BJPS

Brazilian Journal of
Pharmaceutical Sciences

http://dx.doi.org/10.1590/s2175-979020200004181008

Article

Curcumin supplementation in the treatment of patients with cancer: a systematic review

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Feeding with high levels of phytochemicals, including curcumin, may be a therapeutic option for diseases such as cancer which is a public health problem. The aim of this study was to systematically review the results of clinical trials investigating the effect of oral curcumin supplementation on anti-inflammatory and antioxidant profiles, reduction of PSA levels and degree of dermatitis in radiotherapy treatment in cancer patients. The review was carried out based on the items of the PRISMA Statement. A bias risk assessment was performed according to Cochrane Collaboration criteria. Six studies met the eligibility criteria and were included in the systematic review. The results of this study are based on those obtained in the literature on the effect of curcumin on the anti-inflammatory profile, on reducing dermatitis, on PSA alteration and on anti-oxidant profile for a total of 450 individuals, comprising 259 in the intervention group and 191 in the control group. Some studies have reported improvement in biochemical and clinical indicators, with limited adverse effects and good tolerance. It was not possible to determine, with the desired degree of evidence, the effect of curcumin supplementation in the treatment of cancer patients. It is important to consider the great heterogeneity and methodological weaknesses of the studies, and that it was not possible to perform a meta-analysis of the data available in the literature.

Keywords: Curcumin. Cancer. Systematic review. Anti-inflammatory profile. Anti-oxidant profile.

INTRODUCTION

Studies published to date have shown that feeding with high levels of dietary fibers, vitamins, minerals and polyphenols confers a protective role for a number of chronic diseases, including cancer (CA) (Ferlay *et al*., 2015; Tachibana, 2011). The anti-inflammatory and immunomodulator effects of phytochemicals, such as curcumin, may serve as an important complementary therapeutic option in the treatment of these patients (Rezaee *et al*., 2017).

Curcumin is a long-used phytochemical with a large number of biological targets, for which anti-inflammatory, antioxidant, anti-tumor, immunoregulatory, hepatoprotective, anti-ischemic, anti-dyspeptic, anti-depressant, and analgesic effects have been determined (Amalraj *et al*., 2017).

Preclinical studies have reported curcumin as a potent epigenetic regulator, acting in the inhibition of deoxyribonucleic acid (DNA), DNA methyltransferases (DNMTs), regulation of modifications of histone acetyltransferases (HATs) and deacetylases (HDACs) and in regulation of micro ribonucleic acids (miRNA) (Boyanapalli *et al*., 2015; Remely *et al*., 2015). Studies conducted *in vitro* show that curcumin prevents the degradation of nuclear factor erythroid 2-related factor 2 (Nrf2), leading to an increase in antioxidant enzymes such as superoxide dismutase (SOD), catalase and glutathione peroxidase (GPx). In addition, it balances the level of these enzymes and recovers reactive oxygen species (Rezaee *et al*., 2017; Sahebkar, 2013). It was also shown to have an anti-inflammatory effect through negative regulation of several cytokines, such as tumor necrosis factor alpha (TNF-α), interleukins (IL-1, IL-

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6, IL-8, IL-12), monocyte chemoattractant protein-1, cyclooxygenase-2 activity (COX-2), lipoxygenase enzyme and inducible nitric oxide synthase (iNOS) (Aggarwal *et al*., 2007; Gupta *et al*., 2013).

In vitro and *in vivo* investigations have also shown that curcumin reduces the inflammatory process by means of inflammatory transcription factors such as nuclear factor kappa (NF-kB), activator protein-1 (AP-1) and signal transducer and activator of transcription 3 (STAT3) (Panda *et al*., 2017; Imran *et al*., 2016). NF-κB and AP-1 also act as transcription factors that regulate the expression of different genes which affect cellular processes, such as proliferation and apoptosis. Curcumin also inhibited the expression of urokinase plasminogen (uPA), focal adhesion kinase activity (FAK), suppressed expression of matrix metalloproteinases (MMPs), inhibited epidermal growth factor receptor (EGFR) activity, regulating tumor cell invasion and metastasis (Durgaprasad *et al*., 2005; Vadhan-Raj *et al*., 2007; Kim *et al*., 2011; Belcaro *et al*., 2010; Shokes *et al*., 2005; Adhvaryu *et al*., 2008; Biswas *et al*., 2010). Due to these therapeutic properties, curcumin exhibited activities against various types of CA (Gupta *et al*., 2013; Dhillon *et al*., 2008; Golombick *et al*., 2009; Ide *et al*., 2010). The main molecular targets and mechanisms of action of curcumin are summarized in Figure 1.

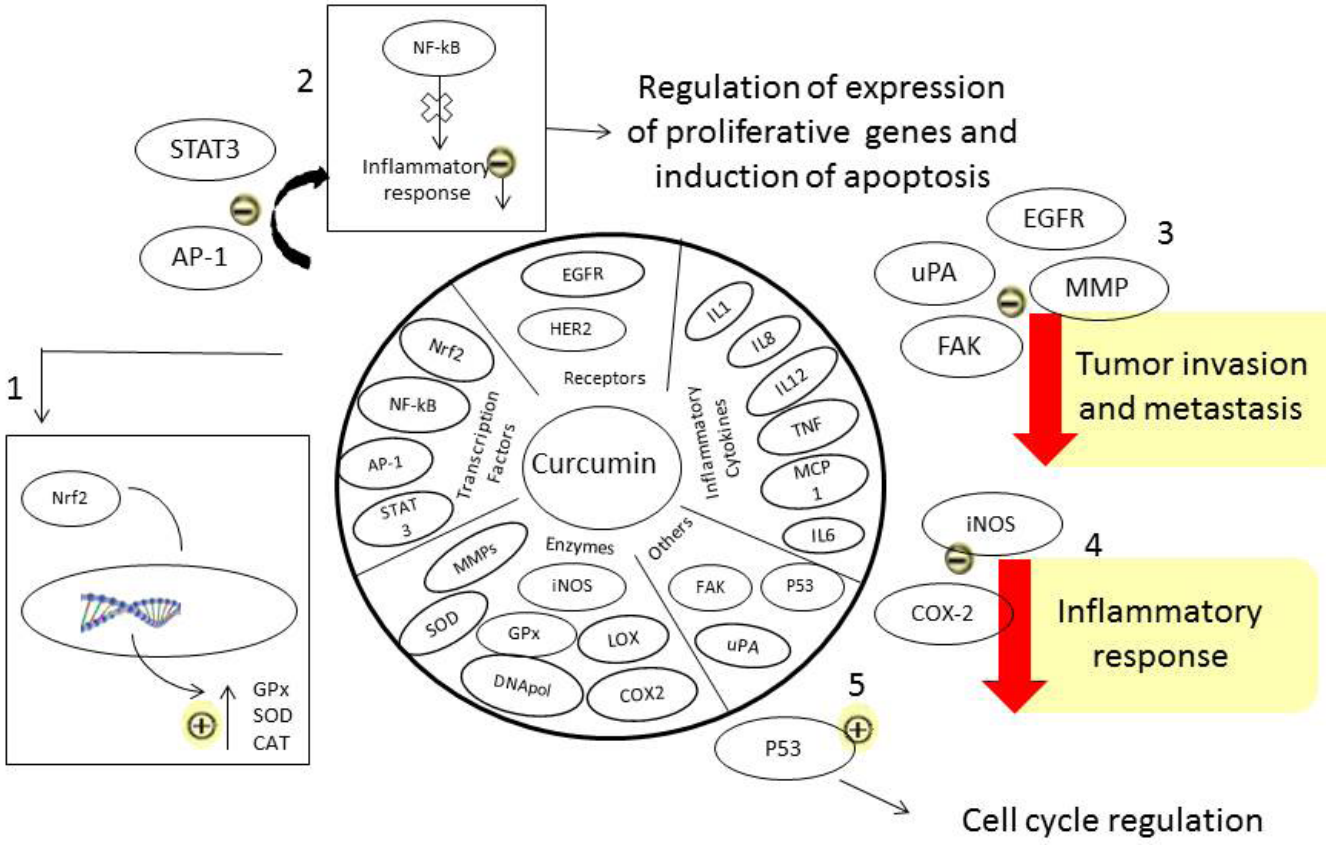

FIGURE 1 – Molecular targets and possible mechanisms of action of curcumin. Adapted from Kunnumakkara *et al.* (2017)
AP-1: Activating Protein-11; COX-2: Cyclooxygenase-2; DNA Deoxyribonucleic Acid; DNA Pol: DNA polymerase; EGF: Epidermal growth factor; FAK: Focal adhesion kinase; GST: Glutathione-S-transferase; HER-2: Human epidermal growth factor receptor 2; IL-1: Interleukin-1; IL-6: Interleukin-6; IL-8: Interleukin-8; IL-12: Interleukin-12; iNOS: Inducible Nitric Oxide Synthase; MCP: Monocyte chemoattractant protein; MMP: matrix metalloproteinase; Nrf2: nuclear factor-erythroid 2–related factor 2; STAT-3: Signal transducer and activator of transcription 3; TNF: Tumor necrosis factor alpha; uPA: Urokinase plasminogen activator. 1 - Curcumin prevents degradation of Nrf2 which leads to an increase in antioxidant enzymes. 2 - Inhibits activation of NF-kB, reducing the inflammatory response, and also inhibits activation of AP-1 and STAT3 by regulating the expression of proliferative genes and inducing apoptosis. 3 - Inhibition of uPA, EGFR, FAK, and MMP leads to air invasion and metastasis of the tumor. 4 - Inhibits iNOS and COX-2, reducing the inflammatory response. 5 - Activates the P53 protein responsible for cell cycle regulation.

However, there is no consensus among specialists on the use of curcumin as a coadjuvant in the clinical treatment of patients with CA. Results of clinical trials are conflicting due to a lack of standardization of methodological aspects, with differences in concentration, type of active principles and intervention time length. Given this scenario, the aim of the present study was to systematically review the results of clinical trials investigating the effect of oral curcumin supplementation in the treatment of patients with CA on antiinflammatory profile, antioxidant activity, decrease in prostate-specific antigen (PSA) levels, and degree of dermatitis in radiotherapy treatment.

MATERIAL AND METHODS

Search strategy

A systematic review of randomized and controlled clinical trials in adult and elderly patients with CA was performed according to recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses: the PRISMA Statement (Moher *et al*., 2009).

The databases Medline/Pubmed, Embase, Cochrane Central Register of Controlled Trials were used in the Cochrane Library, Lilacs, and Clinical Trials. The search was carried out from July 01 to August 31, 2017. The construction of the search strategy was based on the structured PICO process - Population, Intervention, Comparison, Outcome. We used the terms indexed for CA and curcumin, according to the terminology adopted by the site of the Descriptors in Sciences and Health (DeCS), Medical Subject Headings (MeSH) and Embase Subject Headings (Emtree), combined using the Boolean operators "OR" and "AND", without restriction of geographical area, language or year of publication. The terms of outcome were not defined so as to avoid assigning undesirable specificity at this collection stage (Brazil, 2012).

Selection of studies

Two independent reviewers selected randomized and controlled clinical trials including adult and elderly patients with CA of both sexes, who adopted oral use of curcumin in the form of extract, capsule or powder, alone or in combination with other nutrients, collecting information regarding the intervention, such as dose, frequency, duration of intervention and details of the product used. For inclusion, studies also had to present information regarding the anti-inflammatory profile, through interleukins (IL-6, IL-8, IL-10, IL-1), C-reactive protein (CRP) and TNF-α; antioxidant activity, through antioxidant enzymes (catalase, SOD, GPx) and reactive oxygen species; prostate-specific antigen (PSA); and degree of dermatitis associated with anti-neoplastic treatment. We excluded studies involving children, adolescents, review studies, non-randomized, editorial, *in vitro* or *in vivo* model studies. Review articles were used to identify possible additional relevant studies not retrieved by the search strategy.

The selection of studies began independently, by screening titles and abstracts, with subsequent reading of the full texts. Disagreements between the reviewers regarding the eligibility of the articles were resolved by a third reviewer. The data were extracted from the eligible studies independently by the two reviewers using a standard clinical record for data collection of the variables of interest, including information about participants/population, intervention, methods/study design, outcomes, and results, based on the Cochrane Group criteria. In the case of incomplete data, such as the absence of baseline and/or post-intervention data, authors of the articles were contacted via e-mail to obtain information about their studies.

Evaluation of study quality

Eligible studies were analyzed by two external evaluators, according to an instrument recommended by the Cochrane Collaboration for randomized studies, which included identification of selection bias, performance bias, detection bias, friction bias, and reporting bias (Higgins *et al*., 2011; Carvalho *et al*., 2013). Discrepancies were resolved by a third evaluator. Data analysis was performed using Revman 5.3 software (Cochrane IMS, Oxford, UK).

Difference between Protocol and Systematic Review

The protocol of initial research, registered in the International Prospective Register of Systematic Reviews (PROSPERO: CRD42017071650), included performing a meta-analysis, however, this step was not possible due to the insufficient number of studies with the same outcome, different scales in data presentation, great heterogeneity and methodological weakness of the studies. Therefore, the studies identified in the systematic review proved insufficient to perform a meta-analysis on the research question.

RESULTS AND DISCUSSION

The search of the databases resulted in the retrieval of 13,008 studies, with 5,110 replications across the databases. After reading of titles and abstracts, uncontrolled and randomized articles, such as review studies, randomized clinical trials, *in vitro* and *in vivo* studies performed in patients diagnosed with benign tumors were rejected, giving a total of 20 studies eligible for reading in full. After reading of articles, 14 were excluded due to differences such as administration of curcumin through oral, topical or mouthwash routes without subsequent ingestion, no access to the full study, lack of data and non-randomized studies. A schematic diagram of the search strategy is depicted in Figure 2.

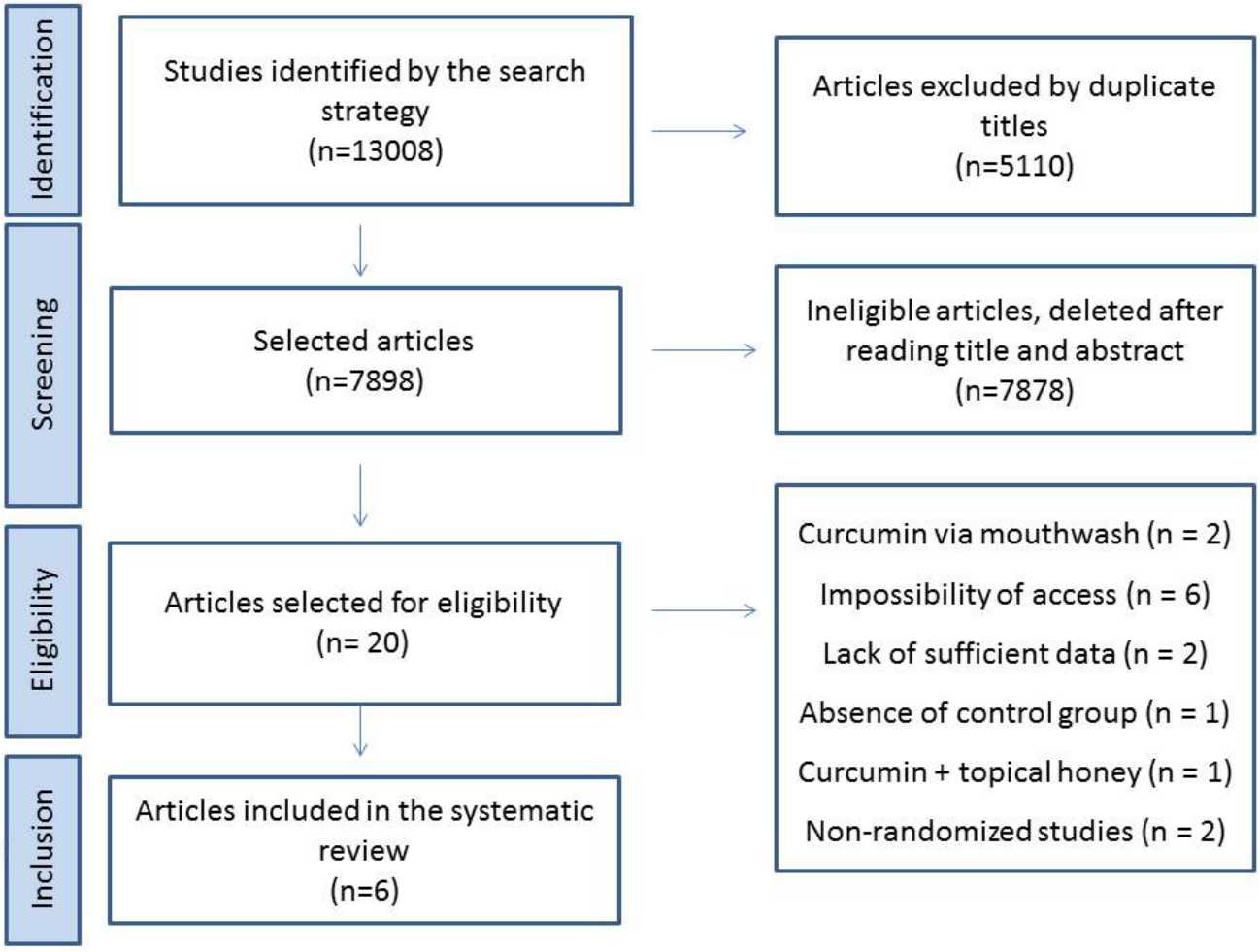

FIGURE 2 – PRISMA illustrative diagram of the systematic search incorporated in this evaluation.

Of the six eligible studies, three reported the effect of curcumin on anti-inflammatory profile (He *et al*., 2011; Panahi *et al*., 2014; Thomas *et al*., 2014), one described reduction in dermatitis after radiotherapy (Ryan *et al*., 2013), three showed modification of PSA (Thomas *et al*., 2014; Hejazi *et al*., 2016; Van Die *et al*., 2017) and one study reported an effect on the profile of antioxidant enzymes (Hejazi *et al*., 2016). A total of 450 adults, comprising 259 individuals in intervention groups and 191 in control groups were included. The age of participants in the studies ranged from 25 to 75 years. The main characteristics of the studies are described in Table I.

TABLE I – Summary of characteristics of clinical trials

Author and location	Intervention duration	Population	Dose	Type of associated treatment	Intervention	Outcomes
He *et al.*, 2011 USA	10, 20 and 30 days (depending on preoperative period)	71 adult patients with colorectal CA	Capsules with 360 mg curcumin 3x/day (1.08g/day curcumin)	Radiotherapy or chemotherapy or combination of both	Curcumin vs. control	Body weight, TNF-α, P-53 protein expression, pro-apoptotic gene levels, and apoptosis death repressor and inducer proteins.
Hejazi *et al.*, 2016 Iran	One week before start of radiotherapy until its conclusion (2 years)	45 patients with prostate CA without metastasis.	Capsules of 500 mg of BCM95, Biocurcumin 6x/day (3g/day of curcumin)	Radiation therapy with 74 Gy dose	Curcumin vs. Control with rice bran	Body weight, PSA levels, SOD, catalase, GPx.
Panahi *et al.*, 2014 Iran	8 weeks	80 patients diagnosed with solid tumors	3x 300 mg Meriva capsules per day (180 mg/day curcumin)	Chemotherapy specific for each CA type	Curcumin vs. control	IL-6, IL-8, calcitonin gene, TNF-α, MCP-1, TGFβ, CRP and quality of life evaluation using the University of Washington scale (UW-QoL).
Ryan *et al.*, 2013 USA	During radiotherapy treatment (16-33 sessions)	35 adult patients with breast CA	4x 500 mg capsules of C3 Complex® 3x/day (2g/day of curcumin)	Radiation therapy with a dose of 42.6-50.4 Gy, not associated with surgical or chemotherapy treatment	Curcumin vs. Dicalcium phosphate control	Severity score of RDS dermatitis and digital image of skin alterations and application of two self-report questionnaires: SI and SF-MPQ.
Thomas *et al.*, 2014 United Kingdom	6 months	199 men with prostate cancer	1 capsule with: powder of broccoli 100 mg, turmeric powder 100 mg, pomegranate 100 mg and green tea extract 100 mg, 3x/day (300 mg/day of curcumin)	No information	Curcumin, Broccoli, Pomegranate and Green Tea vs. Control containing the same volume and anti-caking agent, with 10 mg of watercress extract	Serum levels of PSA

(continuing)

TABLE I – Summary of characteristics of clinical trials

Author and location	Intervention duration	Population	Dose	Type of associated treatment	Intervention	Outcomes
Van Die *et al.*, 2017 Australia	12 weeks	20 adult patients with prostate CA	2 capsules, 2x/day of curcumin (400 mg/d); resveratrol (120 mg/d); green tea (400 mg/d); broccoli (8g/d).	Surgery, radiotherapy or both	Curcumin, Resveratrol, Green Tea and Broccoli vs. Control containing oats	Serum levels of PSA

Legend: Interleukin 6 (IL-6); Interleukin 8 (IL-8); Interleukin 10 (IL-10); Interleukin 1 (IL-1); IL-1 receptor antagonist (IL-1RA); tumor necrosis factor alpha (TNF-α); cyclooxygenase-2 (COX-2); phosphorylated signal transducer and activator of transcription 3 (pSTAT3); Symptom Inventory (SI); -Short Form McGill Pain Questionnaire (SF-MPQ); Radiation Dermatitis Severity (RDS) score; Monocyte Chemotactic Protein-1 (MCP-1); transforming growth factor-β (TGFβ); C-reactive protein (CRP); superoxide dismutase (SOD); glutathione peroxidase (GPx); prostate specific antigen (PSA); insulin-like growth factor 1 (IGF-1); derivatives of reactive oxygen metabolites (D-ROMs).

Four studies used curcumin alone (He *et al*., 2011; Hejazi *et al*., 2016; Panahi *et al*., 2014; Ryan *et al*., 2013), whereas in two studies curcumin was associated with other nutrients (Van Die *et al*., 2017; Thomas *et al*., 2014). Three studies used curcumin in commercially available capsules with standardized formulations (Hejazi *et al*., 2016; Panahi *et al*., 2004; Ryan *et al*., 2013). The main results of these studies are described in Table II.

TABLE II – Summary of main results of clinical trials

Study and year	Outcomes of interest	Main results	Adverse effects
He *et al.*, 2011	TNF- α	Statistically significant reduction in serum TNF alpha levels observed in patients in the curcumin group, but not in those treated with placebo. Administration with curcumin induced apoptosis, increased p53 expression and reduced Bax and Bcl-2 levels in colorectal CA cells.	Reported occurrence of diarrhea in 2 patients, one in the intervention group and one in the placebo group.
Ryan *et al.*, 2013	Decrease in severity of dermatitis	Significant decrease in scores on RDS scale in curcumin group compared to placebo, with decrease after the fourth week. In addition, lower number of patients in the curcumin group had moist desquamation compared to the placebo group, however, with no change in the skin redness. There was no significant difference between groups regarding local pain.	The Symptom Inventory questionnaire was used, where no statistical difference was observed between the curcumin and placebo groups for 17 symptoms present in the questionnaire.

(continuing)

TABLE II – Summary of main results of clinical trials

Study and year	Outcomes of interest	Main results	Adverse effects
Panahi *et al.*, 2014	IL-6, IL-8, TNF- α	Statistically significant reduction in serum levels of TNF-α, IL-6 and IL-8 in both groups. Reductions in TNF-α and IL-6 were significantly higher in the curcuminoid group compared to control group. In contrast, IL-8 reduction was significantly higher in the placebo group, changes in serum IL-8 levels were a predictor of quality of life in the placebo group. In both groups, reduction in TNF-α levels were predictors of quality and life improvement.	Eight patients reported mild gastrointestinal effects. However, there was no abandonment as a result of adverse reactions to treatment.
Thomas *et al.*, 2014	PSA, CRP	There was a significant reduction in serum PSA levels in the intervention group compared to placebo. The mean percentage of PSA increased more slowly in the supplemented group, compared to placebo, a result with statistical significance. An analysis of the subgroup of men under active surveillance also revealed that after the intervention, mean PSA fell while the placebo increased, with a significant difference. For the subgroup of men managed with watchful waiting, PSA had a smaller increase in the intervention group than the placebo group, with statistical difference. Regarding CRP levels, there were no significant differences at the beginning or end of the study between the supplement and control groups.	There were adverse effects such as diarrhea, agitation, tremors and insomnia in both groups, but with no statistical difference.
Hejazi *et al.*, 2016	PSA, SOD, catalase, GPx.	There was a statistically significant increase in total antioxidant capacity and a reduction in SOD activity in the curcumin group. PSA levels were significantly reduced in both groups. There was a decrease in catalase activity, but not statistically significant. There were no changes in GPx activity.	No adverse effects were reported in the two groups.
Van Die *et al.*, 2017	PSA	There was variation in serum PSA levels for both groups. The supplemented group showed a non-significant improvement in PSA values, whereas the placebo group showed no change.	Adverse events were reported in both groups, with no statistical difference, such as "heartburn", and one case of restlessness that persisted throughout the treatment phase. Two men experienced a nocturia increase initially, but this symptom was resolved.

In this review, five studies showed a beneficial effect in the form of improvements in biochemical and clinical indicators among patients with several CA types after curcumin use, such as reductions in IL-6, TNF-α, hs-CRP, and an increase in TAC and improvement in the degree of dermatitis associated with radiotherapy treatment (Panahi *et al*., 2011; Hejazi *et al*., 2014; Ryan *et al*., 2013). Four studies (Panahi *et al*., 2014; Van Die *et al*., 2017; He *et al*,

2011; Thomas *et al*., 2014) showed limited adverse effects and good tolerance to the use of curcumin; data which corroborates those of other similar studies (Imran *et al*., 2016; Rezaee *et al*., 2017).

The clinical trial conducted by Panahi *et al*. (2014) showed a reduction in IL-6 levels in both groups (1.55 to 0.61, p <0.001 in curcumin group vs 1.57 to 1.31, p <0.001 in placebo group), where this reduction was significantly higher in the curcuminoid group compared to the control group (p <0.001). There was also a reduction in IL-8 in the curcumin group (21.64 to 19.78; p = 0.001) vs placebo group (26.23 to 21.38; p <0.001); but levels were significantly higher in the placebo group (p = 0.012). There were no differences between individuals who received radiotherapy or not, or in type of CA (p> 0.05).

Ultra-sensitive CRP levels (hs-CRP) showed a significant decrease in both curcumin (6.96 to 4.63, p <0.001) and placebo (8.54 to 7.92, p = 0.039) groups. There were also significant reductions in serum TNF-α concentrations (28.03 to 15.74, p <0.001) in the curcumin vs placebo group (27.05 to 25.33, p = 0.039), with greater decrease in patients supplemented with curcuminoids compared to placebo (TNF-α p <0.001 and hs-CRP p <0.001) (Panahi *et al*., 2014). It is noteworthy that in this study all patients were undergoing chemotherapy and one of the exclusion criteria was exacerbation of the disease to an uncontrollable level.

In this study by Panahi *et al.* (2014), the quality of life of patients diagnosed with solid tumors supplemented with curcumin was positively correlated with the reduction in hs-CRP (r = 0.25, p = 0.081) and negatively with changes in IL-6 levels (r = -0.53, p = 0.001). Among the patients in the placebo group, there was a negative correlation of quality of life with reduction in TNF-α (r = -0.37, p = 0.020) and IL-8 (r = -0.68, p < 0.001) (Panahi *et al*., 2014).

Despite the low dose of curcumin used in the study by Panahi *et al*. (2014) (180 mg/day) and short intervention time, an improvement in the quality of life of patients diagnosed with solid tumors was observed, accompanied by a significant reduction in serum levels of inflammatory mediators (IL-6, TNFα and hs-CRP). The author attributes the clinical efficacy of adjunctive therapy with curcumin to co-administration of phosphatidylcholine (lecithin) and curcuminoids, shown by several *in vitro* studies to increase bioavailability of this phytochemical (Gupta *et al*., 2013; Shehzad *et al*., 2010). Curcumin is one of the greatest inhibitors of NF-κB and is known to modulate various biomarkers of inflammation, oxidative stress, apoptosis and tumor growth in patients with CA. A limitation of the study by Panahi *et al.* (2014) was that individuals in the curcuminoid group had a significantly lower quality of life score at baseline compared to the placebo group, which may have reflected a more compromised health status and the possibility of greater response to treatment in these patients (Panahi *et al*., 2014).

In the study by He *et al.* (2011), there was a significant reduction in TNF-α percentage levels in patients treated with curcumin after 10 days of treatment (p <0.05). The results showed a negative correlation between body weight gain of patients with colorectal CA in curcumin capsule use and decreased serum levels of TNF-α (r = -0.40 p <0.05).

The study of He *et al.* (2011) also showed a reduction in serum TNF levels and significant improvement in weight loss among adult patients with colorectal cancer after supplementation with 1.08 g/day of curcumin. The hypothesis described by the researchers was that curcumin can increase the apoptosis of cancer cells and positively regulates the p53 molecule (He *et al*., 2011).

It is known that chronic inflammation is present in patients with CA and might be involved in the carcinogenic process, inducing changes in CA-related genes and post-translational modification in signaling proteins involved in the cell cycle, DNA repair and cell apoptosis. Inflammation also produces several symptoms associated with CA progression, such as weight loss and impaired immunity (Hanahan, Weinberg, 2011; Eiro, Vizoso, 2012). Curcumin is considered one of the major inhibitors of NF-κB and is known to modulate various biomarkers of inflammation, oxidative stress and apoptosis (Panda *et al*., 2017; Imran *et al*., 2016).

Total antioxidant capacity (TAC) and antioxidant enzymes were determined in the study by Hejazi *et al.* (2016) one week before the start of radiotherapy and again three months after curcumin treatment of patients with prostate cancer. The patients in the curcumin and placebo groups did not differ significantly in relation to the intake of antioxidant or pro-oxidant foods. After the intervention period, TAC had increased from 10.7U/L to 12.8U/L (p <0.001) in the curcumin group. Patients in the placebo group also exhibited increased TAC, but without statistical significance. The post-treatment increase in TAC was higher in the curcumin group (12.8 vs 10.6, p = 0.014), suggesting that curcumin may be an antioxidant agent (Hejazi *et al*., 2016).

SOD activity decreased from 226U/L to 189.4U/L (p = 0.018) in the curcumin group, whereas no significant change was observed in the placebo group (Hejazi *et al*., 2016).

In some studies involving animal and *in vitro* models, the activity of enzymes such as SOD, catalase, and GPx increased after curcumin supplementation (Huang *et al*., 2012; Tawfik *et al*., 2013). However, in the study by Hejazi *et al.* (2016), curcumin did not increase catalase or GPx activity, and reduced SOD activity; thus, according to the authors, this seems to suggest that, in the presence of curcumin, SOD expression may not necessarily increase (Hejazi *et al*., 2016).

In a clinical study by Thomas *et al.* (2014) evaluating the effect of the use of a dietary supplement on the progression of PSA in men with prostate cancer, in the group supplemented with polyphenols extracted from curcumin, broccoli, pomegranate and green tea, PSA increased from 6.50 to 6.81 ugl, whereas in the placebo group, levels increased from 6.50 to 10.98 ugl. The PSA increase was lower in the supplement group compared to the control group (6.81 vs 10.98, $p = 0.0008$) (Thomas *et al*., 2014).

The percentage of individuals with lower or the same PSA value at the end of the trial was 46% in the supplement group and 14% in the control group, a statistically significant difference ($p = 0.000010$). A sub-analysis of 121 patients in this study, together with active surveillance showed that mean PSA decreased 0.14% in the supplemented group, but increased by 46.98% ($p = 0.001$) in the control group. Analysis of men followed-up with watchful waiting ($n = 78$), a form of symptom-guided treatment, showed that PSA increased by 8.78% in the supplement group, whereas in the placebo group, the level increased by 80.34% ($p = 0.001$). It is noteworthy that the mean levels of sex hormones were normal for both groups (Thomas *et al*., 2014).

The favorable effect in reducing serum PSA levels observed after capsule supplementation with broccoli powder, curcumin, pomegranate and green tea extract was found both in men with primary prostate cancer and those with disease recurrence. The authors argued that foods rich in polyphenols demonstrated anti-neoplastic effects involving angiogenesis, apoptosis and cell proliferation in laboratory models (Thomas *et al*., 2014). It was emphasized that patient characteristics were well balanced and the study had sufficient numbers to ensure adequate statistical power. However, the intervention period (6 months) was short and the study design included men with primary disease besides those who relapsed after radical treatments (Thomas *et al*., 2014).

However, another study failed to demonstrate a significant reduction in PSA after intervention with 500 mg of curcumin three months after completion of radiotherapy (12.98 to 0.12, $p = 0.78$) (Hejazi *et al*., 2016). Similarly, the study by Van Die *et al.* (2017) found no significant changes in PSA levels among supplemented patients after capsule intervention with phenolic compounds extracted from turmeric, resveratrol, green tea and propolis or in the placebo group (Van Die *et al.,* 2017). Notably, the study was not designed to detect effects on change in serum PSA levels. Among the limitations, it should be noted that the PSA tests were not always performed in the same laboratory, and the baseline biochemical data were collected during screening, and not repeated at the time of randomization.

A study of women receiving radiotherapy treatment for CA of the breast evaluated the degree of dermatitis using the RDS (Radiation Dermatitis Severity) scale. The group supplemented with curcumin showed a significant reduction in the degree of dermatitis compared to placebo ($p = 0.008$). Mean RDS scores for patients treated with curcumin were 0.8 lower than those in the placebo group. It was observed that 28.6% of patients treated with curcumin had moist desquamation after radiotherapy, while 87.5% of patients in the control group experienced this adverse effect ($p = 0.002$) (Ryan *et al*., 2013).

There were no statistically significant differences between treatment groups in terms of intensity of perceived pain, sensory pain, or scores on the McGill Pain Questionnaire subscale (Ryan *et al*., 2013). In the evaluation related to individual pain, the curcumin group differed significantly from the placebo group ($p \leq 0.021$), with lower pain for the sensory descriptors of "corroding" and "painful" pain. The authors also observed that women in the curcumin group had lower "depressed" status compared to placebo ($p = 0.023$) (Ryan *et al*., 2013). The authors concluded that administration of oral curcumin significantly reduced the severity of radiation dermatitis and moist desquamation, although did not reduce erythema. Thus, curcumin was ineffective for reducing the severity of dermatitis in women undergoing total mastectomy prior to the commencement of radiation therapy (Ryan *et al*., 2013). It is important to point out that a cream gel containing hydrocortisone was supplied to patients of both groups. Curcumin has previously been studied for its radiomodulatory properties, protecting non-cancerous tumor cells with radiosensitization (Amalraj *et al*., 2017).

In the study by Thomas *et al.* (2014), 24% of the individuals presented adverse events in the supplement group and 34% in the control, but without significant

difference between the groups (p = 0.14). Among these events, diarrhea, flatulence, and abdominal distension occurred in 15.5% of the supplement group compared with 7.5% of the patients in the control group (p = 0.11). In a study carried out by Panahi *et al.* (2014), 16% of patients in the supplement group experienced adverse events such as worsening of urinary flow, renal function decline and non-specific disease, whereas 22% of subjects in the placebo group had these symptoms, with no statistical difference. Despite these adverse events reported, no patient discontinuation was recorded in this protocol (Panahi *et al*., 2014). In another study, 10 patients administered 360 mg of curcumin or placebo, experienced diarrhea with no statistical difference between groups (p> 0.05) (He *et al*., 2011).

In the study conducted by Van Die *et al*. (2017), 12 adverse events were identified among patients supplemented with curcumin, resveratrol, green tea and broccoli. The main symptoms were burns, restlessness and increased nocturia, classified by participants as mild, and heartburn, classified as moderate. There were also 13 adverse events among individuals in the placebo group, such as flatulence and constipation, with no statistically significant difference in severity of symptoms between groups (p = 0.702) (Van Die *et al*., 2017).

It is important to note the widely divergent factors among studies included in this review, where only a small number of clinical trials had well-controlled methodologies, adequate sample size, representativeness of the study population, appropriate intervention time and appropriate statistical analyses. This can directly impact both the positive results and controversial findings, representing an important limitation for conclusions on this topic.

A review of studies has shown that curcumin compound is safe when ingested in daily doses of up to 12g, while toxicity at higher levels has not been established (Imran *et al*., 2016; Rezaee *et al*., 2017). In the present review, the dose of curcumin among the studies ranged from 180 mg to 3 g daily and frequency of ingestion was one to six times a day, used in different formulations, alone or in association with other nutrients. Three studies used curcumin in commercially available capsules with standard formulations (Hejazi *et al*., 2016; Panahi *et al*., 2014; Ryan *et al*., 2013) containing specific information on the amounts and proportions of the curcuminoids present in the formulations. These factors may justify the benefits described in these studies since the addition of curcumin to other agents has been associated with an improvement in its bioavailability. Co-administration of curcuminoids with phosphatidylcholine has been associated with improved bioavailability (Anand *et al*., 2007; Gupta *et al*., 2013; Shehzad *et al*., 2010).

Two studies used donated capsules, however, the authors reported no conflict of interest (Hejazi *et al*., 2016; Panahi *et al.,* 2014). The data from this systematic review suggest that oral curcumin was well tolerated by the patients and the studies analyzed did not report any serious adverse effects in the intervention group, with similar side effects for both curcumin and placebo groups. The main symptoms reported were diarrhea, agitation, tremors, and insomnia, which may be confounded with symptoms associated with antineoplastic treatment. No differences were observed between curcumin supplementation in patients with combination therapy (chemotherapy and radiotherapy) or single therapy.

The present review systematically chose to analyze randomized and controlled clinical trials, considering this design the gold standard among all clinical investigation methods, since it is capable of producing scientific evidence with a lower probability of error to clarify a cause-and-effect relationship between the events (Carvalho *et al*., 2013).

Regarding the quality of the selected papers, in general, there was a low risk of bias in relation to the items of random sequence generation, the blinding of participants and professionals, blinding of outcome assessors, incomplete outcome data and report of a selective outcome. However, information on allocation concealment and other potential biases were unclear in the studies evaluated, which may raise some doubts about the results. Whereas a risk of bias may exist, there is insufficient information to assess whether there is a significant risk, although none of the studies evaluated were considered to be associated with a high risk of injury.

It was not possible to evaluate the publication bias of the studies included in this review, through the analysis of funnel plot and Egger test, since these analyses are recommended for meta-analyses with at least 10 studies, and are therefore not indicated for this study (Higgins *et al*., 2011).

Strengths of this review include the preparing of a sensitive and comprehensive search strategy without restrictions on geographic location, language, year of publication or attribution of outcome at the time of the search to increase search potential; as well as the preparation of the clinical records for data collection and extraction. We also used review articles for the manual

checking of references and identification of possible relevant studies. However, it was not possible to perform a broad search in the gray literature. Despite contacting authors to retrieve missing data in the studies, a large number of articles were excluded.

Analysis of risk of bias

The risk of bias was assessed for randomized clinical trials according to the Cochrane Collaboration criteria for the development of systematic reviews of intervention studies (Higgins *et al*., 2011; Carvalho *et al*., 2013).

The study carried out by Thomas *et al*. (2014) was the only investigation classified as low risk of injuries on all evaluated items. The remaining papers were deemed as having an uncertain risk, since they had one or more answers with information that raised doubts about the results or with insufficient reporting of information, making it impossible to judge adequately.

The study of Van Die *et al.* (2017) had low risk for selection and friction, being classified in the final judgment as having an uncertain risk since it obtained three responses that could not be determined. The study published by He *et al.* (2011) had low risk on three items; generation of random sequence, blinding of participants and professionals and blinding of outcome assessors. In the study by Hejazi *et al.* (2016), the final judgment was classified as uncertain risk due to flaws in concealment of allocation items and other sources of evidence. In the study by Panahi *et al.* (2014), only the item related to data on incomplete outcomes, in the characterization of friction was considered low risk.

The article published by Ryan *et al.* (2013) obtained a low risk of blinding for participants and professionals, blinding of outcome assessors, incomplete outcome data, and other sources of evidence, but two responses were classified as an uncertain risk. The details of this evaluation are given in Figure 3.

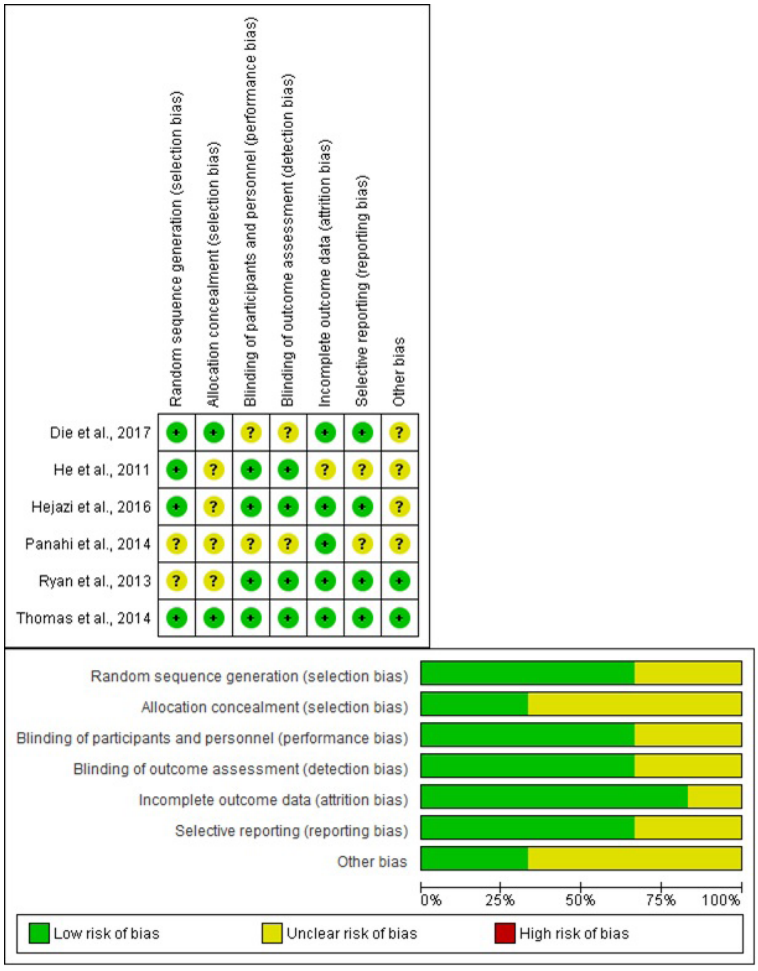

FIGURE 3 – Assessment of bias risk. (a) Bias risk summary: a review of each bias risk item for each included study. (b) Bias risk chart: a review of each bias risk item, expressed in %, for all included studies.

CONCLUSION

This systematic review, which evaluated six eligible clinical trials, demonstrated a potential benefit of curcumin supplementation in the treatment of cancer patients, specifically in the decrease of inflammatory markers, increase in total antioxidant capacity, and reduction of dermatitis severity. However, it is important to consider the great heterogeneity and methodological weakness of the studies, and that it was not possible to perform a meta-analysis of the data available in the literature. The active principle, dosage, and duration of supplementation proved important aspects, with high variability among the evaluated articles. Despite the low risk of bias found for several items, five studies were ultimately classified as having uncertain risk.

Thus, it was not possible to conclude, with the degree of scientific evidence desired, the effect of oral curcumin supplementation in the adjuvant treatment of cancer patients. There is in sufficient evidence for consensus on the use of curcumin in clinical practice or on the dose and supplementation time needed to confer benefits to cancer patients. Despite the growing interest in the use of this phytochemical as a co-adjuvant in the treatment of cancer patients, further clinical trials with more consistent methodological designs are required.

Studies with bioavailable formulations should be conducted to elucidate the relationship between curcumin and its pharmacological activity in neoplastic cells. Such research can yield more consolidated scientific evidence allowing greater safety in the indication and dosage of this phytochemical, thereby helping to improve cancer treatment and quality of life of these patients.

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Received for publication on 02nd December 2018
Accepted for publication on 18th April 2019