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Original Research Article

A 12 weeks, randomized and double-blind evaluation of the efficacy of oral supplements of probiotics (Lactogut and Lactogut Kidz) on atopic dermatitis in adults and children

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ABSTRACT

Background: The primary objective of the study was to evaluate the efficacy and safety of oral probiotics in the treatment of atopic dermatitis (AD) using the scoring atopic dermatitis (SCORAD) index, serum IgE levels and absolute eosinophil count (AEC). The secondary objective of the study was to determine the association of oral probiotic therapy and improvement in AD using global photographs, dermoscopic images (fotofinder) and individual patient satisfaction.
Methods: This was a randomized, double-blind study conducted on 70 patients (20 adults and 50 children) with moderate to severe AD. The participants were randomized into control arm and treatment arm. The treatment arm received conventional and probiotic therapy and only conventional therapy was provided to the control arm. The research was carried out in five visits. For each visit, SCORAD was calculated and response compared using clinical and videodermoscopic images. Patient satisfaction was documented using a quality of life questionnaire during each visit.
Results: Across the treatment arm, the mean serum IgE levels were greatly decreased in contrast to the control arm over the 12 weeks period. SCORAD score was significantly lowered in the treatment arm (55.20%) compared with 18.95% in the control arm. Dermoscopic assessment, global photographic assessment and patient satisfaction in the treatment arm showed statistically significant improvement in AD compared to the control arm.
Conclusions: The decrease in SCORAD scores demonstrated strong associations with the use of probiotics in patients with AD as an adjunct to conventional therapy. Thus, in both adults and children suffering from moderate to severe AD, probiotic supplement can be administered effectively as an adjunct therapy.

Keywords: Atopic dermatitis, SCORAD, Probiotics

INTRODUCTION

Atopic dermatitis (AD) is a chronic, recurrent inflammatory skin disease that usually begins in the childhood and is characterized by variable distribution of pruritic eczematous lesions with flexural predilection; mostly in patients with personal or family history of atopic diathesis. AD has a history of relapsing with frequent exacerbations and remissions. Relapse and remission are associated with elevated levels of serum IgE. AD's natural history is referred to as 'atopic march' involving typical disease progression such as food

allergy, allergic rhinitis (hay fever), and asthma. In fact, it is often clear that 'atopic diathesis' entails personal or family history of bronchial asthma, allergic rhinitis and conjunctivitis, and/or AD, and/or predisposition to overproduction of IgE antibodies. The cumulative incidence of AD varies from 11% to 21%.[1] In a hospital-based survey in the North Indian population, AD was reported as the most common dermatosis with 29.9% prevalence in paediatric dermatology clinic. A typical winter exacerbation was visible in 62% of the AD population.[1] The prevalence of AD in different population ranged from 1-3%.[2]

The pathogenesis of AD is not completely established. It has been proposed that AD arise from the complex interaction of defects in the structure of the skin barrier, immune dysregulation and environmental and infectious agents. Impaired filaggrin gene expression is apparent in AD. This gene codes structural proteins which are important for the creation of skin barriers. Colonization of Staphylococcus aureus is observed in 90% of patients with AD. Deficient innate immune response, chemokine release, and proinflammatory cytokines encourage the development of immunoglobulin E (IgE) with systemic inflammatory responses and pruritic skin inflammation in AD.[3]

Clinical manifestations of AD can be categorized into atopic itch, atopic dryness, atopic eczema and AD's stigmata.[4] Acute cases show red infiltrate with oedema, vesicles, oozing, and crusting; lichenification, excoriation, papules, and nodules dominate the sub-acute and chronic phase. Among infants, the lesions are often found on the face and on the extensors, whereas in children and adults there is predilection for flexors. Chronic hand eczema can be presenting feature of AD in adults. There may be atypical morphologies such as nummular (discoid), prurigo-like, follicular and seborrheic dermatitis-like.[2]

Numerous guidelines for the diagnosis of AD have been established, including Hanifin and Rajka in 1980, which was subsequently updated by the American academy of dermatology, guidelines provided by the UK working group in 1994, and the SCORAD score of AD.[5]

SCORAD (scoring AD) is a clinical tool that is commonly used in dermatology clinics to determine the extent and severity of eczema. This assessment method is used by dermatologists to determine the efficacy of the medication before and after treatment. It considers three elements, area of eczema (A), intensity (B), and subjective symptoms (C), respectively. The rule of nine is used to calculate the area of the eczema (A). The score is added for each region. The total area 'A' is 100% maximum. The criteria for intensity are redness, swelling, oozing or crusting, scratch marks, lichenification and dryness that are graded as none (0), mild (1), moderate (2), or severe (3). The scores of intensities are added together to give the maximum value of 'B' of 18. The patient or caregiver score subjective symptoms such as itch and sleeplessness using a visual analog scale where '0' is neither itch nor sleeplessness and 10 is extreme itching or sleeplessness. Those are added to give 'C' which has a maximum value of 20. For individuals, the cumulative SCORAD is determined using formula A/5+7B/2+C.[6]

Most cases of AD may be managed effectively with topical therapies aimed at reducing inflammation of the skin and alleviating the pruritus. Emollients, topical corticosteroids, topical calcineurin inhibitors and antimicrobial and antiseptic interventions are the most widely used topical treatments. Systemic therapies such as glucocorticoids, cyclosporine, methotrexate, mycophenolate, azathioprine, are usually intended for patients with severe and refractory AD and often cause potential adverse effects.[5] Adjunct treatment such as probiotic therapy may be addressed where AD symptoms become uncontrolled by adequate basic therapy.

Abundant evidence suggests that there are strong antipathogenic and anti-inflammatory properties in different bacterial strains chosen from the healthy gut microbiota. In AD, many targets for the probiotic approach have appeared, such as degradation/structural modification of enteral antigens, normalization of the properties of aberrant indigenous microbiota and gut barrier functions, modulation of the secretion of inflammatory mediators and promotion of immune system growth. Furthermore, the probiotic effects in AD have been attributed to the restoration of increased intestinal permeability and unbalanced intestinal microbiota, improved immunological barrier functions of the intestine, and reduced proinflammatory cytokine generation characteristic of local and systemic allergic inflammation. Therefore, alteration of the gut microbiota by probiotics, together with the immunomodulatory activity of particular probiotic strains, may be used as an approach to having a prophylactic or therapeutic effect in children and adults with atopic dermatitis. Probiotics help to control allergic hypersensitivity reactions by suppressing the Th2-mediated response that tends to balance Th1/Th2 immune responses and by increasing the Treg-mediated immune response. It was proposed that these viable microorganisms may modulate enterocyte TLR (Toll-like receptors) and proteoglycan recognition proteins, contributing to DC (dendric cells) activation and Th1 response. A growing number of reports have studied the possible efficacy of probiotics in preventing and treating AD. Lactobacillus rhamnosus is the probiotic strain tested most commonly for the prevention of AD in children. Another research examined the effect on the treatment of allergic diseases of Bifidobacterium breve and Bifidobacterium longum administration over a span of 1 month prenatally, 6 months during infancy, and 18 months of follow up. Recent review of the role of probiotics in AD prevention suggests a beneficial impact of probiotic therapy for AD treatment.[7-9]

In the current study, Lactogut and Lactogut Kidz oral probiotic supplements which were added to conventional therapy in the treatment arm were used. Considering the above background information, this clinical trial was designed with the primary objective to evaluate the efficacy and safety of oral probiotics in the treatment of atopic dermatitis (AD) using the scoring atopic dermatitis (SCORAD) index, serum IgE levels and absolute eosinophil count (AEC). The secondary objective of the study was to determine the association of oral probiotic therapy and improvement in AD using global photographs, dermoscopic images (fotofinder) and individual patient satisfaction.

METHODS

A 12 weeks randomized, double-blind assessment of the efficacy and safety of oral Lactogut and Lactogut Kidz probiotics for AD in adults and children was conducted at Cutis Academy of Cutaneous Sciences, Bangalore, Karnataka, India from March to December 2018.

This research was undertaken in compliance with the ICH harmonized tripartite guidelines for good clinical practice (GCP) adherence to the Helsinki declaration of ethical standards. The research was initiated after approval by the Cutis institutional ethics committee. The purpose of the research, the procedures to be carried out and the potential hazards that could be experienced during the study, the duration of the study and the follow-up visits were explained to subjects in non-technical terms in the language they knew, before the subjects were evaluated and enrolled in the trial. A study-specific informed consent document has been signed by all participants prior to screening. Enough time was given to read and appreciate the details presented and to ensure that participants were informed of the consequences of enrolling in the research. The informed consent was received in compliance with the ICH-GCP code of ethics.

A total of 70 patients (20 adults and 50 children) with moderate to severe AD were enrolled. Patients were recruited on the basis of the following inclusion and exclusion criteria.

Inclusion criteria

The inclusion criteria used in this study were patients aged 0-60 years (paediatric: 0-18 years; adults: 18-60 years) with moderate to severe AD, with a SCORAD score of ≥15, subjects willing to participate in the study and those participants who consent not to alter the diet, medications or exercise routine considerably.

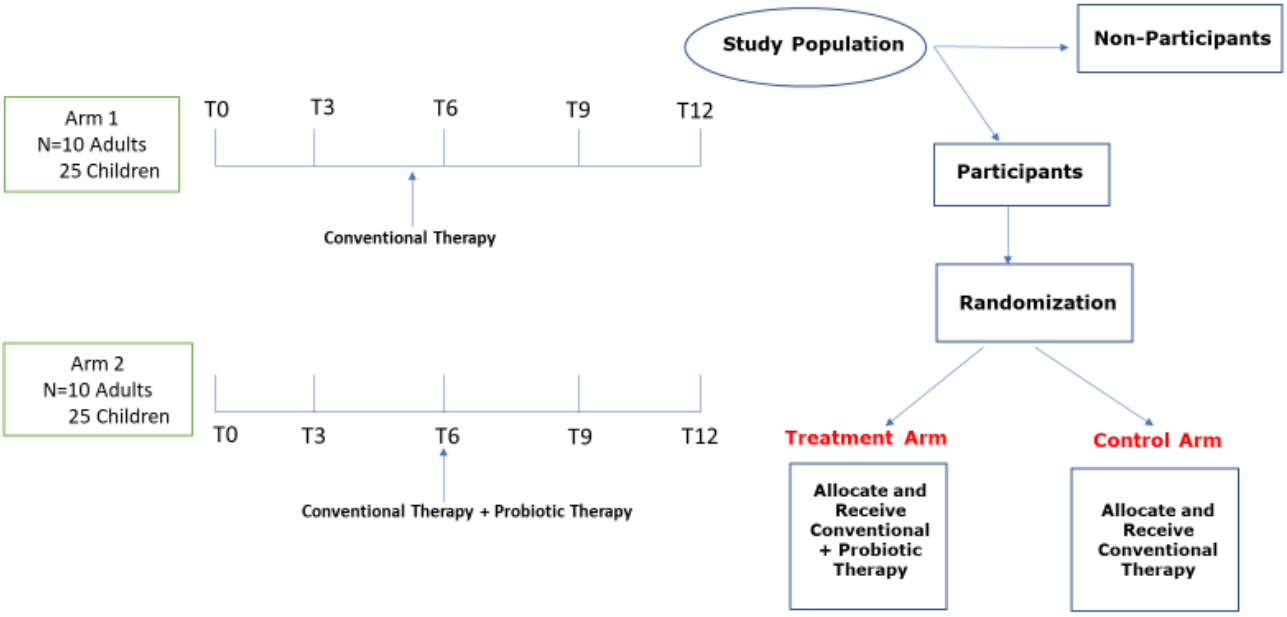

Figure 1: Study plan.

Exclusion criteria

Exclusion criteria were patients using systemic corticosteroids or phototherapy in the previous 1 month, patients on systemic immunosuppressant in the previous 3 months, patients receiving probiotics during the past 4 weeks, patients on systemic antibiotics in past 8 weeks, or topical antibiotics in past 3 weeks prior to commencement of the study, subjects with concomitant skin diseases, chronic skin diseases like psoriasis, SCORAD score <20 after the initial washout period, pregnant or lactating women, subjects with a primary or acquired immunodeficiency, subjects receiving or planning to receive an investigational new drug (IND)

agent, ultraviolet light therapy, monoclonal antibodies, or systemic immunosuppressants, subjects using topical or oral complementary and alternative (CAM) agents within 4 weeks of initiation of treatment, subjects who are currently receiving or have received chemotherapy or radiation for treatment of malignancies within the previous 6 months, patients hypersensitive to any components contained in the probiotic capsules/sachets, subjects participating in a clinical research trial within 30 days prior to randomization. Individuals who are cognitively impaired and/or who are unable to give informed consent were excluded from the study.

The study was performed in five visits, namely visit 1 (day 1, T0), visit 2, (day 21, T3), visit 3 (day 42, T6), visit 4 (day 63, T9) and visit 5 (day 84, T12). 'T' refers to the number of weeks of medication. In T0, prospective patients were screened for inclusion and exclusion parameters after receiving written informed consent from the subjects. At baseline (T0), demographic information, anthropometric parameters, background of other health conditions such as diabetes mellitus, hypertension and any other chronic diseases were reported. Patients were examined during the first visit (T0) clinically as well as using fotofinder and SCORAD score was calculated. SCORAD scores greater than 15 showing moderate to severe AD were chosen for the study. Subjects were randomized to the control arm (arm 1) and the treatment arm (arm 2). The treatment arm received both conventional and probiotic therapy and the control arm conventional therapy only. 10 adults and 25 children were enrolled in each arm. Lactogut probiotic was administered to adults and Lactogut Kidz to children in the treatment arm. Conventional therapy involved moisturizers, topical steroids, topical calcineurin inhibitors, and antihistaminics. Lactogut oral probiotic supplement comprises five billion CFUs of beneficial strains of *Lactobacillus* and *Bifidobacterium*, while Lactogut Kidz oral probiotic supplement is a mixture of one billion CFUs of strains of *Lactobacillus* and *Bifidobacterium* (Table 1).

At visit 2, (day 21, T3), visit 3 (day 42, T6), visit 4 (day 63, T9) and visit 5 (day 84, T12) the decline in SCORAD was measured and response to treatment was compared using clinical and videodermoscopic images. At each visit, clinical photographs, front and lateral views were taken at a distance of 40 cm. AEC and serum IgE levels were recorded at T0 and T12. Patient satisfaction was recorded at each visit using the quality of life questionnaire. Adverse effects and serious adverse events have also been reported in compliance with the procedure.

The primary endpoints of the study were improvement from baseline in the objective SCORAD index, improvement in absolute eosinophilic count (AEC) from baseline, and change in total serum IgE levels from baseline. The secondary endpoints of the study were reduction in pruritus, reduction in AD severity (photographic assessment) and improvement in patient satisfaction of skin condition at each visit using quality of life questionnaire.

Table 1: Composition of Lactogut Kidz and Lactogut oral probiotic supplement.

Lactogut Kidz	Lactogut
Each 1 gm sachet contains proprietary probiotic blend of 1 billion CFU containing	Each gelatine capsule contains proprietary probiotic blend of 5 billion CFU containing
Lactobacillus reuteri UBLRu-87	
Bacillus coagulans unique IS-2	*Bacillus coagulans* unique IS-2
Lactobacillus rhamnosus UBLR-58	*Lactobacillus rhamnosus* UBLR-58
Bifidobacterium longum UBBL-64	*Bifidobacterium longum* UBBL-64
Bifidobacterium bifidum UBBB-55	*Bifidobacterium bifidum* UBBB-55
Bifidobacterium infantis UBBI-01	
Saccharomyces boulardil unique 28	*Saccharomyces boulardii* unique 28
Streptococcus thermophilus UBST-50	*Streptococcus thermophilus* UBST-50
Elemental zinc (as zinc lactate) 10 mg	
Fructooligo sacchorides 20 mg	Fructooligo sacchorides 20 mg
Lactitol 10 mg	Lactitol 10mg

Ethical approval

Ethics approval of the study has been obtained from Institutional Ethics Committee of Cutis Academy of Cutaneous Sciences, Bengaluru, Karnataka, India.

RESULTS

A total of 70 patients were enrolled in the study which includes 20 adults and 50 children. In treatment arm, adult subjects received Lactogut and children received Lactogut Kidz along with conventional therapy and controls received only conventional therapy. 10 adults and 25 children were enrolled in each arm. Demographic details are presented in (Table 2).

Assessment of SCORAD score, IgE levels and AEC values

Children group

The independent 't' test was used to evaluate the outcomes between the control arm and the treatment arm. The mean age in the control arm was 5.76 years with a standard deviation of 3.76 years, while it was 5.28 years

with the standard deviation of 3.85 years in the treatment arm, which is statistically not significant. SCORAD in control arm at T0 is 32.46 with standard deviation of 11.79 while in treatment arm it is 32.23 with SD of 11.66. With 't' value of -0.233 this difference is statistically not significant. SCORAD score between the control arm and the treatment arm is also statistically not significant at T3 and T6. SCORAD scores at T9 and T12 demonstrate statistically significant differences between the two groups with a 't' value of 2.24 and 3.225 respectively and the p value of 0.031 and 0.003.

Table 2: Demographic data.

Characteristics	Treatment arm		Control arm	
	Adults	Children	Adults	Children
Total number of patients enrolled	10	25	10	25
Completed study	9	23	8	22
Male patients	4	9	4	9
Female patients	5	14	4	13
Mean age of male patients	29	7.88	26.75	7.55
Mean age of female patients	22.4	3.57	35	5

Table 3: Independent 't' test values of both groups (children and adults) to compare between control arm and treatment arm.

Variable	Children group				Adult group			
	Control arm (n=25)	Treatment arm (n=25)	t	P value	Control arm (n=25)	Treatment arm (n=25)	t	P value
	Mean±SD	Mean±SD			Mean±SD	Mean±SD		
Age	5.76±3.76	5.28±3.85	0.446	0.657	32.4±10.32	24.6±6.79	1.997	0.061
SCORAD T0	32.46±11.79	33.23±11.66	-0.233	0.816	29.7±11.19	37.7±10.75	-1.631	0.12
SCORAD T3	30.83±11.45	28.83±10.59	0.634	0.529	29.33±11.35	34.11±10.42	-0.93	0.366
SCORAD T6	29.46±12.15	23.85±9.27	1.782	0.081	28.38±12.83	30±10.42	-0.288	0.777
SCORAD T9	26.71±12.14	19.63±8.89	2.24	0.031	27±12.59	25.44±10.17	0.282	0.782
SCORAD T12	24.57±12.27	14.72±7.57	3.225	0.003	24.5±11.81	20.56±9.18	0.774	0.451
SCORAD difference between baseline and T3	1.63±2.41	4.62±2.6	-4.176	<0.001	-0.44±2.35	4.22±1.3	-5.209	<0.001
SCORAD difference between baseline and T6	2.91±2.77	9.59±4.73	-5.946	<0.001	0.63±2.5	8.33±2.74	-6.028	<0.001
SCORAD difference between baseline and T9	4.76±4.24	13.82±5.38	-6.302	<0.001	2±2.56	12.89±3.37	-7.418	<0.001
SCORAD difference between baseline and T12	6.9±5.14	18.14±7.21	-5.998	<0.001	4.5±1.93	17.78±4.89	-7.511	<0.001
IgE T0	563.19±607.94	273.19±505.4	1.834	0.073	216.82±72.9	125.63±65.29	2.946	0.009
IgE T12	559.63±570.19	315.94±696.65	1.281	0.207	174.63±60.43	71.47±21.2	4.584	0.002
IgE T0-T12	61±366.2	-30.61±186.73	1.064	0.293	46.02±69.11	39.12±30	0.273	0.789
AEC T0	709.96±399.76	432.84±201.09	3.096	0.004	429.5±173.21	406.9±147.68	0.314	0.757
AEC T12	556.73±268.67	346.43±224.19	2.856	0.007	391.75±194.17	262.33±103.51	1.745	0.102
AEC T0-T12	192.55±273.51	88.04±109.66	1.696	0.097	30.63±25.17	132.22±81.11	-3.57	0.005

Table 4: Intra group comparison of the SCORAD score, IgE levels and AEC values using paired 't' test in children.

Groups			N	Mean±SD	Mean difference ±SD	t value	P value
Children control arm	Pair 1	SCORAD T0	25	32.46±11.79	1.63±2.41	3.38	0.002
		SCORAD T3	25	30.83±11.45			
	Pair 2	SCORAD T0	23	32.37±12.23	2.91±2.77	5.04	<0.001
		SCORAD T6	23	29.46±12.15			
	Pair 3	SCORAD T0	22	31.47±11.73	4.76±4.24	5.27	<0.001
		SCORAD T9	22	26.71±12.14			
	Pair 4	SCORAD T0	22	31.47±11.73	6.9±5.14	6.30	<0.001
		SCORAD T12	22	24.57±12.27			
	Pair 5	IgE T0	22	620.62±627.11	61±366.2	0.78	0.443
		IgE T12	22	559.63±570.19			
	Pair 6	AEC T0	22	749.27±407.54	192.55±273.51	3.30	0.003
		AEC T12	22	556.73±268.67			
Children treatment arm	Pair 1	SCORAD T0	24	33.45±11.86	4.62±2.6	8.69	<0.001
		SCORAD T3	24	28.83±10.59			
	Pair 2	SCORAD T0	24	33.45±11.86	9.59±4.73	9.94	<0.001
		SCORAD T6	24	23.85±9.27			
	Pair 3	SCORAD T0	24	33.45±11.86	13.82±5.38	12.59	<0.001
		SCORAD T9	24	19.63±8.89			
	Pair 4	SCORAD T0	23	32.86±11.76	18.14±7.21	12.07	<0.001
		SCORAD T12	23	14.72±7.57			
	Pair 5	IgE T0	23	285.34±525.69	-30.61±186.73	-0.79	0.44
		IgE T12	23	315.94±696.65			
	Pair 6	AEC T0	23	434.48±209.95	88.04±109.66	3.85	0.001
		AEC T12	23	346.43±224.19			

Mean SCORAD in the T9 and T12 treatment arm is 19.63±8.89 and 14.72±7.57, in contrast with 26.71±12.14 and 24.57±12.27 in the T9 and T12 control arm respectively. The SCORAD difference between the control and treatment arm from baseline to T3, T6, T9 and T12 indicates statistically significant difference in treatment arm with reduced SCORAD score. The T0 and T12 IgE levels between the control and treatment arm indicate no statistically significant difference. However, AEC at T0 and T12 between the control and treatment arm indicates statistically significant difference in treatment arm with reduced AEC count.

Statistical measures are mentioned in (Table 3). The paired 't' test was used for intragroup comparison of mean SCORAD score, IgE levels, and AEC between control arm and treatment arm. The findings of the paired 't' test for both the control and the treatment arm are statistically significant for SCORAD score and AEC between T0 and T12 visit. Mean IgE levels for both the control and treatment arm before and after treatment do not indicate statistically significant difference. In Table 4, results of the paired 't' test for intra group comparison in children is given.

Adult group

Mean age was 32.4±10.32 years for the control arm and 24.6±6.79 years for the treatment arm, which is not statistically significant. Mean SCORAD score does not indicate statistically significant difference between control and treatment arm for all 5 visits. However, the mean SCORAD score between the control and treatment arm from baseline to T3, T6, T9 and T12 indicates a statistically significant difference, as seen in Table 5. Mean levels of IgE at T0 and T12 between the control and treatment arm indicate statistically significant difference in treatment arm with lower levels of IgE being apparent. Mean AEC between control arm and treatment arm indicates no statistically significant difference; however, comparison between baseline and T12 reveals statistically significant difference. Adult group statistical results are clarified in (Table 3).

Table 5: Intra group comparison of the SCORAD score, IgE levels and AEC values using paired 't' test in adults.

Groups			N	Mean±SD	Mean difference ±SD	t value	P value
Adult control arm	Pair 1	SCORAD T0	9	28.89±11.55	-0.44±2.35	-0.57	0.586
		SCORAD T3	9	29.33±11.35			
	Pair 2	SCORAD T0	8	29±12.34	0.63±2.5	0.71	0.503
		SCORAD T6	8	28.38±12.83			
	Pair 3	SCORAD T0	8	29±12.34	2±2.56	2.21	0.063
		SCORAD T9	8	27±12.59			
	Pair 4	SCORAD T0	8	29±12.34	4.5±1.93	6.60	<0.001
		SCORAD T12	8	24.5±11.81			
	Pair 5	IgE T0	8	220.64±71.86	46.02±69.11	1.88	0.102
		IgE T12	8	174.63±60.43			
	Pair 6	AEC T0	8	422.38±193.01	30.63±25.17	3.44	0.011
		AEC T12	8	391.75±194.17			
Adult treatment arm	Pair 1	SCORAD T0	9	38.33±11.2	4.22±1.3	9.73	<0.001
		SCORAD T3	9	34.11±10.42			
	Pair 2	SCORAD T0	9	38.33±11.2	8.33±2.74	9.13	<0.001
		SCORAD T6	9	30±10.42			
	Pair 3	SCORAD T0	9	38.33±11.2	12.89±3.37	11.47	<0.001
		SCORAD T9	9	25.44±10.17			
	Pair 4	SCORAD T0	9	38.33±11.2	17.78±4.89	10.90	<0.001
		SCORAD T12	9	20.56±9.18			
	Pair 5	IgE T0	9	110.59±47.44	39.12±30	3.91	0.004
		IgE T12	9	71.47±21.2			
	Pair 6	AEC T0	9	394.56±151.06	132.22±81.11	4.89	0.001
		AEC T12	9	262.33±103.51			

Table 6: Photographic assessment of AD lesions using independent 't' test.

Groups			N	Mean	SD	T value	df	P value
Children	Photographic assessment	Control arm	22	18.180	13.052	-8.834	43	<0.001
		Treatment arm	23	56.960	16.148			
Adult	Photographic assessment	Control arm	8	15<0.001	6.547	-10.64	15	<0.001
		Treatment arm	9	55.560	8.819			
Total	Photographic assessment	Control arm	30	17.330	11.651	-11.78	60	<0.001
		Treatment arm	32	56.560	14.337			

A paired 't' test was used for intragroup comparison of mean SCORAD score, IgE levels, and AEC between control arm and treatment arm. The findings of the paired 't' test are statistically significant for SCORAD score for only T0-T12 pair of the control arm, but mean SCORAD score for treatment arm is statistically significant for all pairs (T0-T3, T0-T6, T0-T9, and T0-T12). Mean control arm IgE levels do not demonstrate statistically significant difference for the T0-T12 pair, while mean treatment arm IgE levels display statistically significant difference for the T0-T12 pair. The mean AEC value indicates statistically significant difference for both the control and the treatment arm between the T0-T12 pairs. In Table 5, results of the paired 't' test for intra-group comparison of adult group are seen.

Figure 2 demonstrates the treatment arm SCORAD index versus control arm. This was 32.86 on day 0 in the treatment arm, and 14.72 on day 84 at the end of the study. Thus, the SCORAD index significantly decreased in moderate to severe AD, with a drop of 55.20%.

Table 7: Patient satisfaction before and after treatment using chi-square test.

Child/adult				Group		Total
				Control	Treatment	
Children	Patient satisfaction	Moderate	Count	15	3	18
			% within group	68.2	13.0	40.0
		Good	Count	7	9	16
			% within group	31.8	39.1	35.6
		Very good	Count	0	6	6
			% within group	0.0	26.1	13.3
		Excellent	Count	0	5	5
			% within group	0.0	21.7	11.1
	Total		Count	22	23	45
			% within group	100.0	100.0	100.0
Adult	Patient satisfaction	Moderate	Count	5	0	5
			% within group	62.5	0.0	29.4
		Good	Count	3	5	8
			% within group	37.5	55.6	47.1
		Very good	Count	0	3	3
			% within group	0.0	33.3	17.6
		Excellent	Count	0	1	1
			% within group	0.0	11.1	5.9
	Total		Count	8	9	17
			% within group	100.0	100.0	100.0
Total	Patient Satisfaction	Moderate	Count	20	3	23
			% within group	66.7	9.4	37.1
		Good	Count	10	14	24
			% within group	33.3	43.8	38.7
		Very good	Count	0	9	9
			% within group	0.0	28.1	14.5
		Excellent	Count	0	6	6
			% within group	0.0	18.8	9.7
	Total		Count	30	32	62
			% within group	100.0	100.0	100.0

Chi-square tests

Child/adult		Value	df	P value (<0.05)
Children	Pearson chi-square	19.237	3	<0.001
	Number of valid cases	45		
Adult	Pearson chi-square	9.474	3	0.024
	Number of valid cases	17		
Total	Pearson chi-square	28.197	3	<0.001
	Number of valid cases	62		

Comparision by photographic assessment

Based on the blind assessment of the global photographs (Figure 5) and the dermoscopic assessment using fotofinder images (Figure 6), patients were graded by two independent dermatologists as grade 1 <25% reduction; grade 2 26-50% reduction; grade 3 51-75% reduction; grade 4 >76% reduction. In the treatment arm of dermoscopic assessment using fotofinder, 15.63% had an improvement of grade 4, 34.38% had an improvement of grade 3, 50.00 % had an improvement of grade 2 and none had an improvement of grade 1 while in the control

arm none had an improvement of grade 4 or grade 3, 16.67% had an improvement of grade 2 and 83.33% had an improvement of grade 1. Figure 4 indicates the overall percentage improvement in the treatment arm, based on the assessment of global photographs.

Global photographic assessment in the treatment arm showed grade 4 improvement in 9.38% of patients, an improvement of grade 3 in 40.63% of patients and an improvement of grade 2 in 50.00% of patients. In the control arm none had an improvement of grade 4 or grade 3, 13.33% had an improvement of grade 2 and 86.67% had grade 1 improvement. In the control and treatment arms of children and adult groups, independent 't' test was used to compare the photographic assessment of AD lesions. Mean scores of photographic assessments was statistically significant across arms of control and treatment in both children and adult groups. Table 6 sums up the methodological results.

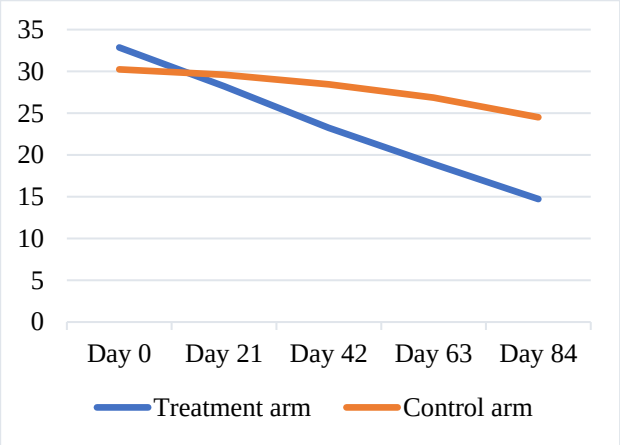

Figure 2: SCORAD index comparison in both groups.

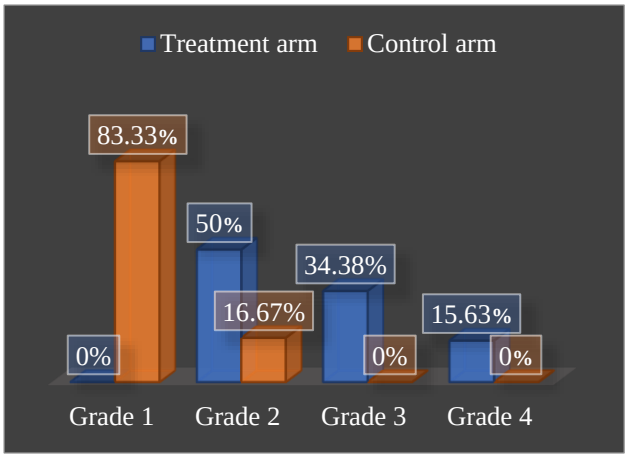

Figure 3: Dermoscopic assessment using fotofinder (overall improvement in both groups).

Assessment of patient satisfaction

Categorical variable 'patient satisfaction' was compared using chi-square test. Scores of patient satisfaction with pre and post treatment demonstrated statistically significant difference in the application of chi-square testing. The statistical results are discussed in depth in (Table 7).

There was overall percentage increase in patient satisfaction in the treatment arm at the end of the therapy. In total it was rated as excellent by 18.75% of patients, 28.13% of patients graded it as very good, 73.75% of patients graded it as good and 9.38% of patients considered it moderate in the treatment arm. In the control arm, none called it excellent or very good although 33.33% of patients thought it good and 66.67% of patients deemed it moderate.

Three children and two adult volunteers in the control arm and two children and one adult volunteer in the treatment arm were among the dropouts from the study.

Adverse events

The therapy was not associated with any relevant adverse events, either in the treatment arm or the control arm.

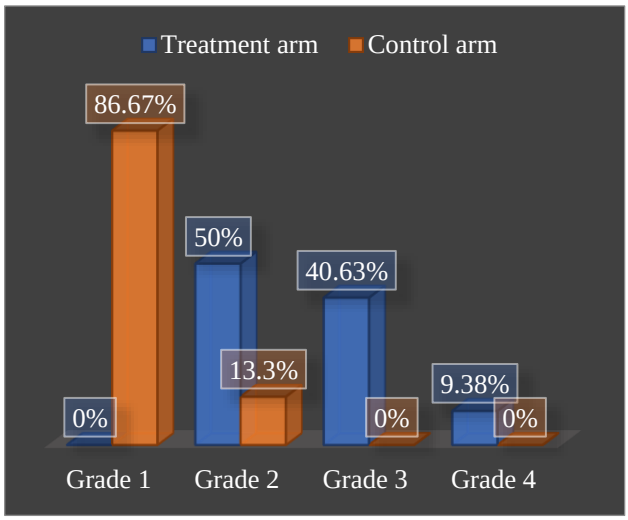

Figure 4: Global photographic assessment (overall percentage improvement in treatment and control arm).

DISCUSSION

AD or atopic eczema is a chronic, recurring, pruritic, inflammatory skin condition with a prevalence of up to 20% in children and 1-2% in adults in both developed and developing countries. AD is a prevalent disease, especially in childhood, but can continue or begin in adulthood. At sites of typical predilection, acute flare-ups and exacerbations as well as chronic eczematous skin lesions on dry skin, such as flexural folds accompanied by intense pruritus, characterize the disease and are quite homogenous, but the disease's trigger factors are diverse and the pathophysiological network involved is complex. The effect of pruritus and the noticeable presence of AD-

related effects has a substantial adverse influence on the quality of life of patients and their families, which may vary from physical and emotional wellbeing loss to impaired social activity. AD's fundamental mechanism and etiology are uncertain, but are suspected to be multifactorial in nature, including hereditary, socio-economic, environmental, and immunological influences culminating in AD being triggered and advanced. Using uniform standards and scoring systems, AD can range from mild to moderate to severe forms and diagnosis, as well as severity may be defined.[1-4]

AD patients are treated effectively using topical therapies that involve topical corticosteroids, emollients, and antihistaminics. Additional immunosuppressants are given in refractory cases. Corticosteroids and immunosupressants can cause adverse effects. Probiotics are used as adjunct therapy. Probiotics include live microorganisms that transmit beneficial results and improve immunity. Probiotics have strong anti-inflammatory and antipathogenic capabilities.[4,5]

In our research, 12 weeks, randomized, double-blind study of the efficacy of Lactogut and Lactogut Kidz probiotics oral supplement on AD in adults and children was conducted, respectively. The research was performed on a total of 70 patients (20 adults and 50 children) with moderate to severe AD over duration of 12 weeks per case. Subjects were double-blindly randomized and obtained a conventional therapy plus study supplement in treatment arm and just conventional therapy in control arm. Subjects were instructed to take two probiotic capsules/sachets (Lactogut/Lactogut Kidz) every day during this study. In the following visits, the study was conducted: visit 1 (day 0, T0), visit 2, (day 21, T3), visit 3 (day 42, T6), visit 4 (day 63, T9) and visit 5 (day 84, T12).

Mean SCORAD score at T9 and T12 in the children's group demonstrated statistically significant difference between the control arm and the treatment arm with lower mean SCORAD score in the treatment arm. IgE levels of the children's group's control and treatment arm indicate little statistically significant difference, yet AEC demonstrated a statistically significant difference between the control arm and the treatment arm. It suggests that probiotic supplements was dramatically effective in lowering AD severity by reducing the T9 and T12 SCORAD score relative to the control arm. Children's group's patient satisfaction score was ranked very good in 26% and excellent in the treatment arm's 21% subjects as opposed to 0% in control arm subjects. This suggests a significant increase in the patient satisfaction score in the group of children in whom oral probiotic supplements are added to conventional therapy. The research performed by Wu et al indicated that supplementing the species *Lactobacillus* and *Bifidobacterium* was substantially helpful in decreasing AD severity in a 1 to 3 years age range of children. Their research also shows a substantial decline in the scores of SCORAD, infant dermatitis quality of life and dermatitis family impact scores.[10] In 1-3 years old children, the supplement of *Lactobacillus salivarius, Lactobacillus casei, Lactobacillus acidophilus* and *Bifidobacterium bifidum* showed prevailing decreases in SCORAD, IgE, IL-6, IL-5 and IFN gamma levels.[11] Another study found that the presence of *Lactobacillus fermentum* alone, *Lactobacillus paracesei* alone and combining of both strains for 12 weeks improved SCORAD, infant dermatology quality of life index and family dermatology quality of life index scoring, urinary 8-oso-2-deoxyguanosine and eosinophil protein X, serum IgE and TNF alfa levels in AD subjects.[12] The study performed by Woo Sl with *Lactobacillus* fermentum species in infants aged 6-18 months reported a significant reduction in SCORAD and severity of AD.[13] *Lactobacillus sakei* (in children aged 2-10 years) and *Lactobacillus plantarum* (in children aged 1-13 years) showed a significant reduction in SOCRAD score over a 12 weeks span.[14] The treatment of children 1 of 3 years old of *Lactobacillus acidophilus*, DDS-1, *Bifidobacterium lactis*, UABLA-12 and fructo-oligosaccharide reported a 33% reduction in SCORAD. Gerasimov et al showed a quality of life score for child dermatitis of 33% and a dermatitis family impact of 35.2%.[15]

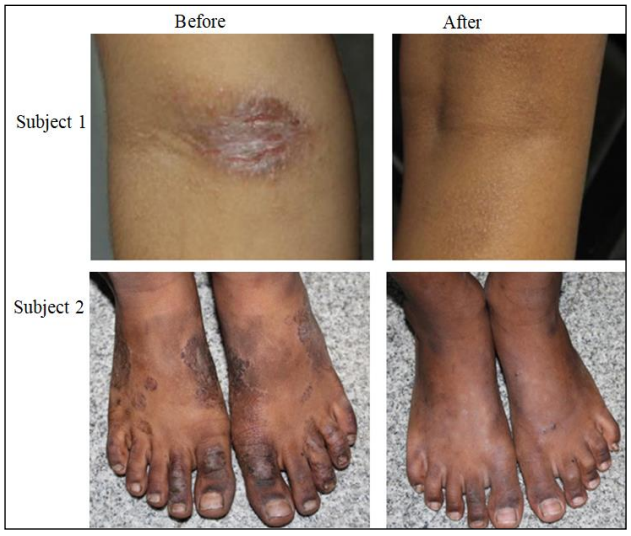

Figure 5: Global photographs of subjects in the treatment arm (before and after treatment).

In our study, SCORAD score in adult group shows no significant difference between control arm and treatment arm. However, a statistically significant difference between baseline SCORAD score at T0 versus mean SCORAD score at T3, T6, T9 and T12 is noted. In addition, a statistically significant difference between mean IgE levels of control arm and treatment arm was observed. AEC values do not indicate any significant difference between the control arm and the treatment arm. Adult patient satisfaction score was very good in 33.3% and excellent in 11.1% for subjects in the treatment group relative to 0% in subjects in the control group. This suggests a significant decrease in SCORAD index and

serum IgE levels and marked increase in the patient satisfaction score in the group of adults in whom oral probiotic supplements are added to conventional therapy. *Lactobacillus salivarius* supplements of 18-46 years old adult patients with AD increased the score for the dermatology life quality index, lowered the SCORAD score and load for *Staphyloccocci* and cytokine levels. Supplementations of *Lactobacillus salivarius* decreased development of Th2 cytokines and preserved levels of Th1.[16,17] *Bifidobacterium animalis* species supplements decreased the itching and the levels of kynurenic acid in subjects with AD. This supplement has strong antipruritic effects.[18]

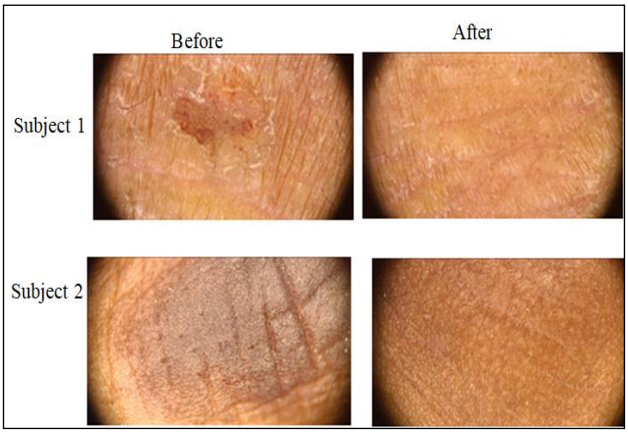

Figure 6: Dermoscopic images of subjects in the treatment arm using fotofinder (before and after treatment).

In our study, dermoscopic assessment using fotofinder scored grade 4 in 15.63% and grade 3 in 34.38% of subjects in the treatment arm in contrast with 0% for both grade 3 and grade 4 scores in subjects in the control arm. Global photography assessment scored 9.38% in grade 4 and 40.63% in grade 3 subjects as opposed to 0% in both grade 3 and grade 4 subjects in the control arm. Thus, both dermoscopic assessments utilizing Fotofinder and global photography assessments showed statistically significant improvement in the treatment arm as opposed to our study control arm. Patient satisfaction scores showed drastic improvement in the treatment arm in contrast to the control arm of our trial.

A growing number of studies have examined the potential efficacy of probiotics in the prevention and treatment of AD.[19] *Lactobacillus rhamnosus* is the most widely tested probiotic strain in children for the prevention of AD.[20] Another research assessed the effect of *Bifidobacterium breve* and *Bifidobacterium longum* administration on the treatment of allergic diseases over a span of 1 month prenatally, 6 months during infancy, and 18 months of follow-up.[21] At the end of four months of treatment of adult AD patients with probiotic strain (*Lactobacillus salivarills* LS01), Drago et al recorded statistically significant improvements in SCORAD ($p<0.0001$) and DLQI ($p= 0.021$) relative to placebo group.[17] Farid et al observed the clinical and immunological impact of a mixture of seven strains of probiotic bacteria (*Lactobacillus casei, Lactobacillus rhamnosus, Streptococcus thermophilus, Bifidobacterium breve, Lactobacillus acidophilus, Bifidobacterium infantis, Lactobacillus bulgaricus*) and fructo oligo saccharide in infants and children (3 months to 6 years) with mild to severe AD for 8 weeks, and showed a significantly greater reduction in SCORAD in the symbiotic group than in the placebo group.[22] In another study, the intake of a mixture of oral probiotics (*Bifidobacterium lactis, B. longum*, and *Lactobacillus casei*) by children aged 4 to 17 years with moderate atopic dermatitis demonstrated statistically significant reduction of SCORAD coupled with decrease in the usage of topical corticosteroids in the treatment group at the end of 12 weeks relative to the placebo group.[23] Some trials struggled to demonstrate the efficacy of probiotics or symbiotic in the treatment of AD.[24-26] Michail et al collected evidence from 10 trials (n=678) to assess if probiotics were successful in the treatment of AD which indicated an overall statistically significant difference in favour of probiotics compared to placebo in reducing the SCORAD score.[27] In the current study, our group used special combinations of bacterial strains of oral probiotic (Table 1) to test the efficacy of oral probiotics in treating AD, to assess the correlation of SCORAD score, serum IgE, AEC, global photography assessment, dermoscopy assessment using fotofinder and patient satisfaction score with probiotic therapy in AD. Thus, this study has explored the association of oral probiotic supplements and various criteria of AD management.

CONCLUSION

The findings of the study concluded that added conventional therapy with Lactogut Kidz supplements demonstrated effective control of SCORAD score and AEC levels in children suffering from AD. For children with both conventional and conventional and probiotic therapy, IgE levels between baseline and at 12 weeks demonstrated effective reduction. Adding to conventional therapy, the Lactogut supplement in adults showed effective control of SCORAD score, IgE levels and AEC values. In addition, the patient satisfaction score and quality of index demonstrated marked improvement after the introduction of Lactogut and Lactogut Kidz probiotic therapy in adults and children respectively. Dermoscopic assessment using fotofinder and global photographs showed notable improvement in treatment arm relative to control arm.. Thus, in both children and adults suffering from moderate to severe AD, probiotic supplements may also be used successfully as an adjunct remedy.

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Conflict of interest: None declared
Ethical approval: The study was approved by the institutional ethics committee

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