

Therapeutic effectiveness of green tea leaf extract on clinical symptoms in children suffering viral gastroenteritis: A randomized clinical trial

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Abstract

The use of tea plant extract has been reported to reduce viral complications, but its role in improving viral gastritis has not been investigated. The aim of this randomized clinical trial was to evaluate the effect of green tea consumption in improving pediatric viral gastroenteritis. This clinical trial study was performed on children aged 12 to 17 years with diarrhea who were not treated within 48 hours of the onset of clinical symptoms during September 2019 to September 2020. The children were randomly assigned to a green tea leaf extract (GTE) tablet. The placebo group was considered as a control. Treatment (prescribing the tablets) was continued until a Bristol Stool Scale of 3 or 4 was obtained. Two groups were compared in terms of clinical symptoms. The complete and partial improvement was revealed in 63.2% and 31.6% respectively in the GTE group while only in 15.8% and 57.9% respectively in control group indicating a significant difference ($p < 0.001$). The increase in the number of tablets led to higher improvement rate in response to GTE prescription. The mean hospital stay in GTE and control groups was also 1.66 ± 0.63 days and 3.36 ± 0.4 days indicated shorter hospitalization in former group ($p < 0.001$). The use of GTE leads to effectively improve the diarrhea as well as to reduce the hospital stay in children suffering viral gastroenteritis.

Key Words: Green tea leaf extract; children; viral gastroenteritis; green tea.

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So far, hundreds of gastrointestinal viruses have been identified, and their number is increasing every day. Due to viral mutations, more severe complications are observable.^{1,2} Intestinal gastritis is an intestinal infection that affects millions of people each year and children with the disease show the most complications in this regard.³ The main symptoms of this disease are diarrhea, nausea, vomiting and abdominal pain.⁴ Treatment and control of acute gastritis through fluid replacement and electrolyte balance (intravenously and orally) do not have a direct effect on the virus itself.⁵ Therefore, it is necessary to find antiviral agents that directly target the virus and consequently reduce the viral titer and severity of clinical symptoms. In the last century, with the advancement of virology and the discovery of the viral cause of many diseases, the need

for research in the field of antiviral therapeutic agents increased. However, therapeutic use of drugs and synthetic chemical compounds has complex problems, including side effects, drug allergies, and development of resistant viral strains. Therefore, with the expansion of research in the field of new therapies, the application of therapeutic effects of medicinal plants has also been considered.^{6,7} Herbal medicine have long been a method of treatment for various diseases in human life,⁸ and their medicinal application has been mentioned in the manuscripts of many world scientists, especially the famous Iranian scientist Avicenna.⁹ The use of medicinal plants due to fewer side effects than chemical drugs in the treatment of many diseases, especially infectious diseases is growing. Plants usually have antimicrobial properties due to the phenolic compounds,

saponins and flavonoids in their structure. These substances affect the permeability of the cytoplasmic membrane and its structural enzymes. Green tea leaves also contain compounds such as catechins, thiamine and caffeine that can play an effective role in creating the antimicrobial properties of this plant.¹⁰ In one study, the effect of green tea leaf extract (GTE) on inhibiting the growth of pathogenic bacteria isolated from farm animals and improving the balance of intestinal microflora and its effects in preventing gastrointestinal and respiratory diseases in calves were investigated. GTE has moderate to extensive inhibitory effects on the growth of pathogenic bacteria, including 7 strains of *Staphylococcus spp*, 7 strains of *Streptococcus*, one strain of *Corynebacterium*, 19 strains of *Escherichia coli* and 26 strains of *Salmonella*,¹¹ however its effect on human models remains unclear. However, when a disease is caused by virus, antibiotics have no effect on viral gastroenteritis.

Evaluation of the properties of green tea plant extract is justified to determine if it could be effective in treating and improving the complications of viral gastritis in children. Thus, this study was performed to determine effect of GTE in improving symptoms of pediatric viral gastroenteritis.

Materials and Methods

Study design

This study was performed as a randomized clinical trial in which a group of patients suffering with diarrhea and which had not been treated within 48 hours of the clinical appearance and thus were admitted to Ali Asghar Hospital in Tehran, Iran in 2019-2020 were included in the study. Patients were diagnosed based on the results of complete blood count and stool exam.

Ethical statement

In this study, codes of ethics were obtained and protocols were approved by the ethics committee at Iran University of Medical Sciences (IR.IUMS.FMD. REC.1397.292). The parents of children gave written

informed consent before study intervention.

Inclusion and Exclusion criteria

Inclusion criteria included Children with age 2-17 years and receiving irrigation solutions 48 hour before intervention.

Children with a history of chronic hypertension, drug abuse, overt or gestational diabetes, history of underlying disease, kidney disease, seizure, prior significant illness and vitamin deficiency were excluded.

Randomization and execution of research

Using random number tables, the patients were assigned into two groups 1) receiving GTE tablet (Dineh Co., Iran) on the first day of the week and irrigation solutions in other days of the week (GTE group); and 2) receiving only irrigation solutions on all days of the week (Control group). Treatment (prescribing the tablets) was continued until a score of 3 or 4 was obtained and thus no limitation was considered to prescribe the number of GTE tablets till achievement of improvement. To assess the effects of interventions on improving viral gastroenteritis, Bristol Stool Scale was used in each time the baby defecation. Acute diarrhea was defined as the occurrence of ≥ 3 stools per day graded as 6 or 7 on the Bristol Stool Scale during a period shorter than 72 hours. The diagnosis was made according to the investigators' judgment based on the clinical picture including objective (stools, vomiting, and fever) and subjective (nausea, abdominal pain, and bloating) symptoms. The study endpoint was to assess the response rate to interventions based on the change in Bristol Stool Scale and also the length of hospital stay.

Statistical analysis

For the statistical analysis, the statistical software SPSS version 25.0 for windows (IBM, Armonk, New York) was used and results were presented as mean \pm standard deviation (SD) for quantitative variables and were summarized by frequency (percentage) for categorical variables. Continuous variables were compared using t

Table 1. Baseline characteristics in intervention and control groups

Item	GTE group (n = 57)	Control group (n = 57)	p value
Age (year)	4.49 \pm 2.88	4.35 \pm 1.50	0.70
Gender	Male	26 (45.6)	0.65
	Female	31 (54.4)	
Weight(kg)	25.20 \pm 11.53	10.24 \pm 27.25	0.45
Digestive problems	Nausea	35 (60.5)	0.13
	Vomit	22 (39.5)	

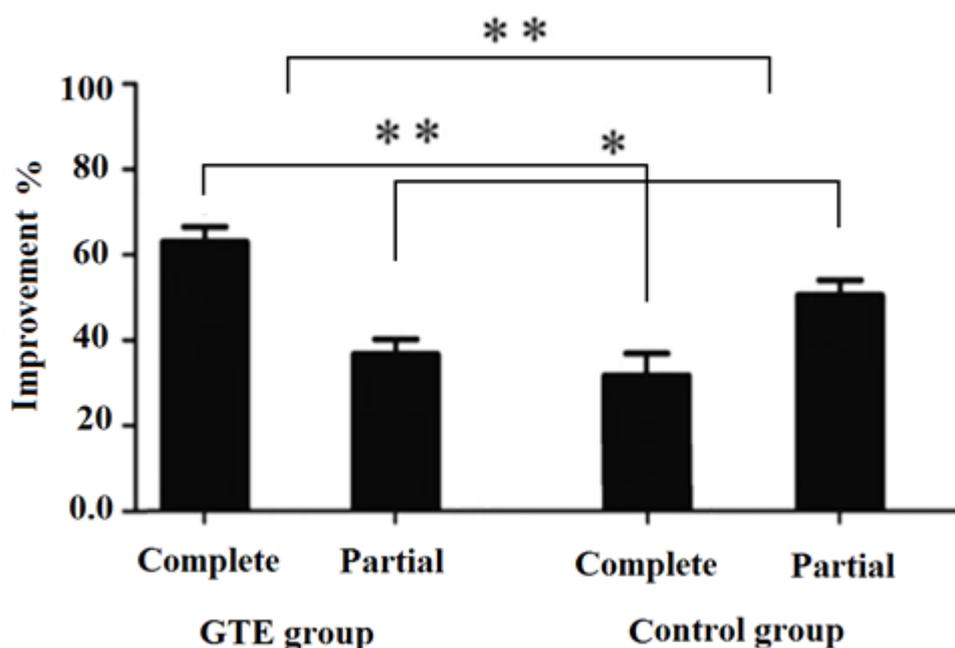


Fig 1. Green tea leaf extract (GTE) improve diarrhea in children: Error bars represent mean±SD, and the symbols * and ** indicate differences from their respective controls at $p < 0.05$, $p < 0.001$ respectively.

test or Mann-Whitney test whenever the data did not appear to have normal distribution or when the assumption of equal variances was violated across the study groups. Categorical variables were, on the other hand, compared using chi-square test. P values of ≤ 0.05 were considered statistically significant.

Results

A total of 114 consecutive patients suffering diarrhea due to viral gastroenteritis were included in the study.⁵⁻⁷ of them received the GTE tablets as the interventional group, while the other 57 did not received the tablets (Control group). The mean age of children was 4.41 ± 2.38 .

Two groups were similar in terms of demographic factors ($p > 0.05$) (Table 1).

Figure 1 show that the rate of improvement of diarrhea, complete or partial improvement were 63.2% and 31.6% respectively in the GTE group, while only 15.8% and 57.9% respectively in the control group with a significant difference ($p < 0.001$).

In the group receiving GTE tablet, 27 patients received the tablet once a week, 29 received the tablet two days a week and 1 received it three days a week. As shown in Table 2, the increase in the number of tablets led to higher improvement rate in response to GTE prescription. The mean hospital stay in GTE and control groups was also 1.66 ± 0.63 days and 3.36 ± 0.4 days indicated shorter hospitalization in the former group ($p < 0.001$).

Discussion

The aim of this clinical trial study was to evaluate the effect of green tea consumption in improving pediatric viral gastroenteritis. Our study shows that not only the use of green tea could result in improvement in clinical symptom, but also led to reduce the hospitalization. It was also found that increasing the number of GTE tablets, the improvement rate significantly increased. Previous studies have shown the dramatic effect of green tea on dangerous viral diseases.^{12,13}. Recent

Table 2. The improvement in diarrhea according to the number of GTE tablets

Improvement	1 GTE tab (n = 27)	2 GTE tabs (n = 29)	3 GTE tabs (n = 1)	p value
Complete improvement	11 (40.7)	24 (82.8)	1 (100)	0.001
Partial improvement	13 (48.1)	5 (17.2)	0 (0.0)	
No improvement	3 (11.2)	0 (0.0)	0 (0.0)	

studies have shown that epigallocatechin-3-gallate (EGCG) in green tea has antiviral effects. Studies by Liu et al.,¹² on the effect of green tea extract in patients with Covid-19 virus have concluded that green tea beverage (GTB) or its main ingredient, epigallocatechin gallate (EGCG), inhibits SARS-CoV- infection. In addition, this drink has antiviral properties in mutated viruses as well as the old species. They stated that among the four beverages with different doses of green tea, pure EGCG had the strongest performance against viruses. The highest inhibitory activity was observed when viruses or cells were pre-incubated with EGCG prior to infection. Their molecular analysis showed that EGCG blocks infection at the entry stage by interfering with the involvement of the receptor binding domain (RBD) of viral spikes to the receptor angiotensin-converting enzyme 2 (ACE2) host cell.¹² Other findings have shown that the tea extract is effective against influenza virus.¹⁴ Jang et al., 2020 found that green tea extract with the composition of EGCG polyphenols inhibits the protease enzyme in Covid-19, which prevents the virus from entering the human cell.¹⁵ The findings of Randazzo et al. (2020) were aimed at investigating the effect of green tea extract on intestinal viruses and its use as a natural disinfectant. During their study, they observed the antiviral effect of green tea extract on the gastritis virus (norovirus). They stated that GTE is a natural disinfectant, able to inhibit intestinal viral infections transmitted by the environment and food.¹⁶ Randazzo et al., 2020, studied the effect of green tea extract on the gastritis virus in the human intestinal enteroids model. They reported that different temperatures showed complete inhibition of human neurovirus GII.4 proliferation at different concentrations. For example, concentrations of 1.5 mg / ml for 37 ° C, 1.75 mg / ml for 21 ° C, and 2.5 mg / ml for 7 ° C.¹⁷ It is suggested that the ability of EGCG to bind to many biological molecules and to influence the activities of different enzymes and signal transduction pathways at the micromolar and nanomolar levels may be responsible, at least in part, for these effects. In this regard, specific antiviral activity of EGCG in green tea has been reported in inhibiting Epstein-Barr virus expression of viral proteins and inhibiting host factors.^{18,19} In a study by Zehtabian et al. (2020) the effect of lemongrass extract on the proliferation of acute gastroenteritis-causing rotaviruses was investigated. They showed that this extract caused membrane changes in the capsid coat of the virus and glycoproteins that have a super antiseptic role, and it disrupts the entry

of the virus by interfering with the effect of antiviral receptors on the spatial structure of these receptors. Finally, the results of this study showed the antiviral effects of lemongrass in the treatment of rotavirus diarrhea and it was found that with the positive and antiviral effect of this plant, it can be very effective as an adjunct therapy.²⁰ Weber et al., 2003 also indicated that EGCG in micromolar concentrations reduces the titer of adenovirus in two models of cell infection and inactivated purified adenoviruses.¹⁹ Colpitts et al. (2014) also showed that EGCG inhibits adenovirus binding by interacting with virion surface proteins.²¹ Rondanelli et al., 2021 have systematically shown that the substances in green tea, in addition to antimicrobial properties, can be effective in improving metabolism and nutrition,²² which indicates the effective role of green tea in human health. It can be said with confidence that in addition to increasing metabolism and antiviral properties, this extract can play an important role in human health. Despite the effect of GTE on viral gastroenteritis, more accurate molecular studies are still needed to identify better doses and conditions for GTE efficacy. Green tea extract can be effective in reducing the complications of gastritis in children. The antiviral role of EGCG in green tea extract has been proven in other studies.

It can be concluded that considering the satisfactory results of using green tea leaf extract in children with viral gastroenteritis, this plant can be considered as an effective and useful drug in the treatment of viral gastroenteritis infections.

List of acronyms

ACE2 - angiotensin-converting enzyme 2

EGCG - epigallocatechin-3-gallate

GTB - green tea beverage

GTE - green tea leaf extract

RBD - receptor binding domain

Contributions of Authors

All authors have approved the submitted and modified version of paper and agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

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Conflict of Interest

The authors declare no conflict of interest.

Ethical Publication Statements

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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