# Effects of Curcumin on Treatment Outcome in Patients with Cancer Diagnosis

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# **Abstract**

Introduction: Treatment options for palliative care in patients with cancer aim to improve quality of life, and, in this context, alternative, complementary treatments are under study to reduce treatment side effects and increase traditional treatment efficacy. Curcumin is a food supplement derived from the plant Curcuma longa, which has recently received increasing attention because of its antioxidant and anti-inflammatory effects. Previous clinical trials, with different results, investigated Curcumin's efficacy in cancer treatment. We aimed to explore the effect of Curcumin on treatment outcomes in patients with cancer diagnosis.

**Methods:** In this systematic mini-review, conducted to answer the research question "What is the effect of curcumin on treatment outcome of cancer patients?" we searched four portals/databases (Pubmed/Medline, BVS/Lilacs, Scielo, and Cochrane). The PICOT strategy adopted was: P - patients with cancer; I - Curcumin; C- not applicable; O - treatment outcome; T- RCT and cohort studies. Independent reviewers checked for eligibility and study quality.

**Results:** We included six studies regarding prostate cancer, head and neck tumors, colorectal cancer, breast cancer, and bladder cancer. Studies showed good tolerability for Curcumin with mild adverse effects. However, it showed no significant difference in survival or tumor progression. On the contrary, researchers observed exciting findings concerning preventing and relieving chemotherapy-related adverse effects.

**Discussion:** Curcumin appears to be an intriguing potential adjuvant therapy in patients with cancer. Further studies on the topic are needed to investigate its possible concrete applications and to address the known problem of its poor bioavailability.

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# Introduction

The World Health Organization (WHO) establishes cancer as the second cause of death and one of the most urgent public health problems worldwide (World Health Organization [WHO], 2023; Siegel et al., 2023; Tomeh et al., 2019). The incidence increases

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every year, and estimates indicate that there will be 1,958,310 new cases in the US only in 2023, about 5,370 new cases per day (Siegel et al., 2023), leading to enormous impact on families, communities, and health systems in every aspect of life, as physical effects, emotional issues and financial repercussions (WHO, 2023). Depending on the case, there are several cancer treatment options related to the type, localization, and stage, such as surgery, chemotherapy, radiotherapy, and combinations of them. One of the treatments in the advanced stage of cancer is palliative care, which is the field of medicine that focuses on the quality of life of cancer patients and their families, a crucial part of treatment (WHO, 2023). Alternative treatments increase efficacy, reduce chemotherapy side effects, and improve quality of life. However, despite all the developments in recent years in cancer therapy, mortality remains high, with approximately 50,000 cancer-related deaths in the United States in 2023 (Siegel et al., 2023; Tomeh et al., 2019). We must develop new, more effective, cost-effective therapies to address this problem, both preventively and therapeutically. Modern anticancer treatments target a specific molecule of the pathophysiology of a particular cancer as a mechanism of action. Besides chemically synthesized anticancer agents, several compounds with potential anticancer effects have been extracted from plant sources: Curcumin is one of them (Tomeh et al., 2019).

Curcumin is a food supplement derived from the turmeric plant, which has received much attention in recent decades for its bifunctionality as an antioxidant and anti-inflammatory effect (Tomeh et al., 2019). A therapeutic regimen of Curcumin can be used for different treatment purposes in cancer: anti-inflammatory, chemopreventive, antimetastatic, and antiangiogenic (Pricci et al., 2020; Nagahama et al., 2016).

Clinical trials have already investigated Curcumin's efficacy as a treatment for cancer, with different results, especially considering the impact of treatment on patient-reported outcomes (Pricci et al., 2020; Howels et al., 2019). Recently, Waure et al. (2023) conducted a systematic review to summarize the evidence related to the therapeutic effects of Curcumin on patients with cancer diagnosis, notably the effects on hard endpoints, like survival, time to tumor progression, and duration of treatment. As far as it is known, no previous systematic review aimed to synthesize evidence related to the potential effect of Curcumin on treatment outcomes, such as quality of life or the occurrence of adverse events, for example. It is, thus, essential to compile data on curcumins' general effect on cancer as patients could greatly benefit from reduced chemotherapy side effects, potentially improving treatment adherence and, subsequently, efficacy and quality of life. This systematic mini-review aims to combine the available empirical evidence to analyze the effects of Curcumin on treatment outcomes in cancer patients.

## Materials and Methods

This is a systematic mini-review of the literature, guided by Cochrane Methodology (Higgins et al., 2019). PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) criteria guided the reported findings (Page et al., 2021).

# Search Strategy

The research question, "Is curcumin effective in improving clinical treatment outcomes in adult cancer patients?" guided the search for published registries. PICOT was adopted to establish the search strategy, considering P (population): patients with cancer; I (intervention): Curcumin; C (comparison): any comparators; O (outcome): treatment outcome; T (time): any restrictions to time. The search strategy was: ((("Neoplasms"[Mesh]) AND "Curcumin"[Mesh]) AND "Treatment Outcome"[Mesh]). It was adapted to each portal/database searched based on MeSH terms (Table 1). We adopted the MeSH definition for treatment outcome as a major topic. Eligibility criteria were defined to include original articles (randomized clinical trials and cohort studies), published in any language, without temporal restrictions, that tested Curcumin as a therapy for any type of cancer and presented information related to the effect of Curcumin on treatment outcome in cancer patients. Articles that did not have complete information regarding the study variables were excluded, as well as other types of publications (conference papers, book chapters, guidelines, etc.)

# Search for Studies

A database search was carried out on 08/07/2023. We consulted the following electronic portals/databases: Pubmed (Medline), BVS (Lilacs), Scientific Electronic Library Online (SciELO), and Cochrane. Two teams of independent reviewers searched.

# Study Criteria and Data extraction

Selection of studies, data extraction, and quality of studies analysis

Portal/Database	Search strategy  (("Neoplasms"[Mesh]) AND				
Pubmed (Medline)	"Curcumin"[Mesh]) AND "Treatment				
	Outcome"[Mesh]				
DVC (Lilear)	Neoplasms AND Curcumin AND				
BVS (Lilacs)	"Treatment Outcome"				
Scientific Electronic Library Online	Neoplasms AND Curcumin AND				
(SciELO)	"Treatment Outcome"				
	Neoplasms OR Cancer in Title Abstract				
6.1	Keyword AND "curcumin" in Title				
Cochrane	Abstract Keyword AND "treatment				
	outcome" in Title Abstract Keyword				

**Table 1:** Search strategy according to portal/database.

After removing duplicate registries, titles, and abstracts were analyzed for the eligibility conference. Two teams of independent reviewers did eligibility checking (Team 1: MAA, FA, SS, KF, AK, CL, LAMJ; Team 2: SN, RPM, JS, OV, IV, RTP), with disagreements solved by a third team of reviewers (RELF, CLE, JC, LGM, DT) whenever they occurred. All the reviewers were blinded to the decisions during the process, using the Rayyan platform (https://www.rayyan.ai/).

We thoroughly read eligible articles to confirm inclusion and exclusion criteria and to analyze the study's quality. Studies that met the inclusion criteria, with all needed available data, and reached methodological quality and a minimum score of 50% in risk of bias analysis were included in this mini-review. The independent reviewers analyzed the quality of included studies using the criteria established in JBI critical appraisal tools for randomized clinical trials and cohort studies (Barker et al., 2023). We also used the Risk of Bias (RoB) tool to classify the quality of the studies.

Data extracted from the studies were: author, year of publication and country where the study was developed; study design, number of cases, gender (n; %), age (mean+SD); body weight (kg); type of cancer; stage of disease (1-4); curcumin posology; standard treatment besides Curcumin (another drug, chemotherapy or radiotherapy); treatment outcome; measurement of outcome; effect on treatment outcome (direction of effect).

Reviewers solved disagreements when they occurred and also analyzed RoB. Publication bias was analyzed qualitatively in each study concerning time to publication, location, and language bias.

## Data Analysis

Study characteristics were analyzed narratively. The impact of curcumin intake on disease progression was reported, evidencing the direction of association of the event. Data extracted from the articles were presented in summary tables format and qualitative synthesis description, grouped by type of cancer.

# Results

The search strategy yielded 133 registries, where 12 were considered eligible. After evaluating the complete text, we included six papers in the review (Figure 1) based on a critical appraisal (Figure 2).

The risk of bias, analyzed during critical appraisal, was considered low for all included studies.

All the included papers were RCT conducted in the USA, France, Iran, United Kingdom, and Korea from 2017 to 2021. Table 1 presents the study characteristics, intervention, and outcome descriptions.

The effects of Curcumin were investigated in five types of cancer: (1) prostate cancer, (2) colorectal cancer, (3) head and neck cancer, (4) breast cancer, and (5) bladder cancer (Table 1). Curcumin was orally administered in all RCT, with posology varying across the studies. Most studies (n=4; 66,7%) compared Curcumin against placebo, and two studies compared it to chemotherapy agents. Only one study did not have a placebo control group (Howells et al., 2019). Detailed information about the studies is reported in Table 2).

Found effects of Curcumin on selected outcomes

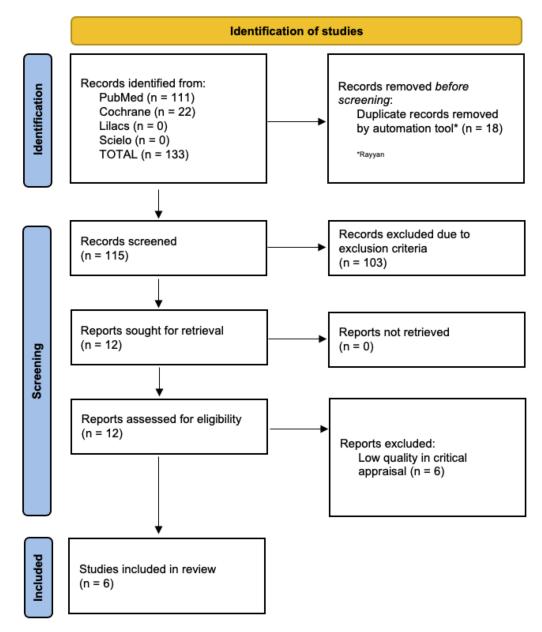


Figure 1: PRISMA Flow diagram systematic review.

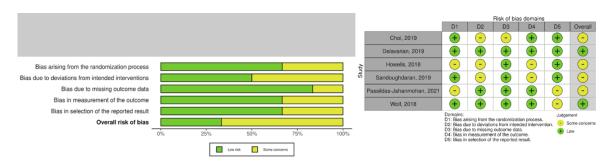


Figure 2: Risk of Bias Assessment.

First author and year of publication	Population and disease	Study Characteristics	Curcumin intake description	Comparator description	Primary outcome measure	Secondary outcome measure	Main Outcomes result	Author's conclusions
Jahanmohan et al., 2021	Prostate cancer in all stages. $n=44$ f=0 m= 44, mean age IG/CG: $69/70$ .	RCT, double-blind, phase II, three French comprehensive cancer centers, n IG: 22 n CG: 22.	Curcumin 500 mg capsules. 2g/8 hours, for 7 consecutive days (from Day -4 to Day +2 with chemotherapy at Day 0) every 3 weeks.	Docetaxel + prednisone. Placebo same frequency as curcumin.	Time to progression (ITTP), I) an increase ≥25% in target lesion or an absolute increase by 2 ng/ml of PSA, 2) an increase of 20%, 3) New lesions, or 4) At least 2 new bone lesions.	curcumin absorption, and quality of life.	Progression-free survival (PFS) between the placebo (5.3 months) and curcumin (3.7 months) groups, p = 0.75. Secondary endpoints: PSA response rate (p=0.88), overall survival (p=0.50), and quality of life (p=0.49 and p=0.47).	Lack of efficacy of adding curcumin to the current mCRPC treatment. Curcumin+docetaxel does not seem to potentiate the chemotherapy effect on cancer cells. No side effects of curcumin were noted.
Wolf et al., 2018	97% stage 0, n= 686 f=	RCT, multisite, double- blinded, placebo- controlled, n IG: 344 n CG: 342.	Gelatin capsule, 500 mg of curcuminoids. 2g 3 times per day, course of RT plus 1 week post-RT.	Placebo (dicalcium phosphate capsule): 4 capsules 3 times per day, during the course of RT plus one week after RT.	Radiation Dermatitis Severity (RDS) scale at the end of RT.	Presence of moist desquamation at the End of RT, pain at RT site (McGill Pain Questionnaire Short Form (SF-MPQ), skin-related quality of life (Skindex-29), and adverse symptoms.	In mixed linear model analyses, there was no reduction in radiation dermatitis severity at the end of RT compared to placebo (B (95% CI) = 0.044 (-0.101, 0.188), p = 0.552). Fewer curcumin patients with RDS > 3.0 suggested a trend toward reduced severity (7.4% vs. 12.9%, p=0.082).	There was no significant difference between the groups. No reduction in the severity of turmeric dermatitis vs placebo.
Choi et al., 2019	Prostate cancer patients with biochemical recurrence or metastasis at initial diagnosis. n= 97. f= 0. m= 97, mean age IG 71.5, CG 72.9.	placebo-controlled, n	Capsule 240 mg of curcuminoid powder, 480mg 3 times per day (1440 mg/day), for 6 months.	Placebo same frequency as curcumin.	Duration of the first interruption of treatment with an LHRH agonist and antiandrogens (androgen deprivation therapy-ADT).	PSA and testosterone levels over 6 months, rate of PSA progression, quality of life scores (HRQoL) at 6 months.	In the curve of off- treatment, there was no difference between groups (P = 0.4816). The PSA progression was significantly lower during the curcumin treatment compared with placebo (10.3% vs 30.2%, P = 0.0259). The testosterone levels during 6 months, the HRQOL scores and PSA changes at 6 months were not different between	No significant differences in the duration curve without treatment between the two groups.
Delavarian et al., 2019	Head and neck cancer (buccal mucosa, tongue, palate, floor of the mouth): Squamous cell carcinoma, adenoid carcinoma, mucoepidermoid carcinoma n= 32 f= 13 m= 19, mean age IG 62.18, CG 55.87.	Oncology Center and Omid Hospital in Mashhad, Iran. n IG: 16. n CG: 16.	Nanocurcumin 80 mg/day oral (1 capsule) during the radiotherapy.	Placebo in a container identical to nanocurcumin, with the same frequency as curcumin.	on OM according to	Measurement of body weight before and after radiotherapy courses.	The difference in severity of mucositis between groups was statistically significant. All control groups developed OM in the second week of radiotherapy, 32% of the case group developed OM with no obvious oral or systemic side effects.	Delayed onset of OM (grade 1) and lower grade of mucositis for the study group compared to the control group.
Sandoughdaran et al., 2021	Localized muscle-invasive bladder cancer (MIBC). T2-T4a, n = $26$ f = 0 m = 97, mean age IG 68.2, CG 64.7.	RCT, double-blind, placebo-controlled trial. n IG: 12. n CG: 14.	Oral capsule nanocurcumin 80 mg twice a day for four weeks.	Chemotherapy (Gemeitabine, carboplatin) + placebo, Placebo same frequency as curcumin.	Complete clinical response (no evidence of primary tumor, 70) on cystoscopic evaluation with biopsy.	Chemotherapy-induced nephrotoxicity, hematologic toxicities, and nadir between the two groups.	The complete clinical response rate was 30.8% in the placebo group and 50% nanocurcumin group. Nanocurcumin was superior to placebo in complete clinical response rate, with no significant difference between the groups (p = 0.417), and between groups, there was no significant difference regard to grade 3/4 renal and hematologic toxicities as well as hematologic nadirs. Nanocurcumin was well tolerated.	Nanocurcumin was superior to placebo for the primary endpoint but with no significant difference between groups (p = 0.417). There are no significant differences in nephrotoxicity, hematological toxicity, or nadir levels between the two groups.
HowellsLM, et al., 2019	Metastatic colorectal cancer, stage IV, n= 27 mean age IG 66.9, CG 68.3.	RCT, phase IIa open- labelled. University Hospitals of Leicester. n IG: 18. n CG: 9.	Curcumin C3 Complex 2 gr per day.	Open-labeled trial, FOLFOX. Placebo is not mentioned.	Safety evaluation and tolerance of daily oral curcumin. Safety using common toxicity criteria and adverse event reporting. Efficacy by progression free survival (PSS) and overall survival (OS).	for any clinical benefit.	Oral curcumin to FOLFOX	chemotherapy was safe and tolerable (primary outcome). Similar adverse event profiles were observed in both arms. There were no significant differences between the arms in terms of quality of life (p = 0.248) or resurrosticity (n =

n, sample size; f, female; m, male; IG, Intervention Group; CG, control group; RCT, Randomized controlled trial; RT: radiotherapy; FOLFOX, folinic acid/5-fluorouracil/oxaliplatin chemotherapy; CUFOX, FOLFOX + 2 g oral curcumin/d; PSA, Prostate-specific antigen; LHRH, luteinizing hormone-releasing hormone; OM, Oral mucositis; CXCL1, C-X-C motif chemokine lingand 1.

**Table 2:** Study characteristics, intervention, and treatment outcome description.

in different types of cancer:

#### Prostate Cancer

Two of the studies included in the mini-review evaluated the efficacy of Curcumin as a treatment for prostate cancer. Passildas-Jahanmohan et al. (2021) assessed the potential therapeutic benefit of docetaxel therapy combined with Curcumin compared to docetaxel plus placebo by assessing time to progression (TTP), defined as 1) an increase of  $\geq$ 25% or an absolute increase by two ng/ml of PSA, 2) a 20% increase in target lesion(s), 3) Appearance of a new lesion, or 4) documentation of at least two new bone lesions. They found that median progression-free survival (PFS) was about 4.4 months, while at six months, the survival rate was 38%. No significant difference was found between the groups. Moreover, Choi et al. (2019) evaluated the off-treatment duration in patients treated with androgen deprivation therapy, which was defined as the period from initiation to the restart of androgen deprivation therapy in months. Their results showed a mean off-treatment duration of 16.3 months (95% CI) in the curcumin group and a mean off-treatment duration of 18.5 months (95% CI) in the placebo group. However, we concluded that there were no statistically significant results in the treatment discontinuation duration curve between the two groups. (P = 0.4816).

# Colorectal Cancer

Howells et al. (2019) described the therapeutic effects of the combined therapy of FOLFOX ((Folinic acid, fluorouracil, and oxaliplatin)) regimen + bevacizumab or curcumin plus FOLFOX regimen + bevacizumab, as a treatment for metastatic colorectal cancer. The authors evaluated the safety and tolerability of the therapeutic combination of Curcumin and the FOLFOX therapeutic regimen and its potential benefit for clinical use. Their results showed that FOLFOX + bevacizumab combined with 2 g oral Curcumin C3 Complex/d (80% curcumin) was generally well tolerated. Adverse effects such as fatigue and peripheral neuropathy were the most commonly reported, which were between grade 1 and 2 in severity. The most common grade 3 or 4 adverse effect was thromboembolic events observed in 3 patients (in the Curcumin + FOLFOX group). The authors concluded that Curcumin associated with a FOLFOX regimen was safe and tolerable. However, no differences between groups were found considering the secondary outcomes of the study (quality of life and adverse events). The most likely

curcumin-related adverse effect reported was related to the gastrointestinal system, with diarrhea being the most common.

#### Head and Neck Cancers

Delavarian et al. (2019) described the influence of oral administration of nano micelle curcumin in patients with head and neck cancers to prevent radiotherapy-induced mucositis. In this investigation, the authors studied the effects of radiotherapy in producing oral mucositis in a randomized group of patients. They divided two groups of 16 participants who would receive radiation therapy of 50 Gy or greater; the radiation field included at least 50% of the patient's oral cavity. The oral nano curcumin dose administered was 80 mg/day in the study group and placebo for the control group during radiation therapy. The National Cancer Institute Common Toxicity Criteria version 2 scale (NCI-CTC v.2) was used to grade oral mucositis. Results showed a statistically significant delay in the development of grade 1 oral mucositis in the study group compared to the placebo group (P=0.002). No patients with oral mucositis were observed in the study group at week 1, while 25% were in the placebo group. A significant reduction when compared to the control group, in which 37.5% at week 1 and 50% of patients with oral mucositis were observed. By week six, all patients had developed oral mucositis; however, participants in the study group showed oral mucositis to a lesser degree than those in the control group (P < 0.05). Additionally, up to 50% of the participants developed stage 4 oral mucositis in the control group, while no one developed stage 4 in the study group.

# Breast Cancer

Wolf et al. (2018) described the efficacy of oral Curcumin as a treatment to reduce radiation dermatitis severity at the end of radiation therapy using the Radiation Dermatitis Severity (RDS) scale. In the study, the authors evaluated the efficacy of curcumin C3 Complex (450mg curcumin, 40mg dimethoxy curcumin, 10mg bisdemethoxy curcumin) in reducing radiation dermatitis severity in breast cancer patients undergoing radiation therapy. The professionals evaluated the participants' skin using the Radiation Dermatitis Severity (RDS) scale, measuring the severity at the end of the radiation therapy. The first analysis between the Curcumin and placebo-controlled groups showed no statistically significant difference (p=0.552).

#### Bladder Cancer

Sandoughdaran et al. (2021) described the potential efficacy of Curcumin in patients with localized muscle-invasive bladder cancer (MIBC) who are receiving chemotherapy treatment. They evaluated the feasibility and efficacy of an oral capsule of nano curcumin 80 mg supplements plus chemotherapy regimen compared to a placebo plus chemotherapy regimen in patients with histologically confirmed muscle-invasive bladder cancer who had previously undergone transurethral resection of bladder tumor (TURBT). Being a multicenter study, the participants were stratified between the two chemotherapies used: 1) gemcitabine/cisplatin and 2) gemcitabine/carboplatin. All 26 study participants welltolerated Curcumin. The results demonstrated a 39.1% reduction in tumor stage in all patients studied. When assessing the complete clinical response, the findings were statistically nonsignificant: 30.8% in the placebo group and up to 50% in the curcumin group (p= 0.417). Similarly, researchers found no significant difference between the groups receiving cisplatin or carboplatin (0.999).

## Discussion

In this mini-review, we found studies that previously evaluated the effects of Curcumin in treating cancer. Results demonstrated that Curcumin has been used as an adjuvant therapy for the treatment of patients with prostate, breast, bladder, head and neck, and colorectal cancer. Results indicate that Curcumin may benefit treatment outcomes, but further studies need to be conducted to confirm not only the direction of the association as its strengths but also its strengths in different types of cancer.

In the case of prostate cancer, Passildas-Jahanmohan et al. (2021) combined curcumin therapy with docetaxel, demonstrating comparable results between curcumin and placebo groups. Choi et al. (2019) identified no statistically significant difference in treatment duration between curcumin and placebo groups in the case of androgen deprivation therapy. In metastatic colorectal cancer, Howells et al. (2019) evaluated the use of Curcumin with the FOLFOX + bevacizumab regimen. They found it well tolerated, although fatigue and neuropathy emerged as side effects. Focusing on head and neck cancers, Delavarian et al. (2019) emphasized the potential of Curcumin to decrease mucositis caused by radiotherapy.

Regarding breast cancer, Wolf et al. (2018) found no statistically significant difference between curcumin and placebo groups when evaluating the role of Curcumin in reducing the severity of radiationinduced dermatitis. For localized muscle-invasive bladder cancer, one study assessed the potential of Curcumin when used with chemotherapy. Although well tolerated, Curcumin did not present a statistically significant difference in tumor stage or clinical response. The main finding of these studies suggests Curcumin's potential in cancer therapy, but they are inconclusive. More studies are needed to understand better its advantages and limitations in various types and treatments of cancer, which was already stated in a previous systematic review (Waure et al., 2023).

Once there were few studies on each of the five types of cancer investigated, the inferences of the present studies are based primarily on single studies that are, per se, very heterogeneous, especially in terms of the study population. This may be an essential limitation of this mini-review for establishing conclusions and extrapolating results. From the results, we can infer that evidence supports the need for further studies rather than using Curcumin as a recommendation for practice.

Besides, only RCTs published in the study databases that aimed to investigate Curcumin's effect on cancer patients' outcomes were included in this mini-review. Cohort studies were not considered in the exclusion criteria but were intentionally excluded from the analysis due to quality issues. Considering gray literature, the not-so-broad search of the literature may be a limitation of the present study as necessary information from articles published elsewhere might have yet to be included. A scoping review can further investigate the effects of Curcumin on treatment outcomes among cancer patients more broadly. However, this mini-review followed a rigorous methodological method from the search of the registries (in four databases/portals) to qualitative data analysis and reached the purpose of mini-review studies. Once mini-reviews are used to provide a concise overview of the available evidence, the findings can be utilized to guide future research directions.

The fact is that with the evidence found, it is possible to infer that Curcumin as an adjuvant treatment needs to be better analyzed. More studies are required in order to discover the best formulation to maximize curcumin bioavailability and establish a narrower therapeutic range. It is also essential to identify patients who are most likely to benefit from this intriguing supplement. Carefully designed studies investigating curcumin pharmaceutical characteristics should further assess its full therapeutic potential and clinical efficacy as monotherapy or an add-on to standard treatment in cancer patients.

Although the studies didn't demonstrate statistical significance regarding the effect of Curcumin on treatment outcomes in cancer patients, the literature shows that the outcome in these patients after using

Curcumin as an adjuvanted treatment improves the occurrence of side effects of the standard treatment. Cancer patients would greatly benefit from reduced side effects that would improve their treatment adherence, efficacy, and quality of life, especially in the advanced stage of the disease.

Future clinical trials could be designed to compare the efficacy of Curcumin plus standard treatment to standard treatment alone in patients with non-metastatic and metastatic types of cancer, on the reduction of tumor size, increase of survival rate, and quality of life. This trial would provide valuable information on identifying patients most likely to benefit from curcumin treatment. The evidence provided in the present study may be assumed to indicate that Curcumin needs to be further studied in cancer patients, especially for whom the possibility of cure is limited.

# Conclusion

Curcumin may have some benefits when used as adjuvant therapy for different types of cancer; however, its effectiveness in improving treatment outcomes still need further investigation.

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# **Conflicts of Interest**

The authors declare no conflict of interest.

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