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Effectiveness of Gelatin Tannate among Children with Acute Diarrhea: A Systematic Review and Meta-Analysis

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Abstract

Gelatin tannate has been proposed as a theoretically effective treatment for treating acute diarrhea in children. Vegetable tannins have attracted a lot of attention in recent years because of their multifunctional properties, such as beneficial to human health and recently, an antidiarrhea effect of gelatin tannate has been reported. However, inconsistency across the studies was reported. This study aims to perform a meta-analysis concerning the efficacy of gelatin tannate administration for treating acute diarrhea in children Published papers from PubMed, Embase, Cochrane, and Google Scholar were collected, and they were analyzed using a fixed or random-effect model. A total of three relevant papers were included in our analysis. Our pooled analysis found that gelatin tannate administration, compared to control, was associated with reduced stool frequency (mean diff: 0.79 [95%CI: 0.44-1.15], p = 0.000). However, duration of diarrhea (mean diff: 10.87 [95%CI: -7.71-29.46], p = 0.25), weight gain (mean diff: 47.22 [95%CI: -22.81-117.24], p = 0.19), vomiting (OR: 0.57 [95%CI: 0.23-1.41], p = 0.22), and side effects (OR: 1.39 [0.42-4.63], p = 0.59) were not affected significantly between treatment and control groups. Gelatin tannate administration provides the efficacy to reduce stool frequency in children with acute diarrhea.

Keywords
Gelatin tannate; acute diarrhea; adjuvant therapy

I. Introduction

Diarrhea is the passage of increased amounts of loose or watery stools caused by impairment in the absorption processes (Lopetuso et al, 2017). Diarrheal diseases constitute one of the primary causes of increased mortality and morbidity rate globally (Global Burden of Disease 2013 Mortality and Causes of Death Collaborators, 2013; Bustreo. 2015; Alexander, 2013). It is attributed to approximately 1.3 million annual deaths,[5] mostly occurring in resource-limited countries; (Global Burden of Diarrhoeal Diseases Collaborators, 2015; Kotloff, 2013; Fiedoruk, 2015). Diarrhea-induced morbidity is further concentrated in marginalized communities (Bulled, 2014). Acute diarrhea in children mostly resolves spontaneously, hence, treatment is based on replacement of lost water and electrolytes together with adequate nutrition (Guandalini, 2008; Koletzko, 2009; Farthing, 2013). (Researchers looked snacks in schools does not meet the nutritional balance, due to the low in vitamins and minerals in these snacks, only high in carbohydrates and fats such as meatball skewers, pop noodles, fried noodles, light snacks, and milk cans. (Adinda, D. 2019)

Furthermore, acute diarrheal disorder treatment, except in cases of severe dehydration or other serious complication, does not require hospitalization (Guarino,

2014). The oral rehydration solution (ORS) is the treatment of choice for diarrhea-induced dehydration However, scientists are interested in adjunctive treatments due to the inadequate effect of this therapy to decrease frequency/duration of diarrhea (Guarino, 2009). Probiotics are living microorganisms that provide various health benefits to humans and constitute one of the alternative approaches for diarrhea prevention and treatment. It is proposed that probiotics produce anti-microbial agents (Cheikhyoussef, 2008), compete with pathogens for nutrient uptake and adhesion sites (Abedi, 2013) and modulate immune response (Matsuzaki, 2000).

Gelatin tannate, a compound produced when tannic acid is suspended in gelatinous solution, is reportedly an effective treatment for pediatric acute gastroenteritis (Farthing, 2000). Over the years, vegetable tannins have attracted much attention due to its multifunctional properties which provides great benefits to human health, as demonstrated via in vitro and in vivo assays. Gelatin tannate has recently been shown to possess, antidiarrhoic effect (Yoshida, 2010; Esteban, 2009). Furthermore, tannins has shown to possess astringent properties, hence, reduces local inflammation through precipitation of proinflammatory proteins such as intestinal mucoproteins (Ashok, 2012). It also demonstrate antibacterial properties by inhibiting the growth of pathogens such as *Bacteroides fragilis, Clostridium perfringens, Escherichia coli, Enterobacter cloacae, Listeria monocytogenes Salmonella typhimurium, and Helicobacter pylori* (*H. pylori*) (Chung, 1993; Scalbert, 1991; De Servi).*In vitro*, tannins have been shown to inhibit certain bacterial toxins such *Vibrio cholera. (Oi H, Matsuura D, 2002).*

In acute colitis mouse model tannate significantly increased disease severity in form of histological score, body weight, as well as disease activity index (DAI) (Scaldaferri, 2014). Besides, it tends to induce undesirable symptoms such as nausea, vomiting, and inhibition of metal absorption when consumed independently. This compound provides mechanical protection for the gut by forming a protein-based membrane that lines the walls of the gut. Hence, it counteracts acid and alkaloid effects resulting from putrefaction during GIT movements or bacterial fermentation (Freli). An RCT study confirmed gelatin tannate as an acute childhood gastroenteritis therapy. Based on the results, GT together with oral rehydration significantly decreased bowel movements after 72h, with shorter disease duration and improved stool consistency in children with acute diarrhea, compared to oral rehydration solution only

II. Research Methods

2.1 Study Design

This was a meta-analysis study conducted from September to October 2020 to determine the effectiveness of gelatin tannate in managing acute diarrhea in children. Published papers were collected from PubMed, Embase, Cochrane, and Google Scholar while the pooled mean difference and 95% confidence interval (95% CI) were calculated using either random or fixed effect model. Furthermore, the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) checklist was applied to ensure different procedures such as statistical analysis, papers selection, quality assessment, as well as data extraction, conforms to the guidelines. This study was carried out in accordance with the Helsinki Declaration Principles. This study was approved by Ethical Committee of MRC with approval number NO: 061/Liv/K.3/309/2021.

2.2 Search Strategy and Data Extraction

Several research websites were accessed to obtain related papers as of October 14, 2020, meanwhile, the publishing language was restricted. Papers that were not published both in English and Indonesia were not included. Furthermore, the systematic search was carried out using the following keywords: [“acute diarrhea”], [“children”] and [“gelatin tannate"]. The following information of interest were also extracted: (1) author's first name, (2) year of publication, (3) sample size of case and control, (4) age of participants, (5) ethnicity, (6) main findings, (7) duration of diarrhea, (8) stool frequency, (9) weight gain, (10) total number of vomiting subjects, and (11) the total of subjects with side effects after drug administration. Moreover, to provide high-validity data, two independent authors performed data extraction to avoid human error (FF, SHZ) while a joint discussion is carried out when discrepancies are found (FF, SHZ, CHA).

2.3 Eligibility Criteria

The papers used in this study were selected based on the following inclusion criteria: (1) assess the effectiveness of gelatin tannate in treating pediatric acute diarrhea; and (2) possess necessary data for calculation of 95% CI and mean differences. In contrast, the exclusion criteria include: (1) reviews and commentaries, (2) unrelated titles and abstracts, (3) ungeneralized and/or incomplete data, (4) low-quality article.

2.4 Outcome Measures

The predictor covariate was gelatin tannate administration while the outcome measures include diarrhea duration, frequency of stooling, weight gain, side effects and vomiting. These variables were determined after conducting an initial search for covariates used for the meta-analysis calculation.

2.5 Assessment of The Methodological Quality

Prior to inclusion, the New Castle-Ottawa scale (NOS) with a score ranging from 0 to 9 was used to access the quality of each paper, with three points: patient selection (4 points), comparability of the groups (2 points) and ascertainment of exposure (3 points). Furthermore, paper was interpreted as having low quality (≤ 4), moderate quality (5-6), or high quality (≥ 7), meanwhile, papers with low quality were excluded from our study. Two independent authors (FF and CHA) performed the NOS assessment while joint discussion was carried out when discrepancy is found.

2.6 Statistical Analysis

The correlation and estimates of gelatin tannate administration on diarrhea duration, frequency of stool, weight gain, vomiting and side effects among children with acute diarrhea were analysed using the Z test. Moreover, data were evaluated prior to the identification of significant factors for potential publication bias and heterogeneity. The latter was assessed using the Q test. When heterogeneity exist between studies ($p < 0.10$), a random effect model was adopted, otherwise, a fixed effect model was applied. To determine reporting or publishing error, the Egger test and funnel plot were used with $p<0.05$ taken as publication bias). The forest plot was then used to present correlation and effect estimates. Moreover, data analysis was performed using Review Manager v.5.3 (Revman Cochrane, London, UK). To avoid methodological errors, two independent authors (FF and SHZ) conducted the statistical analysis.

III. Results and Discussion

3.1 Eligible Studies

The systematic and strategic search identified 178 potential relevant papers. However, 168 were excluded due to irrelevant titles and abstracts. Hence, only 10 papers were included for fulltext review. Among these papers, seven were excluded because of review (n = 4), incomplete data (n = 2), and low quality (n = 1) leaving only three papers which were then included in the analysis. Figure 1 summarizes the selection pathway, while Table 1 outlines the baseline characteristics of the papers included the meta-analysis.

a. Data Synthesis

During the data synthesis, 3, 2, and 3(3) papers investigating the association between gelatin tannate administration and duration of diarrhea, stool frequency, weight gain, vomiting, and side effects were included respectively. The pooled analysis showed that gelatin tannate was associated with stool frequency (mean diff: 0.79 [95%CI: 0.44-1.15], p = 0.000) compared to control. However, duration of diarrhea (mean diff: 10.87 [95%CI: -7.71-29.46], p = 0.25), weight gain (mean diff: 47.22 [95%CI: -22.81-117.24], p = 0.19), vomiting (OR: 0.57 [95%CI: 0.23-1.41], p = 0.22), and side effects (OR: 1.39 [0.42-4.63], p = 0.59) were not significantly affected between the treatment and control groups. The summary of the correlation and effect estimates between treatment and outcome measures is outlined in Table 2.

b. Source of Heterogeneity

1. Heterogeneity among studies

Based on the results, evidence of heterogeneity was observed in diarrhea duration. Therefore, the association between gelatin tannate administration and this parameter was accessed using the random effect model. Conversely, there were no evidence of heterogeneity in stool frequency, weight gain, vomiting and side effects covariate. Therefore, the association between treatment and these variables was evaluated using the fixed effect model. The evidence of heterogeneity among studies is presented in Table 2.

2. Potential publication bias

Publication bias among studies was determined using Egger's test. Overall, there was no publication bias in this study as summarized in Table 2.

Table 1. Baseline characteristics of articles included in our study

Author & year	Sample size		Case setting	Age (month)	Ethnicity	NOS	Main findings
	CON	GT					
Kara et al 2017	73	71	GEA	44.1 ± 33.7	Caucasian	7	GT resulted in a decreased stool frequency at 12 hours in children with acute diarrhea.
Kołodzie et al 2018	33	31	Acute Diarrhea	27.2 ± 28.9	Caucasian	7	GT was ineffective as an adjunct to rehydration therapy.
Mennini et al 2016	29	31	GEA	19 ± 5	Caucasian	6	GT was associated with a significant decrease in bowel movements at 72 hours, early improvement in the stool consistency and shorter disease duration.

Note, NOS, Newcastle-ottawa scale; GEA, Gastroenteritis Acute; CON, Control; GT, Gelatin tannate.

Table 2. Summary of the association between gelatin tannate and outcome parameters among children with acute diarrhea

Outcome parameters	NS	Model	Outcome measure		Mean difference / OR	95%CI	pE	pHet	P
			Control	Gelatin tannate					
Duration of Diarrhea	3	Random	76 ± 20.33	65 ± 17.67	10.87	-7.71-29.46	0.609	0.000	0.25
Stool frequency	3	Fixed	3.33 ± 1.33	2.67 ± 1.67	0.79	0.44-1.15	0.371	0.026	0.00
Weight Gain	2	Fixed	114.5 ± 577.5	135 ± 321	47.22	22.81-117.24	0.301	0.084	0.19
Vomiting	3	Fixed	17.7 %	21 %	0.57	0.23-1.41	0.000	0.491	0.22
Side effects	3	Fixed	5 %	3.7 %	1.39	0.42-4.63	0.000	0.928	0.59

Note, data were presented in mean ± SD; NS, number of studies; CI, confidence interval; pE, p Egger; pHet, p Heterogeneity.

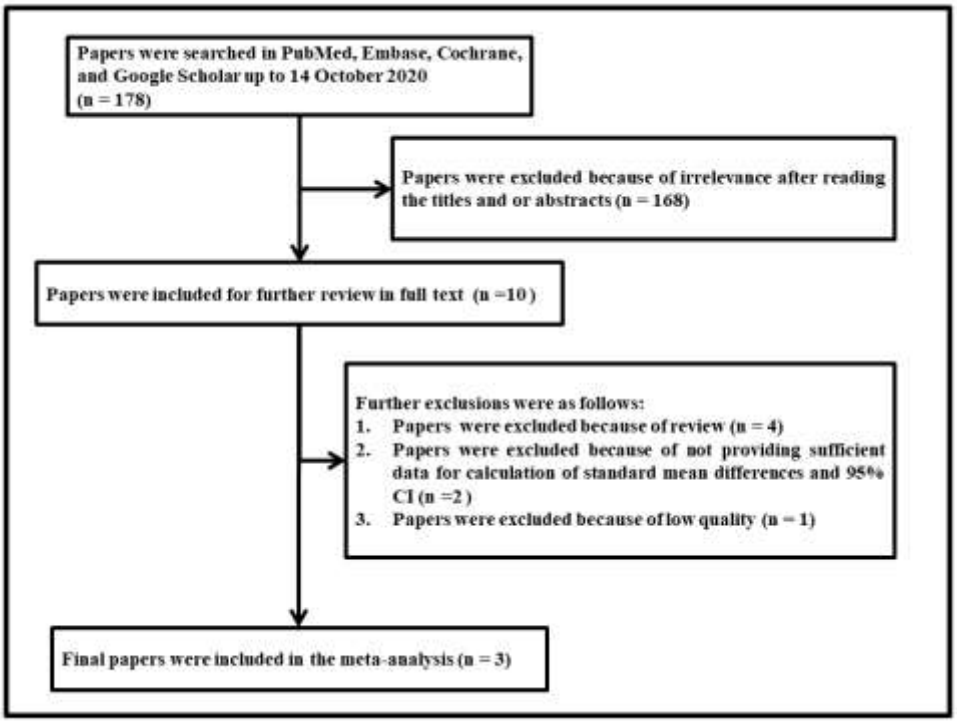

Figure 1. *A flowchart of study selection*

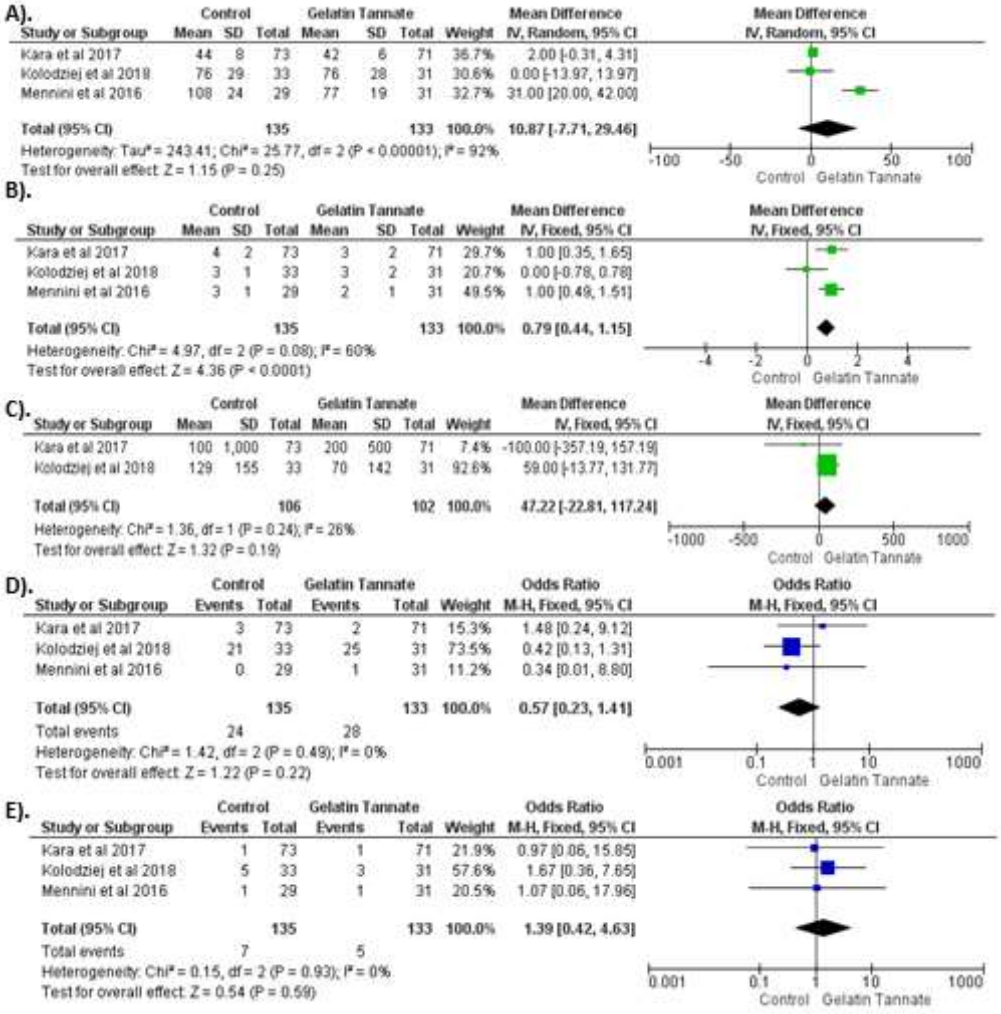

Figure 2. *Forest plot of the association between gelatin tannate and outcome parameters among children with acute diarrhea. A). Duration of diarrhea; B). Stool Frequency; C). Weight Gain; D). Vomiting; E). Side effects*

3.2 Discussion

a. Duration of Diarrhea

A total of three studies were analyzed to assess the correlation between gelatin tannate administration and the duration of diarrhea in children with acute diarrhea. However, this correlation was confirmed by only one of the three studies. According to pooled data, gelatin tannate administration was not correlated with diarrhea duration, and these findings were consistent with previous studies. The results also showed gelatin tannate administration was not correlated to reduced duration of diarrhea (Çağan, 2017; Florez, 2019). These findings were contradictive to previous studies. Furthermore, gelatin tannate was discovered to shorten the duration of diarrhea among children with acute diarrhea (Aloi, 2019; Serban, 2019). This contradiction ought to be clarified in the near future. Viruses, especially rotavirus, are the most common causes of acute gastroenteritis (Karimi, 2014). These viruses replicate in epithelial cell at the tips of the villi in the small intestine, and the epithelial cells in turn undergo atrophy as well as necrosis, and are shedded from the gut, leading to diarrhea (Karimi, 2014). Meanwhile, gelatin tannate, a mucoprotectant, protects the epithelial cells by forming a protective biofilm in the intestinal mucosa and enhancing mucosal resistance to pathological attack. This

mucoprotectant was also found to prevent growth in some bacterial species and preserve the intestinal mucous layer (Florez, 2019), as well as to help re-establish normal physiological function and theoretically, shorten the duration of diarrhea. However, further studies are required to investigate the correlation between these two.

b. Stool Frequency

A total of three studies were analyzed to assess the correlation between gelatin tannate administration and stool frequency in children with acute diarrhea. However, this correlation was confirmed by only one of the three studies. According to pooled data, gelatin tannate administration was correlated with reduced diarrhea stool frequency. These findings were consistent with previous studies. The results also showed that gelatin tannate administration was correlated with reduced diarrhea stool frequency (Florez, 2019; Aloi, 2019; Serban, 2019). These findings were contradictive to previous studies. Also, gelatin tannate was discovered to have no correlation with the stool frequency among children with acute diarrhea (Florez, 2019). This contradiction ought to be clarified in the near future. As previously mentioned, viruses are the most common causes of acute gastroenteritis (Karimi, 2014). These micro-organisms destroy the epithelial cells, leading to reduces absorption and increased osmotic gradient, as well as a component of hypersecretion, contributing to the diarrhea (Karimi, 2014). However, gelatin tannate, a mucoprotectant, helps reduce the number of epithelial cells being destroyed, thus improving absorption within the gut and correcting the osmotic gradient imbalance (Serban, 2019). Balancing the osmotic gradient tends to reduce liquid stools, as well as the stool frequency.

c. Weight Gain

A total of two studies were analyzed to assess the correlation between gelatin tannate administration and weight gain, in children with acute diarrhea. However, only one study showed a correlation, while the other showed no difference. According to pooled data, gelatin tannate administration was not correlated with weight gain. This finding is similar to a previous retrospective observational study by Serban and Manolache, reporting gelatin tannate and ORS with ORS and placebo both promote weight gain, with no significant difference (Serban, 2019). Kara *et al*., (the study confirming correlation) measured participants' weight at 120 hours after intervention, while Kolodziej *et al*., and Serban and Manolache (the study confirming correlation) measured participants' weight at 48 hours and 72 hours after intervention, respectively. The short duration between measurements probably explains the absence of significant difference in weight gain. Galatin tannate, a mucoprotectant tannic acid, binds with albuminoidal and mucilaginous substances from the intestinal content, neutralizing inflammation in gastrointestinal walls (Aloi, 2019). This inflammation is a possible cause of lactose malabsorption, a common diarrhea complication. Therefore, a reduction in thus inflammation, lactose malabsorption ought to be reduced, while weight gain ought to be promoted. However, further studies are required to investigate the correlation between these two.

d. Vomiting

A total of three studies were analyzed to assess the correlation between gelatin tannate administration and vomiting, in children with acute diarrhea, and all studies confirmed no significant correlation between the two. Based on the pooled data, gelatin tannate administration was not correlated with vomiting. This finding is similar to a previous meta-analysis by Florez *et al*., and a retrospective observational study by Serban

and Manolache, reporting gelatin tannate and ORS, with ORS and placebo, both reduce vomiting frequency, with no significant difference. Meanwhile, noroviruses, a type of GEA-causing virus, causes a marked delay in gastric emptying (Sawin-Johnson, 2019). This is believed to be related to the high incidence of vomiting episodes in noroviruses infection. The pathophysiology behind this phenomenon is believed to gastric motor function (hypermotility) alteration, and pyloric junction inflammation between the stomach and intestine (Sawin-Johnson, 2019). Tannins have been found to be effective against these two problems. Furthermore, there are very few studies on tannins regarding intestinal motility, but Liu *et al*., found the compounds to exhibit antidiarrheal activity in mice, including reducing intestinal motility. Tannins also help to reduce gastroinsteninal inflammation, by providing mechanical protection for the inflamed gut walls, in the form of biofilm lining, offering protection against harmful acid from bacterial fermentation or putrefaction, during gastrointestinal transit (Aloi, 2019).

e. Side Effects

A total of three studies were analyzed to assess the correlation between gelatin tannate administration and side effects, in children with acute diarrhea, and all studies confirmed no significant correlation. According to pooled data, gelatin tannate administration was not correlated with side effects. This finding is similar to previous a retrospective observational study by Serban and Manolache, where participants were administered diosmectite ± racecadotril ± Saccharomyces boulardii or Lactobacillus GG ± ORS, as placebo, and no other medication was administered (Serban, 2019). Tannic acids are known to independently induce adverse effects, including nausea and vomiting. However, gelatin tannate, a tannic acid complex hydrolysed to gelatin, prevents these adverse effects in the gastric mucosa, as well as tannic acids' metal chelating (De Servi).

f. Clinical Implication

This study confirmed children with acute diarrhea, treated with gelatin tannate experienced decreased stool frequency, compared to without gelatin tannate. A randomized, controlled, double-blind, parallel-group, single-center study by Cagan *et al*., involving 103 patients, and a retrospective observational study by Serban and Manolache, reported the same results as this study. Previous meta-analyses had been performed to assess the effect of gelatin tannate in patients with diarrhea, and contradictory results were obtained. The results matched the report by Aloi and Mennini, but not with Florez *et al*., and this contradiction requires further assessment further. Further studies are also required to confirm other considerations, in the contexts of pharmacologic, pharmacokinetic, and pharmacogenetic interactions.

g. Study limitations

This study faced several limitations in the form of several unmonitored and omitted important factors in the analysis governing the severity of acute diarrhea in children, including nutritional status, medication compliance, dehydration, congenital disorder, and comorbid factors. In addition, the sample size provided was relatively small, as with previous meta-analyses. Therefore, this study's results ought to be carefully interpreted.

V. Conclusion

This study discovered gelatin tannate administration provides the efficacy to reduce stool frequency in children with acute diarrhea. However, duration of diarrhea, weight gain, vomiting and side effects were not affected by gelatin tannate administration in these children. Therefore, this study probably better clarifies the correlation about gelatin tannate's effectiveness as adjuvant treatment in children with acute diarrhea.

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