

Original Research Article

Evaluation of nano-curcumin oral formulation efficacy in prevention of chemotherapy-induced adverse reactions in metastatic colorectal cancer patients

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Article history:

Received: Nov 21, 2024

Received in revised form:

Feb 10, 2025

Accepted: Feb 27, 2025

AJP, Vol. 16, No. 2, Mar-Apr

2026, 342-355.

<https://dx.doi.org/10.22038/ajp.2025.26317>

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Keywords:

Metastatic colorectal cancer

Nanocurcumin

Chemotherapy toxicity

Cancer progression

FOLFOX/XELOX±Bevacizumab

Abstract

Objective: The aim of the present study is to evaluate the effectiveness of oral formulation of nano-curcumin in prevention of some chemotherapy-induced adverse reactions.

Materials and Methods: In this study, 84 patients with metastatic colorectal cancer were randomly assigned into the nano-curcumin (40 mg capsule) or placebo groups, receiving treatments three times daily, beginning the first day to the end of the sixth cycle of chemotherapy. To investigate various adverse events, including hematologic adverse reactions, diarrhea, hand-foot syndrome (HFS) and neuropathy, the criteria of National Cancer Institute Common Terminology for Adverse Events (NCI-CTCAE) version 5 were implemented after the third and sixth course.

Results: The CTCAE peripheral neuropathy score was significantly different between the two groups at the end of the 6th course ($p=0.029$) but not the third course ($p=0.157$). No significant response was observed for neutropenia, anemia, thrombocytopenia, HFS, or diarrhea at the end of both third ($P=0.267, 0.258, 0.933, 0.377, \text{ and } 0.811$, respectively) and 6th courses ($p=0.456, 0.645, 0.772, 0.34, \text{ and } 0.114$, respectively).

Conclusion: Nano-curcumin in dose of 40 mg thrice daily was not effective in prevention of neuropathy, HFS and hematologic adverse reactions induced by XELOX/FOLFOX-6 regimens. Further research with larger sample size on different nano-curcumin dosing schedules is suggested.

Please cite this paper as:

Jannati Yazdan Abad M, Allahyari A, Kamandi M, Arasteh O, Varmaghani M, Karbasforooshan H, Jaafari M.R, Kheradmand H, Eftekhari A, Elyasi S. Evaluation of nano-curcumin oral formulation efficacy in prevention of chemotherapy-induced adverse reactions in metastatic colorectal patients. Avicenna J Phytomed, 2026; 16(2): 342-355.

Introduction

Colorectal cancer (CRC) represents a significant global health burden as the third most common cancer and second leading cause of cancer-related death worldwide, with 1.85 million new cases and 850,000 deaths annually (Hossain et al. 2022). Among newly diagnosed cases, 20% present with initial metastasis (Biller and Schrag 2021), and 80% of these cases have unresectable metastases requiring palliative chemotherapy (Jeon et al. 2022). While the overall five-year survival rate for CRC is 64%, it drops dramatically to 12% in metastatic colorectal cancer (mCRC) patients (Xie et al. 2020).

Standard chemotherapy regimens for mCRC, including FOLFOX, FOLFIRI, and FOLFOXIRI with/without targeted agents, face significant challenges. These include poor patient adherence, frequent treatment delays (affecting 43% of patients), and high incidence of adverse events (90% of patients experience multiple events) (Keramida et al. 2019; Kogan et al. 2019; Ohishi et al. 2023). These factors, combined with tumor resistance and low drug selectivity, significantly impact treatment outcomes and quality of life (Arafat et al. 2022; Tang et al. 2023).

Curcumin, a bioactive polyphenol from turmeric, has emerged as a promising adjunctive therapy due to its chemosensitizing, antioxidant, and anti-inflammatory properties (Ojo et al. 2022; Tan and Norhaizan 2019). In addition, plant-based compounds could potentiate drug efficacy in lower doses, thus leading to lower systemic toxicities (Cocetta et al. 2021; Gavrilas et al. 2022; Wei et al. 2018). Previous studies have demonstrated curcumin potential in preventing various chemotherapy-induced complications, including hand-foot syndrome, neuropathy, hepatotoxicity, bone marrow suppression, and diarrhea (Chen et al. 2017; Hafez Ghoran et al. 2022; Ruiz de Porras et al. 2023; Sardou et al. 2023; Yao et al. 2013). However, these studies are mostly *in vitro*

or *in vivo* and double-blind randomized clinical trials are scarce.

Curcumin protective effects against chemotherapy-induced adverse events involve multiple complex molecular mechanisms. At the cellular level, curcumin demonstrates significant anti-inflammatory properties by modulating key inflammatory mediators such as Nuclear factor kappa B (NF- κ B), cyclooxygenase (COX), and signal transducer and activator of transcription 3 (STAT3), while inhibiting pro-inflammatory enzymes including xanthine oxidase and inducible nitric oxide synthase (Belcaro et al. 2014; Benzer et al. 2018; Calabrese et al. 2003; Dai et al. 2018; Fetoni et al. 2014). Moreover, it is shown that curcumin plays a significant role in regulating prostaglandin synthesis and modulating the activity of c-Jun/AP-1 transcription factors (Akbari et al. 2020; Zhou et al. 2011). Curcumin has an ability to increase pro-apoptotic molecules like BAK and BID while decreasing anti-apoptotic molecules such as BCL-2, BCL-XL, and MCL-1 (Palipoch et al. 2014). Another crucial aspect of curcumin protective mechanism lies in its antioxidant properties. As an effective reactive oxygen species (ROS) scavenger, curcumin enhances the body's natural antioxidant defense mechanisms (Belcaro et al. 2014; Calabrese et al. 2003; Dai et al. 2018; Mohamad et al. 2009; Palipoch et al. 2014; Sankrityayan and Majumdar 2016).

While traditional curcumin formulations face pharmacokinetic limitations (bioavailability <1%) (Scontre et al. 2018), nano-based formulations show enhanced anticancer activity and improved bioavailability (Al Moundhri et al. 2012). The nano formulation of curcumin potentially enhances these protective mechanisms through improved bioavailability and cellular uptake, though this specific aspect warrants further investigation (Fetoni et al. 2014).

Given the side effect profile of FOLFOX and XELOX regimens and proposed protective properties of curcumin

in previous studies against these adverse reaction, this placebo-controlled, randomized, triple-blind clinical trial was designed to evaluate the efficacy of an oral nano-curcumin formulation in preventing chemotherapy-related adverse events in mCRC patients.

Materials and Methods

Study Design

A randomized, triple-blind, placebo-controlled clinical trial conducted at an outpatient oncology clinic in Mashhad, Iran, between September 2021 and December 2023.

Ethics approval

The study protocol was approved by the Ethics Committee of Mashhad University of Medical Science (IR.MUMS.REC.1399.527). The study was registered at the Iranian Registry of Clinical Trials

(IRCT20200408046990N7) on 2021-03-13

Study Population

Eligible participants included patients aged 18-70 years with confirmed metastatic colorectal cancer (Stage IV) receiving FOLFOX/XELOX+Bevacizumab for six consecutive cycles. Key inclusion criteria encompassed adequate bone marrow, liver, and kidney function, and Eastern Cooperative Oncology Group (ECOG) performance status <2. Exclusion criteria included pregnancy, active infection, hypersensitivity to study components, multiple primary cancers, and use of antioxidant drugs.

Intervention

Patients received either SinaCurcumin® (40 mg nanomicelle-entrapped curcumin) three times daily or identical placebo capsules. The systematic review by Gutsche *et al.* (Gutsche *et al.* 2025) revealed that oral curcumin dosing in previous studies has ranged widely from 500-8000

mg/day for conventional curcumin and 40-180 mg/day for modified curcumin formulations. So, we chose the abovementioned conservative dose within the proven therapeutic range for modified formulations, to maintain both safety and potential efficacy while optimizing patient compliance over the 6-cycle treatment period. Besides, the recommended dose by the manufacturer is 40 mg twice daily and we did not want to give much higher dose. Nanomicelle entrapped curcumin is a registered curcumin product (SinaCurcumin®) for oral administration which has been developed in Nanotechnology Research Center of Mashhad University of Medical Science and marketed by Exir Nano Sina Company in Tehran-Iran (IRC:1228225765). Each soft gel of SinaCurcumin® contains 40 mg of curcumin in the form of nano-micelle. These nano-micelles are prepared from generally recognized as safe (GRAS) pharmaceutical excipients and C3-complex form of curcumin. The curcumin encapsulation rate in nano-micelle is nearly 100% and the particle size is around 10 nm. Compared to curcumin powder nano-enhanced formulation possesses higher bioavailability (Rahimi *et al.* 2015). Soft gels of SinaCurcumin® dissolve in the gastric medium in less than 15 min and are transferred to small intestine as the major site of absorption (Yao *et al.* 2013). After reaching the small intestine, nano-micelles can be released into unstirred water layer and diffused into enterocytes. Moreover, bile salts enhanced nano-micellar formulation by emulsification (Allen *et al.* 1993). Placebo soft gels were prepared by the same company, in exactly the same appearance containing all ingredients of medicine soft gel except curcumin with same dosing.

Protocol

Patients underwent standard chemotherapy regimens: XELOX: capecitabine (1000 mg/m² twice daily for 14 days) + oxaliplatin (130 mg/m² day 1),

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every 21 days. mFOLFOX6: oxaliplatin (85 mg/m² day 1) + calcium folinate (400 mg/m²) + 5-FU (400 mg/m² day 1, then 1200 mg/m² over 46-48 hr), every two weeks ± Bevacizumab (5 mg/kg day 1). Adverse events were assessed using CTCAE v5 criteria at the end of the 3rd and 6th cycles.

Sample size

Since the evaluation of preventive effect of nano-curcumin against chemotherapy adverse reactions is a part a larger project entitled “the oral nano-formulation of curcumin efficacy, as an adjuvant to XELOX/FOLFOX±Bevacizumab regimen for metastatic colorectal cancer”, the sample size was calculated based on the main outcome of that study: the overall response rate. To determine the sample size, taking into account the results of the study by Jeon et al. (Jeon et al. 2022) who stated that the overall response rate of XELOX and FOLFOX regimen in metastatic colorectal cancer is 40%, and considering effect size=10%, type 1 error (α) to be 5% and type 2 error (β) 80%, the calculated sample size for each arm was 29, and the total number of patients in each arm was considered 42 people.

However, while our sample size was primarily calculated for cancer progression outcomes, this sample size is also adequate for selected adverse events analysis. In line with Whitehead et al. recommendations, a pilot trial with 75, 25, 15, and 10 participants per treatment group is sufficient for standardized effect sizes of extra small (≤ 0.1), small (0.2), medium (0.5), or large (0.8), respectively (Whitehead et al. 2016), for a main trial with 90% power and a two-sided 5% significance level. Hence, the standardized effect size for nano-curcumin in this study is expected to be small to medium. Considering a study power of 90% ($\beta = 0.20$) and α error of 5%, a sample size of 15 - 25 per group would be sufficient.

Outcomes

The study evaluated the incidence of chemotherapy-induced side effects, including: neuropathy, hand-foot syndrome (HFS), diarrhea, and hematologic complications (anemia, neutropenia, and thrombocytopenia). These were assessed using NCI-CTCAE v.5 criteria at the end of the 3rd and 6th chemotherapy cycles. Hematologic complications and diarrhea CTCAE grading was not dependent on the investigator but regarding the HFS and neuropathy which are investigator-dependent, all patients were assessed with same person (an oncologist) to minimize inter-observer variability and ensure consistent grading across all study participants.

Randomization and blinding

Randomization was carried out using a computer-generated list of random allocation sequences from the randomization.com. Block randomization with blocks of four patients was used to ensure a balanced distribution of eligible patients between the control and intervention groups. The website randomly selected 24 blocks of four, resulting in a total of 96 patients included in the study. To maintain blinding, nano-curcumin and placebo soft gels, which were indistinguishable in appearance, were placed in boxes labeled with numbers from 1 to 96 according to the allocation sequence (by Exir Nano Sina Company), designating nano-curcumin and placebo as A and B, respectively. These boxes were then delivered to the clinical pharmacist. Patients received the medications in two separate boxes, one at the start of the study and another after four weeks, to facilitate better compliance monitoring. Each box contained 120 soft gels of nano-curcumin or placebo, sufficient for an eight-week period. Patients who met the inclusion criteria were selected by an oncologist and given boxes according to the allocation list. The clinical pharmacist and oncologist, who conducted patient evaluations during

the treatment period, were blinded to the group assignments. The person analyzing the data also remained blinded to the group allocations until the end of study.

Statistical analysis

SPSS version 13 and STATA were used for statistical evaluation. Continuous and non-continuous quantitative data are reported as mean \pm standard deviation and median (prevalence) and for qualitative data as percentage (prevalence). The normality of data was checked by Kolmogorov-Smirnov test or Sapiro-Wilk test. Comparison of the variables between the two groups was made with an independent sample t-test for quantitative variables and Fisher's exact test for qualitative variables. In case of non-normal data distribution, Mann-Whitney quantitative test was used. Intragroup changes were evaluated by Friedman test. The significance level for all tests was < 0.05 .

Results

Demographic and baseline characteristics

A total of 94 patients with metastatic colorectal cancer receiving the FOLFOX/XELOX \pm Bevacizumab regimen who met the inclusion criteria were included in the study after obtaining written consent. Participants were randomly assigned into two groups and received nano-curcumin capsules (n=47) or placebo (n=47). Eight patients in the curcumin group and two patients in the placebo group were excluded. Figure 1 shows the CONSORT subject flow diagram.

Eighty-four patients with a median age of 60.90 ± 6.65 years were analyzed. The baseline demographic, clinical, and laboratory parameters of the two groups are presented in Table 1. There was no significant difference between the two groups in any of these issues. Moreover, there were no significant differences in terms of gender, past medical and drug

history, type of chemotherapy regimen and location of metastasis.

Efficacy of nano-curcumin in prevention of chemotherapy-induced adverse events Neuropathy

After the third course of chemotherapy 79.48 and 77.8% of patients in the treatment and placebo groups experienced neuropathy respectively that were mostly grade 1, with no meaningful difference between the two groups ($p=0.15$). At the end of the 6th course, it increased to 92.27 and 80% and most of cases in the treatment group had neuropathy grade 2, in contrast to the placebo group (mostly grade 1). The difference was significant between two groups ($p=0.029$) (Table 2).

Hand-foot syndrome

At the end of third course, HFS grade 1 was the most common grade in both groups (38.44 and 46.6%, in the treatment and placebo groups, respectively), and this pattern remained after 6 courses. However, 12.82 and 4.4% of patients in the treatment and placebo groups experienced grade 3. The difference between the two groups was insignificant in both assessment points ($p=0.37$ and 0.34) (Table 2).

Diarrhea

Most of patients after three courses of chemotherapy experienced diarrhea in both groups (76.91 and 71.2% in the treatment and placebo groups, respectively) which increased to 89.75 and 80% after 6 courses of chemotherapy, but its occurrence rate was insignificantly different between two groups in both time points ($p=0.81$ and 0.11 , respectively) (Table 2).

Hematologic complications

At the end of third course, neutropenia (79.49 vs. 64.5%) and anemia (59 vs. 57.8%) was most common in the treatment group. However, thrombocytopenia was more common in the placebo group (77.8 vs. 74.4%). But the incidence of none of them was meaningfully different between

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two groups ($p=0.26$, 0.93 and 0.25 , neutropenia, anemia and thrombocytopenia respectively). The difference remained insignificant after 6 courses of chemotherapy ($p=0.45$, 0.77 and 0.64 , respectively). Anemia was the most common hematologic adverse drug reaction (ADR) after the 6th course in both groups (88.9 and 79.5%, in the placebo and treatment groups respectively) (Table 2).

Adverse events of nano-curcumin

No adverse events specifically attributable to nano-curcumin were reported during the study period. Moreover, distinguishing between chemotherapy-induced gastrointestinal effects and those potentially influenced by nano-curcumin was not feasible based on the data collected.

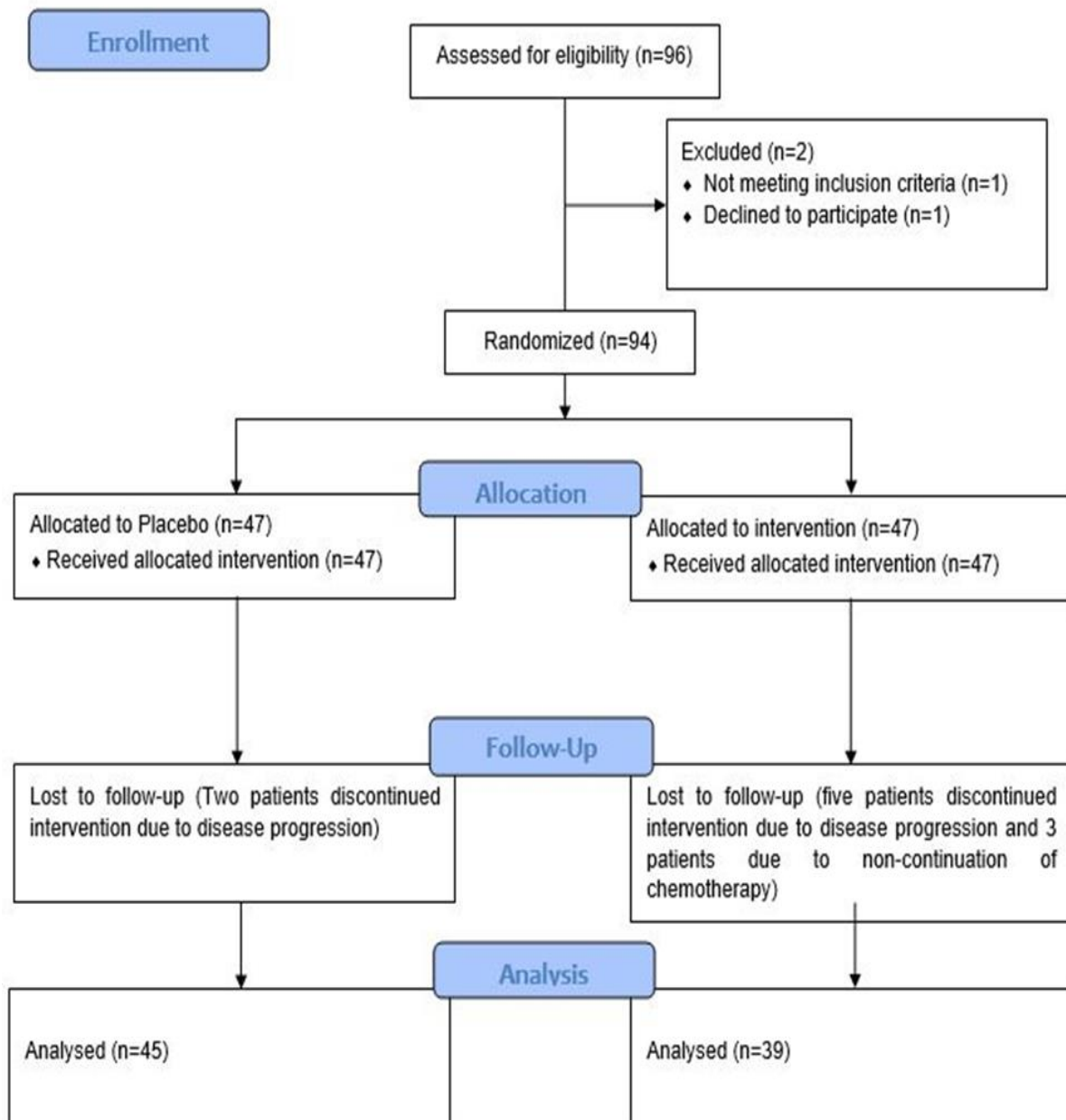


Figure 1. CONSORT flow diagram of the study

Table 1. Comparison of the baseline demographics, characteristics and laboratory data between the treatment and placebo groups.

variable	Placebo	Nano-curcumin	p value	Test result
Age, years ¹	60.2±7.52	61.71±5.47	0.3	t = -1.04*
Weight, kg ¹	73.42±8.68	73.46±10.05	0.98	t = -0.019
Height, cm ¹	170.48±8.98	171±9.23	0.79	t = -0.2567
Body surface area, m ² (mean ± SD)	1.80±0.15	1.81±0.16	0.69	t = -0.3977
Gender, number (%) N	Male (53.3) 24	(61.5) 24	0.449	Chi ² = 0.5744**
Comorbid illness (%) N	Diabetes Mellitus (13.33) 6	(20.51) 8	0.388	Chi ² =3.02
	Hypertension (20) 9	(7.69) 3		
	Cardiovascular disease (8.8) 4	(5.1) 2		
Past medical history (%) N	Anti-diabetics agents (37.78) 17	(38.46) 15	0.747	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, number (%) N	1 (37.8) 17	(30.8) 12	0.5	Chi ² =0.45
	2 (62.2) 28	(69.2) 27		
Chemotherapeutic regimen, number (%) N	FOLFOX (44.4) 20	(35.9) 14	0.2133	F=1.53
	XELOX (6.7) 3	(15.4) 6		
	FOLFOX+BEV (33.3) 15	(43.6) 17		
	XELOX+BEV (15.6) 7	(5.1) 2		
Liver metastasis (%) N	yes (93.3) 42	(89.7) 35	0.553	Chi ² = 0.3524
	no (6.7) 3	(10.3) 4		
Serum creatinine, mg/dl ¹	1.0±0.11	1.0±0.10	0.7	t = 0.376
Blood urea nitrogen, mg/dl ¹	16.6±1.81	16.4±1.42	0.53	t = 0.629
White blood cell count ²	7,928.8	7,933.3	0.981	t = -0.023
	7,659.4 – 8,198.3	7,654.2 – 8,212.4		
Hemoglobin, grams per liter ²	11.3	11.5	0.51	t = -0.652
	11.0 – 11.7	11.1 – 11.8		
Platelet count ²	21522.2	211025.6	0.402	t = 0.84
	208,421– 222,02	203,568-218,214		
CEA, ng/ml ²	4017.9	5242.2	0.17	t = -1.36
	2844.8-5191.0	3847.7-5479.3		
AST, international unit per liter ²	22.5	22.8	0.63	t = -0.483
	21.4-23.5	21.7-23.9		
ALT, international unit per liter ²	26.7	27.2	0.605	t = -518
	25.6-27.9	26.0-28.3		
ALP, international unit per liter ²	80.2	80.1	0.92	t = 0.097
	78.75-540	100-650		

CEA (Carcinoembryonic antigen), ECOG (Eastern Cooperative Oncology Group), AST (Aspartate transaminase), ALT (Alanine transaminase), ALP (Alkaline phosphatase), SD (Standard deviation), NSAID (Non-steroidal anti-inflammatory drug), XELOX: capecitabine (1000 mg/m² twice daily for 14 days) + oxaliplatin (130 mg/m² day 1), every 21 days. mFOLFOX6: oxaliplatin (85 mg/m² day 1) + calcium folinate (400 mg/m²) + 5-FU (400 mg/m² day 1, then 1200 mg/m² over 46-48 hr), every two weeks ± Bevacizumab (5 mg/kg day 1). *Two sample T test **Pearson's chi-squares test ***ANOVA, ¹mean±SD, ²average, interquartile range.

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Table 2. Comparison of the adverse reactions between the treatment and placebo groups based on NCI-CTCAE V5. scores

Group	CTCAE V5. score						p-value*
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	
	(percent) number	(percent) number	(percent) number	(percent) number	(percent) number	(percent) number	
Neuropathy- 3 rd cycle							
Nanocurcumin	(20.51%) 8	(38.46%) 15	(41.02%) 16	0	0	0	0.157
Placebo	10 (22.2%)	25 (55.6%)	10 (22.2%)	0	0	0	
Neuropathy- 6 th cycle							
Nanocurcumin	3 (6.8%)	13 (33.3%)	23 (58.9%)	0	0	0	0.029*
Placebo	9 (20%)	22 (47.8%)	14 (31.2%)	0	0	0	
HFS- 3 rd cycle							
Nanocurcumin	(34.28%) 12	(38.44%) 15	(34.28%) 12	0	0	0	0.377
Placebo	8(17.8%)	18(60%)	21(46.6%)	16(35.6%)	0	0	
HFS- 6 th cycle							
Nanocurcumin	(17.14%) 6	(51.42%) 18	(26.64%) 10	(12.82%) 5	0	0	0.340
Placebo	5(11.2%)	20(44.4%)	18(40%)	2(4.4%)	0	0	
Diarrhea- 3 rd cycle							
Nanocurcumin	9(23.1%)	16(41%)	14(35.9%)	0	0	0	0.811
Placebo	13(28.8%)	18(40%)	14(31.2%)	0	0	0	
Diarrhea- 6 th cycle							
Nanocurcumin	4(10.3%)	14(35.9%)	13(33.3%)	8(20.5%)	0	0	0.114
Placebo	9(20%)	17(37.7%)	17(37.7%)	2(4.6%)	0	0	
Neutropenia- 3 rd cycle							
Nanocurcumin	(20.51%) 8	(43.58%) 17	(35.89%) 14	0	0	0	0.267
Placebo	16(35.6%)	18(40%)	11(24.4%)	0	0	0	
Neutropenia- 6 th cycle							
Nanocurcumin	10(25.6%)	13(33.4%)	14(34.6%)	2(2.4%)	0	0	0.456
Placebo	12(26.6%)	18(40%)	15(33.4%)	0	0	0	
Anemia- 3 rd cycle							
Nanocurcumin	8(20.5%)	18(46.2%)	13(13.3%)	0	0	0	0.258
Placebo	13(28.8%)	13(28.9%)	19(42.3%)	0	0	0	
Anemia- 6 th cycle							
Nanocurcumin	8(20.5%)	14(36%)	12(30.7%)	5(12.8%)	0	0	0.645
Placebo	5(11.1%)	20(44.4%)	19(33.4%)	5(11.1%)	0	0	
Thrombocytopenia- 3 rd cycle							
Nanocurcumin	10(25.6%)	18(46.5%)	11(28.2%)	0	0	0	0.933
Placebo	10(22.2%)	22(48.8%)	13(29%)	0	0	0	
Thrombocytopenia- 6 th cycle							
Nanocurcumin	9(23.1%)	12(30.7%)	17(43.6%)	1(2.6%)	0	0	0.772
Placebo	14(31.1%)	15(33.3%)	15(33.3%)	1(2.3%)	0	0	

*ANOVA test

Discussion

The current study aimed to assess the efficacy of nanomicelle-entrapped curcumin (SinaCurcumin®) in prevention of some chemotherapy-induced adverse events in patients with metastatic colorectal cancer undergoing treatment with XELOX or mFOLFOX6 ± Bevacizumab regimens. Our findings suggested that administration of SinaCurcumin® 40 mg trice daily for 6 courses of chemotherapy did not significantly show protective effect against some chemotherapy-induced adverse events including hematologic complications, diarrhea, neuropathy and HFS.

Peripheral neuropathy is considered the most common and dose limiting adverse events of oxaliplatin-based chemotherapy regimens, such as XELOX and mFOLFOX6 (Mendonça *et al.* 2013). Nearly 30-40% of patients undergoing chemotherapy develop peripheral neuropathy (Rahimi and Kazemi Oskuee 2014). Curcumin neuroprotective characteristics have recently shown efficacy in the mitigation of various types peripheral neuropathies and possess several protective actions in neural cell lines and tissues (Liu *et al.* 2018; Yang *et al.* 2014; Zhang *et al.* 2020). Preclinical studies, including those by Zhang *et al.* (Zhang *et al.* 2020), Caillaud *et al.* (Caillaud *et al.* 2022), and Al Moundhri *et al.* (Al Moundhri *et al.* 2012), have demonstrated curcumin ability to improve nerve conduction, prevent hypersensitivity, and enhance nerve histology in animal models subjected to chemotherapeutic agents. However, in the current study, patients in the treatment group experienced neuropathy with higher grades and difference with the placebo group was significant. Howells *et al.* also found no significant difference in neuropathy between standard and cufox (curcumin-enhanced) groups based on the partially validated Gynecologic Oncology Group Neurotoxicity questionnaire, though patient-reported outcomes suggested fewer neuropathy-related symptoms with

curcumin (Howells *et al.* 2019). Belcaro *et al.*, in a pilot placebo-controlled study evaluated the lecithinized formulation of curcumin (Meriva: 500 mg) to mitigating chemo- and radio-therapy adverse events, observed reduced local pain rating based on visual analogue scale due to radiotherapy in curcumin arm (Belcaro *et al.* 2014). So, they assessed radiotherapy induced neuropathy and they used a different scale, which could make the difference. Besides, the nanomicelle-based formulation of curcumin may play a major role in alleviating oxidative stress and inflammation through stabilizing the curcumin in serum by binding to albumin, and betterment of cellular uptake, blood brain barrier permeability and tissue distribution (Bertoncini-Silva *et al.* 2024). This study breaks new ground by being the first to analyze nano-based formulation of curcumin in prevention of chemotherapy-related adverse effects, making our findings a unique contribution to existing literature.

Regarding hematologic complications, including anemia, neutropenia, and thrombocytopenia, no significant differences were observed between the nano-curcumin and placebo groups. Studies toward curcumin preventive effects on myelosuppression are scares and limited to preclinical studies (Akbari *et al.* 2020; Liu *et al.* 2018). In a study by Panahi *et al.*, in a randomized placebo-controlled trial evaluating the effects of a curcumin capsule containing 500 mg curcuminoids plus 5 mg piperine for 3 month in 80 patients on standard chemotherapy regimens, researchers observed no statistical differences between two groups regarding white blood cell and platelets counts and hemoglobin serum level and at the end of the trial ($p > 0.05$) (Panahi *et al.* 2021). In another placebo-controlled study by Goyal *et al.*, investigating the role of curcumin in decreasing standard chemotherapy related toxicities in locally advanced and metastatic breast cancer patients, curcumin was administered 1 g after breakfast and dinner for 4-6 courses of chemotherapy.

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They found no significant reduction in anemia occurrence in the treatment group (Goyal et al. 2019). So, the findings of these two studies were also in line with ours.

HFS is most frequently associated with pegylated liposomal doxorubicin (PLD), docetaxel, and fluoropyrimidines such as intravenous 5-fluorouracil (5-FU), capecitabine, and S-1 (Kwakman et al. 2020). In a pilot study by Scontre et al., in a pilot study evaluated the effects of turmeric 4 g/day (2 pills 12 hr apart) for 6 weeks on the incidence and severity of HFS in 40 patients undergoing treatment with capecitabine. The authors emphasized that despite they did not meet primary outcomes, the rates of HFS grades 2 or higher were very low compared to the values in the literature (Scontre et al. 2018). In addition, they concluded that anti-inflammatory effects of curcumin may play no role in prevention of HFS due to lack of significant changes in inflammatory variables (including Interleukin-6 (IL-6), Tumor necrosis factor (TNF)- α , C-reactive protein (CRP) and albumin) during six weeks of treatment (Scontre et al. 2018). We also did not find a meaningful reduction in CTCAE HFS grade in the nano-curcumin group in comparison with the placebo group.

Regarding diarrhea occurrence, which we again did not find considerable difference between the two groups, nano-curcumin was only investigated in in-vivo studies for enterotoxicity mediated by irinotecan and a reduction in intestinal mucosal damage was shown (Akbari et al. 2020). In an *in-vivo* study by Ouyang et al., evaluated curcumin effect on late-onset diarrhea of irinotecan. Eighteen BALB/c mice were administered 75 mg/kg intraperitoneal irinotecan for four days and curcumin (100 mg/kg) intragastrically administered 8 days before irinotecan. Authors concluded that curcumin exerts protective effects against irinotecan-related intestinal injury (Ouyang et al. 2019). Further research may explore different formulations, dosages, or combinations of

curcumin with other protective agents to determine if there can be a broader protective effect.

To add value to future trials, a useful scenario may involve multiple shared sites as part of a "Curcumin Consortium" that evaluates dosing strategies for various disease states. A consensus opinion on trial designs regarding dosing strategies could significantly enhance the clinical applicability of curcumin and provide a strong evidence base that can be easily translated among regulatory bodies and international approvals (Howells et al. 2021). Future research should focus on larger, multi-center trials with extended follow-up periods, explore combination therapies with nano-curcumin, and conduct mechanistic studies to better understand its neuroprotective actions.

So, as the current dosing schedule was not effective in prevention of assessed ADRs, it seems that further studies on higher dose of nano-curcumin for longer duration are necessary for better judgment. Moreover, it may be better to start nano-curcumin use some days before the initiation of chemotherapy for better response. It also suggested assessing the proposed nano-curcumin mechanism of action in future studies. Considering the high incidence of chemotherapy-induced adverse events which could result in treatment discontinuation or dose reduction, and consequently treatment failure, it is worthy to find some herbal cheap compounds with good safety profile for prevention of these events.

The current study suffered from several limitations. Although our follow-up duration of 6 chemotherapy cycles (approximately 3 months) exceeds the average previous study duration of 2.6 months, longer-term follow-up would be valuable to assess the persistence of protective effects, late-onset adverse events, potential cumulative benefits or risks and long-term safety profile of nano-curcumin. Moreover, several potential confounding factors, despite

randomization, may influence our results: Dietary factors, including consumption of turmeric-containing foods, use of other supplements or complementary medicines, variations in lifestyle factors (exercise, sleep patterns), and individual genetic variations affecting drug metabolism. Additionally, while our single-center design allowed standardized procedures and consistent follow-up, it may limit the generalizability of our findings to different geographic populations, varied healthcare settings, different chemotherapy protocols and diverse ethnic groups with varying genetic profiles. Finally, the sample size, while comparable to other curcumin studies (average 60 participants), may have limited our ability to detect smaller effect sizes, particularly in subgroup analyses.

Future multi-center studies with longer follow-up periods, larger sample sizes, and more comprehensive assessment of potential confounding factors would help address these limitations and provide more robust evidence for the role of nano-curcumin in managing chemotherapy-induced adverse events.

In conclusion, this randomized controlled trial demonstrates that nanomicelle-entrapped curcumin 40 mg capsule trice daily for 6 courses beside XELOX/6-FOLFOX6 chemotherapy regimens did not show significant preventive effects on hematologic complication, diarrhea, and HFS induced by these regimens and even significant higher grade of neuropathy was seen in the curcumin group. These findings suggest that while nano-curcumin may have potential preventive effects against chemotherapy ADRs based on some previous preclinical studies, its role as a broad supportive therapy requires further investigation. Future research should focus on optimizing formulations and dosing strategies, conducting larger, multi-center trials with longer follow-up periods, investigating potential mechanistic pathways, and identifying specific patient

subgroups who may benefit most from this intervention.

Acknowledgment

This study is part of a research thesis for a Ph.D. degree at Mashhad University of Medical Sciences.

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.

Funding

This work was supported by the Research Council of Mashhad University of Medical Sciences, Mashhad, Iran.

Ethical Considerations

The study protocol was approved by the Ethics Committee of Mashhad University of Medical Science.

Code of Ethics

(IR.MUMS.REC.1399.527)

Authors' Contributions

Mahdi Jannati Yazdan Abad, Hedyieh Karbasforooshan, Hamidreza Kheradmand and Abolfazl Eftekhari performed experiments, collected data. Sepideh Elyasi and Omid Arasteh designed the experiments, supervised, directed and managed the study. Mostafa Kamandi and Abolghasem Allahyari helped in patients' selection process. Mehdi varmaghani analyzed the data. Mahmoud Reza Jaafari provided the medications. Mahdi Jannati Yazdan Abad wrote the first version of the manuscript. All authors approved the final version of article to be published.

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