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Ameliorative effect of *Curcumin* on chemo radiotherapy induced Enteritis in colorectal cancer: a randomized, double blinded, placebo- controlled study

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Abstract.

Background: Cancer is the second leading cause of death in the world. Chemotherapy and radiotherapy are common cancer treatments. However, the development of adverse effects resulting from chemotherapy and radiotherapy hinders clinical use and negatively reduces the quality of life in cancer patients. Natural products, such as Curcumin prepared from herbs besides herbal formulas have been proved to prevent adverse effects of chemo radiotherapy in several studies. This study focuses on the impact of Curcumin on the prevention and treatment of adverse chemo radiotherapy effects in patients with colorectal cancer.

Method: This randomized, double-blinded, placebo-controlled trial study was performed on patients with colorectal cancer who received 28 days of radiation therapy. The participants were randomly assigned to the curcumin or placebo group with a chemo-radiation indication. Patients received oral curcumin (500 mg/day)or placebo for the entire treatment period. Patients in two groups were evaluated for intestinal symptoms and every two weeks after chemo-radiation and after the end of treatment.

Results: All 48 participants were randomly assigned 1:1 to curcumin (24 patients) and placebo group (24patients). Among them, 44 patients were evaluated for analysis (22 patients and 22 patients in the curcumin group and placebo group). The treatment period was the total radiotherapy duration (28 days) in the curcumin and placebo groups. The proportion of patients with symptoms of complications during the treatment period in the curcumin group (7 patients 31%) was not significantly less than the placebo group (9patients 40%). There was no significant difference in adverse drug reaction between the two groups (31%versus 40%, P =0.17).

Conclusion: Consumption of the curcumin for six weeks did not significantly reduce the adverse effects of chemo-radiotherapy in the study population. Curcumin is tolerated and safe in these patients. We could not conclude that curcumin is a potential therapeutic perspective for the prevention and treatment of chemotherapy and radiotherapy-induced side effects. Further studies are required to validate the efficacy of natural products in cancer patients and elucidate potential underlying mechanisms.

Keywords: Rectal cancer- Curcumin- Enteritis- Radiation Therapy

Introduction:

Cancer is one of the most common causes of death all over the world. Colorectal cancer is the third most prevalent type of cancer with the second high death incidence (1-2). Besides surgery, chemotherapy and

radiotherapy are the most effective and extensive approaches for this cancer management. However, chemo-radiotherapy causes adverse effects such as oral mucositis, hepatotoxicity, nephrotoxicity, neurotoxicity, hematopoietic system injury, and gastrointestinal toxicity. Many of these side effects are due to inflammatory reactions, oxidative stress, and oxygen free radicals production. These adverse effects often reduce the quality of life in the patient with cancer (3-4). Enteritis caused by chemo-radiotherapy is accompanied by increased intestinal permeability, decreased transit time, hypertrophic villi, mucosal atrophy, sub mucosal edema, inflammation of lamina propria, and ulcer following by nausea, vomiting, abdominal cramp, frequent rejection, watery diarrhea, mucosal secretion, pain, rectorrhagia, and weight loss (5-6). It is important to develop effective management strategies against these side effects (1). Curcumin, extracted from the Turmeric plant, has anti-oxidant and anti-inflammatory properties. Besides, the anti-cancer effect of curcumin is known to may have chemo-radio protective effects and it is established in phase I clinical trials without side effects (7). Curcumin regulates the anti-inflammatory effect due to NF-kB suppression. NF-kB suppression permit anti-oxidants to inhibit radiation-induced lipid peroxidation and endothelial function improvement. Available studies show 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-alpha (TNF-a), interleukin (IL) -1, -2, -6, -8, and -12, monocyte chemoattractant protein (MCP), and migration inhibitory protein; and down-regulates mitogen-activated and Janus kinase (8-11). Based on promising protective effects of Curcumin, the present study performed to evaluate the chemo radio-protective effect of curcumin in the intestine.

Method and material:

This randomized, double-blinded clinical trial study (RCT) was conducted on patients with colorectal cancer between 2017 and 2018 in the radiation-oncology department of Seyed-al-Shohada Hospital in Isfahan (Iran). The patients with pelvic inflammatory disease, allergy to curcumin, metabolic or hepatic disease, were excluded. And they did not take Cinamon during the study. All participants signed an informed written consent form. Forty-four patients by simple randomization method were selected. Patients were evaluated with demographic characteristics (age, sex, BMI), liver function tests, and the stage of cancer. They all underwent neo-adjuvant chemo-radiotherapy, with whole pelvic radiation therapy with 6 MV photon [5040 cGy to whole pelvic or 4500 cGy to whole pelvic + 540 cGy boot to the rectum] and chemotherapy by capecitabine [850mg /m2 all radiation days] or 5-FU [1000 mg/ m2 first and last week] as standard protocol. They were randomly divided into two groups, A (Curcumin N=22) and B (Placebo N=22). In group A, patients received Curcumin Capsules daily (www. Karenpharma.com turmeric extract 95%, 500 mg /cap) from one week before chemo-radiation and it lasted up to six weeks. In group B, patients received Placebo capsules in the same shape and the same method. All of them were visited every two weeks through eight weeks by a specialist. All complications, signs, and symptoms were noted. SPSS version 23 (SPSS Inc., Chicago, IL, USA) software was used for statistical analysis.

Results

All Patients in two groups received 28 days of chemo-radiotherapy. Both groups underwent evaluation variables such as age, sex, body mass index (BMI), stage of cancer, the dosage of chemotherapy drugs, and the dose of radiotherapy in this study .by using Mann-Whitney and chi-square analyzing method we realized that both groups did not have any significant differences among mentioned parameters. As a result, we could entirely relate the study results to the type of medicine, which we used on patient groups (Table 1).

Intestinal side-effects including abdominal cramp, frequent rejection, watery diarrhea, mucosal secretion, pain, rectorrhagia are noted in Table 2, and there are no significant differences between groups. We divided

intestinal complications into four groups due to severity, Grade 1: no obvious sign and symptom. Grade 2: abdominal pain, mucosal secretion, or mild rectorrhagia. Grade 3: severe abdominal pain, bowel obstruction, and peritoneal signs. Grade 4: life-threatening condition. There are no significant differences between the two study groups in the grades of intestinal disease (P=0/17) (Table 3).

We compared the frequency of complications during the time between the two groups. There are no significant differences between groups, and after eight weeks, all patients were cured (p=0/22) (Chart 1).

There were no differences between age and stage of disease with a prevalence of complications between groups. (p=0/31) (Table 4).

In the patient with grade 3 intestinal disease, we found a significantly large intestine in the radiation field compared with grade 1 and 2 in both groups (p=0/03) (Table 5).

Loperamide was administered for the treatment of diarrhea in all affected patients.

Discussion:

There is no recent study that shows the effectiveness of curcumin in controlling side effects of chemo-radiotherapy in the intestine. We found some similar studies about other types of cancers and other body organs. In this study, we tried to eliminate any bias, and we paired patients in several variables such as cancer stage, age, BMI, gender, used medication, dosage, and duration of chemotherapy and radiotherapy .

Consequently, we can note that the results of this study, are based on the type of medicine (curcumin & placebo) that used on patients. However, there were no significant differences between the function of Curcumin and placebo which we used in two study groups .

Intestinal complications between weeks 2-4 were at the most severity and frequency in both groups. And after eight weeks, all patients were cured. The most prevalent complication was in grade 1. And there was no side effect of Curcumin in patients .

Vivek Verma in 2016 performed a review article concerning interactions of curcumin with radiation Therapy. He pointed to different previous studies that demonstrated the benefits of curcumin against radiotherapy toxicities. For example, resolve dermatitis in breast cancer, prevention of memory and cognitive decline in brain tumors, treatment of soft tissue mucositis in head and neck cancer, he noted that curcumin action is due to decreasing oxidative stress, pro-inflammatory cytokines, NF-κB expression, and fibrogenic cytokines. All of which tend to occur both simultaneously and sequentially (12).

Curcumin protects the myocardium against doxorubicin-induced cardiotoxicity in mouse hearts and primary cardiomyocytes, probably via upregulating 14-3- 3g expression (13). In 2017, Rezaee et al. provide a summary of the studies done to show the protective effects of curcumin against cisplatin-induced neurotoxicity, nephrotoxicity, and ototoxicity (14). Curcumin mouthwash is observed to be better than chlorhexidine mouthwash in terms of rapid wound healing in adult patients with chemotherapy and radiotherapy-induced oral mucositis (15). Turmeric and curcumin are known to have hepatoprotective action. They antagonize chemotherapy-induced hepatotoxicity (16-17). Pre-treatment with a combination of curcumin and a-tocopherol regulates liver enzyme and lipid peroxidation biomarker and alleviates liver histopathology change in rats, showing the protection against cisplatin-induced hepatotoxicity via abrogating oxidative stress (18). Curcumin and its analog difluorinated curcumin potentially reduce cisplatin-induced nephrotoxicity, thereby enhance the therapeutic window of cisplatin, the latter also decreases inflammatory factors NF-kB and COX-2, oxidative stress as well as multi-drug resistance markers (19-20). In 2020, Dheyauldeen et al. evaluated the protective effect of Curcumin in radiotherapy dermato-toxicity in rats, they divided 40 rats into 4 groups: control group, curcumin 150mg/kg daily, radiation 10 GY /single dose, and a combination of curcumin and radiation. In treatment groups, rats received curcumin one day before radiation till three days after that. Then rats were sacrificed and their skin was examined. They founded reception of curcumin before and after radiotherapy leading to an increase in anti-oxidase enzymes, significantly. They concluded that curcumin could decrease radiotherapy oxidative stress(7). Although there were no significant changes in the two study groups in this study, we recommended further evaluations, especially molecular changes and microscopic investigations, in the effectiveness of curcumin in patients with adverse effects of chemo-radiotherapy.

Conclusion:

Unlike the above-mentioned studies, we didn't find the antioxidant effect of Curcumin in the prevention or treatment of chemo radiotherapy-induced enteritis in colorectal cancer, in our examination, and gross signs and symptoms occurred like placebo group in patients received curcumin during the study. However, probably, the examination of the direct intestinal tissue with microscopic characteristics and the existence of anti-inflammatory factors in tissue cells could show us somethings we expected. On the other hand, more dosage and duration of treatment with curcumin for the appearance of this natural product ameliorative effect against chemoradiotherapy toxicity in the intestine is needed, but we should regard curcumin side effects .

Finally, as this study is the first in this context, we suggest further evaluations with more sample size, long duration of treatment, molecular investigation, and microscopic examination of the intestine in rats and human beings.

Clinical Characteristics		Group B (Placebo) N=22	GroupA (Curcumin) N=22	*P Value
Age (y)		57.41 ± 11.08	52.59 ± 12.87	0/364
BMI(kg/m^2)		25.316 ± 2.88	24.579 ± 3.56	0/358
Gender	**male**	10 (45.4%)	11 (50%)	
	female	12 (54.5%)	11 (50%)	
Stage	**Stage II**	6(27.3%)	3(13.6%)	0/559
	Stage III	16(72.7%)	19 (86.4%)	
chemptherapy	**Capecitabine**	19 (86.4%)	18 (90%)	0/132
	5FU	3 (13.6%)	2(10%)	
Radiation Dose (cGy) + Boost		4698 + 471 ± 453	4642 + 518 ± 230	0/131

Table 1: different demographic characteristics in groups

*p value<0/05 is statistically significant

intestinal side effect	Group B (Placebo) N=22 N (%)	Group A (Curcumin) N=22 N(%)	P value
Blood in stool	1 (4/5%)	1 (4/5%)	0/17
Abdominal pain	0(0%)	1 (4/5%)	
nausea	4(18%)	3 (13%)	
Mucus in stool	2 (9%)	0(0%)	
Diarrhea	1 (4/5%)	2 (9%)	
Total	9(40 %)	7 (31%)	

Table 2: Different intestinal side effect after radiotherapy in groups

*p value<0/05 is statistically significant

Intestine disorder	Group B (Placebo) N=22 N(%)	GroupA (Curcumin) N=22 N(%)	*P Value
Grade 1	4 (18%)	3 (13%)	0/17
Grade 2	3(13%)	3(13%)	
Grade 3	1 (4%)	1(4%)	
Grade 4	0	0	

Table 3: comparing different garde of intestine disorder between groups

*p value<0/05 is statistically significant

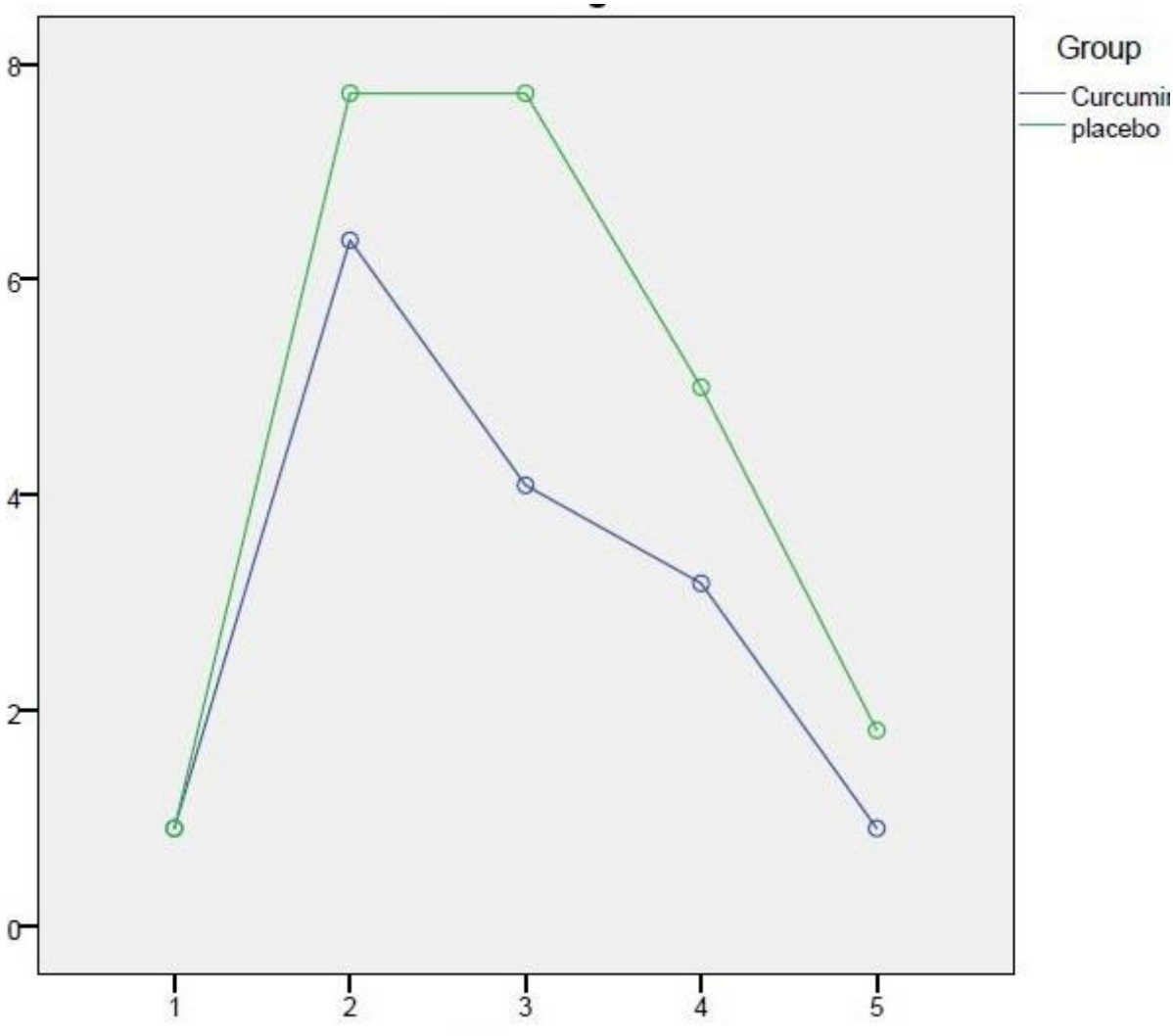

Chart 1:frequency of complications during time between two groups

Clinical Characteristics	Group B (Placebo) N=22 N(%)	GroupA (Curcumin) N=22 N(%)	*P Value
age	57.41 ± 11.08	52.59 ± 12.87	0/364
Stage II	3	0	0/321
Stage III	6	6	

Table 4: compare Clinical Characteristics and intestinal disorder between groups
*p value<0/05 is statistically significant

	Grade I,II Intestine Volume (cc)	Grade III Intestine Volume (cc)	P value *
Group B (Placebo) N=22	221/2	465/5	0/03
GroupA (Curcumin) N=22	218/1	458	0/03

Table 5: intestine Valume in different garde of intestinal disorder

*p value<0/05 is statistically significant

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