or 150 mg of purified curcumin for 8w. The patients in both groups received mesalamine 2.4 g/d	No significant difference was observed in the rates of clinical remission (31.3% vs 27.3%), clinical response (20.7% vs 36.4%), mucosal healing (34.5% vs 30.3%), and treatment failure (25% vs 18.5%) between curcumin and placebo at 8 weeks.	Curcumin in a low dose (450 mg/d) was not adequate to induce remission in mild to moderate cases of UC
Masoodi et al. 2018 (Masoodi et al. 2018)	Iran	Randomized double-blind controlled trial with 56 patients, 28 ♀ and 28♂ (> 18 y) with the final diagnosis of mild/moderate UC according to the SCCAI	The patients received curcuminoids nanomicelles (80 mg, 3xd, orally) plus mesalamine (3 g/24 hours, orally) The severity of disease was assessed at baseline and at the end of the second and fourth weeks of the treatment according to the SCCAI	The score for the urgency of defecation reduced significantly more in the case group as compared with control at 4w of treatment. The treated patients experienced better general condition than the control. SCCAI score was significantly lower in the *Curcuma* group	Curcuminoids nanomicelles is related with improvement of the frequency of urgent defecation, well-being and clinical activity of UC
Sadeghi et al 2018 (Sadeghi et al. 2019)	Iran	Single-centre, Randomized, double-blind, placebo-controlled trial with 70 patients (21♀, 49♂; 30-63 y) with mild/moderate UC (SCCAI < 12)	Patients received 500 mg curcumin 3x/d	Decrease of ≥ 3 points in the SCCAI and reduction of body weight loss, decrease in TNF-α levels, CRP, and ERS	Curcumin improves the quality of life, clinical outcomes, decrease in CRP, and ERS in UC subjects

SZ: sulfasalazine; CAI: clinical activity index; UC: ulcerative colitis; UCDAI: ulcerative colitis disease activity index; SCCAI: Simple Clinical Colitis Activity Index; 5ASA: 5-aminosalicylate; SMEDDS: Self- Micro Emulsifying Drug Delivery System.; ERS: Erythrocyte Saturation Rate.

Discussion

Inflammatory bowel disease and Curcuma longa

The etiology of IBD is not fully understood, but genetic factors, diet, stress, modifications in the gut microbiome are closely related to the pathogenesis of these diseases. The intestinal epithelial cells express the TLR sensitive to pathogens. When there is an imbalance in the epithelial barrier, the hyperactivation of NFκβ leads to further increase in the synthesis of proinflammatory interleukins, TNF-α and IFN-γ resulting in significant impact for the patient who is plagued by fatigue, fever, abdominal pain, bloating, bleeding and diarrhea that reduces the quality of life (Mazieiro et al. 2018; Karimi et al. 2020).

The therapies commonly used in the therapeutic approach of IBD include corticosteroids, aminosalicylates, immunosuppressants, and biological agents. Although they can help patients in the relief of pain and other symptoms, many patients do not benefit from these therapies due to the lack of response or due to the occurrence of numerous adverse effects (Marton et al. 2019).

Due to the need to develop other new and effective therapies to IBD, many studies have focused attention on alternative therapies such as naturally occurring indanes (Frankish, McHale, and Sheridan 2018; Frankish and Sheridan 2012). *Curcuma longa* or its derivatives are known for the anti-inflammatory and antioxidant properties, mainly due to the inhibition of the transcriptional NFκβ (Jobin et al. 1999),

Table 2. Randomized clinical trials showing the effects of curcumin in osteoarthritis.

Reference	Local	Model and patients	Intervention	Outcomes	Conclusion
(Heidari-Beni et al. 2020)	Iran	Double-blind, randomized controlled trial (two-arm parallel-group) with 60 subjects with mild/moderate OA, 27 ♀ and 33 ♂, 35–75 y	Patients were divided to receive Naproxen (250 mg/2xd) or a herbal formulation (300 mg of curcumin, 3.75 mg of piperine and 7.5 mg of gingerols)/2xd for 4 months	Levels of PGE2 reduced significantly in both groups, and no significant differences were observed between groups	The use of the herbal formulation can improve the levels of PGE2 with chronic knee OA similar to Naproxen
(Pinsornsak and Niempoog 2012)	Thailand	Double-blind prospective randomized control trial with 88 patients with OA; 15 ♂ and 73 ♀ (≥ 45 y)	44 patients were randomized to take NSAIDs (diclofenac) 75 mg/d with placebo and the other 44 took NSAIDs (diclofenac) 75 mg/d with curcumin 1,000 mg/d for 3 months. The authors evaluated the VAS for pain and KOOS every month for 3 months. At the end of the study, 36 patients were completed for the first group and 37 for the study group.	Both groups showed improvement in pain. The pain scale decrease was better in the group treated with curcuminoids at the end of the study. KOOS and pain showed better improvement in the curcuminoid group	Curcumin and diclofenac combined has the additive improvement in the improvement of pain and KOOS
(Madhu, Chanda, and Saji 2013)	India	Randomized, single-blind, placebo-controlled, comparative study with 120 patients (37♂and 83 ♀; 40 y or older) with a clinical diagnosis of knee OA	They received a placebo (400 mg twice daily) or NR-INF-02 (500 mg twice daily) or GS (750 mg twice daily) alone or a combination of NR-INF-02 and GS for 42 days. Efficacy was evaluated during the treatment period on the 21st and 42nd d	The post-treatment scores using VAS, WOMAC, and CGIC at each clinical visit showed a significant decrease compared to placebo. NR-INF-02 group showed a significant decrease in the use of rescue medication, along with clinical and subjective improvement compared to placebo	The study demonstrates the safety and efficacy of NR-INF-02 as a useful treatment option for patients with primary painful knee OA
(Kuptniratsaikul et al. 2014)	Thailand	Randomized clinical trial with 367 primary knee OA patients with a pain score ≥ 5, 296 ♀ and 35 ♂, 60–68 y	185 and 182 patients were assigned into *C. domestica* extracts (1,500 mg/day) and ibuprofen (1,200 mg/day). The patients were asked to take two capsules after meals 3xd / 4 w and not to use other medications (if they presented severe pain, they could have tramadol)	The mean of WOMAC scores at 0, 2, and 4w showed significant improvement when compared with the baseline in both groups. Patients that developed AEs were no difference between groups. However, the number of abdominal pain/discomfort was significantly higher in the ibuprofen group	*C. domestica* extracts are non-inferior to Ibuprofen in the treatment OA (AE profile was similar but with fewer GI)
(Panahi et al. 2014)	Iran	Randomized double-blind placebo-controlled trial with 53 patients who met the inclusion criteria, under 80 y, 9♂and 44 ♀	40 subjects (19 in the curcuminoids and 21 in the placebo group) completed the 6-week study duration. Patients were assigned to curcuminoids (1500 mg/day in 3 divided doses) or placebo for 6 w. Efficacy measures were changes in WOMAC, VAS and LPFI scores	There was no significant difference in VAS, WOMAC, and LPFI scores between the groups at baseline. Treatment with curcuminoids showed significant reductions in WOMAC, VAS, and LPFI scores compared with placebo. In WOMAC subscales, there were significant improvements in the pain and physical function scores	Curcuminoids represent an effective and safe alternative treatment for OA.
(Nakagawa et al. 2014)	Japan	Randomized, double-blind, placebo-controlled prospective study with 41 patients with knee OA of Kellgren–Lawrence	Placebo or Theracurmin containing 180 mg/day of curcumin was administered dailly/8w orally. Knee symptoms were evaluated at 0, 2, 4, 6, and 8 w by the	At 8 w of treatment, knee pain VAS scores were significantly lower in the Theracurmin group than in the placebo, except in the patients with initial VAS scores of 0.15	Theracurmin was significantly effective in decreasing pain and NSAID necessity with no major adverse events.

(*continued*)

Table 2. Continued.

Reference	Local	Model and patients	Intervention	Outcomes	Conclusion
		grade II or III and; ≥ 40 y, 9 ♂ and 32 ♀	Japanese Knee OA Measure, the knee pain VAS, the knee scoring system of the Japanese Orthopedic Association, and the need for non-steroidal anti-inflammatory drugs	or less. Theracurmin lowered the celecoxib dependence more than the placebo. No major side effects were observed	
(Rahimnia et al. 2015)	Iran	Randomized double-blind placebo-control parallel-group clinical trial with 40 subjects with mild-to-moderate degree knee OA	Patients were allocated to receive either pure curcuminoids (1,500 mg/day in 3 divided doses; n = 19) or matched placebo (n = 21) for 6 w. Curcuminoids were associated with piperine (15 mg/day). Serum levels of IL-4 and IL-6, TNF-α, TGF-β, and hs-CRP, together with ESR were determined at the baseline and at the end of the trial	IL-4, IL-6, and hs-CRP were significantly reduced in both groups	Improvement of clinical symptoms in treated subjects cannot be attributed to the systemic anti-inflammatory effects of these phytochemicals
(Sterzi et al. 2016)	Italy	Multicenter, prospective, randomized, double-blind, placebo-controlled clinical trial with 53 patients, ≥ 50 y, 17 ♂ , and 33 ♀.	Experimental subjects (n = 26) received two tablets of CartiJoint Forte (glucosamine hydrochloride (500 mg), chondroitin (400 mg), and bio-curcumin BCM-95 (50 mg) /d/8w, or placebo (n = 27). Both groups received 20 sessions of physical therapy during the trial. The primary outcome was pain intensity, measured by VAS. The secondary outcome was knee function by WOMAC and Lequesne Index, knee ROM, and two inflammation markers (C-reactive protein and erythrocyte sedimentation rate). Assessments were carried out at 0, 8 and 12w	No differences in VAS at rest was found between groups. The Lequesne Index showed reductions at 8 and 12w compared to 0w, along with group effect, and the experimental group presented a lower score at 8w. No significant changes were found in the knee ROM and inflammation markers	CartiJoint Forte, added to physical therapy, ameliorate pain and help to improve functional score in knee OA
(Srivastava et al. 2016)	India	Randomized, double-blind, placebo-controlled trial with 160 patients, ≥ 50 y, 57 ♂ and 103 ♀, of KOA	Patients of knee OA were randomly enrolled to receive either CL extract (500 mg) or placebo along with the standard treatment of Diclofenac 50 mg/day. VAS and WOMAC were assessed on 0, 60, and 120d. Radiographs were taken for Kellgren, and Lawrence grading and blood samples were collected for assessing IL-1β and biomarkers of oxidative stress (reactive oxygen species and MDA)	Overall significant improvement was observed in treated patients with CL. Clinically, the WOMAC and WOMAC scores became better, and the levels of biomarkers, viz, IL-1β, ROS, and MDA were also significantly improved	Chronic administration of CL reduces inflammation and brings clinical improvement in patients of KOA
(Panahi et al. 2016)	Iran	Randomized double-blind placebo-controlled parallel-group trial with 40 patients with degenerative primary knee OA with mild/	Patients were allocated to receive curcuminoids 1500 mg/day in 3 divided doses (n = 19); or placebo (n = 21) for 6 w. Curcuminoid capsule	Serum SOD, GSH, and MDA were comparable between the study groups at baseline, but the curcuminoid group showed significant elevation in SOD and	Short-term use of curcumin can attenuate systemic oxidative stress in patients with OA

(*continued*)

Table 2. Continued.

Reference	Local	Model and patients	Intervention	Outcomes	Conclusion
		moderate severity, bilateral OA, age < 80 years	also contained 5 mg piperine	GSH, and a significant reduction in MDA	
(Haroyan et al. 2018)	Armenia	Comparative, randomized, double-blind, placebo-controlled study with 201 subjects, 40–77 y, 187 female and 14 male with degenerative hypertrophic OA of knee bone joints	The participant received Curamin, CuraMed or placebo capsule (500 mg) orally, 3xd /12w. CuraMed capsules contain 552–578 mg of BCM-95® as a dry extract, (DERnative, 25:1) from CL rhizome corresponding to 500 mg curcuminoids; capsule of Curamin contains 350 mg BCM-95® and 150 mg *Boswellia serrata* Roxb	The beneficial effects of both preparations compared to placebo were observed after only 3 m of treatment. Compared to placebo, Curamin® improved both physical performance tests and the WOMAC joint pain index, while the maximum efficacy of CuraMed vs placebo was sen only in physical performance tests. The effects were comparable to placebo for both treatment groups but were superior in the Curamin® group	Use of curcumin complex or its combination reduces pain-related symptoms in patients with OA
(Karlapudi et al. 2018)	India	Placebo-controlled double-blind study with 105 patients (70 ♂ and 35 ♀, 45–70 y with unilateral or bilateral knee OA suffering for more than 6w	Subjects were distributed into three groups to receive LI73014F2-200 or LI73014F2-400mg/d or placebo. Capsules were administered before breakfast and before dinner/90d. LI73014F2 is a synergistic composition comprising the aqueous extract of *T. chebula* fruit, an alcohol extract of CL rhizome, and *B. serrata* extract at 2:1:2 ratio	Subjects were evaluated for pain and physical function (VAS, Lequesne's Functional Index, and WOMAC) at the baseline and on day 14–3, 30–3, 60–3, and at the end of the study (day 90–3). At the end of the study period, LI73014F2 conferred significant pain relief, improved physical function, and quality of life in OA patients	Preclinical and clinical data suggest that LI73014F2 is a safe and effective for the management of joint discomfort, demonstrating efficacy as early as 14d
(Panda et al. 2018)	India	Randomized, double-blind, placebo-controlled, parallel-group study with 50 patients, 40–75 y with unilateral or bilateral knee OA for more than 3 m (ACR criteria)	Participants received one capsule of 500 mg once daily of placebo or Curene® (bioavailable formulation of CL). Each subject acknowledged a questionnaire providing details regarding their symptoms of pain, stiffness, and physical function at day −7 to 0 (screening visit), day 1 (randomization visit), day 7 (visit 2), day 14 (visit 3), day 30 (visit 4), and day 60 (visit 5), respectively	The decrease in total WOMAC score (also subscale scores) and VAS score resulted in a statistically significant difference when comparing the treated group with placebo. It was also found to be safe and well-tolerated	Curene® results in a significant reduction in pain, stiffness, and improvement in physical functioning in subjects with knee OA
(Shep et al. 2019)	India	Randomized open-label parallel-arm study with 139 patients, 52–58 y, 93 ♂ and 46 ♀	139 participants with knee OA were divided to receive either a curcumin 500-mg (BCM-95®) capsule 3xd or a diclofenac 50-mg tablet 2xd for 28 d. Patients underwent assessment at 0, 7, 14, and 28d. The primary outcome measure was the severity of pain using VAS score at days 14 and 28	At days 14 and 28, subjects receiving curcumin showed similar improvement in the severity of pain and KOOS scale when compared with diclofenac. On day 7, patients receiving curcumin experienced a significantly higher reduction in the number of episodes of flatulence compared with diclofenac. On day 28, a weight-lowering effect and anti-ulcer effect of curcumin were	Curcumin has similar efficacy to diclofenac but better tolerance.

(*continued*)

Table 2. Continued.

Reference	Local	Model and patients	Intervention	Outcomes	Conclusion
				observed. Side effects were significantly reduced in the curcumin group	
(Gupte et al. 2019)	India	Randomized pilot clinical study with 42 patients, ≥65 y, 8 ♂ and 34 ♀	The treated group received SLCP in the form of capsules 2xd (80 mg/ capsule) post meals /90d. The control group received Ibuprofen capsule (400 mg) once in the morning followed by placebo (dextrin) in the evening post meals / 90 d	Patients from the Ibuprofen and SLCP group showed significant improvements in VAS and WOMAC scores indicating comparable efficacy of SLCP in alleviating pain with Ibuprofen	SLCP (160 mg/d) was effective and safe in alleviating symptoms in patients suffering from knee OA
(Henrotin et al. 2019)	Belgium	Double-blind, multicenter randomized placebo-controlled three-arm study with 141 patients, 113 ♀ and 28 ♂, 45–80 y with primary femorotibial and/or femoropatellar symptomatic knee OA	Patients were divided in three groups with a ratio of 1:1:1: (1) placebo 2 × 3 caps/day, (2) bio-optimized BCL (46.67 mg of CL extract) low dosage (2 × 2 caps/ day) plus placebo, and (3) BCL high dosage 2 × 3 caps/day/ 3 m	Low and high doses of BCL resulted in a more significant decrease of PGADA than placebo. The global KOOS significantly decreased over time, but changes were comparable across treatment arms	BCL seems to be safe and well-tolerated with no evidence of severe AE

OA: osteoarthritis; VAS: Visual Analog Scale; KOOS: Knee injury and Osteoarthritis Outcome Score; GS: glycosamine sulfate; NR-INF-02: Bioactive Turmerosaccharides from *Curcuma longa* Extract; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; AE: Adverse events; LPFI: Lequesne's pain functional index; NSAID: non-steroidal anti-inflammatory drugs; IL-4: interleukins 4; IL-6: interleukins 6; TNF- α: tumor necrosis factor-α; TGF- β: transforming growth factor-β; hs- CRP: high-sensitivity C-reactive protein; ESR: erythrocyte sedimentation rate; KOA: Osteoarthritis of the knee; LC: *Curcuma* longa; MDA: malondialdehyde; ROS: reactive oxygen species; ACR: American College of Rheumatology; SOD: superoxide dismutase; GSH: glutathione; MDA: malondialdehyde; K-L: American College of RheumatologyKellgren-Lawrence; KOOS: Knee Injury and Osteoarthritis Outcome Score; SLCP: solid lipid curcumin particles; BCL: *Curcuma* longa extracts; PGADA: Patient Global Assessment of Disease Activity; AE: adverse events; BSE: Boswellin Super; PGE2: prostaglandin E2.

and have been considered for the treatment of different inflammatory conditions, including IBD, especially UC (Mazieiro et al. 2018; Cunha Neto et al. 2019). Figure 4 shows some pathophysiological aspects of IBD and the effects of curcumin.

Table 1 shows the studies that evaluated the effects of *Curcuma longa* in patients with IBD. Only studies with Ulcerative Colitis were found. Except for one study (Hanai et al. 2006) all the patients presented mild-to-moderate UC and maintained the use of conventional therapy for UC (sulfasalazine, mesalamine, and 5-aminosalicylate). One study does not mention the conventional therapy that patients were using during the trial (Sadeghi et al. 2019).

There were variations in the mode of administration of curcumin among the RCT varying from oral forms (Hanai et al. 2006; Sadeghi et al. 2019; Lang et al. 2015; Banerjee et al. 2017; Kedia et al. 2017; Masoodi et al. 2018) to enema (Ahuja et al. 2011). Some of the studies used purified curcumin (Lang et al. 2015; Kedia et al. 2017) and others used Self-Micro Emulsifying Drug Delivery System (SMEDDS) (Banerjee et al. 2017) or nanomicelles (Masoodi et al. 2018). Substantial variations were also noted with regards the doses of curcumin used, which varied from 150 mg (Kedia et al. 2017) up to 3000 mg (Lang et al. 2015). Lower doses of oral curcumin have showed not to be effective in inducing clinical remission in patients with mild to moderate UC (Kedia et al. 2017). With regards the administration time it was also noted a significant variation that ranged from 4 weeks up to 6 months.

The effects of the use of the plant were evaluated according to the following disease scores Ulcerative Colitis Disease Activity Index (UCDAI), Clinical Activity Index (CAI), and Simple Clinical Colitis Activity Index (SCCAI). After the administration of curcumin the studies showed CAI improvements (Hanai et al. 2006), LCDAI reduction and remission rates of 78.5% (Ahuja et al. 2011), 38% (Lang et al. 2015), and 26.3% (Banerjee et al. 2017). Moreover, the SCCAI index was significantly lower after the use of the plant (Sadeghi et al. 2019; Masoodi et al. 2018).

Overall, the addition of the curcumin to the conventional therapy for the treatment of IBD, especially UC, seems to be associated to the improvement of symptoms (reduced frequency of urgent defecation), clinical outcomes, quality of life, remission in mild and moderate cases, and may be a safe and promising agent for the treatment of these conditions. The curcumin doses that brought benefits to the patient with psoriasis ranged from 20 to 500 mg (orally administrated) (Goulart et al. 2020).

Osteoarthritis and Curcuma

The pathogenesis of the disease is related to the increase in the enzymes related to cartilage degradation, including disintegrin and metalloproteinases. Associated with the increase of enzymes is the increase of pro-inflammatory biomarkers such as IL-1β, IL-6, IL-18, IL-17, and TNF-α, resulting in cartilage degradation, osteophyte formation, subchondral bone remodeling, and modifications in the synovium and

Table 3. Randomized clinical trials showing the effects of curcumin in *Lupus erythematosus*.

Reference	Local	Model and patients	Intervention	Outcomes	Conclusion
(Khajehdehi et al., 2012)	Iran	Randomized and placebo-controlled study with 24 patients with relapsing or refractory biopsy-proven lupus nephritis; 2 groups (trial and control), 32–45 y, 22 ♀ and 2 ♂	With each meal, subjects in the treated group received 1 capsule (500 mg turmeric, with 22.1 mg was the active ingredient curcumin)/ 3m, (3 capsules daily). The control group received capsules with starch	A significant decrease in proteinuria, systolic pressure, and hematuria were met when comparing pre and 1, 2, and 3 months supplementation in the trial group. No adverse effect related to turmeric was observed during the trial	Short-term turmeric supplementation can bring benefits for patients with relapsing or refractory lupus nephritis and can be used as a safe adjuvant therapy
(Singgih Wahono et al. 2017)	Indonesia	Double-blind randomized controlled trial with 39 patients diagnosed as SLE based on the criteria of ACR, 27–40 y	The subjects were divided into a group receiving 3 × 400 IU cholecalciferol and 3 × 1 tablet placebo (group I, n = 20) and the group receiving 3 × 400 IU and curcumin (*Curcuma xanthorrhiza*) 3 × 20 mg/3m (group II, n = 20)	There were no significant differences in SLEDAI, IL-6, and TGF-β1 serum among groups after the treatment.	*Curcuma xanthorrhiza* supplementation and vitamin D3 had no effects on SLEDAI and serum levels of IL-6 and TGF-β1

SLE: Systemic Lupus Erythematosus; ACR: American College of Rheumatology; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index

joint capsule. These degenerative processes are related to severe pain and reduced mobility, leading to reduced quality of life and an increase in the socioeconomic burden with these patients (Akuri et al. 2017; Chow and Chin 2020).

The traditional therapies are the use of corticosteroids, nonsteroidal anti-inflammatory drugs, and analgesics. Nevertheless, the use of these drugs can lead to substantial side effects such as gastrointestinal problems, primarily if they are used for long periods. In this view, *Curcuma longa* and its derivatives can be auxiliary in the therapeutic approach once it promotes inhibition of the signaling mediated by NFkß. With the inhibition of IKK (inhibitor of nuclear factor kappa-B kinase subunit beta), no phosphorylation and degradation of IkBα (nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor-α) occurs (Nicoliche et al. 2020; Billesberger et al. 2020). Figure 5 shows some pathophysiological aspects of osteoarthritis and the effects of curcumin.

Table 2 shows the RCTs that evaluated the effects of *Curcuma* in patients with OE. An overview of these studies shows heterogeneity in the duration of the study, where the follow-up time ranged from 28 days to 12 weeks. The doses used also varied between studies (approximately 100 mg to 1500 mg/day of curcumin). Regarding administration, all studies used *Curcuma* orally, but it was observed that the plant was used in the form of rhizome extract in capsules, in the form of different commercial formulations that included solid lipid oil (Gupte et al. 2019), or a mixture of curcumin with different plant extracts like *Boswellia serrata*, piperine and gingerols (Heidari-Beni et al. 2020; Karlapudi et al. 2018; Haroyan et al. 2018), *T. chebula* (Karlapudi et al. 2018) and piperine (Panahi et al. 2016; Rahimnia et al. 2015).

The studies compared the effects of using turmeric (or formulations with the plant, or with curcuminoids) with placebo and with or without glucosamine sulfate (Madhu, Chanda, and Saji 2013), diclofenac (Pinsornsak and Niempoog 2012; Srivastava et al. 2016), ibuprofen (Gupte et al. 2019; Kuptniratsaikul et al. 2014), or naproxen (Heidari-Beni et al. 2020; Shep et al. 2019). Except for the work of Rahimina et al (Rahimnia et al. 2015), who found no differences between the treated group and the placebo in the levels of C Reactive Protein, Prostaglandin E2, IL-4, and IL-6, all studies indicate that the plant or its bioactive compounds can be used in the treatment of OA. The results show that the use of *Curcuma longa* leads to decreased pain, improves stiffness, physical function and different standardized scores such as Visual Analog Scale (VAS), Knee injury and Osteoarthritis Outcome Score (KOOS), Lequesne's pain functional index (LPFI), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), and Patient Global Assessment of Disease Activity (PGADA). All studies also indicate that the use of the plant may be considered safe and well-tolerated. CL also is related to the decrease of oxidative stress, which, together with inflammation, contributes to the evolution and clinical worsening of OA.

Furthermore, studies comparing turmeric with ibuprofen (Gupte et al. 2019; Kuptniratsaikul et al. 2014) and diclofenac (Pinsornsak and Niempoog 2012; Srivastava et al. 2016; Shep et al. 2019) have shown that the plant has effects equivalent to these drugs, without the adverse effects generally reported by patients as gastrointestinal events.

The studies show improvement of OE scores with curcumin doses that varied from 500 to 1500 mg a day (orally administrated) or curcumin-based formulations (theracurcumin) in the dosage of 180 mg a day.

Lupus erythematosus and Curcuma

SLE has unknown etiology, but genetics, epigenetic, and environmental risk factors play an essential role. Hormonal factors, ultraviolet light, viruses, and drugs can be related to the pathogenesis (Little and Vesely 2020).

The disease activity is actuated by abnormalities in the dendritic cell, in the balance TH1, TH2, TH17, Treg cells,

Table 4. Randomized clinical trials showing the effects of curcumin in Psoriasis.

Reference	Local	Model and patients	Intervention	Outcomes	Conclusion
(Sarafian et al. 2015)	Iran	Randomized, prospective, right-left comparative, placebo-controlled, double-blind clinical trial with 34 patients with mild/moderate bilateral symmetrical lesions of stable plaque psoriasis on legs and arms (♂ to ♀ ratio of 14 to 20; 18–60 y)	Both active and placebo preparations were made identical and supplied in a 50 g tubes for a maximum of 3 w supply at a time. Patients were instructed to use 2xd. Treatment was maintained for 9w. The PASI score, photography, and quality of life questionnaire known as DLQI were used.	All subjects completed the 9 w of active treatment, and it was observed progressive reduction of thickness, decrease erythema, and pruritus, resulting in moderate to acceptable improvement and, in some cases, the significant resolution of psoriatic lesions.	Microemulgel may an alternative in some patients and most likely as an add-on therapeutic option for many patients suffering from plaque psoriasis.
(Carrion-Gutierrez et al. 2015)	Spain	Randomized, double-blind, placebo-controlled, pilot clinical trial with 21 patients with moderate to severe psoriasis, 37–56 y, 13 ♂ and 8 ♀	Patients received 100 mg of *Curcuma* extract orally, with 12 mg of curcumin per tablet with VLRT or VLST in the experimental area, while the rest of the body surface was treated with UVA radiation. The outcomes were the number of responders and the temporal course of the response, and safety	No participants included in the VLRT group exhibited moderate or severe plaques at the end of the treatment when comparing to the patients in the VSLT group. The evolution of BSA, PGA, and PASI scores was evaluated. 76% of patients showed a response in the BSA exposed to UVA. Lesions in the experimental area showed a response in 81% in the VLRT group and 30% VLST group	Oral *Curcuma* if activated with visible light phototherapy can be effective to treat moderate to severe plaque psoriasis
(Antiga et al. 2015)	Italy	Randomized, double-blind, placebo-controlled clinical trial, with 63 patients with mild/moderate plaque psoriasis with a PASI $<$ 10; 32 ♂ and 31 ♀, 19–62 y	Patients consumed tablets of 500 mg Meriva (Indena SpA, Milan) 2xd, for an overall daily dose of 2 g or with topical steroids alone both for 12 w. Meriva is a delivery dietary phenolic curcumin, with lecithin to boost the absorption and bioavailability.	After 12w, both groups achieved a significant reduction of PASI (but value for patients treated with both topical steroids and oral curcumin was higher than those patients treated only with topical steroids. IL-22 levels were significantly reduced in patients that used oral curcumin	Curcumin is effective as adjuvant therapy for the treatment of *Psoriasis vulgaris*
(Ramírez-Boscá et al. 2017)	Spain	Randomized, with third party blind evaluation, Unicenter, open pilot clinical trial with 24 patients with moderate to severe psoriasis	Participants were randomized to receive 600 mg/day of *Curcuma* extract and visible blue light or conventional PUVA therapy with methoxsalen for 12w.	85% of the *Curcuma* group and 91% of PUVA group showed psoriasis area and severity Index reduction (higher than 75%), but the speed of response was slower in the *Curcuma* group. The SE related to *Curcuma* extract combined with visible blue light treatment were rare and mild, while in the PUVA group, patients required sun protection, and some of them showed gastric distress	Treatment with *Curcuma* is effective and safe, although the speed of this improvement may be slower than that with PUVA
(Bahraini et al. 2018)	Iran	Randomized, placebo-control clinical trial with 30 patients with mild/moderate scalp psoriasis, 18–75 y, 21 ♀ and 9 ♂	The case group received turmeric tonic 2xd for 9 w, and the other group received a placebo. Evaluations at week 3, 6 and 9 using DLQI questionnaire, PASI scores, and medical photos	*Curcuma* tonic significantly reduced the scaling, erythema, and induration of lesions (PASI score), when compared to placebo and aso, improved quality of life.	The clinical effects of *Curcuma* lotion on scalp psoriasis were beneficial overall and can be considered as a treatment for scalp psoriasis
(Bilia et al. 2018)	Italy	Placebo-controlled, double-blind, randomized clinical	The first group was treated orally with acitretin (0.4 mg/kg/	The decrease in PASI was significantly higher in the curcumin group, and serum	Nanourcumin is an effective adjuvant therapy in moderate-

(*continued*)

Table 4. Continued.

Reference	Local	Model and patients	Intervention	Outcomes	Conclusion
		trial with 30 patients (16 ♂s, 14 ♀s, 24–63 years) randomized into arm 1 and 2	day) and nanocurcumin (3 g/day), and the other group was treated with acitretin, for 12 w	levels of total cholesterol remained unchanged in subjects treated with acitretin plus nanocurcumin	to-severe psoriasis patients treated with oral acitretin, improving their lipid serum profile

CL: *Curcuma* longa; PASI: psoriasis area and severity index; DLQI: Dermatology Life Quality Index; VLRT: real visible light phototherapy; VLST: simulated visible light phototherapy; UVA: ultraviolet A; ITT: intention-to-treat; PGA: Physician Global Assessment; BSA: Body Surface Area Affected; DLQI: dermatology life quality index

and dendritic cells, and on the levels of anti-inflammatory and proinflammatory cytokines (such as IL-17 and IL-23) and their receptors in the body. This scenario results in inflammation and tissue destruction (Parikh et al. 2020; Singgih Wahono et al. 2017).

Corticosteroids and immunosuppressive drugs are the main drugs used in the treatment of SLE, and antihypertensive drugs, hydroxychloroquine, and anti-osteoporosis drugs also are crucial in the management of the disease. However, these medications are associated with significant side effects. Considering that the pathogenesis of SLE is yet to know, many studies have been performed to evaluate the impact of diet on the disease activity. In this context, curcumin shows several actions that can benefit SLE, both in terms of triggering or modifying the course of the disease (Momtazi-Borojeni et al. 2018; Constantin et al. 2019).

Table 3 shows the two RCTs that investigated the use of *Curcuma* and Lupus erythematosus. Both studies used *Curcuma* orally for three months and with doses that varied from 500 mg of turmeric (with 22.1 mg of active curcumin) (Khajehdehi et al., 2012) and 20 mg of *Curcuma xanthorrhiza* associated with vitamin D (Singgih Wahono et al. 2017). Khajehdehi et al (2012) found that the use of short-term supplementation with turmeric is associated with benefits in subjects with relapsing or refractory lupus nephritis and could be used as safe adjuvant therapy. On the other hand, Singgih Wahono et al. (2017) did not find changes in the Systemic Lupus Erythematosus Disease Activity Index and the levels of IL-6 and TGF-β after supplementing *Curcuma xanthorrihiza*. One of the explanations of these findings could be related to the low dosage of *Curcuma* used in the study and to the bioavailability of curcumin administered per oral route.

The curcumin doses that brought benefits to the patient with lupus ranged from 20 to 500 mg (orally administrated).

Psoriasis and Curcuma

The pathogenesis of psoriasis involves a complex interplay between the innate and adaptive immune system, with a central driver IL-23/IL-17 axis. Although the underlying molecular mechanisms have not been fully clarified, targeting the pro-inflammatory cytokines is the milestone of the treatment options that are currently available. This condition is predominantly managed with steroids, which are associated with various side effects. Vitamin D analogs can cause skin irritation and hypocalcemia, while corticosteroids are associated with local adverse events, including skin atrophy, striae, and telangiectasia, as well as systemic adverse events such as adrenal suppression. *Curcuma longa*, has properties (anti-inflammatory, antimicrobial, antioxidant, and antineoplastic) that can be helpful to treat psoriasis (Castaldo et al. 2020; Di Meglio, Villanova, and Nestle 2014; Bahraini et al. 2018; Gooderham et al. 2014). Figure 6. Shows some pathophysiological aspects of Psoriasis and the effects of curcumin.

Table 4 presents the six studies that evaluated the effects of *Curcuma* in psoriasis. Many variations in the treatment and severity of the disease were found among these studies that enrolled patients with mild to moderate psoriasis or with a severe stage of the disease (Carrion-Gutierrez et al. 2015). The treatments were oral or topic microemulgel (Sarafian et al. 2015) or tonic (Bahraini et al. 2018) and included the use of curcumin alone or activate (real visible light phototherapy or simulated visible light phototherapy), or associated with steroids (Antiga et al. 2015), acitretin (Bilia et al. 2018), visible blue light or conventional PUVA therapy with methoxsalen (Ramírez-Boscá et al. 2017). The dose of oral *Curcuma* varied from 100 mg/day (Carrion-Gutierrez et al. 2015) to 3 g (Bilia et al. 2018). The RCTs outcomes suggest that the use of *Curcuma*, orally, or topic can bring benefits as an adjuvant to treat psoriasis.

The doses of curcumin that brought benefits to the patient with psoriasis ranged from 100-600 mg of turmeric extract (orally administrated) a day, 3 g of nanocurcumin a day or even a tonic prepared with plant extract.

Sclerosis and Curcuma

There is no cure for MS. Currently, available therapies are aimed primarily at reducing the number of relapses and slowing the progression of disability. Conventional agents including corticosteroids; recombinant interferon (IFN)-β-1a, 1b; glatiramer acetate; natalizumab; fingolimod; and other medications are partially effective but often result in serious side effects, such as infections or secondary malignancy liking treatment-related acute leukemia (Wingerchuk and Carter 2014; Salehi et al. 2020).

Besides that, reactive CD4+ T cells (TH1, TH17, and Treg phenotypes) are crucial to MS. The TH1 phenotype can promote major histocompatibility complex-II expression, and TH17 can induce inflammatory gene expression. Curcumin has been reported to show great potential in MS treatment, once it could inhibit CD4+ T cell proliferation and effector cell activation. Besides the anti-inflammatory properties, curcumin is also related to the reduction of oxidative stress. These characteristics may bring crucial benefits

Table 5. Randomized clinical trials showing the effects of curcumin in Sclerosis.

Reference	Local	Model and patients	Intervention	Outcomes	Conclusion
(Ahmadi et al. 2018)	Iran	Pilot Randomized Clinical Trial with 54 patients, age range of 18–85 years, 39 ♂ and 15 ♀.	Patients were randomized to receive either nanocurcumin 80 mg daily or placebo during 12 m	After 12 m, events occurred in 3.7% in the nanocurcumin group and in 22.2% in the placebo. Kaplan–Meier evaluation showed a significant difference between the study groups regarding survival curves. No significant differences were found for the other outcomes. No severe side effects or treatment-related deaths were detected.	Nanocurcumin might improve the probability of survival as an add-on treatment in patients with ALS. Also it is safe for patients
(Dolati, Aghebati-Maleki, et al. 2018)	Iran	Randomized, double-blind, placebo-controlled trial with 50 patients with RRMS (28–51, 42 ♀, 8 ♂, EDSS score $<$ 5/5) and 35 controls (26–50 y, 22 ♀ and 13 ♂)	Patients received nanocurcumin capsules (80 mg oral) or placebo capsules /6 m. Blood samples were collected prior and after administration of nanocurcumin or placebo	The expression of several microRNAs is regulated by nanocurcumin indicating restoring of the expression pattern of dysregulated miRNAs in patients with MSIs	Nanocurcumin may be used as a beneficial approach to improve therapeutic outcomes for MS
(Chico et al. 2018)	Italy	Randomized double-blind, placebo-controlled trial with 42 patients (20 ♂ and 22 ♀; 39–83 y. 38 patients were sporadic cases, and 4 were familiar ALS (one A total of them with G41S and SOD1 mutation	Patients were divided in group 1 (Brainoil: curcumin 600 mg + 100 mg Coenzyme Q10 /day/3m); and group 2 (Brainoil/600 mg/day/ 6m). The evaluations were conducted at baseline, 3 m of Brainoil or placebo, and after the 3 m open-label phase. Clinical evaluations and oxidative stress biomarkers (AOPPs, FRAP, T-SH, and lactate) were evaluated. Patients continued to take regular therapy for ALS (Riluzole 50 mg/2xd)	Over the entire study, Group 2 showed a stable ALS-FRS-r score in parallel with a reduction of AOPPs, which was not detected in Group 1. FRAP remained stable in Group 2, while in Group 1 they were reduced. Compared to controls, the whole ALS population showed greater oxidative stress; those treated with curcumin exhibited decreased exercise AOPPs at T2 with values approaching those of controls.	Use of curcumin shows a slight slowdown in the disease progression, improving aerobic metabolism and oxidative damage
(Dolati, Aghebati-Maleki, et al. 2018)	Iran	Randomized, placebo, clinical trial with 50 patients (31 ♀ and 19 ♂; 28–51 y; diagnoses of MS (Mc Donald Criteria). All patients were in RRMS (EDSS $<$ 5/5) and no relapses occurred for at least 3 m before the study	All patients received INF-β1a injections/3m before the intervention. 25 patients received nanocurcumin capsules (80 mg of curcumin in nanomicelle)/day or placebo for 6 m. Additionally, a healthy control group was also used	The use of curcumin showed a significant reduction of mRNA expression of miR-145, miR-132, miR-16, STAT1), TNF-α, AP-1, IL-1β, IL-6, IFN-γ, CCL2, CCL5, NF-κB, and also a significant increase in expression of miRNAs targets; sirtuin-1, Foxp3, Sox2, PDCD1. IFN-γ, CCL2, and CCL5 were reduced dramatically in the test group compared with the placebo group	Nanocurcumin is effective on the inflammatory features of MS
(Dolati et al. 2019)	Iran	Randomized, double-blind, placebo-controlled trial with 50 patients (31♀ and 19♂), 28–51 y; BMI 19–30; EDSS 0–5.5, and no relapses occurred for at least 4 m before the study	MS patients were divided into 2 subgroups to received a daily dose of 80 mg oral nanocurcumin or placebo/6m	A significant reduction was observed in peripheral Treg cell and FoxP3, IL-10, TGF-β expression in subjects with RRMS. The results showed that the frequency of Treg cells, the expression of FoxP3, TGF-β, and IL-10 and the secretion levels of the TGF-β and IL-10 in cultured PBMCs are increased in nanocurcumin treated group compared to the placebo group.	The results indicated that nanocurcumin could restore the frequency and function of Treg cells in MS patients

MS: Multiple Sclerosis; SE:RRMS: relapsing-remitting multiple sclerosis; EDSS: expanded disability status scale; ALS: Amyotrophic Lateral Sclerosis; ALS-FRS-r: revised ALS Functional Rating Scale; AOPPs: oxidative protein products; FRAP: ferric reducing ability; T-SH: total thiols; mRNA: messenger RNA; miR-145: microRNA encoded by the MIR145 gene; miR-132: microRNA encoded by the MIR132 gene; miR-16: microRNA encoded by the MIR16 gene; STAT1: Signal Transducer and Activator of Transcription 1; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; AP-1: Activator protein 1, IL-1β: interleukin 1β; IL-6: interleukin 6; IFN-γ: interferon γ, CCL2: chemokine ligand 2; CCL5: chemokine ligand 5; RRMS: Relapsing-Remitting Multiple Sclerosis; TNF-α: Tumor necrosis factor α; BMI: body mass Index; Treg cell: The regulatory T cells; TGF-β: Transforming growth factor-beta; IL-10: interleukin 10; FoxP3: forkhead box P3; PBMCs: peripheral blood mononuclear cell.

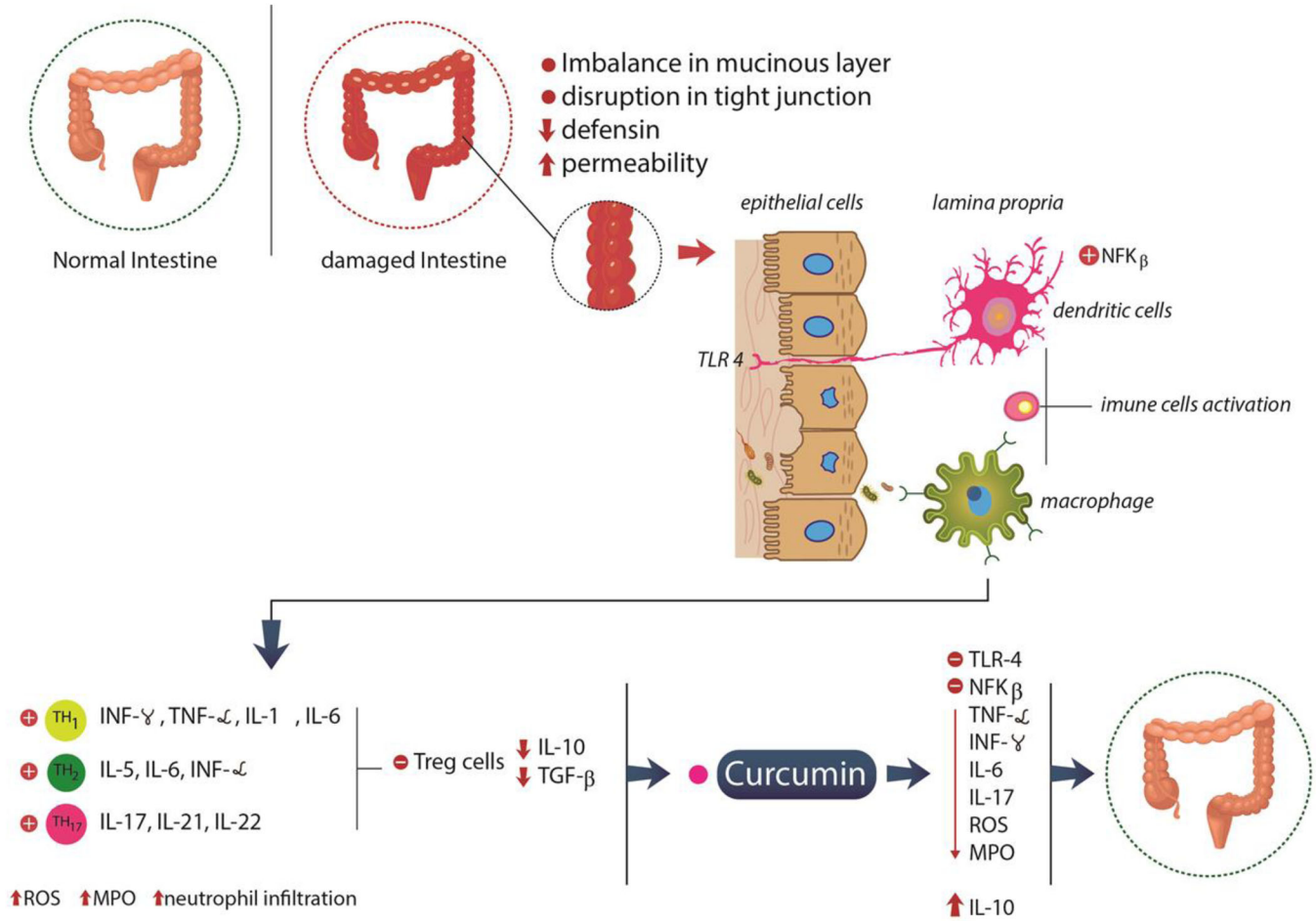

Figure 4. Pathophysiological aspects of Inflammatory Bowel Disease and the effects of curcumin. Damaged intestine shows imbalance in the mucinous layer, decreased defensin, and interruption in the tight junction, resulting in increased permeability, and activation of dendritic cells and macrophages. This scenario is accompanied by the increased release of INF-γ, TNF-α, IL-1, IL-6, IL-5, IL-21, IL-17 and IL-22 and decreased release of IL-10 and TGF-β. Curcumin inhibits TLR-4 and NFK- β, decreasing the release of pro-inflammatory cytokines, ROS, MPO and increasing anti-inflammatory cytokines such as IL-10, improving inflammatory aspects and decreasing intestinal damage. TLR: Toll Like Receptor; NF$\kappa\beta$: Nuclear Factor $\kappa\beta$; TH: T helper cell; TReg: T Regulatory cells; INF-γ: Interferon-γ; TNF-α: Tumor necrosis factor alpha; IL: Interleukin; TGF-β: Transforming Growth Factor-β; ROS: Reactive oxygen species; MPO: metalloproteinase.

in the therapeutic approach of MS (Liu et al. 2019; Jelcic et al. 2018; Fetoni et al. 2015).

Five RCTs involved the use of *Curcuma* and sclerosis (Table 5). Four of them used nanocurcumin 80 mg, and one used curcumin 600 mg (Chico et al. 2018). Curcumin was used alone or in association with Coenzyme Q or brainoil (Chico et al. 2018), and follow-up varied from 6 to 12 months. The outcomes showed that the use of curcumin shows an increase of survival rates (Ahmadi et al. 2018), slowdowns the disease progression (Chico et al. 2018; Dolati, Aghebati-Maleki, et al. 2018), improves aerobic metabolism and oxidative damage (Chico et al. 2018), and reduces pro-inflammatory pattern in multiple sclerosis (Dolati, Aghebati-Maleki, et al. 2018; Dolati et al. 2019).

As a therapeutic adjuvant to sclerosis, positive effects were observed using 600 mg of curcumin or 80 mg of nanocurcumim orally administrated.

Other comments

Several studies have shown that *Curcuma* species (*C. longa, C. domestica,* and *C. xanthorrhiza*) can bring benefits in the therapeutic approach of inflammatory diseases both used alone or in combination with other therapies. However, there is no standardization of the doses used, the form of administration, and duration of treatment. Many studies are unclear regarding the presentation of demographic data, and the small number of patients involved in the RCTs may be significant biases in these studies.

Despite the above limitations, a considerable part of the studies indicate that the use of *Curcuma* sp/curcumin can be beneficial in patients with inflammatory bowel disease, osteoarthritis, psoriasis, lupus and sclerosis, in addition to not producing (or producing less) side effects when compared to other pharmacological therapies available to date.

Conclusion

Adding curcumin to the traditional drug therapy seems to be promising and safe for the treatment of autoimmune and inflammatory diseases. More studies are needed to elucidate how and to what extent *Curcuma* or its derivatives can be used safely and efficiently as adjuvants or as a main therapy for these diseases that increase year by year in the world population.

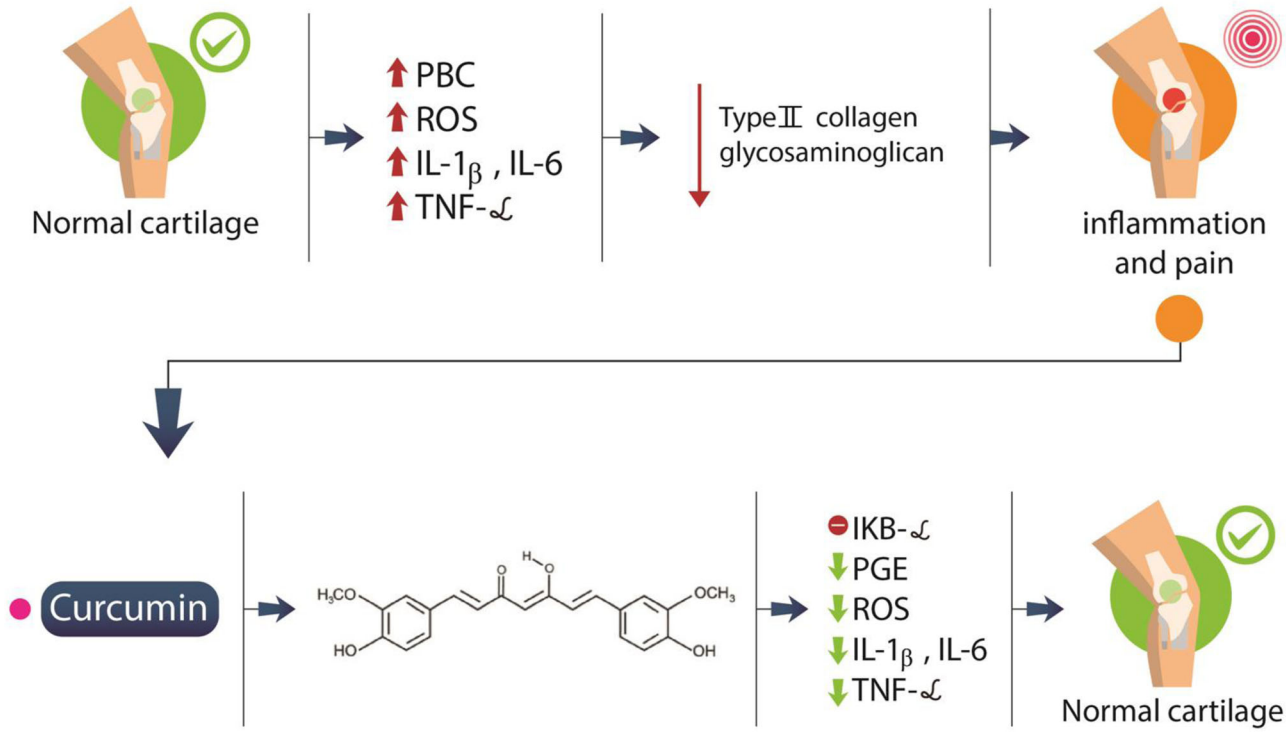

Figure 5. Pathophysiological aspects of osteoarthritis and the effects of curcumin. In normal cartilage, there is an increase in PBC, ROS, IL-1β, IL-6 AND TNF-α, causing a decrease in type 2 glycosaminoglycan collagen that causes inflammation and pain. Curcumin inhibits IKB-α, decreasing PGE, ROS, IL-1β, IL-6 and TNF-α, consequently decreasing inflammation and pain. PGE: prostaglandin; IKB-α: nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor-α; TNF-α: Tumor necrosis factor alpha; IL: Interleukin; ROS: Reactive oxygen species; MPO: metalloproteinase.

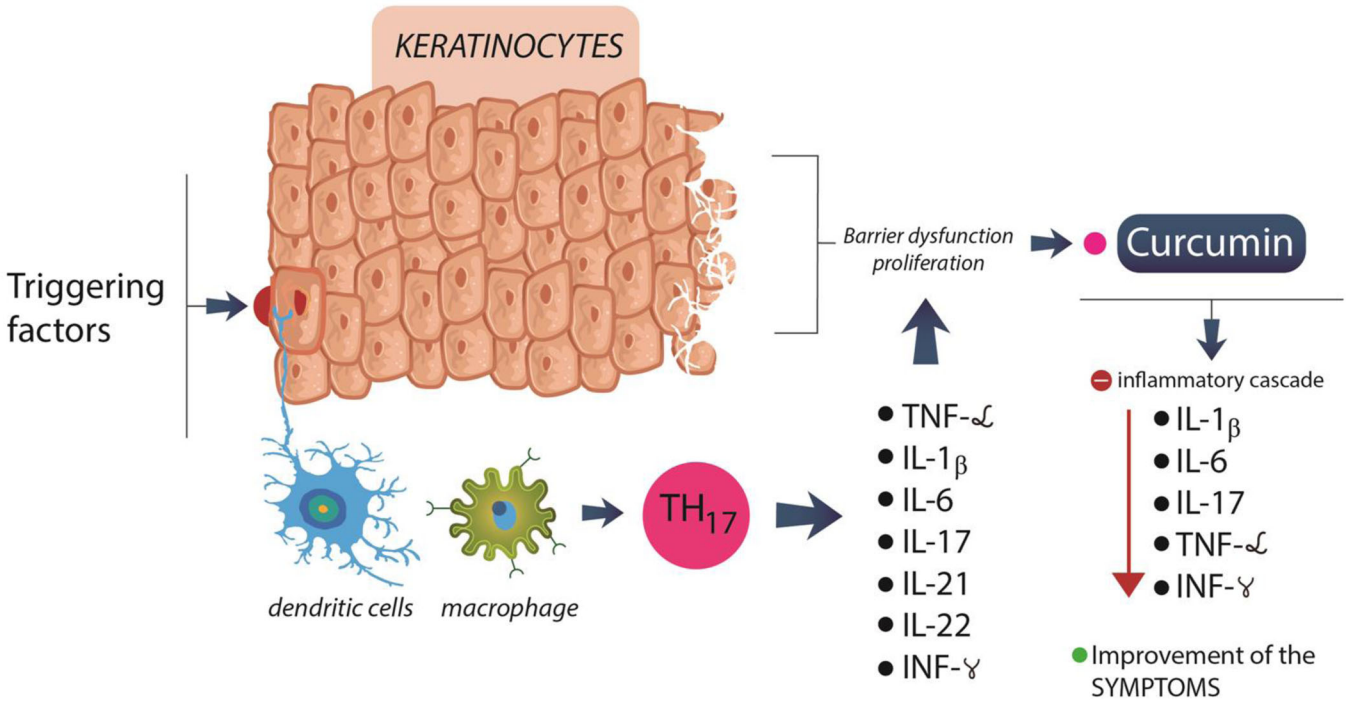

Figure 6. Pathophysiological aspects of Psoriasis. Triggering factors act on keratinocytes causing activation of dendritic cells and macrophage that stimulate TH17 to produce pro-inflammatory cytokines such as TNF-α, IL-1β, IL-6, IL-27, IL-21, IL-22 and INF-γ, leading to a barrier dysfunction proliferation. Curcumin inhibits the inflammatory cascade, decreasing cytokines IL-1β, IL-6, IL-17, TNF-α, INF-γ, and improvement of the symptoms. TH: T Helper Cell; TNF-α: Tumor necrosis factor alpha; IL: Interleukin; INF-γ: Interferon-γ.

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