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**REVIEW ARTICLE**

# Gelatin Tannate: A Selective Biofilm-Forming, Gut Mucoprotectant for Acute Gastroenteritis in Children. A Short Narrative Review

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**Abstract:** ***Background*:** Gelatin tannate is bowel selective, safe and effective, and acts locally to form a biofilm. As an adjuvant to oral rehydration solution (ORS), gelatin tannate acts as a mucoprotectant in the management of acute diarrhea in children.

***Objective*:** To provide an up-to-date review of the pharmacological profile of gelatin tannate, and its efficacy and safety in the treatment of children with acute gastroenteritis.

***Methods*:** A medical literature review was conducted using the PubMed database, analyzing all gelatin tannate preclinical research and clinical reports, and post-marketing surveillance data.

***Results*:** *In vitro* studies have demonstrated that gelatin tannate protects biological membranes against corrosive substances. *In vivo*, gelatin tannate acts not only as a gut mucoprotectant but also as an anatomical and physiological modulator. Moreover, gelatin tannate is an intestinal barrier enhancer endowed with gut homeostatic recovering properties. Clinical studies have shown that the combination of gelatin tannate and ORS has a fast onset of action and is effective and safe in the relief of acute diarrheal conditions in children.

***Conclusion*:** Although ongoing clinical studies will address current clinical gaps with gelatin tannate, the findings highlighted in this overview may have particular implications for the use of gelatin tannate in resource-poor, developing countries to treat cases of pediatric acute gastroenteritis.

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## INTRODUCTION

Diarrhea, characterized by increased stool volume and reduced stool consistency, is defined as a volume of daily stools >10 mL/kg (children aged <2 years) or daily stools weighing >200g (children aged >2 years). From a clinical perspective, diarrhea presents as loose-to-watery stools passed ≥3 times daily. However, individual stool patterns can vary; breastfed infants, for example, often produce5-6 stools daily. Assessing stool color, consistency, frequency, and volume can assist in the clinical determination of the diarrheal source (*e.g.* small or large bowel) [1].

According to the latest World Health Organization reports, approximately 2 billion cases of diarrhea occur globally on an annual basis, and almost 2 million children aged <5 years (mainly in developing countries) fail to thrive due to diarrhea. These estimates equate to 18% of all deaths in children aged <5 years, with >5000 children dying every day as a consequence of diarrheal diseases. Seventy-eight percent of all diarrhea-related deaths in children occur in Africa and South-East Asia [2].

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It is estimated that children aged <5 years have an average of three acute diarrhea episodes annually. On a worldwide basis, acute diarrhea represents one of the leading causes of death in this population (second only to pneumonia). Indeed, although the incidence and risk of mortality associated with diarrheal diseases decline in older children, they are highest in children aged <5 years, particularly during infancy. In developing countries, childhood diarrhea is also directly associated with malnutrition, growth faltering, and impaired cognitive development; however, in developed countries, family life comfort disruption is a direct consequence of diarrhea in children [2].

A range of factors has contributed to a reduction in the diarrhea-related mortality rate in the last 30 years, including the broad availability of oral rehydration solutions (ORS), and improvements in breastfeeding rates, nutrition, sanitation/hygiene, and immunization coverage [2].

ORS and improvements in nutrition have had a great impact on reducing mortality rates on a global scale. However, despite some improvements in nutrition, developing countries continue to experience a high incidence of diarrhea due to poor living conditions and a lack of tangible progress with regard to safe water, personal hygiene, and sanitation. Factors which are likely to have a positive and simultaneous impact on diarrhea-related mortality and morbidity in developing countries include breastfeeding (exclusive and continuous until the infant is aged 2 years), improved complementary feeding (*via* improved nutrition), and better sanitation [2].

In contrast to the situation in developing countries, there are relatively few diarrhea-related deaths in children in developed countries; nevertheless, diarrhea remains a notable cause of morbidity which is associated with significant costs to healthcare and society. Diarrhea negatively impacts quality of life (QoL) for parents and family members of affected children and can lead to increased stress levels and higher rates of work absenteeism. The economic burden on families includes contracting caregivers as baby sitters and disrupting normal family functioning and comfort by having to rely on other family members (*e.g.* grandparents) to care for children with diarrhea who cannot attend their day care centers or schools. In the US alone, it has been reported that an estimated $US70 million in working hours/year are lost due to acute gastroenteritis (AGE).

In the US, for example, acute childhood diarrhea accounts for approximately 5% of all pediatric hospitalizations and a cost of nearly $US1 billion [1]. Moreover, in children aged <2 years or <3 years, acute diarrhea is responsible for 20% and 10% of physician referrals, respectively, in addition to resources required for nurse and pharmacist consultations, and searching for internet-based health information.

A new product class, termed “mucoprotectors”, has been developed for use in combination with ORS in the treatment of gastroenteric disorders [3, 4]. Mucoprotectors, including gelatin tannate, form a bio-protective film on the intestinal mucosa, improving the resistance of the mucosa to pathologic aggression, and helping to restore normal function [3, 4]. In this article, we provide an up-to-date narrative review of the pharmacological profile of gelatin tannate, describing its unique, selective intestinal mucoprotectant mechanism of action, as well as providing an overview of clinical efficacy and safety data for gelatin tannate in children with AGE.

## METHODS

We conducted a medical literature review using the PubMed database, analyzing all gelatin tannate preclinical research and clinical reports, and post-marketing surveillance data.

## PHARMACOLOGY

Gelatin tannate is a selective locally-acting biofilm-forming, non-absorbable, safe and effective gut mucoprotectant [5]. It is composed of tannic acid and gelatin collagen, forming a stable complex which reaches the intestinal intact where it acts after being ingested as a powder. At gastric pH, gelatin tannate is insoluble. Gelatin tannate acts topically, forming a biofilm, *via* an intestinal mucosal protectant mechanism which potentiates the gut barrier function and contributes to re-establishing normal homeostatic gut physiology.

The selective mechanism of action of gelatin tannate in the gut mucosa results from the topical formation of physical non-covalent links with mucin, resulting in the formation of a mucoprotec-

tant biofilm which acts as a defense against intestinal secretions and enteropathogenic gut bacteria.

There are scientific data showing that the selective intestinal mucosal protective action of gelatin tannate impedes bacterial adhesion and proliferation in the gut epithelium. In cases of gut bacterial infection and/or inflammatory conditions, tight junctions may become permeable; by covering the tight junctions, gelatin tannate also prevents gut bacterial translocation.

*In vitro* studies show that gelatin tannate acts as well as a biological membrane protectant in the presence of corrosive substances. As a result of their astringent properties, tannins can precipitate pro-inflammatory mucoproteins from the intestinal mucus and aid in their fecal elimination. Gelatin tannate has been defined as one of the most novel and promising gut barrier modulator agents with mucosal protective activity [6].

In an *in vitro* study, Frasca *et al*., showed that gelatin tannate reduced the lipopolysaccharide (LPS)-induced inflammatory response in human intestinal cells, assigning the anti-inflammatory effect to the action of tannic acid (according to the state-of-the-art at that time) [7]. In a subsequent *in vivo* study, it was shown that the mechanistic effect of tannic acid is minor. The mode of action is strictly physical/mechanical, a mucoprotectant action by the undissociated gelatin tannate complex, forming a biofilm that prevents infectious agents and toxins from stimulating the immune system and the onset of inflammatory reactions [8].

*In vivo*, gelatin tannate acts not only as an intestinal mucoprotectant against microbiological agents but also as an anatomical and functional modulator for the intestinal barrier [6]. It has also been reported that gelatin tannate potentiates the intestinal barrier in re-establishing homeostasis, recovering mucosal permeability and modulating the composition of the gut microbiota [9].

According to Bueno *et al.*, gelatin tannate forms a mechanical mucoprotectant biofilm which prevents the *in vitro* leakiness of the tight junctions and bacterial-related mucosal gut inflammation. The combination is also preventive against *in vivo* insult by *Escherichia coli* LPS [8].

## CLINICAL FINDINGS

Clinical trials conducted in children show that gelatin tannate is effective and safe in pediatric patients as a complement to (or in combination with) ORS in unspecific AGE.

In a comparative study performed by Esteban Carretero *et al.*, two cohorts of children (aged 3 months to 12 years) with acute diarrhea were evaluated: ORS-only group (mean age 2.3 years; 114 patients analyzed), and ORS + gelatin tannate (mean age 2.6 years; 97 patients) [5]. Acute diarrhea was defined as ≥3 liquid stools per day and with a duration of less than 72 hours. The main clinical outcome variables were the number of stools (absolute number from baseline to 12 hours, and as the stool decrease index [SDI]). Secondary clinical variables included weight, fever, vomiting, stool characteristics, and signs of peritonitis/sepsis. The study reported SDI values of 18% and 60% in the ORS and ORS + gelatin tannate groups, respectively. At 12 hours, the combination of gelatin tannate and ORS resulted in a clinically and statistically significant reduction in the number of bowel movements (Fig. **1**) and an increase in stool consistency (Fig. **2**), compared with the ORS-only group [5]. The authors of the study concluded that the treatment of acute diarrhea with ORS + gelatin tannate complies with the Edelman criteria for the ideal antidiarrheal agent: it is effective, safe and has an early onset of action.

From a pharmacoeconomic perspective, the combination of ORS and gelatin tannate is cost effective, allowing for a reduction in the total administered dose of ORS [10]; this provides an advantage in counteracting or diminishing the disruption to the family's QoL (*e.g*. work absenteeism, parental anxiety) that can frequently be associated with acute diarrhea in children.

Durban Reguera *et al*., conducted a prospective, multicenter, observational study in infants and children with acute diarrhea treated with gelatin tannate [11]. Primary study endpoints were the number and characteristics of bowel movements, patient weight, and symptoms such as fever and vomiting. A total of 97 patients with three or more watery stools per day were included in the study. Children were excluded from the study if they had chronic diarrhea or were immunosuppressed and/or taking antidiarrheal agents or antibiotics. After 12 hours of treatment with ORS + gelatin tannate, the main variables improved markedly from baseline: the proportion of patients with ≥4 bowel movements decreased from 98.9% at baseline to 7.9% ($p<0.0005$); the mean number of

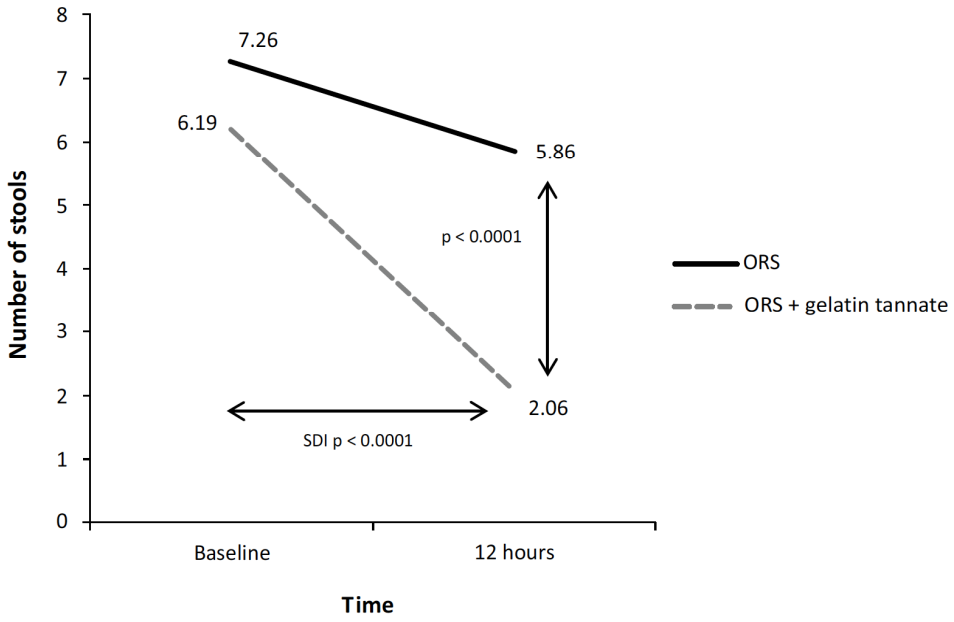


**Fig. (1).** Number of stools between the groups at baseline and after 12 hours in a comparative study in pediatric patients with acute diarrhea [5]. Patients received oral rehydration solution (ORS) or ORS + gelatin tannate. **SDI**: stool decrease index.

stools was reduced from 5.72 to 2.1; stool consistency progressed from watery in 97.9% of cases at baseline to 28.3%; vomiting was reduced from 72.6% of cases at baseline to 35% ($p<0.0005$); weight gain was 300g [11].

An open-label, non-randomized, non-controlled pilot study evaluated the efficacy and safety of gelatin tannate in 19 children presenting with AGE [12]. To be included in the study, children had to be diagnosed with ≥3 watery stools in the prior 24 hours and a score of >20 mm using a visual analog scale (0−100 mm). Children receiving ongoing treatment with antidiarrheal agents were excluded. Patients received a 250 mg sachet of gelatin tannate six times daily for 2 days. Investigators assessed the reduction in the frequency of diarrheal stools and abdominal pain relief. Safety was evaluated by recording adverse reactions. Treatment was safe, with no side effects being reported. Clinical response was statistically significant for both efficacy outcomes at 48 hours (daily frequency of diarrheal stools and abdominal pain) and the overall treatment response rate was 89.5% at 48 hours [12].

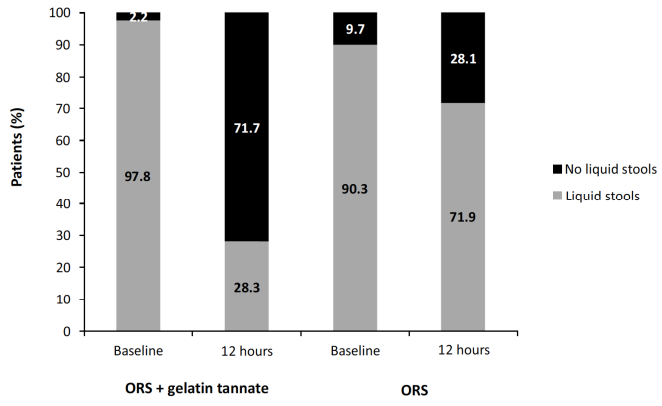


**Fig. (2).** Improvements in stool consistency at baseline and after 12 hours in pediatric patients with acute diarrhea who received oral rehydration solution (ORS) or ORS + gelatin tannate [5].

The use of adjuvant gelatin tannate has also been reported in a case report of a female baby (aged 4 months) with AGE [13]. Despite a 2-day history of severe watery diarrhea, fever and dehydration, the patient was otherwise healthy. Her weight 2 weeks before admission was 4,390g. On physical examination the patient was conscious but irritable, with an overall ill aspect. Her vital signs were: temperature 39.9ºC, heart rate 170-190 beats/min, respiratory rate 40-80 breaths/min, blood pressure 102/55 mmHg and oxygen saturation (pulse oximetry) 100%. Moreover, the patient lost 10% of her previously reported weight and presented signs of dehydration, including decreased urine output. A routine stool specimen tested positive for rotavirus antigen. Intravenous and oral fluid therapy was initiated as soon as the patient was hospitalized. Due to diarrhea-related liquid loss, metabolic acidosis persisted during the first 48 hours. However, the baby had digestive tolerance which allowed enteral nutrition. On day

3 after being admitted to hospital (5 days after the onset of diarrhea), adjuvant treatment with gelatin tannate (one sachet every 6 hours) was initiated. The patient responded to treatment with a marked decrease in stool output and a subsequent improvement in metabolic acidosis. In the first 24 hours after starting gelatin tannate, a reduction in the total number of daily stools was observed (from 10 watery stools/day to 4 at 12 hours and 3 at 24 hours). Diarrhea diminished progressively and, after 3 days of gelatin tannate administration, diarrhea was practically resolved (only three stools of near-normal consistency). The authors concluded that, although AGE is usually self-limiting, some antidiarrheal agents, including gelatin tannate, are useful for treating more severe cases in infants and children when symptoms such as severe diarrhea, vomiting or fever can aggravate dehydration [13].

Aloi *et al*., presented an abstract of a prospective, randomized, open, parallel study which included 60 AGE patients aged from 3 to 36 months (mean: 21.9±12.3 months): 29 patients received ORS, 31 patients received ORS plus gelatin tannate (ORS+GT) [14]. The primary outcome measure was the number of bowel movements 48 and 72 hours after initiating treatment. Secondary outcomes were the duration of diarrhea (days), stool characteristics, and adverse events.

At 48 hours, ORS+GT-treated patients showed a significant improvement in stool consistency compared with those in the ORS-only group ($p=0.02$). At 72 hours, a significant reduction in the number of bowel movements was reported in the ORS+GT group compared with the ORS-only group (1.07±1.3 vs. 2.05±1.7; $p=0.01$). Tolerability was good in both treatment groups. The authors concluded that, when used as adjuvant therapy to ORS in infants and children with AGE, gelatin tannate was associated with a significant reduction in the number of stools at 72 hours, with an early improvement in stool consistency [14].

Data from the latest gelatin tannate post-marketing surveillance report (1 January 2014 to 31 December 2014) show that only three mild adverse events have been reported in children. Gelatin tannate is currently marketed in 45 countries, and the total number of administered doses (at the time of the report) was 30,363,676 [15]. According to the gelatin tannate Summary of Product Characteristics, a number of infrequent adverse reactions are listed, including constipation, abdominal pain, allergic reactions and intestinal obstruction [16].

The importance of mucoprotectants in the management of diarrhea is growing. In a recently published review article, mucosal protectants are included as future agents in the management of diarrhea [3]. Although current clinical data with gelatin tannate remain somewhat limited [4], clinical trials are ongoing and our experience with using it continues to expand. For example, an ongoing randomized, double-blind, placebo-controlled clinical trial is evaluating the efficacy and safety of gelatin tannate in acute unspecific pediatric gastroenteritis. The protocol of this clinical trial has been published recently [17, 18].

## CONCLUSIONS

Based on this narrative review of the pharmacological and clinical literature, and safety data on file from the manufacturer, we conclude that gelatin tannate is a selective locally-acting, biofilm-forming, gut mucosal protectant against the insults that usually play a role in the pathogenesis of AGE in children. Gelatin tannate is not absorbed, does not induce an inflammatory response in the gut, has a rapid onset of therapeutic action and is very safe and well-tolerated, with no related clinically-relevant adverse events reported to date. From the pharmacoeconomic perspective, gelatin tannate is cost effective, with an excellent benefit-to-risk relationship, and this has particularly positive implications in resource-poor, developing countries. From a practical point of view, one can hypothesize that, in day-to-day outpatient or ambulatory practice, gelatin tannate could be a useful adjuvant to ORS to treat AGE, selectively alleviating diarrhea. In doing so, gelatin tannate may also help to ease the emotional and financial burden which is frequently present in families with children experiencing AGE.

## CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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