# Evaluation of Nano-curcumin Oral Formulation Efficacy as an Adjuvant Treatment in Metastatic Colorectal Patients

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***Received: 2025-01-10, Revised:2025-03-01, Accepted: 2025-03-05, Published:2025-03-31***

## Abstract

***Background:*** Globally, colorectal cancer ranks as the second cause of mortality and the third most diagnosed cancer. Curcumin has been investigated as an adjunct therapy in various cancers, mostly in pre-clinical studies, particularly by acting as a chemo-sensitizer.

***Objectives:*** The present study aimed to evaluate the effectiveness of oral formulation of nano-curcumin as an adjuvant treatment in patients with metastatic colorectal cancer receiving the XELOX/FOLFOX±Bevacizumab regimen.

***Methods:*** In this study, 94 patients with metastatic colorectal cancer who completed the inclusion and exclusion criteria were randomized into the nano-curcumin and placebo groups. 40 mg nano-curcumin capsules were administered three times a day after each meal, beginning the first day to the end of the sixth cycle of chemotherapy. Carcinoembryonic antigen (CEA) level and radiological response based on Response Evaluation Criteria in Solid Tumors (RECIST version 1.1) were evaluated. The data were analyzed using SPSS version 13.

***Results:*** All baseline demographic, clinical, and laboratory variables were comparable between placebo and nano-curcumin groups. The administration of nano-curcumin showed no significant impact on carcinoembryonic antigen (CEA) levels. There was also no significant difference in both arms regarding RECIST criteria at the end of the 3rd and 6th cycle.

***Conclusion:*** TOur findings suggest that nano-curcumin with the prescribed dose did not show considerable efficacy in the radiologic response of metastatic colorectal cancer based on RECIST criteria. The CEA serum level also did not change significantly in comparison with the placebo. Further research is needed to assess various nano-curcumin formulations, dosing, and timing for initiating curcumin for better judgment.

J Pharm Care 2025; 13(1): 14-25.

**Keywords:** Metastatic Colorectal Cancer; Nano-curcumin; Chemotherapy Toxicity; Cancer Progression; FOLFOX/ XELOX ± Bevacizumab

## Introduction

According to GLOBOCAN 2020, colorectal cancer (CRC) ranks third in cancer diagnoses and second in cancer-related deaths globally (1-3), with 20% of patients presenting with metastatic disease at diagnosis (4). While surgery is preferred for resectable cases, chemotherapy remains the primary intervention for unresectable metastatic CRC (mCRC) (5, 6). Standard regimens include FOLFOX, FOLFIRI, and FOLFOXIRI with/without targeted agents (7,8). Treatment

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challenges include poor adherence (9), frequent delays (43% of patients) [10], and high toxicity rates (90% experience adverse events) (11,12).

Natural compounds, particularly curcumin, have been investigated as adjunct therapy (13-15). Curcumin demonstrates multiple therapeutic properties (16) and acts as a chemo-sensitizer (17,18). Pharmacokinetic disparities including low bioavailability (<1%), rapid metabolism (digestive and hepatic) along with poor physicochemical properties (low solubility, chemical instability) are major withdraws of oral curcumin formulations (19). Several studies on nano-based formulation development aim to tackle the issues (18). Moreover, curcumin nanoparticles show stronger anticancer activity than curcumin (20). Its modulatory effects on the efflux transporter Pgp, primarily the main cause of multidrug resistance in cancer cells, make it a suitable adjunctive therapy in combination therapy (18).

Despite the availability of several in-vitro and in-vivo experiments on the anti-cancer properties of curcumin as an adjuvant along with chemotherapeutic drugs in various cancers, there are a limited number of well-designed randomized clinical trials examining the possible impact of curcumin, emphasizing the need for additional investigation on this subject. Moreover, considering the poor oral absorption of curcumin, the utilization of nano-curcumin in clinical research might be advantageous. The primary purpose of this triple-blind, randomized clinical trial was to assess the efficacy of oral nano-curcumin as a supplement to XELOX or m-FOLFOX6 regimen in treating mCRC patients.

## Methods

### *Study Design*

This study was a randomized, triple-blind, placebo-controlled clinical trial in an outpatient oncology clinic in Mashhad, Iran, investigating the preventive effect of nano-curcumin on the progression of cancer as an adjuvant agent beside standard chemotherapy regimen in patients with mCRC, which was performed between September 2021 and December 2023. The study was registered at the Iranian Registry of Clinical Trials (IRCT20200408046990N7) on 2021-03-13.

### *Ethics approval*

The study protocol was approved by the Ethics Committee of Mashhad University of Medical Science (IR.MUMS.REC.1399.527). It was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Informed consent was obtained from all individual participants.

### *Study population*

Inclusion criteria:

- Age 18-70 years
- Confirmed stage IV colorectal cancer
- Receiving FOLFOX/XELOX±Bevacizumab for 6 cycles
- Adequate organ function: Hb≥9g/dL, WBC≥1.5×103/µL, PLT≥10×104/µL, AST/ALT≤5×ULN, bilirubin≤2×ULN, GFR>30ml/min
- ECOG performance status<2
- Sign of the written consent

Exclusion criteria:

- Pregnancy/lactation
- Candidates for curative surgery
- Active infection
- Hypersensitivity to study medications
- Multiple primary cancers
- Heart failure, autoimmune diseases, immunodeficiency
- Hepatitis B/C
- Concomitant antioxidant regular use including dietary supplements (Vitamin C: >500 mg/day, Vitamin E: >400 IU/day, Beta-carotene: >5,000 IU/day, Selenium: >100 mcg/day, N-acetylcysteine (NAC): >600 mg/day, Alpha-lipoic acid: >300 mg/day, Coenzyme Q10 >100 mg/day), antioxidant-rich herbal supplements (Green tea extract: >500 mg/day, Resveratrol supplements: >100 mg/day, Grape seed extract: >100 mg/day, Pine bark extract: >100 mg/day) or during 2 weeks before study initiation
- *Regular use defined as ≥3 times per week for the past month, exceptions: Standard multivitamins containing RDA levels of antioxidants are permitted Dietary sources of antioxidants through normal food consumption are allowed (19-22)
- Gallstones/active GI ulcer

Exit criteria:

- Participation in other trials
- The patient's unwillingness to continue the study or their inability to swallow the capsule
- Worsening (progression) of the patient's cancer on the prescribed chemotherapy regimen requiring a change in the chemotherapy regimen Intolerable adverse events induced by nano-curcumin
- Intolerable side effects based on the Common Terminology CTCAE v5 (23) due to chemotherapy that require discontinuation of treatment
- Starting antioxidant drug use

### *Study Protocol*

Patients with histologically confirmed stage 4 colorectal cancer receiving XELOX or mFOLFOX6 ±Bevacizumab were enrolled. The intervention used SinaCurcumin® (developed at Mashhad University of Medical Science, marketed by Exir Nano Sina Company) (24), containing 40mg curcumin in nano-micelle form (~10nm particle size). This formulation enhances bioavailability by overcoming the unstirred water layer barrier (25), dissolving within 15 minutes (26), and utilizing bile salt emulsification (27). Patients received three 40mg capsules daily after meals or an identical placebo during six chemotherapy cycles (each cycle lasting 3 weeks). The placebos were designed to match active treatment in size, shape, and appearance, containing microcrystalline cellulose and lactose as inert ingredients by the same company (Exir Nano Sina). Both active and placebo capsules were stored at room temperature (20-25°C) in identical opaque containers protected from light and moisture. Compliance (≥80% consumption) was monitored during each cycle. Baseline demographics, medical history, laboratory data (CEA, liver function, serum creatinine (Scr), blood urine nitrogen (BUN)), and radiological findings were recorded.

### *Sample size*

This study was primarily designed to evaluate the oral nano-formulation of Curcumin efficacy, as an adjuvant to XELOX/FOLFOX±Bevacizumab regimen for mCRC. To determine the sample size, taking into account the results of the study by Jeon et al. (9) who stated that the overall response rate of XELOX and FOLFOX regimen in metastatic colorectal cancer is 40%, with the acceptable assumption of additional effectiveness caused by curcumin at the rate of 10% and considering Power Study equal to 0.8 and significant level equal to 0.95 confidence interval and using the Pocock formula, the calculated sample size for each arm was calculated as 29 people, and the total number of patients in each arm was considered 47 people, considering a possible dropout rate of 40%, considering that patients are outpatients.

$$n = \frac{[P_1(1-P_1) + P_2(1-P_2)]}{(P_1-P_2)^2} (Z_\alpha+Z_\beta)^2$$

$$n = \frac{[0.4(1-0.4)+0.1(1-0.1)]}{(0.4-0.1)^2} (1.96+0.84)^2 = 2=28.74$$

### *Outcomes*

Primary outcomes will consist of radiographic examination for metastatic extent according to RECIST criteria at the completion of six courses, along with serum CEA level assessments at the end of both three and six courses of chemotherapy (28). Partial Response (PR) is defined as at least a 30% decrease in the sum of diameters of target lesions, taking the baseline sum diameters as reference, with no new lesions appearing and no unequivocal progression of non-target lesions (28).

Stable Disease (SD) refers to a state where neither sufficient shrinkage to qualify for Partial Response (less than 30% decrease) nor sufficient increase to qualify for Progressive Disease (less than 20% increase) has occurred, taking as reference the smallest sum diameters while on study. Additionally, there should be no new lesions and no unequivocal progression of non-target lesions (28).

### *Randomization and blinding*

Randomization was performed using randomization. com, employing block randomization (blocks of 4) to ensure balanced group allocation. Ninety-six patients were randomized into 24 blocks. Identical-appearing nano-curcumin and placebo soft gels were numbered 1-96 and labeled A or B by the manufacturer. A clinical pharmacist managed medication distribution. Patients received two boxes (120 soft gels each) at baseline and week 4. The oncologist selected eligible patients and provided medications according to the allocation list. In addition to patients, the clinical pharmacist, oncologist, and data analyst remained blind throughout the study.

### *Statistical analysis*

Statistical analysis was performed using SPSS v13 and STATA. Data normality was assessed using Kolmogorov-Smirnov or Shapiro-Wilk tests. Continuous data were presented as mean±SD or median, and categorical data as percentage (prevalence). Between-group comparisons used independent t-tests (normal data) or Mann-Whitney U tests (non-normal data) for continuous variables, and Fisher's exact test for categorical variables. Intragroup changes were analyzed using Friedman test. Statistical significance was set at $P<0.05$.

## Results

Over the 2-year study period, a total of 96 patients with metastatic colorectal cancer receiving FOLFOX/XELOX±Bevacizumab regimen were initially screened. Two patients were excluded (one due to not meeting inclusion criteria and one declining to participate), resulting in 94 eligible patients. They were randomly divided into two groups and received either nano-curcumin capsules (n=47) or placebo (n=47). In the nano-curcumin group, 5 patients were excluded due to disease progression requiring chemotherapy regimen changes, and three patients due to discontinuation of chemotherapy. In the placebo group, 2 patients were excluded due to disease progression requiring chemotherapy regimen changes (Figure 1). Data from 84 patients who completed the study were included in the statistical analysis (per protocol analysis).

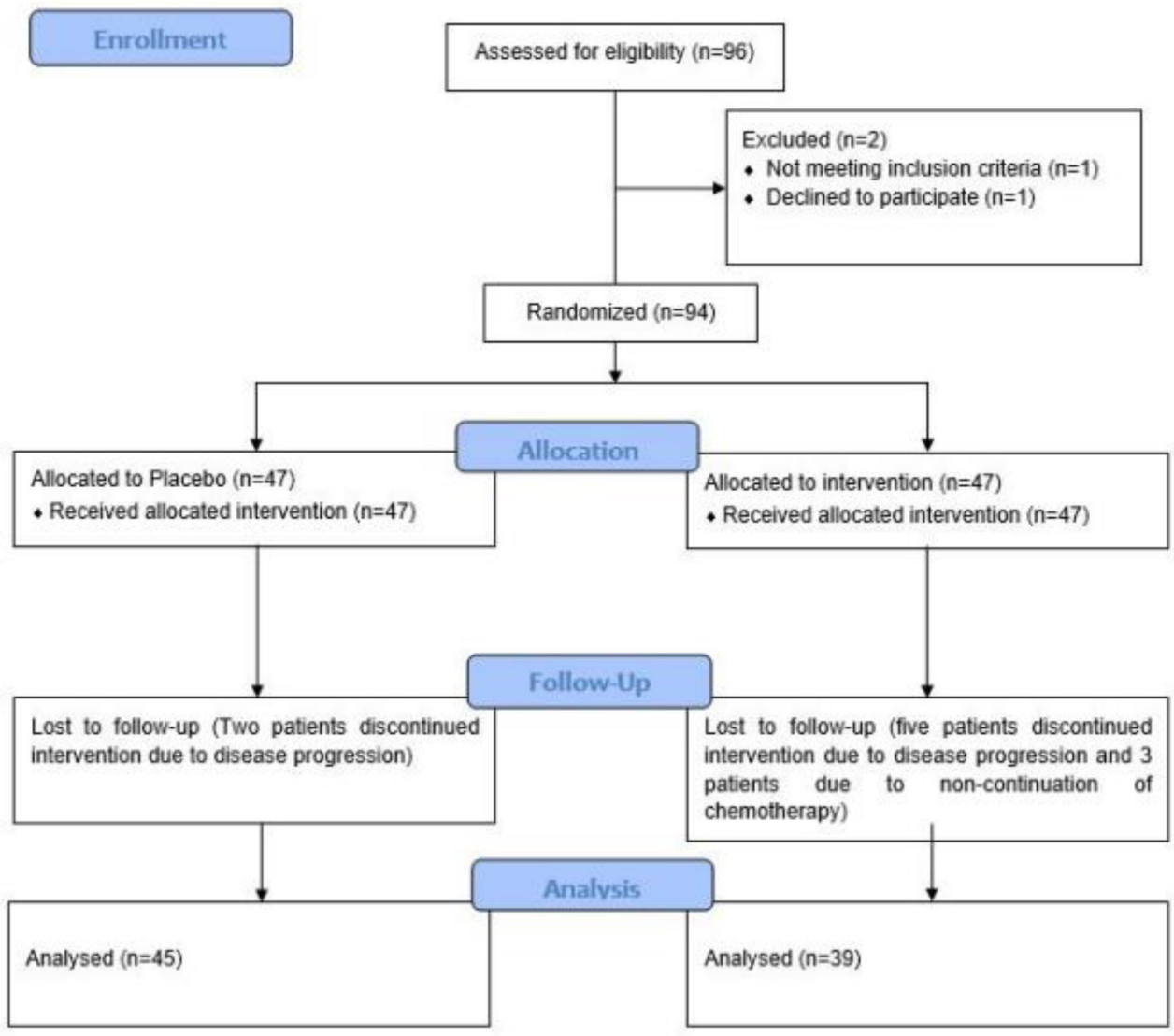


**Figure 1. CONSORT flow diagram of the study**

### *Baseline Demographic, Clinical, and Laboratory Characteristics of Patients*

The mean age of patients enrolled in the study was 60.90±6.65 years. The initial demographic, clinical, and laboratory parameters of the two groups are presented in Table 1. Comparison of the two groups in terms of weight, height, body surface area, age, creatinine and BUN, white blood cell count, platelet count, hemoglobin, and initial CEA was performed using an independent t-test, and there were no significant differences between the two groups in any of these parameters. The nano-curcumin and placebo groups also showed no significant differences in terms of gender, concurrent diseases, concurrent medications, type of chemotherapy regimen, and metastasis location.

**Table1. Baseline demographics, clinical characteristics, and laboratory data in placebo and nano-curcumin groups**

| Variable | | Placebo | Nano-curcumin | P value | Test result |
|---|---|---|---|---|---|
| Demographics (Mean ± SD) | Age, years | 60.2±7.52 | 61.71±5.47 | 0.3 | t = -1.04* |
| | Weight, kg | 73.42±8.68 | 73.46±10.05 | 0.98 | t = -0.02 |
| | Height, cm | 170.48±8.98 | 171±9.23 | 0.79 | t = - 0.25 |
| | Body surface area, $m^2$ | 1.80±0.15 | 1.81±0.16 | 0.69 | t = - 0.39 |
| Gender, N (%) | Male | (53.3) 24 | (61.5) 24 | 0.449 | $Chi^2$= 0.57** |
| Comorbid illness, N (%) | Diabetes Mellitus | (13.33) 6 | (20.51) 8 | 0.39 | $Chi^2$=3.02 |
| | Hypertension | (20) 9 | (7.69) 3 | | |
| | Cardiovascular disease | (8.8) 4 | (5.1) 2 | | |
| Past medication history, N (%) | Anti-diabetics agents | (37.78) 17 | (38.46) 15 | 0.75 | $Chi^2$=1.93 |
| | Anti-hypertensive agents | (13.33) 6 | (7.69) 3 | | |
| | NSAIDs | (11.11) 5 | (10.26) 4 | | |
| | Anti-ischemic agents | (17.78) 8 | (12.82) 5 | | |
| | Other | (20) 9 | (30.77) 12 | | |
| ECOG, N (%) | 1 | (37.8) 17 | (30.8) 12 | 0.5 | $Chi^2$=0.45 |
| | 2 | (62.2) 28 | (69.2) 27 | | |
| Chemotherapeutic regimen, N (%) | FOLFOX[1] | (44.4) 20 | (35.9) 14 | 0.21 | F=1.53 |
| | XELOX[2] | (6.7) 3 | (15.4) 6 | | |
| | FOLFOX+BEV[3] | (33.3) 15 | (43.6) 17 | | |
| | XELOX+BEV[4] | (15.6) 7 | (5.1) 2 | | |
| Liver metastasis, N (%) | Yes | (93.3) 42 | (89.7) 35 | 0.55 | $Chi^2$= 0.35 |
| | No | (6.7) 3 | (10.3) 4 | | |
| Kidney function test, mg/dL (Mean±SD) | Serum creatinine | 1.0±0.11 | 1.0±0.10 | 0.7 | t = 0.37 |
| | Blood urea nitrogen | 16.6±1.81 | 16.4±1.42 | 0.53 | t = 0.63 |
| Laboratory test (Median, Interquartile range) | White blood cell count | 7,928.8 | 7,933.3 | 0.981 | t = -0.02 |
| | | 7,659.4 – 8,198.3 | 7,654.2 – 8,212.4 | | |
| | Hemoglobin, g/L | 11.3 | 11.5 | 0.51 | t = -0.65 |
| | | 11.0 – 11.7 | 11.1 – 11.8 | | |
| | Platelet count | 21522.2 | 211025.6 | 0.4 | t = 0.84 |
| | | 208,421– 222,002 | 203,568-218,214 | | |
| | CEA, ng/ml | 4017.9 | 5242.2 | 0.17 | t = -1.36 |
| | | 2844.8-5191.0 | 3847.7-5479.3 | | |
| | AST, IU/L | 22.5 | 22.8 | 0.63 | t = -0.48 |
| | | 21.4-23.5 | 21.7-23.9 | | |
| | ALT, IU/L | 26.7 | 27.2 | 0.6 | t= -51 |
| | | 25.6-27.9 | 26.0-28.3 | | |
| | ALP, IU/L | 80.2 | 80.1 | 0.92 | t = 0.09 |
| | | 78.75-540 | 100-650 | | |

SD: Standard deviation, N: Number, ECOG: Eastern Cooperative Oncology Group Performance Status, NSAIDs: Non-steroidal anti-inflammatory drugs, CEA: Carcinoembryonic antigen, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, ALP: Alkaline Phosphatase.

1FOLFOX: Consists of oxaliplatin 85 mg/$m^2$ given intravenously over 2 hours on day 1, leucovorin 400 mg/$m^2$ IV over 2 hours on day 1, followed by 5-FU 400 mg/$m^2$ IV bolus, and then 2400 mg/$m^2$ as a continuous IV infusion over 46 hours starting on day 1. This regimen is repeated every 2 weeks.

2XELOX: Combines oxaliplatin 130 mg/$m^2$ given intravenously over 2 hours on day 1 with oral capecitabine 1000 mg/$m^2$ taken twice daily on days 1-14. This regimen runs on a 3-week cycle.

3FOLFOX+BEV: Adds bevacizumab 5 mg/kg given intravenously over 30-90 minutes on day 1 to the standard FOLFOX regimen described above. This combination is given every 2 weeks.

4XELOX+BEV: Incorporates bevacizumab 7.5 mg/kg administered intravenously over 30-90 minutes on day 1 along with the standard XELOX regimen outlined above. This combination follows a 3-week cycle.

***Comparison of CEA Serum Level Between Two Groups***

After three and six courses of chemotherapy, there was no significant difference between the two groups in terms of CEA values (Table 2).

**Table 2. Comparison of CEA (Carcinoembryonic antigen) level in 3rd and 6th cycle of chemotherapy in placebo and nano-curcumin groups**

| ng/mL (Median, (Interquartile Range)) | Placebo | Nano-curcumin | P- value |
|---|---|---|---|
| 3rd Cycle | | | |
| **CEA** | 769 | 653 | 0.1 |
| | (497-1430) | (529-1320) | |
| 6th cycle | | | |
| **CEA** | 239 | 326 | 0.95 |
| | (123-338) | (149-410) | |

CEA: Carcinoembryonic antigen

***Comparison of Disease Progression Based on RECIST Criteria in Two Groups***

There was no significant difference in both arms regarding RECIST criteria at the end of the 3rd and 6th cycle (Table 3).

**Table 3. Comparison of RECIST criteria in 3rd and 6th cycle of chemotherapy in placebo and nano-curcumin groups**

| Variable | | Placebo | Nano-curcumin | P- value |
|---|---|---|---|---|
| **3rd cycle** | **Partial Response** | 17(37.7%) | 14(35.8%) | 0.86 |
| | **Stable Disease** | 28(62.2%) | 25(64.1%) | |
| **6th cycle** | **Partial Response** | 21 (46.6%) | 20 (51.2%) | 0.67 |
| | **Stable Disease** | 24 (53.3%) | 19 (48.7%) | |

***Intragroup Effectiveness Comparison Between Two Groups***

Analysis of CEA levels showed a consistent decrease across all treatment regimens in both nano-curcumin and placebo groups. In the nano-curcumin group, FOLFOX demonstrated the most pronounced reduction from baseline (4553.28 ng/mL) to Cycle 6 (88.00 ng/mL). Similar trends were observed in the placebo group, with FOLFOX showing a reduction from 3359.10 ng/mL to 68.00 ng/mL. Statistical analysis revealed no significant differences between regimens at any time point in either group (all p-values>0.05). The addition of bevacizumab did not significantly impact CEA reduction patterns. While all regimens effectively lowered CEA levels by Cycle 6, the magnitude of reduction was comparable across treatment strategies, suggesting that a specific regimen did not significantly influence CEA outcomes (Table 4).

**Table 4. Comparison of CEA (Carcinoembryonic antigen) Levels by treatment group and time point**

| Treatment Arm | Regimen | Baseline (Median [IQR]) | Cycle 3 (Median [IQR]) | Cycle 6 (Median [IQR]) | P-value* |
|---|---|---|---|---|---|
| **Nano-curcumin** | FOLFOX | 4553.28 (1395.76-6542.11) | 545.00 (196.00-2281.50) | 88.00 (40.00-342.00) | 0.847 |
| | BEV+FOLFOX | 4326.67 (2456.42-8694.89) | 2489.00 (672.00-4561.00) | 118.00 (32.00-420.00) | 0.456 |
| | XELOX | 5251.72 (1876.23-9865.21) | 3298.00 (782.00-4532.00) | 59.00 (28.00-156.00) | 0.623 |
| | BEV+XELOX | 4181.83 (3578.21-4784.89) | 1185.75 (132.00-2239.00) | 168.00 (26.00-310.00) | 0.745 |
| **Placebo** | FOLFOX | 3359.10 (768.33-7583.67) | 768.00 (456.50-4823.00) | 68.00 (15.00-196.00) | 0.912 |
| | BEV+FOLFOX | 3296.32 (894.43-8764.56) | 2487.00 (894.00-8764.50) | 85.00 (36.00-190.00) | 0.834 |
| | XELOX | 2487.23 (432.22-6093.44) | 2487.00 (432.00-6093.00) | 72.00 (32.00-85.00) | 0.745 |
| | BEV+XELOX | 2308.56 (743.54-4823.11) | 2308.00 (743.50-4823.50) | 82.00 (42.00-410.00) | 0.623 |

CEA: Carcinoembryonic antigen, IQR: Interquartile range

*P-values represent the comparison between regimens within each treatment arm at each time point using Kruskal-Wallis test.

Analysis of treatment responses across different chemotherapy regimens revealed varying patterns. In the FOLFOX group, nano-curcumin showed a higher partial response rate compared to placebo (57.1% vs 45%, P=0.48). The BEV+FOLFOX regimen demonstrated similar response rates between nano-curcumin and placebo groups (47.1% vs 46.7%, P=0.98). For XELOX, nano-curcumin achieved a higher PR rate (50% vs 33.3%, P=0.62), though the sample size was limited. The BEV+XELOX group had too few patients in the nano-curcumin arm (n=2) for meaningful comparison (50% vs 57.1%, P=0.85) (Table 5).

**Table 5. Comparison of Response rate based on RECIST criteria by regimen type between two groups at Cycle 6**

| Regimen | Treatment | Total, N | Partial Response, N (%) | Stable Disease, N (%) | P-value |
|---|---|---|---|---|---|
| **FOLFOX** | Placebo | 20 | 9 (45%) | 11 (55%) | 0.48 |
| | Nano-curcumin | 14 | 8 (57.1%) | 6 (42.9%) | |
| **BEV+FOLFOX** | Placebo | 15 | 7 (46.7%) | 8 (53.3%) | 0.98 |
| | Nano-curcumin | 17 | 8 (47.1%) | 9 (52.9%) | |
| **XELOX** | Placebo | 3 | 1 (33.3%) | 2 (66.7%) | 0.62 |
| | Nano-curcumin | 6 | 3 (50%) | 3 (50%) | |
| **BEV+XELOX** | Placebo | 7 | 4 (57.1%) | 3 (42.9%) | 0.85 |
| | Nano-curcumin | 2 | 1 (50%) | 1 (50%) | |

N: Number

Longitudinal analysis showed that the nano-curcumin group had a slightly higher improvement rate (23.1% vs 17.8%) and lower worsening rate (7.7% vs 8.9%) compared to the placebo. However, these differences were not statistically significant (P>0.05) (Table 6).

**Table 6. Comparison of the response rates based on RECIST criteria from Cycle 3 to Cycle 6**

| Group | Improved (Stable disease to Partial Response) | Worsened (Partial response to Stable disease) | No change | P-value* |
|---|---|---|---|---|
| Placebo (n=45) | 8 (17.8%) | 4 (8.9%) | 33 (73.3%) | 0.24 |
| Nano-curcumin (n=39) | 9 (23.1%) | 3 (7.7%) | 27 (69.2%) | 0.14 |

*McNemar's test for within-group changes Between-group comparison at cycle 6: p = 0.677 (Chi-square test)

### *Safety of Treatment*

There were no adverse reactions noticed in either the treatment or placebo group of patients.

## Discussion

The present study was conducted to evaluate the efficacy of curcumin nanomicellar formulation (SinaCurcumin®) in enhancing the effectiveness of standard chemotherapy regimens and reducing chemotherapy-related side effects in patients with mCRC undergoing treatment with XELOX/mFOLFOX6 ± Bevacizumab. Our findings showed that the administration of curcumin nanomicellar formulation had no significant effect on CEA, which was considered a laboratory criterion for evaluating disease progression in these patients. Additionally, nano-curcumin administration did not have a significant effect on RECIST criteria, which indicates radiological progression during treatment.

Based on our findings, while nano-curcumin showed some promising trends, particularly in the FOLFOX group (57.1% vs 45% PR rate), the differences did not reach statistical significance (P>0.05). The longitudinal analysis revealed that nano-curcumin-treated patients showed a higher rate of improvement from SD to PR (23.1% vs 17.8%) and a lower rate of disease progression (7.7% vs 8.9%) compared to the placebo, but these differences were not statistically significant. Similarly, Greil et al.'s 2018 study (29) evaluating intravenous liposomal curcumin (100-300 mg/minute) in 32 advanced cancer patients showed limited efficacy. Of 23 patients evaluated, only 8 completed an 8-week assessment, all showing progressive disease. Among 15 patients evaluated between weeks 4-8, 14 had

progressive disease and one maintained stable disease. Five patients discontinued due to deteriorating condition, and two withdrew consent (29). Purbadi et al.'s double-blind, placebo-controlled trial (30) evaluated BCM-95 (biocurcumin) in stage IIIB cervical cancer patients. Despite administering 1000mg oral biocurcumin thrice daily for 9 weeks, no significant differences in RECIST criteria were observed between intervention and control groups (30).

The current study found no significant intergroup differences in CEA levels. Similarly, Sharma et al.'s 2001 study (31) of 15 advanced colorectal cancer patients showed limited impact of curcumin on CEA. Only one patient receiving 440mg curcuma extract (36mg curcumin) daily demonstrated CEA reduction (from 310±15 to 175±9 μg/L) after 2 months, with mixed response showing stable colonic disease but liver progression (31).

The trial evaluated curcumin's efficacy in metastatic CRC using CEA as a primary endpoint. Results showed no significant impact on CEA levels. While CEA is traditionally used for monitoring CRC progression and treatment response (32), its reliability as a marker for curcumin's therapeutic effects may be limited, as CEA levels can be influenced by various factors including inflammation, and may not directly reflect tumor response (32).

This lack of correlation demonstrates a vital limitation in relying solely on CEA as an endpoint in trials investigating agents like curcumin, known for their anti-inflammatory effects. The relationship between inflammation and cancer is well-established, particularly in CRC, where inflammatory processes play a crucial role in tumor progression. Curcumin is known for its ability to modulate inflammatory pathways, particularly through inhibition of key signaling molecules like NF-kB and pro-inflammatory cytokines including IL-6 and TNFα. These inflammatory mediators play a role in CRC pathogenesis; for example, IL-6 is associated with pre-cancerous inflammatory responses (33). Moreover, curcumin demonstrates multiple anti-cancer mechanisms in colorectal cancer treatment. It acts as an immunomodulator by suppressing immune responses through CD28/CD80 regulation and CTLA-4 expression while enhancing NK cell activity. At the molecular level, curcumin targets key pathways by suppressing NF-κB, AP-1, and EGFR signaling, leading to reduced cancer cell growth and increased apoptosis through p53 activation (34). It also exhibits strong antioxidant properties by increasing superoxide dismutase and catalase activity while scavenging free radicals. Additionally, curcumin modulates enzyme systems by inhibiting cytochrome p450 and increasing Phase II enzymes, while decreasing VEGF activity through PPAR receptor inhibition. These combined mechanisms make curcumin a promising therapeutic agent for colorectal cancer prevention and treatment (34).

Cancer trials comprise 9% of curcumin-related complementary/alternative treatment studies (35). Mansouri et al.'s systematic review of 22 clinical studies demonstrated curcumin's benefits as an adjunct therapy in common cancers, including reduced side effects, improved survival rates, quality of life, and treatment effectiveness (36). Various formulations showed safety at doses up to 8g/day for 11 months. However, diverse study designs, outcome measures, and concurrent treatments make specific dosing recommendations challenging (37).

Given the compelling evidence supporting curcumin's role as an anti-inflammatory agent, considering a broader spectrum of biomarkers that reflect these mechanisms is essential. Recent meta-analyses have emphasized the need to use inflammatory biomarkers in curcumin clinical trials, as only 30% of studies have done so to date (33). This research gap limits our ability to translate preclinical findings into clinical relevance, particularly in understanding how curcumin affects molecular targets that could lead to meaningful clinical outcomes.

A recent meta-analysis by Tabrizi et al. highlighted curcumin's potential to reduce inflammatory markers such as TNFα, IL-6, and high-sensitivity C-reactive protein (hsCRP) in various conditions, including obesity-related diseases. However, curcumin's effect on CRC specifically has not been examined in relation to inflammatory biomarkers (38).

Most curcumin and cancer studies were conducted in past decades, but less than half were double-blind clinical trials using bioavailability-enhanced products. The average sample size and study duration in these trials were 60 people and 2.6 months, respectively. The ultimate study objective varied across different cancers, with most studies focusing on reducing chemotherapy-related side effects. Colorectal cancer citations in different populations have focused on prevention (which was ineffective), response to chemotherapy or radiotherapy (ineffective), or tolerability of this compound in metastatic colorectal cancer (35).

In a systematic review conducted by de Waure et al., the results did not sufficiently support the use of curcumin, either as monotherapy or as an add-on to standard treatment in patients with metastatic or locally advanced solid tumors. Multiple factors, including low sample sizes, limited clinical studies in this area, different formulations and administration routes, and tumor stage, can explain this lack of conclusive results (39).

In a systematic review by Howells et al., curcuminoid delivery systems were classified into 23 different types, with most studies using enhanced bioavailability curcumin

formulas (including studies adding piperine for increased availability) (35.8%) or standard curcumin capsules/tablets (29.7%). In studies involving patients at higher cancer risk, however, 11 out of 23 studies (47.8%) used capsules/tablets not formulated for enhanced bioavailability, compared to 6 studies (26.1%) that used enhanced bioavailability formulations. Interestingly, all 6 studies using enhanced bioavailability curcumin (in capsule form) showed positive results (1 for oral leukoplakia, 3 for oral submucosal fibrosis, 1 for Crohn's disease, and 1 for ulcerative colitis); while only 4 of 11 studies using non-enhanced formulations showed positive outcomes (2 for oral lichen planus; 2 for ulcerative colitis). Oral dosing regimens used various doses, with standard curcumin formulation ranging from 45 to 6000 mg daily, and enhanced-bioavailability curcumin formulation ranging between 50 to 6000 mg. The most common duration of treatment was 12 weeks (21.7%), 8 weeks (16.8%), 4 weeks (12.0%), or a single dose (8.1%). The maximum reported treatment duration was 72 weeks (33).

In de Waure's systematic review of seven cancer-related curcumin trials, researchers cite non-uniform formulations across different studies as the possible reason for inconclusive results. The wide dose range (minimum 1.44 grams daily for 6 months and maximum 8 grams daily for 6 weeks) and varying pharmacokinetic properties make comparing formulation efficacy difficult. Beyond irregular oral absorption, high curcumin uptake by malignant cells results in inadequate concentration in these tissues (39). In this regard, Gunther et al. (40) and Garcea et al. (41), treating colorectal tumor patients with oral curcumin C3 complex (8 grams daily for 6 weeks and 3.6 grams daily for one week, respectively), found mean curcumin concentrations in tumor tissue of 33.7 ng and 12.7 ± 5.7 nmol per gram tissue, respectively.

Additionally, in the rectal mucosa of healthy volunteers treated with curcumin-phosphatidylcholine formulation, mean curcumin levels were even lower at 2.8 ng/mL. These concentrations, in the low nanomolar range, are several times lower than concentrations used in cell-based studies to exert biological activities and may explain curcumin's varied effects in humans compared to laboratory systems (39). Collectively, these observations suggest that formulation and administration routes are key determinants of curcumin's therapeutic efficacy.

The authors of the Howells et al. study note that the enormous variance between trial protocols in terms of dose and intervention duration observed throughout this review may limit the value of outcome data even where potential clinical benefits have been observed. To add value to future trials, a useful scenario might include multiple shared sites as part of a "curcumin consortium" evaluating dosing strategies for different disease conditions. A consensus opinion on trial design regarding dosing strategies could greatly advance curcumin's clinical application and provide a strong evidence base that is readily translatable among international regulatory and approval bodies (33).

Several significant limitations must be considered when interpreting this study's findings on curcumin's effects on colorectal cancer. The inadequate follow-up period hampered the ability to assess long-term safety and efficacy outcomes, potentially missing delayed therapeutic responses or adverse effects. The limited frequency of CEA measurements reduced the capacity to monitor disease progression accurately and may have overlooked important temporal changes in tumor marker levels. Statistical under-powering due to insufficient sample size weakened the reliability of conclusions and increased the risk of Type II errors. Additional constraints included a potential lack of standardization in curcumin formulations, unresolved bioavailability and absorption issues, limited patient population diversity, and possible uncontrolled confounding factors. These limitations collectively suggest that while the findings are promising, larger, well-designed studies with extended follow-up periods and more frequent monitoring are necessary to definitively establish curcumin's role in colorectal cancer treatment.

## Conclusion

Our findings suggest that nano-curcumin with the prescribed dose did not show considerable efficacy in the radiologic response of metastatic colorectal cancer based on RECIST V1.1 criteria. CEA serum level also did not change significantly in comparison with the placebo. While CEA has been the cornerstone of colorectal cancer monitoring, our findings suggest it may not be an appropriate biomarker for evaluating curcumin efficacy. The lack of association between clinical disease activity and reported biomarkers of effectiveness suggests considering inflammatory markers that more accurately reflect the biological processes involved in CRC. Future studies should focus on optimizing the treatment protocol, including investigation of alternative nano-curcumin dosing strategies and timing of therapeutic interventions to enhance clinical efficacy.

## Conflicts of Interest

Dr. Mahmoud Reza Jaafari, one of the manuscript authors, is the founder of Exir Nano Sina Company which produced the studied medication. Other authors have nothing to declare.

**Acknowledgments**

No funding was received to assist with the preparation of this manuscript.

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**PLEASE CITE THIS PAPER AS:**

Jannati Yazdan Abad M, Allahyari A, Kamandi M, Arasteh O, Varmaghani M, Karbasforooshan H, et al. Evaluation of Nano-curcumin Oral Formulation Efficacy as an Adjuvant Treatment in Metastatic Colorectal Patients. J Pharm Care. 2025;13(1):14-25.