

Original Article

Running Title: Effect of Curcumin on Chemoradiotherapy-Induced Enteritis

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A Randomized, Double-Blinded, Placebo-Controlled Study on the Protective Effects of Curcumin against Chemoradiotherapy-Induced Enteritis

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Abstract

Background: Colorectal cancer ranks as the third most prevalent cancer type globally. In addition to surgery, chemotherapy, and radiation therapy, being the foremost efficacious and all-encompassing treatment modalities for cancer, pelvic chemoradiotherapy is known to precipitate adverse effects, notably intestinal inflammation. This study delves into assessing the impact of curcumin on the prophylaxis and amelioration of chemoradiotherapy-induced enterocolitis in colorectal cancer patients.

Method: This randomized study encompassed 44 colorectal cancer patients undergoing standard pelvic chemoradiotherapy, allocated to either curcumin treatment (22 patients) or placebo (22 patients) groups. Patients were administered oral curcumin capsules at a daily dosage of 500 mg commencing one week before baseline and extending throughout the standard treatment regimen, adhering to the same schedule. Subsequently, patients were subjected to biweekly evaluations encompassing demographics, clinical characteristics, and manifestations of enterocolitis, with statistical analysis employing Mann-Whitney and chi-square tests. A significance threshold of $P < 0.05$ was employed in the study for statistical significance.

Results: The incidence of complications exhibited no statistically significant disparity between the two cohorts across diverse disease stages. Furthermore, there were no discernible discrepancies in the manifestation of varying grades of intestinal complications between the curcumin-treated and placebo groups. Predominantly, both groups experienced the most pronounced side effects during the initial two weeks of treatment. Additionally, there was no statistically significant distinction in the prevalence of adverse drug reactions between the two groups, with figures standing at 31% versus 40% ($P = 0.17$).

Conclusion: Even though 500 mg/day of curcumin over a six-week duration did not engender a statistically significant reduction in the adverse effects of chemoradiotherapy, it was well-tolerated and deemed safe in this patient cohort.

Keywords: Rectal neoplasms, Curcumin, Enteritis, Radiation therapy

Introduction

Cancer is one of the most common causes of death worldwide. Recently, radiation therapy has formed a significant part of the treatment regimen for various human malignancies and is frequently applied in the palliative management of several other incurable ones. It is estimated that approximately 50%–70% of all cancer patients are being treated with radiation therapy or a combination of chemotherapy and radiation therapy schedules.¹⁻² Colorectal cancer is the third most prevalent type with the second highest death incidence.³⁻⁴ Besides surgery, chemotherapy and radiotherapy are the most effective and extensive approaches for cancer management. However, chemoradiotherapy causes adverse effects such as oral mucositis, hepatotoxicity, nephrotoxicity, neurotoxicity, hematopoietic system injury, and gastrointestinal toxicity. These side effects are due to inflammatory reactions, oxidative stress, and oxygen-free radical production. These adverse effects often reduce the quality of life in a patient with cancer.⁵⁻⁶ Enteritis caused by chemoradiotherapy is accompanied by increased intestinal permeability, decreased transit time, hypertrophic villi, mucosal atrophy, submucosal edema, inflammation of lamina propria, and ulcer. Nausea, vomiting, abdominal cramps, frequent rejection, watery diarrhea, mucosal secretion, pain, rectorrhagia, and weight loss follow these.⁷⁻⁸ Acute radiation enteritis manifests in up to 50% of individuals undergoing abdominal or pelvic radiotherapy.⁹ It is essential to develop effective management strategies against these side effects. Curcumin, extracted from the Turmeric plant, has antioxidant and anti-inflammatory properties. In addition, the chemo-radio protective effects of curcumin, known for its anticancer properties, were established in phase I clinical trials without side effects.¹⁰ Curcumin is a hydrophobic

molecule with a logP of 3.2 and is practically insoluble in water.¹¹

Curcumin regulates the anti-inflammatory effect due to NF- κ B suppression. NF- κ B suppression permits antioxidants to inhibit radiation-induced lipid peroxidation and improve endothelial function. Studies show that curcumin is a highly pleiotropic molecule capable of interacting with numerous molecular targets involved in inflammation. Curcumin modulates the inflammatory response by down-regulating the activity of cyclooxygenase-2 (COX-2), lipoxygenase, and inducible nitric oxide synthase (iNOS); inhibits the production of the inflammatory cytokine's tumor necrosis factor- α (TNF- α), interleukin (IL) -1, -2, -6, -8, and -12, monocyte chemoattractant protein (MCP), and migration inhibitory protein; and down-regulates mitogen-activated and Janus kinase.¹²⁻¹⁵ Based on the promising protective effects of Curcumin, the present study evaluated the chemo radio-protective effect of curcumin in the forty-four colorectal cancer patients on intestine side effects.

Materials and Methods

Trial design

This study employed a randomized, double-blinded clinical trial (RCT) conducted on patients diagnosed with colorectal cancer at the Radiation-Oncology Department of Seyed-al-Shohada Hospital in Isfahan, Iran.

Sample size

Initially, the sample size was calculated using the ratio comparison formula, considering statistical data from the study by Ryan et al.¹⁶ A total of 56 rectal cancer patients participated in this trial between 2017 and 2018, drawn from all rectal cancer patients eligible for chemo-radiation (Figure 1).

Inclusion and exclusion criteria

Inclusion criteria encompassed adult patients (> 18 years old) diagnosed with adenocarcinoma by biopsy, with tumors

located within fifteen centimeters from the anal verge. Patients with pelvic inflammatory disease, allergies to curcumin, or metabolic or hepatic diseases were deemed ineligible. Exclusion criteria included mortality during the study, voluntary participation withdrawal, and curcumin sensitivity.

Intervention

Ultimately, 44 evaluable patients were randomly allocated into two groups using systematic randomization with a sampling distance of 2, determined based on the estimated number of previous colorectal cancer patients at the hospital, utilizing random allocation software. All participants provided informed written consent.

Patients' demographic characteristics, such as age, sex, and cancer stage, were assessed. All patients were candidates for neoadjuvant chemoradiotherapy in line with their respective stages. Both groups underwent a standard 28-day course of chemoradiotherapy, consisting of radiation therapy with 6 MV photon [4500 to 5040 cGy to the whole pelvis, five days a week, along with a 540 cGy boost dose to the rectal tumor] and concurrent chemotherapy with Capecitabine [850mg/m² daily during radiation] or 5-FU [1000 mg/m², continuous infusion, five days during the first and last week of the course]. Gross target volume in the neoadjuvant setting, clinical target volume (CTV), and organs at risk (including the bladder, femoral heads, small bowel, and uterus in women or prostate in men) were contoured following the RTOG Consensus for contouring rectal cancer in 2008. Finally, a 3-millimeter margin was added to the CTV to create the planning target volume. Loperamide was administered to manage diarrhea in affected patients.

In group A, patients received Curcumin Capsules twice daily [Curcuma (curcumin glucuronide) from Dineh Company, www.dinehiran.ir] one week before commencing chemo-radiation, which

spanned six weeks. In group B, patients received placebo capsules manufactured by the Isfahan School of Pharmacy, matching the shape and method of the curcumin capsules.

All participants were assessed at baseline and visited every two weeks throughout the eight-week study period by a specialized healthcare provider. Patient assessments included a radiation enteritis severity score, measured using the NIH Common Terminology Criteria for Adverse Events (CTCAE) scales, version 4. This scoring system evaluated acute radiation enteritis toxicity, including abdominal cramps, frequent bowel movements, watery diarrhea, mucosal secretion, pain, rectorrhagia, and all associated complications, signs, and symptoms. As depicted in table 1, intestinal complications were categorized into five groups based on severity: Grade 1, no apparent signs and symptoms; Grade 2, abdominal pain, mucosal secretion, or mild rectorrhagia; Grade 3, severe abdominal pain, bowel obstruction, and peritoneal signs; Grade 4, life-threatening condition; and Grade 5: death.¹⁷

Statistical analysis

Following this, both groups underwent an evaluation of variables including age, sex, body mass index (BMI), cancer stage, interstitial signs grade, chemotherapy drug dosage, and radiotherapy dose, employing the Mann-Whitney and chi-square analysis methods. Statistical analysis was performed using SPSS version 23 (SPSS Inc., Chicago, IL, USA) software. The primary outcome measures included the severity of acute radiation-induced enteritis after chemoradiotherapy. $P < 0.05$ was considered statistically significant in the study.

Ethical considerations

This study received approval from the Ethics Committee of Isfahan University of Medical Sciences (Approval ID: IR.MUI.REC.1396.3.588). It was also

registered under clinical trial registration number (IRCT20220429054699N1) in the Iranian Clinical Trials Registry (WHO subgroup). All data generated or analyzed during this study are included in this published article, and all the patients provided informed consent.

Results

A total of 44 rectal cancer patients participated in this trial between 2017 and 2018, with 22 patients in each group: group A (Curcumin, N = 22) and group B (Placebo, N = 22). The baseline demographic and clinical characteristics of the participants are summarized in table 2. The mean differences in parameters, including age, sex, BMI, cancer stage, chemotherapy drug dosage, and radiotherapy dose, were not statistically significant ($P = 0.364, 0.358, 0.559, 0.132,$ and $0.131,$ respectively). The mean age of the Curcumin group was $52.59 \pm 12.87,$ and for the Placebo group, it was 57.41 ± 11.08 ($P = 0.364$). In the Curcumin group, 50% were male, and 50% were female. In the Placebo group, 45.4% were male, and 54.5% were female.

Table 3 presents intestinal side effects. Although nausea and mucosal secretion were slightly more common in the placebo group, there were no significant differences between the two groups.

Table 4 illustrates that there were no significant differences in the grades of intestinal complications categorized into five groups based on severity between the two groups ($P > 0.05$).

The prevalence of complications between the two groups did not significantly differ across various stages of the disease ($P = 0.321$). As shown in table 5, among patients with grade 3 enteritis, a more significant extent of intestinal involvement in the radiation field was observed than in grades 1 and 2 ($P = 0.03$).

Figure 2 compares the frequency of complications between the two groups over time. It demonstrates that although the most prominent side effects occurred in the first two weeks in both groups, they persisted until the third week in the placebo group while exhibiting a declining trend in the Curcumin group. However, there was no significant difference between the two groups in this regard, and after eight weeks, all patients were cured ($P = 0.22$).

Discussion

In this study, curcumin was administered with the expectation that it would prevent or treat chemoradiotherapy-induced enteritis in colorectal cancer through its anti-inflammatory effects. A total of 44 rectal cancer patients were randomly divided into two groups: group A (Curcumin) and group B (Placebo). Patients in group A received 500 mg/day of Curcumin Capsules one week before the commencement of standard chemo-radiation and continued for six weeks. In group B, patients received Placebo capsules following the same regimen. Ultimately, the study's results did not reveal any significant anti-inflammatory effect of curcumin in preventing or treating chemoradiotherapy-induced enteritis in colorectal cancer. No noteworthy differences between the two groups were observed in enteritis across various grades (Intervention and Control). The prevalence of enteritis signs and symptoms did not significantly differ among the various stages of the disease. Most side effects were observed in the first two weeks in both groups. However, while these side effects persisted until the third week in the placebo group, they exhibited a declining trend in the Curcumin group. Nevertheless, no significant

difference was noted between the two groups in this regard, and by the end of eight weeks, all patients had recovered. Most cases of enteritis were of the first grade, and no side effects of curcumin were observed in the patients.

For several years, curcumin, a potential anticancer agent, has undergone extensive exploration in numerous clinical trials for the treatment or prevention of various cancers, including pancreatic cancer, colorectal cancer, and osteosarcoma. However, concerns have arisen regarding the potential for antioxidants to diminish the efficacy of radiotherapy by protecting tumor cells from radiation-induced cell death, leading to the general recommendation that patients avoid antioxidants during radiotherapy. This precaution is taken to minimize the risk of cancer recurrence following radiotherapy.¹⁸

Conversely, in a review article by Vivek Verma et al. in 2016 on the interactions of curcumin with Radiation Therapy, they highlighted previous studies demonstrating the benefits of curcumin in mitigating radiotherapy toxicities. Notable examples include its efficacy in resolving dermatitis in breast cancer, preventing memory and cognitive decline in brain tumors, and treating soft tissue mucositis in head and neck cancer. These benefits are attributed to curcumin's ability to reduce oxidative stress, pro-inflammatory cytokines, NF- κ B expression, and fibrogenic cytokines.¹⁹ In adults with oral mucositis caused by chemotherapy and radiation therapy, it has been observed that curcumin mouthwash promotes faster wound healing compared with chlorhexidine mouthwash.²⁰ Ramezani et al. 2023 demonstrated that curcumin mouthwash and nanocapsules were effective, safe, and well-tolerated in treating radiation-induced oral mucositis²¹. Furthermore,

Dheyauldeen et al. conducted a study to evaluate curcumin's protective effect in radiotherapy dermato-toxicity in rats, and they found that pre- and post-radiotherapy administration of curcumin significantly increased anti-oxidase enzymes. They concluded that curcumin could reduce radiotherapy-induced oxidative stress.¹⁰

Based on the reviewed literature, it can be concluded that the disparities between the results and those of other studies may stem from the insufficient dosage of curcumin administered to the patients. Moreover, designing a study with a larger sample size and a more diverse representation of disease stages could yield more precise conclusions. The authors suggest that future research should focus on determining the optimal curcumin dosage. Identifying successful systemic and topical treatments for radiation-induced enteritis remains crucial.

Conclusion

In contrast to similar studies, the investigation did not identify an anti-inflammatory effect of curcumin in the prevention or treatment of chemoradiotherapy-induced enteritis in colorectal cancer. To unveil its natural ameliorative potential, higher dosage and prolonged duration of curcumin consumption are requisite, all while maintaining vigilance regarding curcumin's potential side-effects. As a subsequent step, further assessments could be conducted with a larger sample size, an extended treatment period, molecular analyses, and microscopic scrutiny of the intestinal tissues in both rat and human subjects. Direct examination of the intestinal tissue may be pivotal in elucidating the anticipated outcomes.

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Conflict of Interest

None declared.

References

1. Ballas LK, Elkin EB, Schrag D, Minsky BD, Bach PB. Radiation therapy facilities in the United States. *Int J Radiat Oncol Biol Phys.* 2006;66(4):1204-11. doi: 10.1016/j.ijrobp.2006.06.035.
2. Wang J, Boerma M, Fu Q, Hauer-Jensen M. Significance of endothelial dysfunction in the pathogenesis of early and delayed radiation enteropathy. *World J Gastroenterol.* 2007;13(22):3047-55. doi: 10.3748/wjg.v13.i22.3047.
3. Zhang QY, Wang FX, Jia KK, Kong LD. Natural product interventions for chemotherapy and radiotherapy-induced side effects. *Front Pharmacol.* 2018;9:1253. doi: 10.3389/fphar.2018.01253.
4. Wong KE, Ngai SC, Chan KG, Lee LH, Goh BH, Chuah LH. Curcumin nanoformulations for colorectal cancer: a review. *Front Pharmacol.* 2019;10(152). doi: 10.3389/fphar.2019.00152.
5. Shapiro CL. Highlights of recent findings on quality-of-life management for patients with cancer and their survivors. *JAMA Oncol.* 2016;2(11):1401-2. doi: 10.1001/jamaoncol.2016.3620.
6. Turcotte LM, Liu Q, Yasui Y, Arnold MA, Hammond S, Howell RM, et al. Temporal trends in treatment and subsequent neoplasm risk among 5-year survivors of childhood cancer, 1970-2015. *JAMA.* 2017;317(8):814-24. doi: 10.1001/jama.2017.0693.
7. Pía de la Maza M, Gotteland M, Ramírez C, Araya M, Yudin T, Bunout D, et al. Acute nutritional and intestinal changes after pelvic radiation. *J Am Coll Nutr.* 2001;20(6):637-42. doi: 10.1080/07315724.2001.10719161.
8. Galland RB, Spencer J. The natural history of clinically established radiation enteritis. *Lancet.* 1985;1(8440):1257-8. doi: 10.1016/s0140-6736(85)92322-0.
9. Yeoh EK, Horowitz M, Russo A, Muecke T, Robb T, Chatterton BE. Gastrointestinal function in chronic radiation enteritis--effects of loperamide-N-oxide. *Gut.* 1993;34(4):476-82. doi: 10.1136/gut.34.4.476.
10. Shabeeb D, Musa AE, Abd Ali HS, Najafi M. Curcumin protects against radiotherapy-induced oxidative injury to the skin. *Drug Des Devel Ther.* 2020;14:3159-63. doi: 10.2147/DDDT.S265228.
11. Sharma RA, Steward WP, Gescher AJ. Pharmacokinetics and pharmacodynamics of curcumin. *Adv Exp Med Biol.* 2007;595:453-70. doi: 10.1007/978-0-387-46401-5_20.
12. Kunnumakkara AB, Diagaradjane P, Guha S, Deorukhkar A, Shentu S, Aggarwal BB, et al. Curcumin sensitizes human colorectal cancer xenografts in nude mice to gamma-radiation by targeting nuclear factor-kappaB-regulated gene products. *Clin Cancer Res.* 2008;14(7):2128-36. doi: 10.1158/1078-0432.CCR-07-4722.
13. Xiao Y, Xia J, Wu S, Lv Z, Huang S, Huang H, et al. Curcumin inhibits acute vascular inflammation through the activation of heme oxygenase-1. *Oxid Med Cell Longev.* 2018;2018:3295807. doi: 10.1155/2018/3295807.
14. Sreejayan N, Rao MNA, Priyadarsini KI, Devasagayam TPA. Inhibition of radiation-induced lipid peroxidation by curcumin. *Int J of Pharm.* 1997;151(1):1127-30. doi:10.1016/S0378-5173(97)04900-4.
15. Goel A, Kunnumakkara AB, Aggarwal BB. Curcumin as "Curecumin": from kitchen to clinic. *Biochem Pharmacol.* 2008;75(4):787-809. doi: 10.1016/j.bcp.2007.08.016.

16. Ryan JL, Heckler CE, Ling M, Katz A, Williams JP, Pentland AP, et al. Curcumin for radiation dermatitis: a randomized, double-blind, placebo-controlled clinical trial of thirty breast cancer patients. *Radiat Res.* 2013;180(1):34-43. doi: 10.1667/RR3255.1.
17. Yeoh EK, Horowitz M. Radiation enteritis. *Surg Gynecol Obstet.* 1987;165(4):373-9.
18. Bairati I, Meyer F, Gélinas M, Fortin A, Nabid A, Brochet F, et al. Randomized trial of antioxidant vitamins to prevent acute adverse effects of radiation therapy in head and neck cancer patients. *J Clin Oncol.* 2005;23(24):5805-13. doi:10.1200/JCO.2005.05.514.
19. Verma V. Relationship and interactions of curcumin with radiation therapy. *World J Clin Oncol.* 2016;7(3):275-83. doi: 10.5306/wjco.v7.i3.275.
20. Patil K, Guledgud MV, Kulkarni PK, Keshari D, Tayal S. Use of Curcumin mouthrinse in radio-chemotherapy induced oral mucositis patients: a pilot study. *J Clin Diagn Res.* 2015;9(8):ZC59-62. doi: 10.7860/JCDR/2015/13034.6345.
21. Ramezani V, Ghadirian S, Shabani M, Boroumand MA, Daneshvar R, Saghafi F. Efficacy of curcumin for amelioration of radiotherapy-induced oral mucositis: a preliminary randomized controlled clinical trial. *BMC Cancer.* 2023;23(1):354. doi:10.1186/s12885-023-10730-8.

Table 1. Standard Terminology Criteria for Adverse Events v4.0 (CTCAE): Panel A: The severity of chemo-radiation enteritis was assessed using this scoring system, ranging from 0.0 to 5.0. Panel B: Definition of various recommendations characterizing inflammation of the small and large intestines, known as Enterocolitis

Panel A:

Grade 1	Mild: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate: Minimal, local, or non-invasive intervention indicated; limiting age-appropriate instrumental ADL*
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

Panel B:

Adverse event	1	2	3	4	5
Enterocolitis	Symptomatic; clinical or diagnostic observations only; intervention not indicated	Abdominal pain; mucus or blood in stool	Severe or persistent abdominal pain; fever; ileus; peritoneal signs	Life-threatening consequences; urgent intervention indicated	Death

*ADL: Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc. **Self-care ADL refers to bathing, dressing, and undressing, feeding self, using the toilet, taking medications, and not being bedridden; ADL: Activities of daily living

Table 2. Demographic and clinical characteristics in group A (Curcumin) and group B (Placebo)

Clinical characteristics		Group A (Curcumin) N=22	Group B (Placebo) N=22	*P-value
Age (y)		52.59 ± 12.87	57.41 ± 11.08	0.364
BMI (kg/m ²)		25.316 ± 2.88	24.579 ± 3.56	0.358
Gender	Male	11 (50%)	10 (45.4%)	0.559
	Female	11 (50%)	12 (54.5%)	
Stage	Stage II	3(13.6%)	6(27.3%)	0.559
	Stage III	19 (86.4%)	16(72.7%)	
Chemphtherapy	Capecitabine	18 (90%)	19 (86.4%)	0.132
	5FU	2(10%)	3 (13.6%)	
Radiation dose (cGy) + Boost		4642 + 518 ± 230	4698 + 471 ± 453	0.131

*P value<0.05 is statistically significant

Table 3. Different intestinal side effects after radiotherapy in group A (Curcumin) and group B (Placebo)

Intestinal side-effect	Group A (Curcumin) N=22 N (%)	Group B (Placebo) N=22 N (%)	*P-value
Blood in stool	1 (4/5%)	1 (4/5%)	0.17
Abdominal pain	1 (4/5%)	0(0%)	
Nausea	3 (13%)	4(18%)	
Mucus in stool	0(0%)	2 (9%)	
Diarrhea	2 (9%)	1 (4/5%)	
Total	7 (31%)	9(40 %)	

*P value<0.05 is statistically significant

Table 4. Comparison of different grades of intestinal disorders between group A (Curcumin) and group B (Placebo)

Intestine disorder	Group A (Curcumin) N=22 N (%)	Group (Placebo) N=22 N (%)	*P-value
Grade 1	3 (13%)	4 (18%)	0.17
Grade 2	3(13%)	3(13%)	
Grade 3	1 (4%)	1(4%)	
Grade 4	0	0	

*P-value<0.05 is statistically significant

Table 5. Intestinal volume in different grades of intestinal disorders

	Grade I, II intestine volume (cc)	Grade III intestine volume (cc)	P-value*
Group A (Curcumin) N = 22	221/2	465/5	0.03
Group B (Placebo) N = 22	218/1	458	0.03

*P-value<0.05 is statistically significant

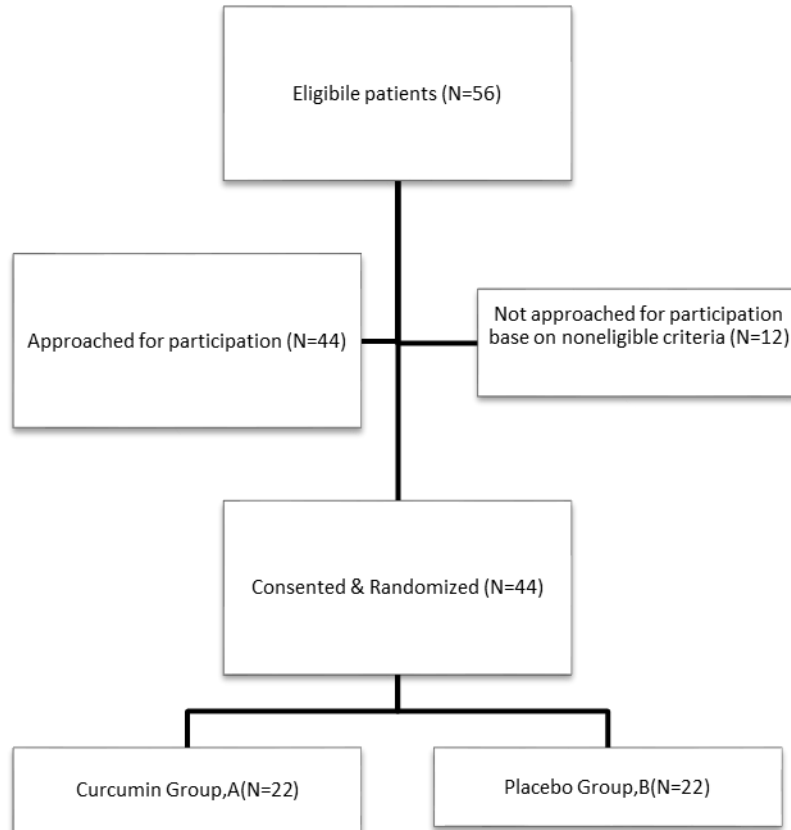


Figure 1. Consort diagram: This diagram documents the patient flow for the clinical trial. Only 44 out of 56 (78.57%) patients prescribed chemoradiotherapy for rectal cancer were eligible for this trial, and all of them were approached for participation. Among them, 44 out of 56 (78.57%) consented. There was no withdrawal rate for the study.

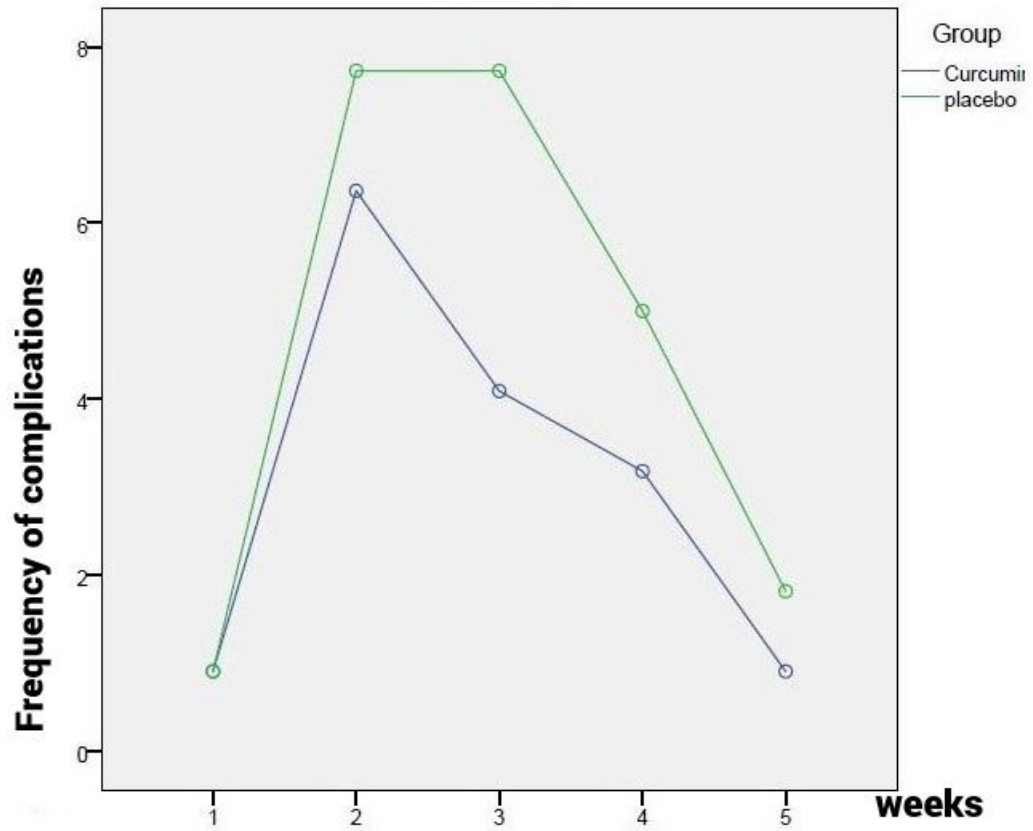


Figure 2. This figure illustrates the frequency of complications between group A (Curcumin) and group B (Placebo).