Avicenna Journal of Phytomedicine (AJP)

Original Research Article

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

Mahdi Jannati Yazdan Abad[1], Abolghasem Allahyari[2], Mostafa Kamandi[2], Omid Arasteh[1], Mehdi Varmaghani[3,4], Hedyieh Karbasforooshan[1], Mahmoud Reza Jaafari[5,6], Hamidreza Kheradmand[7], Abolfazl Eftekhari[8], Sepideh Elyasi[1,*]

[1]*Department of Clinical Pharmacy, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran*
[2]*Department of Hematology-Oncology, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran*
[3]*Social Determinants of Health Research Center, Mashhad University of Medical Sciences, Mashhad, Iran*
[4]*Department of Management Sciences and Health Economics, School of Health, Mashhad University of Medical Sciences, Mashhad, Iran*
[5]*Nanotechnology Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Iran*
[6]*Department of Pharmaceutical Nanotechnology, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran*
[7]*Mashhad University of Medical Sciences, School of Medicine, Mashhad, Iran*
[8]*Babol University of Medical Sciences, School of Medicine, Babol, Iran*

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, 148-161.
https://dx.doi.org/10.22038/ajp.2025.26317

**** Corresponding Author:***
Tel: +985131801588
Fax: +985138823251
elyasis@mums.ac.ir

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, and 0.811, respectively) and 6th courses (p=0.456, 0.645, 0.772, 0.34, 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): 148-161.

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 chemo-sensitizing, 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-κB), 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),

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 (ß) 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% (β = 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 ± 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±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

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.

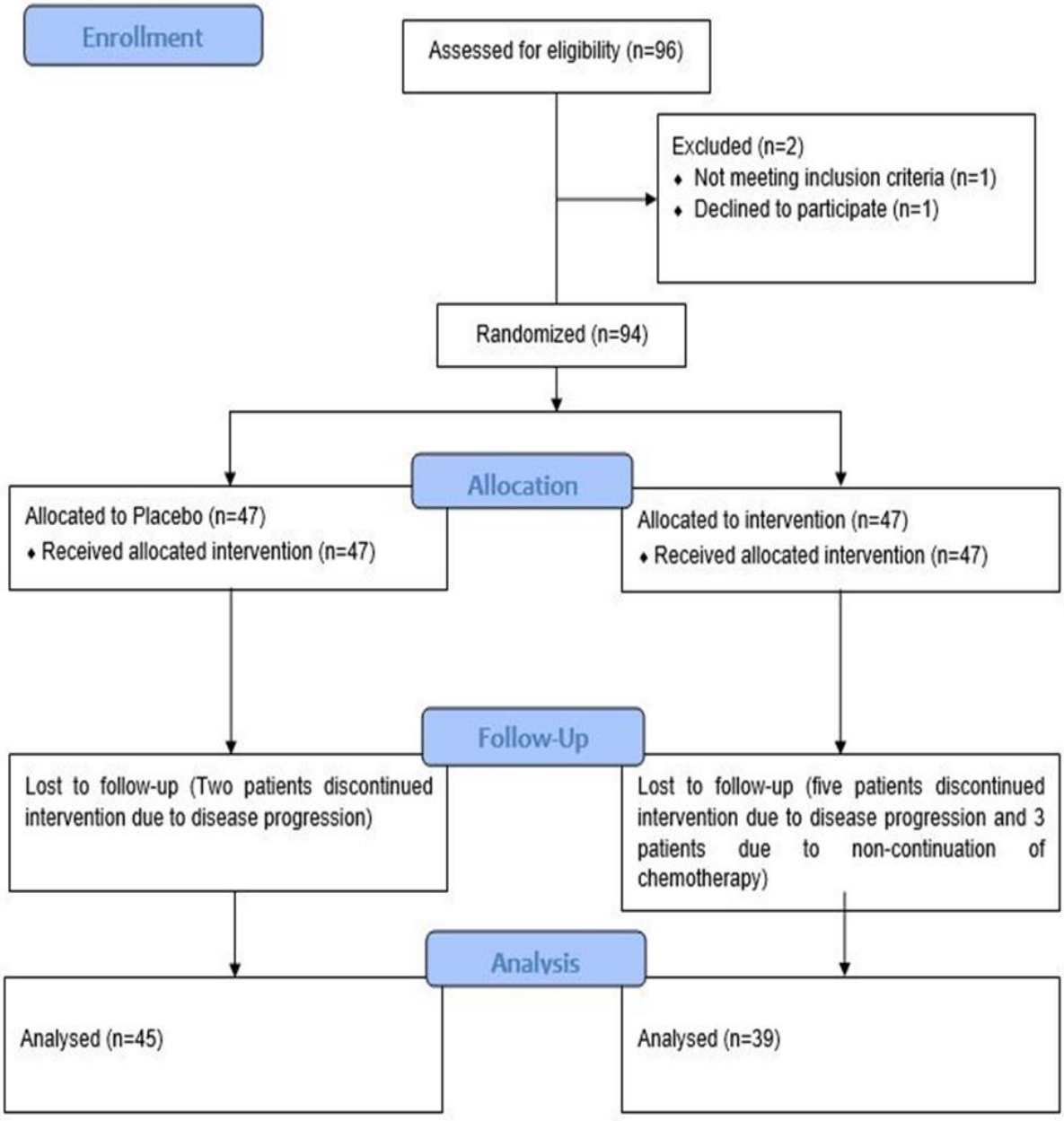

Figure 1. CONSORT flow diagram of the study

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	FOLFOX	(44.4) 20	(35.9) 14	0.2133	F=1.53
regimen, number (%) N	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, [1]mean±SD, [2]average, interquartile range.

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 (percent) number	**Grade 1 (percent) number**	**Grade 2 (percent) number**	**Grade 3 (percent) number**	**Grade 4 (percent) number**	**Grade 5 (percent) number**	
			Neuropathy- 3rd 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- 6th cycle							
Nanocurcumin	3 (6.8%)	13 (33.3%)	23 (58.9%)	0	0	0	0.029*
Placebo	9 (20%)	22 (478.8%)	14 (31.2%)	0	0	0	
HFS- 3rd 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- 6th 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- 3rd 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- 6th 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- 3rd 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- 6th 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- 3rd 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- 6th 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- 3rd 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- 6th 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.

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.

References

Akbari S, Kariznavi E, Jannati M, Elyasi S, Tayarani-Najaran Z (2020) Curcumin as a preventive or therapeutic measure for chemotherapy and radiotherapy induced

adverse reaction: A comprehensive review. Food Chem. Toxicol. 145:111699

Al Moundhri MS, Al-Salam S, Al Mahrouqee A, Beegam S, Ali BH (2012) The Effect of Curcumin on Oxaliplatin and Cisplatin Neurotoxicity in Rats: Some Behavioral, Biochemical, and Histopathological Studies. J. Med. Toxicol. 9:25 - 33

Allen A, Flemstrom G, Garner A, Kivilaakso E (1993) Gastroduodenal mucosal protection. Physiological reviews 73(4):823-857

Arafat Y, Loft M, Cao K, et al. (2022) Current colorectal cancer chemotherapy dosing limitations and novel assessments to personalize treatments. ANZ Journal of Surgery 92(11):2784

Belcaro G, Hosoi M, Pellegrini L, et al. (2014) A controlled study of a lecithinized delivery system of curcumin (Meriva®) to alleviate the adverse effects of cancer treatment. Phytother. Res. 28(3):444-450

Benzer F, Kandemir FM, Ozkaraca M, Kucukler S, Caglayan C (2018) Curcumin ameliorates doxorubicin-induced cardiotoxicity by abrogation of inflammation, apoptosis, oxidative DNA damage, and protein oxidation in rats. J. Biochem. Mol. Toxicol. 32(2):e22030

Bertoncini-Silva C, Vlad A, Ricciarelli R, Giacomo Fassini P, Suen VMM, Zingg J-M (2024) Enhancing the Bioavailability and Bioactivity of Curcumin for Disease Prevention and Treatment. Antioxidants 13(3):331

Biller LH, Schrag D (2021) Diagnosis and treatment of metastatic colorectal cancer: a review. Jama 325(7):669-685

Caillaud M, Thompson D, Toma W, et al. (2022) Formulated Curcumin Prevents Paclitaxel-Induced Peripheral Neuropathy through Reduction in Neuroinflammation by Modulation of α7 Nicotinic Acetylcholine Receptors. Pharmaceutics 14(6):1296

Calabrese V, Butterfield DA, Stella A (2003) Nutritional antioxidants and the heme oxygenase pathway of stress tolerance: novel targets for neuroprotection in Alzheimer's disease. The Italian J. Biochem. 52(4):177-181

Chen X, Wang J, Fu Z, et al. (2017) Curcumin activates DNA repair pathway in bone marrow to improve carboplatin-induced myelosuppression. Sci. Rep. 7(1):17724

Cocetta V, Quagliariello V, Fiorica F, Berretta M, Montopoli M (2021) Resveratrol as chemosensitizer agent: state of art and future perspectives. Int. J. Mol. Sci. 22(4):2049

Dai C, Ciccotosto GD, Cappai R, et al. (2018) Curcumin attenuates colistin-induced neurotoxicity in N2a cells via anti-inflammatory activity, suppression of oxidative stress, and apoptosis. Mol. Neurobiol. 55:421-434

Fetoni AR, Eramo SL, Paciello F, et al. (2014) Curcuma longa (curcumin) decreases in vivo cisplatin-induced ototoxicity through heme oxygenase-1 induction. Otology & Neurotology 35(5):e169-e177

Gavrilas LI, Cruceriu D, Mocan A, Loghin F, Miere D, Balacescu O (2022) Plant-derived bioactive compounds in colorectal cancer: Insights from combined regimens with conventional chemotherapy to overcome drug-resistance. Biomedicines 10(8):1948

Goyal S, Beniwal SK, Kumar HS, Kumar D, Das BC (2019) P1-189 - Role of Curcumin in reducing toxicity and adverse effects in locally advanced and metastatic breast cancer patients. Annals of Oncology 30:vi126-vi127 doi:https://doi.org/10.1093/annonc/mdz343.041

Gutsche LC, Dörfler J, Hübner J (2025) Curcumin as a complementary treatment in oncological therapy: a systematic review. Eur J Clin Pharmacol 81(1):1-33

Hafez Ghoran S, Calcaterra A, Abbasi M, Taktaz F, Nieselt K, Babaei E (2022) Curcumin-based nanoformulations: A promising adjuvant towards cancer treatment. Molecules 27(16):5236

Hossain MS, Karuniawati H, Jairoun AA, et al. (2022) Colorectal cancer: a review of carcinogenesis, global epidemiology, current challenges, risk factors, preventive and treatment strategies. Cancers 14(7):1732

Howells L, Malhotra Mukhtyar R, Theofanous D, et al. (2021) A Systematic Review Assessing Clinical Utility of Curcumin with a Focus on Cancer Prevention. Molecular Nutrition & Food Research 65(13):2000977 doi:https://doi.org/10.1002/mnfr.202000977

Howells LM, Iwuji COO, Irving GRB, et al. (2019) Curcumin Combined with FOLFOX

Chemotherapy Is Safe and Tolerable in Patients with Metastatic Colorectal Cancer in a Randomized Phase IIa Trial. J Nutr 149(7):1133-1139 doi:10.1093/jn/nxz029

Jeon Y, Sym SJ, Yoo BK, Baek J-H (2022) Long-term survival, tolerability, and safety of first-line bevacizumab and FOLFIRI in combination with ginsenoside-modified nanostructured lipid carrier containing curcumin in patients with unresectable metastatic colorectal cancer. Integrative Cancer Therapies 21:15347354221105498

Keramida K, Charalampopoulos G, Filippiadis D, Tsougos E, Farmakis D (2019) Cardiovascular complications of metastatic colorectal cancer treatment. J Gastrointest Oncol 10(4):797

Kogan LG, Davis SL, Brooks GA (2019) Treatment delays during FOLFOX chemotherapy in patients with colorectal cancer: a multicenter retrospective analysis. J Gastrointest Oncol 10(5):841

Kwakman JJM, Elshot YS, Punt CJA, Koopman M (2020) Management of cytotoxic chemotherapy-induced hand-foot syndrome. Oncol. Rev. 14(1):442 doi:10.4081/oncol.2020.442

Liu Z, Huang P, Law S, Tian H, Leung W, Xu C (2018) Preventive Effect of Curcumin Against Chemotherapy-Induced Side-Effects. Front. Pharmacol. 9 doi:10.3389/fphar.2018.01374

Mendonça LM, da Silva Machado C, Teixeira CCC, de Freitas LAP, Bianchi MdLP, Antunes LMG (2013) Curcumin reduces cisplatin-induced neurotoxicity in NGF-differentiated PC12 cells. Neurotoxicol. 34:205-211

Mohamad RH, El-Bastawesy AM, Zekry ZK, et al. (2009) The role of Curcuma longa against doxorubicin (adriamycin)-induced toxicity in rats. J Med Food 12(2):394-402

Ohishi T, Kaneko MK, Yoshida Y, Takashima A, Kato Y, Kawada M (2023) Current targeted therapy for metastatic colorectal cancer. Int. J. Mol. Sci. 24(2):1702

Ojo OA, Adeyemo TR, Rotimi D, et al. (2022) Anticancer properties of curcumin against colorectal cancer: a review. Front. Oncol. 12:881641

Ouyang M, Luo Z, Zhang W, et al. (2019) Protective effect of curcumin against irinotecan-induced intestinal mucosal injury via attenuation of NF-κB activation, oxidative stress and endoplasmic reticulum stress. Int J Oncol 54(4):1376-1386 doi:10.3892/ijo.2019.4714

Palipoch S, Punsawad C, Koomhin P, Suwannalert P (2014) Hepatoprotective effect of curcumin and alpha-tocopherol against cisplatin-induced oxidative stress. BMC Complement Altern Med 14(1):111 doi:10.1186/1472-6882-14-111

Panahi Y, Vahedian-Azimi A, Saadat A, et al. (2021) The Effects of Curcumin on the Side Effects of Anticancer Drugs in Chemotherapy: A Randomized Controlled Trial. *Adv Exp Med Biol*. 2021;1328:255-273. doi:10.1007/978-3-030-73234-9_17

Rahimi HR, Jaafari MR, Mohammadpour AH, et al. (2015) Curcumin: reintroduced therapeutic agent from traditional medicine for alcoholic liver disease. Asia Pac. J. Med. Toxicol. 4(1):25-30

Rahimi HR, Kazemi Oskuee R (2014) Curcumin from traditional Iranian medicine to molecular medicine. Razavi Int J Med 2(2):e19982

Ruiz de Porras V, Figols M, Font A, Pardina E (2023) Curcumin as a hepatoprotective agent against chemotherapy-induced liver injury. Life Sci 332:122119 doi:https://doi.org/10.1016/j.lfs.2023.122119

Sankrityayan H, Majumdar AS (2016) Curcumin and folic acid abrogated methotrexate induced vascular endothelial dysfunction. Can J Physiol Pharmacol 94(1):89-96

Sardou HS, Nazari SE, Abbaspour M, et al. (2023) Nano-curcumin formulations for targeted therapy of colorectal cancer. J Drug Deliv Sci Technol 88:104943

Scontre VA, Martins JC, de Melo Sette CV, et al. (2018) Curcuma longa (turmeric) for prevention of capecitabine-induced hand-foot syndrome: a pilot study. J Diet Suppl 15(5):606-612

Tan BL, Norhaizan ME (2019) Curcumin combination chemotherapy: The implication and efficacy in cancer. Molecules 24(14):2527

Tang Y-L, Li D-D, Duan J-Y, Sheng L-M, Wang X (2023) Resistance to targeted therapy in metastatic colorectal cancer: Current status and new developments. World J Gastroenterol 29(6):926

Wei Y, Yang P, Cao S, Zhao L (2018) The combination of curcumin and 5-

fluorouracil in cancer therapy. Arch Pharm Res 41:1-13

Whitehead AL, Julious SA, Cooper CL, Campbell MJ (2016) Estimating the sample size for a pilot randomised trial to minimise the overall trial sample size for the external pilot and main trial for a continuous outcome variable. Stat Methods Med Res 25(3):1057-1073

Xie Y-H, Chen Y-X, Fang J-Y (2020) Comprehensive review of targeted therapy for colorectal cancer. Signal Transduct Target 5(1):22

Yang Z, Zhao T, Zou Y, Zhang JH, Feng H (2014) Curcumin inhibits microglia inflammation and confers neuroprotection in intracerebral hemorrhage. Immunology letters 160(1):89-95

Yao Q, Ye X, Wang L, et al. (2013) Protective effect of curcumin on chemotherapy-induced intestinal dysfunction. International journal of clinical and experimental pathology 6(11):2342

Zhang X, Guan Z, Wang X, et al. (2020) Curcumin alleviates oxaliplatin-induced peripheral neuropathic pain through inhibiting oxidative stress-mediated activation of NF-κB and mitigating inflammation. Biol Pharm Bull 43(2):348-355

Zhou H, S Beevers C, Huang S (2011) The targets of curcumin. Curr Drug Targets 12(3):332-347