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Effect of Supplementation of Zinc, Glutamine, Fiber, and Prebiotics in Presumed Healthy Indonesian Children Aged 1–3 Years

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ABSTRACT

Purpose: Impaired intestinal mucosal integrity may affect the gastrointestinal function, especially in relation to nutrition, absorption, and barrier function. The purpose of this study was to measure the prevalence of impaired intestinal mucosal integrity in presumed healthy children aged 1–3 years and assess the effects of zinc, glutamine, fiber, and prebiotic supplementation in them.
Methods: A cross-sectional study was conducted in 200 children aged 1–3 years in Pasar Minggu, South Jakarta, Indonesia. A randomized double-blind parallel group method clinical trial was then performed to assess the effects of zinc, glutamine, fiber, and prebiotic supplementation.
Results: Elevated calprotectin was found in 91/200 subjects (45.5%) at the onset of the study. After 10 months, 144 subjects completed the study: 72 subjects received the trial formula, whereas the other 72 received the standard formula. A transitory decrease in fecal calprotectin (FC) was observed after 6 months in the subgroup with normal FC levels, who were fed the test formula (p=0.012).
Conclusion: The prevalence of impaired intestinal mucosal integrity in this group of Indonesian children aged 1–3 years was high. Supplementation with zinc, glutamine, fiber, and prebiotics during 6 months reduced FC only in those who had low levels at baseline but not in those with impaired integrity.

Keywords: Zinc; Glutamine; Prebiotics; Membrane

INTRODUCTION

According to the Basic Health Research Data of the Ministry of Health in Indonesia, the prevalence of being underweight in 2018 in Indonesian children was 17.7%: 13.8% were malnourished and 3.9% were severely malnourished. The prevalence of malnutrition has

Conflict of Interest
The authors have no financial conflicts of interest.

been more or less stable, with 13.5% in 2008, 13.9% in 2013, and 13.8% in 2018. Low intake and malabsorption caused by diseases, especially diarrhea, are the major causes of malnutrition [1]. Disturbance of the gut mucosal integrity is at the center of the pathogenesis of malnutrition in diarrheal disease inducing malabsorption, hormonal imbalance, bacterial overgrowth, secondary protein allergy, and disturbed villous regeneration. Gut mucosal integrity disturbance may cause inflammation [2], and nutritional factors that may modulate gut mucosal integrity include zinc, glutamine, fiber, and inulin [3].

Zinc is a component of more than 300 enzymes and is required for DNA synthesis, cell replication, and protein synthesis. Signs and symptoms of zinc deficiency are unclear, especially for mild deficiency. The prevalence of zinc deficiency in Indonesia is high (approximately 17%) [4]. According to a cohort study, the incidence of diarrhea is 47% higher in children with zinc deficiency [5]. However, studies in developing countries found that zinc supplementation might reduce the incidence of acute and persistent diarrhea [5,6]. Glutamine has a vital role in maintaining gut mucosal integrity and activating the immune system of the gastrointestinal tract [7,8].

The nutritional content of insoluble fiber may be low, but fiber has an important role that cannot be replaced by other compounds. Inulin is a prebiotic, an oligosaccharide, which is not digested but is fermented in the colon, resulting in the development of a bifidobacteria-dominated microbiota, enhancing the production of short chain fatty acids such as butyrate, which are very important nutritional substrates for the colonic mucosa [9,10].

To date, to the best of our knowledge, there have been no studies reporting the effect of zinc, glutamine, and fiber supplementation on gut mucosal wall integrity.

Fecal calprotectin (FC) and alpha-1-antitrypsin (α1AT) are markers of mucosal integrity in toddlers [11,12]. Increased levels of FC may indicate inflammation and lead to decreased mucosal integrity. However, FC levels are age-dependent, and they decrease with age. In a Swedish population, the upper limits for normal values were 233, 615, 136, and 57 μg/mg for infants aged 0, 6, 12 and 24 months, respectively [13]. The FC levels of infants aged 0–6 months reduced with age and were higher than the normal levels observed in healthy older infants [14]. This study aimed to measure the prevalence of intestinal mucosal integrity disturbance in presumed healthy children aged 1–3 years and assess the potential benefits of these supplements.

MATERIALS AND METHODS

This study was conducted in Pasar Minggu district, South Jakarta, from August 2015 to June 2016.

A total of 200 subjects were recruited by consecutive sampling, and they were presumed healthy children aged 1–3 years. Nutritional status was determined based on weight/height using the World Health Organization's child growth standards. Children with a history of cows' milk allergy or children who took medication that could modify the results of the study such as anti-inflammatory drugs or pre-, pro- and synbiotics were excluded from this study.

This study consisted of two phases

The first phase was a cross-sectional analysis to evaluate the prevalence of abnormal intestinal mucosal integrity in presumed healthy children aged 1–3 years by measuring FC

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and α1AT. The cut-off point for FC was 214 mg/kg [11]. The cut-off for α1AT was 26.8 mg/dL (Phical; Immundiagnostik, Bensheim, German).

The second phase was a double-blind randomized clinical trial. The 200 subjects were divided using block random sampling into two groups of 100 subjects each; the first group received formula supplemented with zinc, glutamine, fiber, and inulin (Test formula), whereas the second group (control) received the standard formula (**Table 1**: composition of formulas). All subjects were given 2×200 mL formula per day for 10 months, and they were not allowed to drink other formula.

Physical examination and anthropometric measurements were performed every month, whereas laboratory FC and α1AT were measured every 2 months. Weekly and monthly forms were used to record fecal consistency and frequency for evaluation of constipation and diarrhea.

Per-protocol analysis was performed for all outcomes and for all eligible children who were randomly allocated and had consumed the intervention formula. Analyses were conducted according to a predefined data analysis protocol. The independent *t*-test and Mann–Whitney test were used for statistical analyses for the first phase of this study. A *p*-value <0.05 was considered statistically significant. For the second phase, the Mann–Whitney U-test and

Table 1. Composition of the test formula and standard formula

Nutrient	Unit	Test formula	Standard formula
		Per 100 mL	Per 100 mL
Energy	kcal	74	74
Protein	g	2.6	2.6
Fat	g	2.8	2.8
Multi fiber*	mg	950.5	0.0
Inulin*		480	
Cellulose*		203	
Arabic GUM*		122	
Resistant starch*		115	
FOS*		30.5	
Mineral			
Calcium (Ca)	mg	91.0	91.0
Phosphor (P)	mg	61.8	61.8
Magnesium (Mg)	mg	11.1	11.1
Sodium (Na)	mg	55.3	55.3
Potassium (K)	mg	161.7	161.7
Chloride (Cl)	mg	92.6	92.6
Iron (Fe)	mg	1.4	1.4
Zinc (Zn)*	mg	1.5	0.2
Iodium (I)	mcg	24.4	24.4
Mangane (Mn)	mcg	108.1	108.1
Selenium (Se)	mcg	3.2	3.2
Amino acids			
Isoleusine	g	0.16	0.16
Leusine	g	0.26	0.26
Lysine	g	0.23	0.23
Metionine	g	0.07	0.07
Phenylalanine	g	0.11	0.11
Treonine	g	0.16	0.16
Tryptophane	g	0.05	0.05
Valine	g	0.18	0.18
L-glutamine*	G	0.175	0.0
Total amino acids	G	1.39	1.22

Test formula: SGM Digestive, Sari Husada, FOS: fructo-oligosaccharide.
*The difference between both formulas.

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Wilcoxon test were applied for data that were not distributed normally. SPSS PASW Statistic for Windows, Version 17.0.3 (SPSS Inc., Chicago, IL, USA) was used for all analyses.

This study was approved by the ethical review from the Permanent Committee on Medical/Health Research Ethics, Faculty of Medicine, University of Indonesia (number 117/UN2.F1/ETIK/2015) and informed consent was obtained.

RESULTS

The characteristics of the 200 included children are listed in **Table 2**; none of the characteristics showed a significant difference suggesting adequate randomization. After 10 months, 144 subjects completed the study, with 72 in each group.

FC ranged at baseline in the 200 children from 10.62 to 805.83 mg/kg feces with a median of 199.02 mg/kg; 91 (45.5%) had an FC above the cut-off limit of 214 mg/kg. Fecal α1AT ranged from 3.44 to 237.14 mg/dL, with a median of 30.22 mg/dL; in 116 (58.0%) subjects, fecal α1AT was above the cut-off of 26.8 mg/dL. After 10 months, 72 out of the 100 subjects from each group completed the study. There were no significant differences between the test and placebo groups in relation to FC and α1AT during the 10 months of study as shown in **Table 3**.

Among 144 subjects who completed the study, there were 66 (45.8%) with FC levels above the cut-off value at baseline. The data were à posteriori re-analyzed excluding those subjects with FC baseline >214 mg/kg. Data from 41 subjects in the test formula group and 37 subjects in the control group were re-analyzed. A statistically significant difference in the decrease in calprotectin levels between the test and control group at baseline in 6 months was observed, which disappeared at 10 months. Data were also posteriori re-analyzed for children with FC levels that are above the cut-off limit at baseline. In this subgroup, there was no statistical significant difference at any measuring time point. However, there was a trend for a larger decrease in the control than in the test group (**Table 4**).

Table 2. Subject's characteristics

Variable	Test formula (n=100)	Standard formula (n=100)	*p*-value
Sex			0.777**
Male	48 (51.1)	46 (48.9)	
Female	52 (49.1)	54 (50.9)	
Age (mo)	23.6 (6.18)	24.2 (6.40)	0.748***
Birth weight (g)	3,141.2 (477.71)	3,112.8 (467.72)	0.974***
Birth length (cm)	48.9 (2.03)	48.7 (2.15)	0.546***
Lactation history			0.098**
Exclusive breastmilk	68 (68.0)	67 (67.0)	
Breastmilk and formula	27 (27.0)	27 (27.0)	
Never got breastmilk	5 (5.0)	6 (6.0)	
Weight (kg)	11.1 (2.0)	10.9 (1.9)	0.330*
Height (cm)	83.7 (6.5)	83.6 (6.0)	0.470*
Head circumference (cm)	46.5 (1.4)	46.5 (1.7)	0.051*
Nutrition status			0.129**
Undernutrition (wasted)	6 (6.0)	1 (1.0)	
Normal	92 (92.0)	98 (98.0)	
Overweight	2 (2.0)	1 (1.0)	

Values are presented as number (%) or mean (SD).
*Independent *t*-test, **χ^2 test, ***Mann–Whitney test.

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Table 3. Effect of supplementation of zinc, glutamine, fiber, and prebiotics on fecal calprotectin, α1AT

Marker	Test formula (n=72)	Standard formula (n=72)	*p*-value
Calprotectin			
V_0 (mg/kg)	197.9 (38.1–798.5)	248.8 (31.0–805.8)	*p*=0.897‖
V_6 (mg/kg)	99.2 (20.1–479.4)	125.6 (15.9–358.0)	*p*=0.102‖
V_{10} (mg/kg)	148.3 (26.9–412.8)	173.2 (31.4–808.5)	*p*=0.169‖
p (0-6)*	*p*<0.001	*p*<0.001	p (0-6)‡=0.29
p (0-10)†	*p*=0.002	*p*=0.12	p (0-10)§=0.33
α1AT mg/dL			
V_0 (mg/dL)	28.3 (6.48–190.13)	32.6 (3.4–237.1)	*p*=0.441‖
V_6 (mg/dL)	13.3 (1.13–114.14)	14.4 (1.0–59.5)	*p*=0.790‖
V_{10} (mg/dL)	21.1 (2.46–63.32)	25.0 (3.1–51.6)	*p*=0.085‖
p (0-6)*	*p*<0.001	*p*<0.001	p (0-6)=0.39¶
p (0-10)†	*p*<0.001	*p*<0.001	p (0-10)=0.97¶

Values are presented as median (range).
α1AT: alfa-1-antitrypsin, V_0: month-0, V_6: month-6, V_{10}: month-10.
Results in median with confidence of 95%; *p*-value shows interaction among groups and the difference of laboratory results between month-0 and month-10.
*Significance between month-0 and month-6 in each group. †Significance between month-0 and month-10 in each group. ‡Significance between the changes of month-0 and month-6 between trial group and placebo group. §Significance between the changes of month-0 and month-10 between trial group and placebo group. ‖Wilcoxon test, ¶Mann–Whitney test.

Table 4A. Analysis in subgroups with fecal calprotectin cut-off of 214 mg/kg

Calprotectin <214 mg/kg	Test formula (n=41)	Standard formula (n=37)	*p*-value*
Diff calprotectin 6-0 (mg/kg)			
Median	−34.9200	27.0335	0.023
Diff calprotectin 10-0 (mg/kg)			
Median	16.2800	41.7350	0.127 (NS)

Diff calprotectin 6-0: Difference calprotectin month-6 and baseline, Diff calprotectin 10-0: Difference calprotectin month 10 and baseline; NS: not significant.
*Mann–Whitney test.

Table 4B. Analysis in subgroups with fecal calprotectin cut-off of 214 mg/kg

Calprotectin >214 mg/kg	Trial formula (n=31)	Standard formula (n=35)	*p*-value*
Diff calprotectin 6-0 (mg/kg)			
Median	−225.47	−175.14	0.500 (NS)
Diff calprotectin 10-0 (mg/kg)			
Median	−197.89	−132.33	0.386 (NS)

Diff calprotectin 6-0: Difference calprotectin month-6 and baseline, Diff calprotectin 10-0: Difference calprotectin month 10 and baseline; NS: not significant.
*Mann–Whitney test.

At baseline, 16.7% of the children in the test group and 4.2% in the control were constipated. According to the collected information, no child was constipated after 6 and 10 months. Regarding diarrhea, an incidence of 6.9% in the test and 13.9% in the control group at baseline was reported. After 6 months, this was 4.2% in both groups, and at 10 months, the incidence of diarrhea was 0 in the test group and 2.8% in the control group. None of the differences were statistically significant (**Table 5**).

There was no significant difference of z-score mean of anthropometry indicators between trial formula group and placebo group both after 6 months and 10 months (**Table 6**). As for increment of weight, there is a similar number of median weights raise count for both group, which is 1.65 kg for 10 months.

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Table 5. Effect of supplementation of zinc, glutamine, fiber and prebiotics to intestinal morbidity (diarrhea and constipation)

Morbidity	Test formula (n=72)	Standard formula (n=72)	χ^2 test
Constipation			
V_0			
Yes	12 (16.7)	3 (4.2)	
No	60 (83.3)	69 (95.8)	
V_6			
Yes	0 (0.0)	0 (0.0)	
No	72 (100.0)	72 (100.0)	
V_{10}			
Yes	0 (0.0)	0 (0.0)	
No	72 (100.0)	72 (100.0)	
p (0-6)*			*p*=0.029
Cured	12 (16.7)	3 (4.2)	
Stable	60 (83.3)	69 (95.8)	
Not cured	0 (0.0)	0 (0.0)	
Worsened	0 (0.0)	0 (0.0)	
p (0-10)†			*p*=0.029
Cured	12 (16.7)	3 (4.2)	
Stable	60 (83.3)	69 (95.8)	
Not cured	0 (0.0)	0 (0.0)	
Worsened	0 (0.0)	0 (0.0)	
Diarrea			
V_0			
Yes	5 (6.9)	10 (13.9)	
No	67 (93.1)	62 (86.1)	
V_6			
Yes	3 (4.2)	3 (4.2)	
No	69 (95.8)	69 (95.8)	
V_{10}			
Yes	0 (0.0)	2 (2.8)	
No	72 (100.0)	70 (97.2)	
p (0-6)			*p*=0.48 (NS)
Cured	5 (6.9)	9 (12.5)	
Stable	64 (88.9)	60 (83.3)	
Not cured	0 (0.0)	1 (1.4)	
Worsened	3 (4.2)	2 (2.8)	
p (0-10)			*p*=0.13 (NS)
Cured	5 (6.9)	10 (13.9)	
Stable	67 (93.1)	60 (83.3)	
Not cured	0 (0.0)	0 (0.0)	
Worsened	0 (0.0)	2 (2.8)	

Values are presented as number (%).
V_0: month-0, V_6: month-6, V_{10}: month-10, NS: not significant.
Results in mean, *p*-value shows difference morbidity of constipation and diarrhea between groups.
*Significance between the changes of month-0 and month-6 between trial group and placebo group.
†Significance between the changes of month-0 and month-10 between trial group and placebo group.
Independent *t*-test.

DISCUSSION

FC is a protein used as a diagnostic marker for inflammatory bowel diseases and is thus a fecal marker in gastrointestinal inflammation [13]. Calprotectin is a calcium- and zinc-binding protein of the S100 family expressed mainly by neutrophils with important extracellular activity. Increasing evidence suggests the implication of FC in the diagnosis, follow-up, assessment of relapses, and response to treatment in pediatric pathological conditions, such as inflammatory bowel disease, necrotizing enterocolitis, celiac disease, and many other inflammatory gastrointestinal conditions. In a Chinese cohort, the following median levels of FC in healthy

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Table 6. Anthropometric status of subjects in each group

Mean z-score	Parameter	Test formula (n=72)	Standard formula (n=72)	*p*-value*
Baseline	W	−0.48	−0.70	0.319
	H	−0.57	−0.71	0.442
	W/H	−0.29	−0.49	0.304
Month-6	W	−0.28	−0.33	0.660
	H	0.11	−0.146	0.962
	W/H	−0.34	−0.39	0.745
Month-10	W	−0.52	−0.56	0.69
	H	−0.66	−0.55	0.54
	W/H	−0.41	−0.46	0.57

W: weight, H: height.
Results in mean z-score.
*p-value shows difference mean z-score between groups, on baseline, month-6 and month-10.
Independent t-test.

children were reported, according to age: 12–24 months, 96.14 μg/g; 24–36 months, 81.48 μg/g; and 36–48 months, 65.36 μg/g [12]. This non-invasive test is useful for screening children with gastrointestinal symptoms to avoid unnecessary invasive procedures [15]. Our study shows that the prevalence of intestinal mucosal integrity disturbance in this cohort of presumed healthy children aged 1–3 years was 45.5% according to FC levels. The baseline median FC in this study was relatively higher (199 mg/kg feces) than that reported in two Chinese studies with a median of 83.19 and 104 mg/kg in children aged 1–4 years and 12–18 months, respectively [12,16]. Given that all the subjects in our study were presumed healthy children, the high level of FC at baseline raises the possibility that there may be intestinal inflammation in apparently healthy Indonesian children. After 6 months intervention with the test formula, FC decreased significantly, but only in those children with a FC below the cut-off. Furthermore, no change was observed in the group with high FC. If a true beneficial effect would be induced by the addition of the different supplements, a decrease would have been expected in those with elevated FC levels. The natural evolution of FC is a decrease over time in infants and toddlers. The younger the infant, the higher and the wider the range of FC [11,12,17,18].

Prebiotics are known to stimulate the development of bifidobacteria in the gastrointestinal microbiome, which may strengthen the mucosal resistance toward gastrointestinal infection [19,20]. Prebiotics aside, zinc supplementation is known to increase the immunocompetence that affects the clearance of diarrhea-causing pathogens [21]. Guerrant et al. [22] showed that glutamine is a key component of cell replication and that glutamine improves and stimulates gut crypt cell proliferation. Accordingly, the supplementation of formula with prebiotics, zinc, and glutamine might reasonably be considered significant in reducing the intestinal inflammation in subjects of intervention group. An important limitation of this study is that overall daily nutrition was not registered.

We could not confirm the results from a meta-analysis by Mayo-Wilson et al. [23] showing that zinc supplementation to healthy children may reduce the incidence of diarrhea by 13% (95% confidence interval 0.85–0.89). This meta-analysis also measured zinc supplementation dosage; low dose zinc supplementation (0–5 mg/day) lowered the incidence of diarrhea by 5% [23]. In our trial, zinc supplementation was given at 6 mg/day in the intervention group and 0.8 mg/day in the control group.

In conclusion, there appeared to be a high prevalence of mucosal integrity disturbance in apparently healthy Indonesian children aged 1–3 years. Supplementation of infant formula with zinc, glutamine, fiber, and prebiotics failed to show a clinical benefit.

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REFERENCES

1. Badan Penelitian dan Pengembangan Kesehatan Kementerian Kesehatan Republik Indonesia. Hasil Utama RISKESDAS 2018. Jakarta: Kementerian Kesehatan Republik Indonesia, 2018.
2. Lebenthal E. Prolonged small intestinal mucosal injury as a primary cause of intractable diarrhea of infancy. In: Lebenthal E, ed. Chronic diarrhea in children. New York: Raven Press, 1984:5-9.
3. Duggan C, Gannon J, Walker WA. Protective nutrients and functional foods for the gastrointestinal tract. Am J Clin Nutr 2002;75:789-808.
PUBMED | CROSSREF
4. Dijkhuizen MA, Wieringa FT, West CE, Muherdiyantiningsih, Muhilal. Concurrent micronutrient deficiencies in lactating mothers and their infants in Indonesia. Am J Clin Nutr 2001;73:786-91.
PUBMED | CROSSREF
5. Folwaczny C. Zinc and diarrhea in infants. J Trace Elem Med Biol 1997;11:116-22.
PUBMED | CROSSREF
6. Black RE. Zinc deficiency, infectious disease and mortality in the developing world. J Nutr 2003;133(5 Suppl 1):1485S-9S.
PUBMED | CROSSREF
7. Lima AA, Brito LF, Ribeiro HB, Martins MC, Lustosa AP, Rocha EM, et al. Intestinal barrier function and weight gain in malnourished children taking glutamine supplemented enteral formula. J Pediatr Gastroenterol Nutr 2005;40:28-35.
PUBMED | CROSSREF
8. Neu J, DeMarco V, Li N. Glutamine: clinical applications and mechanisms of action. Curr Opin Clin Nutr Metab Care 2002;5:69-75.
PUBMED | CROSSREF
9. Malkki Y. Physical properties of dietary fiber as keys to physiological functions. Cereal Foods World 2001;46:196-9.
10. Boehm G, Stahl B. Oligosaccharides. In: Mattila-Sandholm T, ed. Functional dairy products. Volume 1. Cambridge: Woodhead Publishing Ltd, 2003:203-43.
CROSSREF
11. Oord T, Hornung N. Fecal calprotectin in healthy children. Scand J Clin Lab Invest 2014;74:254-8.
PUBMED | CROSSREF
12. Zhu Q, Li F, Wang J, Shen L, Sheng X. Fecal calprotectin in healthy children aged 1-4 years. PLoS One 2016;11:e0150725.
PUBMED | CROSSREF
13. Peura S, Fall T, Almqvist C, Andolf E, Hedman A, Pershagen G, et al. Normal values for calprotectin in stool samples of infants from the population-based longitudinal born into life study. Scand J Clin Lab Invest 2018;78:120-4.
PUBMED | CROSSREF
14. Lee YM, Min CY, Choi YJ, Jeong SJ. Delivery and feeding mode affects fecal calprotectin levels in infants <7months old. Early Hum Dev 2017;108:45-8.
PUBMED | CROSSREF
15. Noebauer B, Ramic L, Konstantin A, Zachbauer C, Einwallner E. Analytical evaluation of a fully automated immunoassay for faecal calprotectin in a paediatric setting. Biochem Med (Zagreb) 2017;27:030710.
PUBMED | CROSSREF
16. Li F, Ma J, Geng S, Wang J, Liu J, Zhang J, et al. Fecal calprotectin concentrations in healthy children aged 1-18 months. PLoS One 2015;10:e0119574.
PUBMED | CROSSREF
17. Song JY, Lee YM, Choi YJ, Jeong SJ. Fecal calprotectin level in healthy children aged less than 4 years in South Korea. J Clin Lab Anal 2017;31:e22113.
PUBMED | CROSSREF
18. Velasco Rodríguez-Belvís M, Viada Bris JF, Plata Fernández C, García-Salido A, Asensio Antón J, Domínguez Ortega G, et al. Normal fecal calprotectin levels in healthy children are higher than in adults and decrease with age. Paediatr Child Health 2019.
CROSSREF
19. Turner JR. Intestinal mucosal barrier function in health and disease. Nat Rev Immunol 2009;9:799-809.
PUBMED | CROSSREF
20. Catalioto RM, Maggi CA, Giuliani S. Intestinal epithelial barrier dysfunction in disease and possible therapeutical interventions. Curr Med Chem 2011;18:398-426.
PUBMED | CROSSREF

21. Larson CP, Roy SK, Khan AI, Rahman AS, Qadri F. Zinc treatment to under-five children: applications to improve child survival and reduce burden of disease. J Health Popul Nutr 2008;26:356-65.
PUBMED

22. Guerrant RL, Oriá RB, Moore SR, Oriá MO, Lima AA. Malnutrition as an enteric infectious disease with long-term effects on child development. Nutr Rev 2008;66:487-505.
PUBMED | CROSSREF

23. Mayo-Wilson E, Junior JA, Imdad A, Dean S, Chan XH, Chan ES, et al. Zinc supplementation for preventing mortality, morbidity, and growth failure in children aged 6 months to 12 years of age. Cochrane Database Syst Rev 2014;(5):CD009384.
PUBMED | CROSSREF