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The Impact of Silymarin on the Symptom Severity in Pediatric Patients with Inflammatory Bowel Disease: A Randomized Clinical Trial

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Abstract

Background: Inflammatory Bowel Disease (IBD) is a multifactorial disease, posing significant challenges to public health. The aim of this study is to determine the effect of silymarin on the symptom severity in pediatric patients with IBD.

Methods & Materials: This randomized clinical trial was conducted on children aged 5-18 diagnosed with IBD referred to the GI clinic at Akbar Children's Hospital in Mashhad. Those who met the inclusion criteria were randomly allocated into either the intervention or placebo group, each group consisting of 20 participants. In the intervention group, silymarin was administered three times daily in divided doses for three months. The control group received a placebo. To assess the efficacy of silymarin, PUCAI and PCDAI were evaluated for all patients at three different time points: before the intervention, during the first visit, and after the intervention. Data were analyzed utilizing the SPSS version 25, with a significance level set at $p < 0.05$.

Results: The comparison of the disease activity index scores in patients with IBD between the silymarin and placebo groups revealed that during the initial evaluation, no significant difference was observed in the disease activity index score between the two groups before the intervention ($p>0.05$). However, a statistically significant difference was observed in the disease activity index score between the two groups during the second, and third evaluations ($p<0.05$).

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Conclusion: The findings indicate that silymarin has a significant effect on alleviating the symptom severity in pediatric patients with IBD.

Key Words: Crohn's disease, Inflammatory bowel disease, Silymarin, Ulcerative colitis.

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1- INTRODUCTION

Inflammatory Bowel Disease (IBD) is a chronic and idiopathic condition characterized by intestinal inflammation (1). Over the years, IBD has emerged as a global health concern, with its prevalence growing steadily (2). The disease encompasses two primary manifestations: ulcerative colitis and Crohn's disease, both of which are chronic inflammatory disorders whose etiology remains unidentified (3, 4).

IBD is associated with debilitating symptoms including fatigue, abdominal pain, diarrhea, and weight loss (5, 6). Patients with IBD often experience extra intestinal symptoms, with approximately one-third reporting at least one such symptom. These extra intestinal symptoms encompass a wide range, including skin, eye, rheumatologic, renal, blood, cardiac, pulmonary, and neurological manifestations (7). When IBD begins in early life, it can lead to inadequate growth, delayed puberty, and psychosocial difficulties (8). Psychological distress, anxiety, and depression are prevalent among individuals with IBD (9). Given the physical and psychosocial impact of this disease, it significantly affects the patient's quality of life (10, 11). Furthermore, IBD patients generally have a shorter lifespan compared to the general population (12). The mortality associated with IBD is primarily concentrated in the initial years of the disease and later on, with an increased risk of colon cancer contributing to this outcome (13).

The prevalence of IBD has shown a significant increase in recent years, affecting millions of individuals worldwide (3, 14). In industrialized countries, the reported prevalence of IBD exceeds 0.3% of the population (15). Specifically, more than 2 million Europeans and 1.5 million Americans are suffering from this condition (14). IBD affects both genders equally and typically presents between the ages of 15 and 35; however, the rising incidence among children raises significant concerns within the realm of public health (16). Relapses and disease regression occur in approximately 50-80% of patients, with varying degrees of severity (17). The burden of IBD extends not only to the affected individuals' quality of life but also to the healthcare system, with an annual hospitalization rate ranging from 2.8 to 17 per one hundred thousand people and treatment costs estimated at 6.8 billion dollars (18). Recent evidence has revealed an escalating trend in the incidence and prevalence of IBD, particularly over the past two decades in developing countries like Iran (19, 20). Projections indicate that by 2035, the prevalence of IBD in Iran is expected to rise to 2.5 times, expected to reach 69,000 cases in 2020. Similarly, the Middle East is expected to experience a 2.3-fold increase, amounting to 220,000 cases of IBD. These findings highlight the emergence of an epidemic regarding IBD prevalence in Asian regions, necessitating urgent action to control this alarming trend (21).

IBD presents a multifactorial etiology that involves interactions between various

environmental factors, including diet, microbial composition, genetics, and the immune system, resulting in immune response dysregulation and chronic inflammation (15). Several determinants, such as infectious diseases, lifestyle choices, smoking habits, hygiene practices, and intestinal pathogens, contribute to the exacerbation of IBD symptoms in affected individuals (22).

Currently, the conventional approach for managing this disease involves the usage of anti-inflammatory medications like corticosteroids and aminosalicylates. However, these drugs are associated with notable side effects (23). The adverse effects of medicinal compounds, including headaches, diarrhea, abdominal pain, and nausea, can lead to reduced treatment adherence among patients, thereby aggravating the disease condition (24). Furthermore, the efficacy of these treatments in promoting and sustaining mucosal healing remains unverified (25), and a substantial proportion of patients do not respond favorably to existing therapies (16, 23). Consequently, medical management presents challenges, necessitating research into novel treatment approaches that offer enhanced effectiveness and minimized adverse effects (18, 23). Simultaneously, patients' desire to attain greater control over this condition has compelled them to explore alternative treatment approaches (10).

In recent years, there has been growing interest in the potential of flavonoids, particularly silymarin, for managing symptoms associated with IBD (26, 27). Silymarin is a flavonoid compound derived from milk thistle (28). It has hepatoprotective properties, and exhibits antioxidative, anti-inflammatory, and cellular glutathione-enhancing attributes (29). Additionally, this compound demonstrates the ability to modulate inflammatory cytokines such as TNF-α, interleukin-1β, and interleukin-6 (18). Notable therapeutic properties of silymarin encompass the treatment of gastrointestinal disorders, enhancement of immune function, alleviation of nausea in cirrhotic patients, mitigation of chemotherapy-induced side effects, and the potential for gallstone prevention or treatment (30).

An experimental study on rats demonstrated a significant increase in angiogenesis, cell proliferation, and collagen deposition scores in the silymarin treatment group, as compared to the control group. Based on these findings, the researchers concluded that oral administration of silymarin following colonic anastomosis in rats effectively enhanced structural indices of wound healing (31). Furthermore, a randomized clinical trial involving patients with ulcerative colitis investigated the impact of silymarin. The intervention group exhibited a decrease in disease activity index, along with improvements in hemoglobin and ESR levels. Additionally, a majority of the patients achieved complete remission, which was sustained for up to six months after the treatment. Considering that remaining in remission is an integral aspect of managing IBD, this study successfully demonstrated the beneficial effects of silymarin in accomplishing therapeutic goals (27). Moreover, the administration of silymarin at therapeutic dosages has been considered safe for human consumption, with only transient side effects such as gastrointestinal disturbances being reported (30).

Given the increasing utilization of herbal medicines by patients with IBD, it is essential for both physicians and patients to possess knowledge regarding the efficacy and safety associated with these remedies (9). Considering the substantial impact of IBD on the children’s quality of life, the significant financial burden it poses on patients, families, and healthcare systems, and the potential adverse effects

stemming from conventional treatments, the exploration of alternative treatment options becomes imperative. Silymarin, being a chemical-free herbal product recognized for its safety, presents itself as a viable method for managing and preventing IBD recurrence. Consequently, this study was conducted with the objective of determining the effects of silymarin on the symptom severity in patients with IBD.

2- MATERIALS AND METHODS

2-1. Design and participants

This parallel double-blind clinical trial was carried out at the GI clinic of Akbar Children's Hospital during the period of 2022-2023. The samples included children presenting gastrointestinal symptoms at the GI clinic, who were subsequently diagnosed with IBD. Diagnosis of IBD was established based on a comprehensive assessment conducted by a pediatric gastroenterology specialist, incorporating clinical, laboratory, endoscopic, histological, and imaging findings. In accordance with current guidelines, the classification of these children encompassed three categories: ulcerative colitis, Crohn's, and unspecified colitis. The specific type of the disease in each child was determined by a pediatric gastroenterologist.

2-1.1. Inclusion and exclusion criteria

Inclusion criteria encompassed children aged 5-18 years with ulcerative colitis and a PUCAI score below 65, or children with Crohn's disease and a PCDAI score below 55, having parental consent to participate in the study. Exclusion criteria included a PUCAI score above 65 or PCDAI score above 55, occurrence of silymarin-related side effects or drug interactions, arbitrary discontinuation of treatment, and patient refusal to attend regular follow-up appointments at the GI clinic for assessments and check-ups.

2-1.2. Sample size

The sample size of the study was determined through a pilot study. Initial data from the pilot study provided activity index scores for the patients in two groups: 18.12 ± 11.49 in the experimental group and 26.50 ± 9.61 in the placebo group. To calculate the required sample size, the Gpower software was utilized, considering an alpha level of 0.05 and a beta level of 0.80. Based on these calculations, a sample size of 18 people per group was estimated. Factoring in a potential dropout rate of 10%, it was decided to include 20 participants in each group for the final study. This study involved two groups, with the silymarin group as group A and the placebo group as group B. Quadruple blocks were established and numbered accordingly: AABB (1), ABAB (2), ABBA (3), and BBAA (4). Randomization was then conducted using the random number table method via the website http//www.graphpad.com/quickcalcs/index.cfm. Numbers between 1 and 4 were generated (e.g., 1, 4, 3, and so on). Subsequently, the treatment allocation list was determined based on the previously generated random numbers (e.g., AABB-BBAA-BABA-...), continuing until the desired sample size of 40 participants was reached.

2-2. Procedure

The participants in this study were recruited through the convenient sampling method and assessed for compliance with the inclusion criteria. Those who met the criteria were then randomly assigned to either the intervention group or the placebo group. The parents were assured that the researchers would maintain the confidentiality of their child's information, with no disclosure of their personal details. Each group consisted of 22 patients initially, but after the follow-up period, the analysis included 20 individuals. Patient enrollment and treatment assignment are presented in **Fig. 1**.

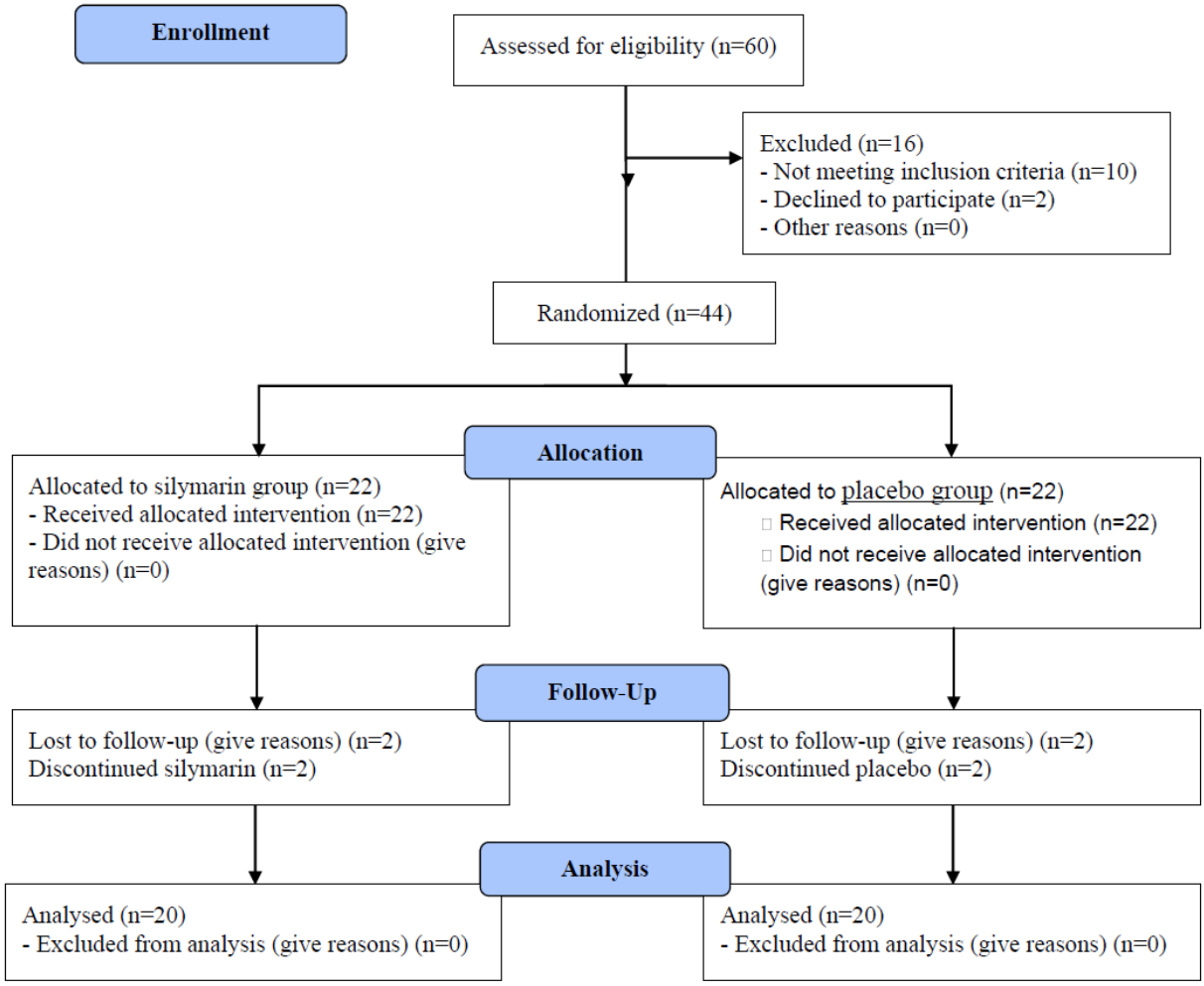

Fig. 1: Flow diagram of the randomized sampling

Allocation concealment was done using sequentially numbered sealed opaque envelopes to ensure unbiased assignment of participants. In the intervention group, which comprised an equal number of Crohn's disease and ulcerative colitis patients, daily administration of tablets containing silymarin extracted from the milk thistle plant was carried out. The dosage was 5 mg per weight, divided into three doses per day for a duration of three months. The recommended dosage was based on the pediatric call book and previous studies conducted in children, which provided evidence of the drug's safety. The tablets used in the control group were placebos, designed to resemble the silymarin tablets in shape and form. These placebos were prepared by the Faculty of Pharmacy in Mashhad University of Medical Sciences.

To investigate the effect of silymarin on children, PUCAI (Pediatric Ulcerative Colitis Activity Index) and PCDAI (Pediatric Crohn's Disease Activity Index) scores were calculated for all patients at three different visits: prior to the intervention, at the beginning of the intervention, and post-intervention. A checklist was utilized to collect demographic information, clinical symptoms, laboratory results, histology findings, endo colonoscopy outcomes, and imaging records for each patient. Additionally, the standard treatments administered, along with their

corresponding dosages, were recorded. Throughout the examination period, close monitoring of any potential side effects of the medication was carried out. If any side effects were experienced by the children, they were excluded from the study. Moreover, the patients' adherence to the prescribed medication was assessed.

2-3. Outcome measures

The primary outcome measure focused on evaluating the severity of symptoms associated with IBD. The parameters included in PUCAI and PCDAI encompassed various aspects. In PCDAI, these aspects consisted of assessing abdominal pain, frequency of bowel movements per day, weight, linear growth, as well as physical findings such as tenderness or the presence of an abdominal mass, perianal disease, extraintestinal manifestations. Additionally, laboratory findings including hemoglobin/hematocrit levels, ESR (erythrocyte sedimentation rate), albumin levels, and overall improvement and functional improvement were taken into account, with evaluations conducted on a weekly basis. On the other hand, the PUCAI focused on abdominal pain, number of bowel movements per day, stool consistency, amount of blood in stool, presence of nocturnal bowel movements, tenderness or the presence of an abdominal mass. The PUCAI and PCDAI each have their own scoring system, enabling a comprehensive evaluation of disease severity. For the PCDAI, scores range from 0 to 100, with the following categorizations: scores between 0 and 10 indicate inactive disease, scores between 10 and 30 indicate mild illness, and scores greater than 30 indicate moderate to severe disease. Similarly, the PUCAI utilizes a scoring range of 0 to less than 85, with the following classifications: scores between 0 and 9 indicate inactive disease, scores between 10 and 34 indicate mild disease, scores between 35 and 64 indicate moderate disease, and scores between 64 and 85 indicate severe illness. These indices are used to assess disease activity, ensuring that patients experiencing periods of remission or intense disease activity were not included in the study.

2-4. Data Analysis

Data analysis was performed using SPSS version 25, employing the following statistical methods. Descriptive statistics, such as mean, standard deviation, and frequency distribution, were utilized to describe the characteristics of the participants. Kolmogorov-Smirnov test was conducted to assess the normality of the distribution of quantitative variables PUCAI and PCDAI. To address the primary objective of comparing the effect of silymarin on the IBD symptoms severity, statistical tests including Chi-square test, Fisher's exact test, paired t-test for intra-group comparisons, and t-test for inter-group comparisons were employed. The repeated measures analysis of variance was employed to evaluate the progression over time in two follow-ups. A confidence level of 95% was considered in all conducted tests.

3- RESULTS

The findings indicated that no statistically significant differences ($p>0.05$) were observed between the patients with IBD in silymarin and placebo groups in terms of demographic characteristics (**Table 1**). Similarly, there were no significant differences ($p>0.05$) observed between the silymarin and placebo groups regarding hospitalization rates, as shown in **Table 2**. Moreover, there was no statistically significant difference in hemoglobin and hematocrit levels between the two groups before and after the intervention ($p>0.05$).

Before the intervention, ESR, CRP, Albumin and fecal calprotectin levels were similar between the two groups ($p>0.05$).

Table-1: Comparison of the demographic characteristics of patients with IBD in silymarin and placebo groups

Variable	Silymarin	Placebo	P value
	Mean ± SD	Mean ± SD	
Age (year)	11.71 ± 3.41	11.05 ± 2.72	.494
Weight before the intervention	37.03 ± 14.97	35.47 ± 10.99	.710
Weight after the intervention	38.52 ± 14.89	37.44 ± 11.93	.802
Height before the intervention	143.55 ± 20.59	143.25 ± 13.55	.957
Weight after the intervention	143.55 ± 20.47	143.35 ± 13.69	.971

Table-2: Comparison of hospitalization rates of the patients with IBD in silymarin and placebo groups

Variable	Silymarin	Placebo	P value
	N (%)	N (%)	
Hospitalization, no	17 (85.0)	13 (65.0)	Chi 2= .602, df= 1, p= .144
Hospitalization, yes	3 (15.0)	7 (35.0)	
Total	20 (100)	20 (100)	

The silymarin group had a higher percentage of patients with ESR >10 (75%) compared to the placebo group (55%), which decreased to 60% in the silymarin group and 50% in the placebo group after the intervention. Among the silymarin group, 15% of patients had CRP > 40 before the intervention, which decreased to 5% after the intervention. In contrast, the placebo group had 5% of patients with CRP > 40 before the study, which increased to 10% after the intervention. Albumin levels of 45% of the patients in the silymarin group was less than 3.5, which decreased to 40% after the intervention. In the placebo group, 25% of patients had albumin levels less than 3.5, which decreased to 15% after the intervention. When considering fecal calprotectin levels >100, 65% of the silymarin group had fecal calprotectin >100, which decreased to 45% after the intervention. In comparison, in the placebo group, 50% of the patients had fecal calprotectin >100 before the study, which decreased to 45% after the intervention (**Table 3**).

There were changes in drug dosage for 15% of the patients in the silymarin group and 35% of those in the placebo group; but there was no significant difference in the frequency of dosage changes between the two groups ($p>0.05$). As shown in **Table 4**, 15% of the patients in the silymarin group experienced a decrease in drug usage, while 30% of patients in the placebo group required an increase in drug dosage (**Table 4**).

In relation to the disease activity index, there was no statistically significant difference between the silymarin and placebo groups before the intervention during the initial evaluation ($p<0.05$). However, during the second and third evaluations, a statistically significant difference in the disease activity index was observed between the two groups ($p>0.05$) (**Table 5**).

Table-3: Comparison of paraclinical characteristics of the patients with IBD in silymarin and placebo groups

Variable		Silymarin	Placebo	P value
		N (%)	N (%)	
ESR	ESR > 10 before the intervention	15 (75.0)	11 (55.0)	0.185
	ESR > 10 after the intervention	10 (50.0)	12 (60.0)	0.525
CRP	CRP > 6 before the intervention	14 (70.0)	14 (70.0)	0.742
	CRP > 40 before the intervention	3 (15.0)	1 (5.0)	
	CRP > 6 after the intervention	14 (70.0)	13 (65.0)	0.831
	CRP > 40 after the intervention	1 (5.0)	2 (10.0)	
Albumin	Albumin < 3.5 before the intervention	9 (45.0)	5 (25.0)	0.185
	Albumin < 3.5 after the intervention	8 (40)	3 (15.0)	0.077
Fecal calprotectin	FC > 100 before the intervention	13 (65.0)	10 (50.0)	0.335
	FC > 100 after the intervention	9 (45.0)	9 (45.0)	1.000

Table-4: Comparison of changes in drug dosage in patients with IBD in silymarin and placebo groups

Variable		Silymarin	Placebo	P value
		N (%)	N (%)	
Changes in drug dosage	No	17 (85.0)	13 (65.0)	Chi 2= .602, df= 1, p= .144
	Yes	3 (15.0)	7 (35.0)	
Increase in dosage		0 (0.0)	6 (30.0)	
Decrease in dosage		3 (15.0)	1 (5.0)	

Table-5: Comparison of the disease activity index in patients with IBD in silymarin and placebo groups

Variable	Silymarin	Placebo	P value
	Mean ± SD	Mean ± SD	
The disease activity index before the intervention	24.12 ± 8.36	24.35 ± 10.53	0.941
The disease activity index at the first visit	17.37 ± 10.53	24.50 ± 10.50	0.039
The disease activity index at the second visit	17.95 ± 12.75	25.80 ± 11.30	0.046
Tests of Within-Subjects Contrasts= .501			
Tests of Between-Subjects Effects=.441			

4- DISCUSSION

The current study represents the first double-blind randomized clinical trial conducted in Iran, aimed at investigating the therapeutic effect of silymarin on the symptom severity in pediatric patients with IBD. The study results revealed no significant difference between the silymarin and placebo groups in terms of demographic characteristics (including age, gender, height and weight), and hospitalization rates before and after the intervention for patients with IBD.

Despite the lack of statistically significant differences in hemoglobin and hematocrit levels between the silymarin and placebo groups before and after the intervention, the patients receiving silymarin showed variations compared to the placebo group in other paraclinical characteristics (such as ESR, CRP, Albumin, and FECAL CALPROTECTIN). Similarly, recent

studies have also demonstrated the efficacy of silymarin in improving paraclinical characteristics (27, 32).

Furthermore, the comparison of drug dosage change in patients with IBD revealed that 15% of patients in the silymarin group and 35% of those in the placebo group experienced alterations in their drug dosage. However, this difference between the two groups did not reach statistical significance. Furthermore, in the silymarin group, 15% of patients observed a reduction in the drug consumption, without any need for dosage increment. In contrast, the placebo group exhibited a clinical necessity for a dosage increase among 30% of the patients.

Comparing the disease activity index scores in the silymarin and placebo groups revealed that there was no statistically significant difference in the initial assessment before the intervention. However, in subsequent evaluations, specifically during the second and third assessments, a significant statistical difference was observed between the two groups.

Oxidative stress is recognized as one of the underlying mechanisms contributing to the development of IBD (18). So, silymarin has gained significant attention as a controversial plant extract with potential benefits for managing gastrointestinal diseases (24).

Silymarin exhibits antioxidant properties, effectively scavenging free radicals. Its antioxidative mechanism involves stimulating the activity of the superoxide dismutase enzyme, augmenting cellular glutathione levels, and inhibiting lipid peroxidation. Moreover, silymarin acts as an anti-inflammatory agent by hindering neutrophil migration towards the site of inflammation and suppressing the function of Kupffer cells, prostaglandins, leukotrienes, and the NF-κB factor. These factors regulate various genes involved in the inflammatory process (33).

Additionally, silymarin demonstrates inhibitory effects on TNF-a, interferon, interleukin-2, and iNOS (26).

Several recent studies have suggested the utilization of silymarin as a potential approach for managing colitis (26, 27). A randomized clinical trial involving patients with ulcerative colitis demonstrated that administering 140 mg of silymarin led to improvements in hemoglobin levels and ESR. Additionally, the silymarin group experienced a significant reduction in the disease activity index, with a majority of patients achieving complete remission after a six-month period (35 out of 38 in the silymarin group, compared to 21 out of 32 in the control group) (27). An experimental study investigating the impact of silymarin on colon ulcers induced by acetic acid in rats indicated a significant reduction in the intestinal microscopic damage and the intensity of inflammation compared to the control group (34). In another study conducted on rats, the consumption of silymarin alone or in combination with celecoxib was found to improve histopathological damages, such as duodenal villous atresia and alleviate the inflammatory cells infiltration. This beneficial effect of silymarin can be attributed to its anti-inflammatory and antioxidant properties (35). Moreover, a double-blind clinical trial showed that the administration of 140 mg of silymarin twice a day for 12 weeks can significantly reduce the volume of endometrioma lesions, interleukin-2 levels, and pain-related symptoms in women with endometriosis (33).

The anti-inflammatory effect of silymarin appears to be dose-dependent. In a study examining the effect of silymarin on acetic acid-induced colitis in rats, it was revealed that the administration of 100 mg of silymarin resulted in a decrease in microscopic damage and the intensity of

inflammation. However, the administration of 50 mg of silymarin did not show any effect in reducing crypt damage and the inflammation intensity (36).

Due to the chronic nature of inflammatory bowel disease, it is common for patients to experience periodic flare-ups and a limited duration of remission. Therefore, achieving long-term remission constitutes an essential therapeutic objective in the management of this condition (15). Silymarin, as demonstrated in our study, has been shown to contribute to advancements in symptom relief among pediatric patients diagnosed with IBD.

4-1. Limitations of the study

Our study has several limitations. Firstly, there were potential side effects associated with the consumption of silymarin and its drug interactions. Secondly, we faced challenges in obtaining parental consent for participation in the study. Additionally, treatment discontinuation and the patient's reluctance to regularly visit the GI clinic for check-ups were factors that impacted our study. Moreover, the patients' history of allergies, their non-cooperation, and the age range limitation of 5-18 years also affected this study.

5- CONCLUSION

Our findings indicate that silymarin has a significant effect on managing symptoms associated with IBD, and alleviating the symptom severity in pediatric patients. Further research is needed to explore the application of silymarin in the population of children aged 5-18 years diagnosed with IBD.

Consequently, it is recommended to investigate the effect of silymarin using varied dosages and an extended treatment duration in a larger cohort. It is also suggested to follow up patients for additional variables, and to monitor the reoccurrence of disease symptoms following the administration of silymarin.

6- ETHICAL CONSIDERATIONS

This research project was granted approval by the ethics committee of Mashhad University of Medical Sciences. To ensure informed consent, the study's purpose and details about the treatment procedure and potential side effects were explained to the parents of the children in simple language. If they agreed to participate, the patients were included in the study, and written consent was obtained from the parents. It is important to note that the resulting data of this study are strictly confidential and accessible only to authorized researchers. This research is based on the research project number 4010272, along with the permission of the ethics committee, marked as IR.MUMS.MEDICAL.REC.1401.590. Furthermore, the study has been registered under the IRCT registration Code: IRCT20101107005123N3.

7- CONFLICT OF INTEREST

None.

8- FUNDING

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