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Anti-diarrheal and thrombolytic activity of the leaf extract of *Phyla nodiflora*

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Abstract: *Phyla nodiflora* (PNF), a medicinal plant, may offer a safer, more accessible alternative to synthetic drugs with fewer side effects. This study aimed to investigate the anti-diarrheal and thrombolytic properties of PNF leaf extract using *in vivo* and *in vitro* models, respectively. The anti-diarrheal activity of PNF was evaluated in *Swiss* albino mice using a castor oil-induced diarrhea model. Mice were administered PNF orally at 300 and 600 mg/kg, with loperamide (LOP) (3 mg/kg) as the positive control and distilled water (DW) as the negative control (NC). For thrombolytic activity, an *in vitro* clot lysis assay was conducted using human blood samples. Our result demonstrated that PNF possesses significant anti-diarrheal effects in a dose-dependent manner, reducing defecation by 27.27% and 63.64% at 300 and 600 mg/kg, respectively ($p < 0.05$), compared to 72.73% inhibition by LOP. Additionally, PNF exhibited notable clot lysis activity (44.59%), surpassing the NC (8.06%) but lower than streptokinase (STK) (74.25%) ($p < 0.005$). However, PNF leaf extract shows promising anti-diarrheal and thrombolytic activities, suggesting its potential as a natural therapeutic agent. Further research is needed to clarify its mechanisms and confirm clinical effectiveness.

Keywords: Diarrhea; Loperamide; *Phyla nodiflora*; Streptokinase; Thrombotic disorders

1. Introduction

Diarrheal disease is a global burden characterized by an increase in the water content, volume, or frequency of stools, affecting normal bowel movement (Jahan et al., 2025). Diarrhea is primarily caused by an imbalance of gut microbiota (Li et al., 2021), drug-drug interaction (Moon et al., 2015), food poisoning (Cangemi, 2011), and malnutrition (Nel, 2010), resulting in dehydration and discomfort (Ghosh et al., 2025). In the poor world, diarrhea is thought to be the cause of about 1.6 million child deaths annually, which is about one out of every five child fatalities (Manetu et al., 2021). Unfortunately, the prevalence of diarrhea ranges from 8.39% to 18.21% in Southeast Asian countries (Murugesan et al., 2022). Diarrhea prevalence correlates with low socioeconomic status (Sumampouw et al., 2019), population density, education levels (Stoltzfus et al., 2014), poor drinking water, sanitation (Abu & Codjoe, 2018), and flooding (Liu et al., 2018).

Atherothrombosis is a condition where blood clots form on atherosclerotic plaques within an artery, causing blood flow restriction (Sah et al., 2025). According to WHO statistics, cardiovascular disease (CVDs) leads to 17.9 million deaths worldwide, which is 31% of all deaths. Coronary artery disease and stroke are responsible for 85% of these deaths, with over 75% of deaths occurring in Southeast Asian nations (Vagare et al., 2024). The prevalence of CVDs is linked to several key risk factors, including diabetes, obesity, smoking, poor diet, and high blood pressure (Mozaffarian et al., 2008). Thrombolysis is a medical treatment involving intravenous clot-busting drugs to dissolve blood clots, thereby improving blood flow and preventing tissue and organ damage that can lead to heart attacks and strokes (Yadav et al., 2024).

Currently available medications, such as LOP, Asim Doline, and Casokefamide, are frequently used to treat diarrhea because they inhibit μ-opioid receptors in the gastrointestinal tract, resulting in

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reduced fluid release and bowel movements (Graven-Nielsen et al., 2023). Although synthetic diarrhea medications are effective in controlling diarrhea, they have mild to severe adverse effects (Schiller, 2017). For example, taking LOP can result in toxic megacolon, Stevens-Johnson syndrome, constipation, nausea, arrhythmia, and cardiac arrest (Sahi et al., 2024). In medicinal science, thrombolytic agents like tissue plasminogen activator, urokinase, and STK are effective for treating life-threatening conditions such as myocardial infarction, pulmonary embolism, and stroke (Yadav et al., 2024). However, its application is restricted due to its possible side effects, such as hypotension (Khalid et al., 2021), serum sickness (Shrestha et al., 2024), severe allergic reaction, and limitation of administration of multiple doses during thrombolytic therapy (Yadav et al., 2024). Therefore, it is necessary to find a safe, efficient, and cost-effective option for thrombolysis and diarrheal management that minimizes adverse effects.

Natural products from plants, animals, or microbes offer effective, safe alternatives to synthetic drugs (Hasan et al., 2025). Studies on *Alocasia indica* and Bangladeshi medicinal plants revealed notable pharmacological and anthelmintic properties (Islam et al., 2013; Islam et al., 2015). Additionally, *Xylocarpus granatum* leaves exhibited strong antioxidant and antibacterial activities (Mahmud et al., 2024). Several plant extracts, like *Zingiber officinale* (Kim et al., 2024), *Cinnamomum cassia* (Park et al., 2023), *Cheilanthes tenuifolia* (Rakib et al., 2024), *Psidium guajava* (Liu et al., 2024), and *Camellia sinensis* (Sadino et al., 2024), exhibited outstanding antidiarrheal properties in clinical trials by reducing gut motility. Additionally, a number of plant extracts, such as *Curcuma longa* (Katiyar, 2018), *Zingiber officinale* (Manju & Pushpa, 2020), and *Camellia sinensis* (Hossain & Mahmood, 2014), have been shown to have thrombolytic activity in research, providing alternatives for treating thrombotic conditions by breaking up blood clots.

Phyla nodiflora (PNF) (Family: Verbenaceae), commonly known as frog fruit, mostly native to tropical and subtropical climates of the world, including America, Asia, Africa, India, and Sri Lanka (Al-Snai, 2019). According to various published papers, PNF displayed several therapeutic properties, including antibacterial (Khan, 2013), anticancer (Teoh et al., 2019), antioxidant (Liau et al., 2017), anti-inflammatory (Ahmed et al., 2004), antiproliferative (Cheong & Teoh, 2014), antidiabetic (Balamurugan & Ignacimuthu, 2011), anti-hepatotoxic (Sudha et al., 2013), and gastroprotective effects (Khalil et al., 2007). Consequently, PNF exhibits several pharmacological properties that would make it a promising drug candidate for diarrheal management and as a thrombolytic agent.

The objective of this study was to evaluate the properties of anti-diarrheal and thrombolytic activity of PNF leaf extract with possible underlying mechanisms using *in vivo* and *in vitro* models.

2. Methods and materials

2.1. In vivo study

2.1.1. Chemicals and reagents

LOP is used as a standard, which was kindly provided by Square Pharmaceutical Ltd., Bangladesh. Castor oil was purchased from a local market in Gopalganj, Bangladesh. Tween 80 and NaCl were purchased from Merck India. STK (30,000 IU) used as a standard was kindly provided by Beacon Pharmaceutical Ltd., Bangladesh.

2.1.2. Preparation of test and controls

The leaf extract of PNF was administered at dosages of 300 and 600 mg/kg body weight, following protocols established in earlier research with some modification (Rahman et al., 2021; Abdur Rahman et al., 2017). As a reference treatment, the standard drug LOP was used at a dose of 3 mg/kg (Jahan et al., 2025), while the NC group received a vehicle composed of 0.9% sodium chloride in DW with 0.5% Tween 80.

2.1.3. Experimental animals

For this study, *Swiss* albino mice (both sexes) weighing between 18 and 22 g were obtained from the animal facility at Jahangirnagar University in Savar, Bangladesh. The mice were housed in the pharmacology laboratory of Khulna University, under standardized conditions. They were given free access to food and water and kept in a controlled environment with a 12-h light/dark cycle. The study was conducted between 8.00 AM and 3.00 PM, followed by a 20-h observation period to monitor any adverse effects or signs of toxicity. The experimental protocol was reviewed and approved by the Pharmacy Discipline of Khulna University.

2.1.4. Castor oil-induced diarrheic in mice

To evaluate anti-diarrheal activity, we followed a modified version of the method described by Islam et al, (2020). In this study, 20 mice were allocated into four groups; each group contained five animals (n=5). Each group received vehicle, LOP, PNF, and combination therapy, as outlined in **Table 1**. After 30 minutes of treatment administration, diarrhea was induced in the mice by oral administration of castor oil (5 ml/mouse). The mice were then placed in enclosures lined with absorbent paper and monitored for four hours to assess diarrheal secretion. The antidiarrheal efficacy was calculated using the following formula.

$$\% \text{ of diarrheal inhibition} = \frac{C-D}{C} \times 100$$

Where C= mean number of diarrheal secretions in the NC group and D = mean number of diarrheal secretions in the standards and test groups.

Table 1. Different treatment groups and their administered doses.

Treatment Groups	Description	Dose (mg/kg)
NC (Vehicle)	Distilled water containing 0.9% NaCl and 0.5% tween 80	10 ml/kg
LOP-3	Standard: Loperamide	3 mg/kg
PNF-300	Lower dose	300 mg/kg
PNF-600	Higher dose	600 mg/kg

NC: Negative control (vehicle: 0.9% NaCl dissolved in 0.5% tween 80); LOP: Loperamide; PNF: Phyla nodiflora

2.2. In vitro study

2.2.1. Selection of test concentration and preparation of test and controls

PNF was administered at 300 and 600 mg/kg. To prepare both 300 mg/kg and 600 mg/kg doses of PNF leaf extract, 600 mg of the extract was first dissolved in 10 mL of DW to create a 600 mg/kg stock solution. From this, the 600 mg/kg dose was administered directly, while the 300 mg/kg dose was prepared by taking an equal volume of the stock solution and diluting it 1:1 with DW to achieve a final concentration of 300 mg/kg. Both solutions were freshly prepared and mixed thoroughly before administration.

2.2.2. Blood sample

We collected blood samples from physically fit human volunteers (n=3) who had no history of oral contraceptive or anticoagulant use while ensuring aseptic conditions were maintained. A volume of 0.5 ml of blood was transferred into microcentrifuge tubes that had been pre-weighed, allowing the formation of clots. The experimental protocol was reviewed and approved by the Pharmacy Discipline of Khulna University.

2.2.3. Thrombolytic activity

A total of 5 ml of venous blood was collected from each volunteer and distributed into three separate pre-weighed sterile microcentrifuge tubes (W1), designated for each concentration of the test sample or standard drug. Additionally, 0.5 ml of blood was added to a control-labeled tube for each volunteer. The tubes were then incubated at 37°C for 45 minutes. Once clot formation occurred, the remaining fluid was gently removed from each microcentrifuge tube. The weight of the clot was calculated by subtracting the weight of the empty tube (W1) from the weight of the tube with the clot (W2), i.e., (W2 - W1). The previously prepared dilutions of PNF and STK were utilized as the test samples and positive controls, respectively, while 100 µL of DW was used as the non-thrombolytic control. All tubes were re-incubated at 37°C for 90 minutes and subsequently observed for clot lysis. After incubation, the released fluid was discarded, and the tubes were weighed again (W3) to assess the weight difference (W2 - W3) following clot disruption. Finally, the percentage of clot lysis was calculated using the following formula:

Percentage of Clot lysis = [{*Lysis wt. (W2-W3)*} ÷ {*Clot wt. (W2-W1)*}] × 100

2.3. Statistical analysis

All values are presented as the mean ± standard error of the mean (SEM) from three replicates. Data were analyzed using one-way ANOVA followed by Tukey's *post hoc* test for multiple comparisons, considering a 95% confidence interval at $p < 0.05$. GraphPad Prism version 9.5 was used for the statistical analysis of the research data.

3. Results

3.1. In vivo study

In this *in vivo* study, we noticed all animals consistently induced diarrhea after administration of castor oil. A vehicle solution at a dose of 10 ml/kg was administered to the NC group, which exhibited no inhibition and served as a reference point for comparison with the LOP-3, PNF-300, and PNF-600 treatment groups. However, LOP-3 significantly ($p < 0.05$) inhibited defecation at 72.73%, outpacing all other examined animal groups. On the other hand, PNF suppressed defecation at doses of 300 and 600 mg/kg in a dose-dependent manner at 27.27% and 63.64%, respectively. All *in vivo* results are shown in **Table 2**.

3.2. In vitro study

The thrombolytic activity of PNF extract (300 µg/ml) was evaluated and compared to the NC and the positive control (STK, 30,000 IU). The NC group demonstrated minimal clot lysis (8.06%), whereas STK exhibited significantly higher clot lysis activity (74.25%) ($p < 0.05$). The PNF extract produced moderate thrombolytic activity, achieving 44.59% clot lysis, indicating statistically significant activity compared to the NC but lower than STK. Each sample was tested at a volume of 100 µl. These results suggest that PNF possesses notable clot dissolving potential. A summary of the data is presented in **Table 3**.

Table 2. % Inhibition of defecation in test and control groups.

Treatment groups	Dose	% Inhibition of defecation
NC (Vehicle)	10 mL/kg	-
LOP-3	3 mg/kg	72.73%[bc]
PNF-300	300 mg/kg	27.27%
PNF-600	600 mg/kg	63.64%[b]

Values are the mean ± SEM (standard error of the mean) (n = 5); One-way ANOVA followed by Tukey post hoc test with multiple comparison considering 95% intervals at $p < 0.05$ compared to the *NC (vehicle), [a]LOP-3; [b]PNF-300, [c]PNF-600; NC: Negative control (distilled water containing 0.9% NaCl and 0.5% tween 80); LOP: Loperamide; PNF: *Phyla nodiflora*

Table 3. Thrombolytic activity of *Phyla nodiflora* extract and streptokinase.

Treatment groups	Concentration	% Of lysis of clot
NC (Vehicle)	100 µl	8.06%
STK (30,000 IU)	100 µl	74.25%
PNF extract-300	100 µl	44.59%

Values are the mean ± SEM (standard error of the mean) (n=3); one-way ANOVA followed by Tukey post hoc test with multiple comparison considering 95% intervals at $p < 0.05$ compared to the *NC (vehicle), [a]STK: streptokinase; [b]PNF-300, *NC: Negative control (distilled water containing 0.9% NaCl and 0.5% tween 80); PNF: *Phyla nodiflora*

4. Discussion

Osmotic and secretory diarrhea are two types of diarrhea that result from an imbalance in the gastrointestinal tract's absorption and release of water and electrolytes (Kelly et al., 2018). Secretory diarrhea is caused by excessive fluid secretion in the intestinal mucosa, whereas osmotic diarrhea is produced by the osmotically ingested nonabsorbable active material in the lumen (Schiller, 1999). Although drugs like oral rehydration solution (ORS) are essential for treating diarrhea, medicinal plants provide supporting alleviation and promote healing (Njume & Goduka, 2012; Damtie, 2023). Numerous naturally occurring substances that are derived from plants, like chamomile, have shown promise in reducing diarrhea (Srivastava et al., 2010). However, shortage of awareness of the causes of diarrhea in society, especially in developing countries, leads to inadequate medical care, which worsens dehydration and promotes the risk of death (Noor & Hira, 2017).

Castor oil, which is extracted from *Ricinus communis* seeds, is used to test antidiarrheal medications in animal models (Akindele & Adeyemi, 2006). After consumption, pancreatic lipases convert castor oil into ricinoleic acid (RA) in the intestines that produces diarrhea in animals (Islam et al., 2020). RA triggers diarrhea by irritating the intestinal lining, causing inflammation, and promoting prostaglandins, which alter the intestinal mucosa's electrolyte permeability via promoting peristaltic activity in the gut. Additionally, it promotes the secretion of platelet-activating factor and endogenous prostaglandins (DE GARDE et al., 2023; Umer et al., 2013), leading to vasodilation, smooth muscle contraction, and mucous secretion (Islam et al., 2020). It also activates adenyl cyclase and NO, which enhances the levels of cyclic adenosine monophosphate (cAMP). Increased cAMP levels influence electrolyte transport by diminishing Na^+ and k^+ absorption, ultimately affecting water absorption (Rakib et al., 2024). The *in vivo* study showed that PNF at 600 mg/kg significantly suppressed defection at 63.64%, which was nearly to LOP-0.1 (72.73%), despite PNF-300 showing a lower inhibition rate. This indicates that PNF may be therapeutically effective and a promising drug candidate for the management of diarrhea due to their remarkable clinical reports, but more research is needed to explore the specific mechanism. However, the possible antidiarrheal mechanism of PNF is shown in **Fig. 1**.

STK is a thrombolytic enzyme used in managing arterial thromboembolism, acute myocardial infarction, and acute pulmonary embolism (Qureshi et al., 2014). The extent of lysis is affected by the time elapsed between symptom onset and treatment, the severity of the blockage, the thrombus's location, and the presence of a plasma proteolytic state (Rogers & Lutcher, 1990). It works by binding to plasminogen and turning it into active plasmin, which degrades fibrinogen, fibrin clots, and other plasma proteins (Sah et al., 2025). Our *in vitro* analysis revealed that the PNF extract showed significantly higher clot lysis (44.59%) than the NC but was less effective than STK (74.25%). This indicates moderate thrombolytic potential of PNF compared to STK. PNF exhibited consistent lytic action, indicating that it could offer a natural and efficient alternative treatment option, particularly in light of the high expense and illness linked to STK. Thus, more investigation is required to examine the underlying process and its potential applications as a therapeutic drug. However, the thrombolytic effect of PNF leaf extract is shown in **Fig. 1**.

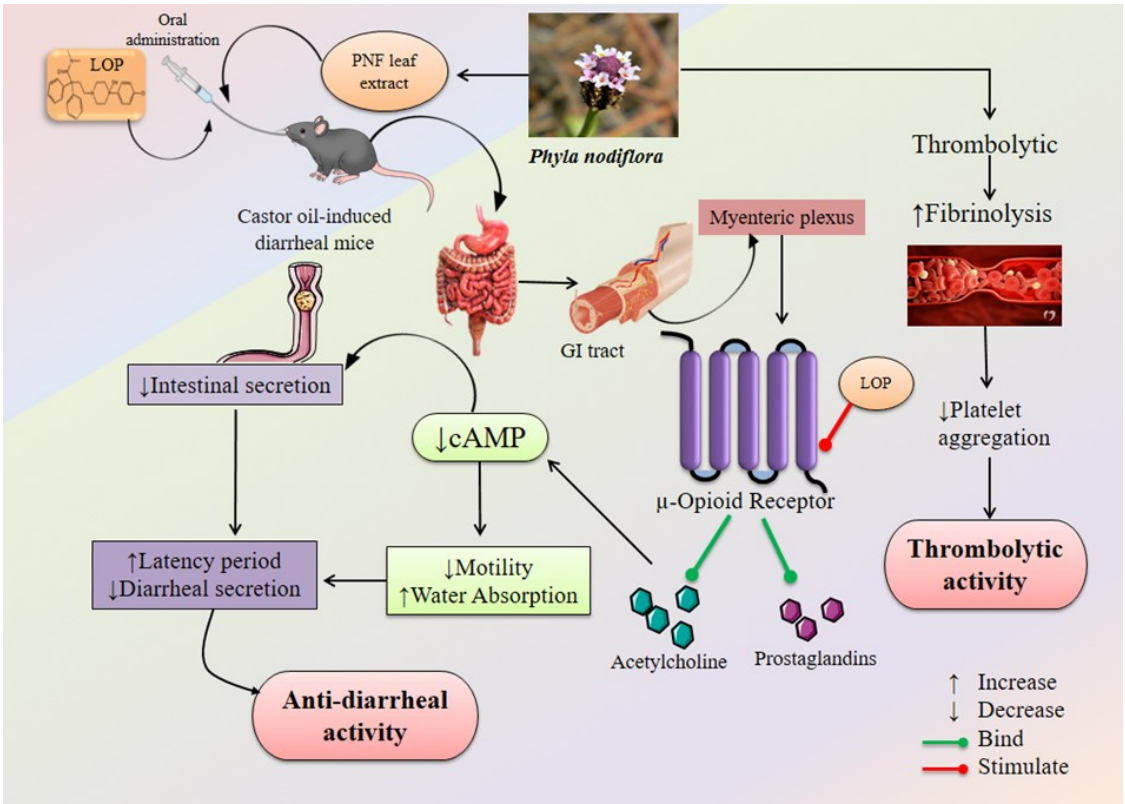

Fig. 1. The possible anti-diarrheal and thrombolytic effects mechanism of *Phyla nodiflora* leaf extract. [The figure depicts the anti-diarrheal and thrombolytic effects of *Phyla nodiflora* (PNF) leaf extract. When orally administered to castor oil-induced diarrheal mice, the extract reduces intestinal secretion and cAMP levels, increasing water absorption and decreasing motility. This action leads to increased latency and reduced diarrheal secretion, indicating anti-diarrheal activity. The mechanism involves μ-opioid receptor binding, which inhibits acetylcholine and prostaglandin activity. Additionally, PNF exhibits thrombolytic effects by promoting fibrinolysis and reducing platelet aggregation. Together, these actions contribute to both anti-diarrheal and thrombolytic therapeutic potential].

Overall, *in vitro* and *in vivo* results hint at several possible outcomes. Initially, *in vivo* research shows that PNF inhibits diarrheal secretion in a dose-dependent manner. Secondly, PNF displayed reliable thrombolytic action in an *in vitro* study. This study's anti-diarrheal evaluation was limited by a small sample size, short observation period, and lack of detailed mechanistic or toxicological analysis, which may affect the generalizability of findings. For thrombolytic assessment, the use of a single *in vitro* dose without *in vivo* validation or identification of active compounds restricts the understanding of efficacy and potential clinical relevance. These limitations must be addressed in future studies to fully elucidate PNF's pharmacological potential and clinical applicability.

5. Conclusion

This study evaluated the anti-diarrheal and thrombolytic activities of PNF leaf extract using both *in vivo* and *in vitro* models. The extract significantly reduced diarrheal symptoms in a dose-dependent manner in castor oil-induced mice. Using an *in vitro* study, PNF demonstrated moderate but notable clot lysis activity, outperforming the NC though less potent than streptokinase. These findings suggest that PNF possesses promising therapeutic potential for managing diarrhea and thrombotic conditions. Therefore, comprehensive research encompassing phytochemical profiling, chronic toxicity evaluations, and *in vivo* thrombolytic assessments is crucial to establish the clinical relevance and safety of PNF as a potential natural therapeutic agent. Furthermore, advanced *in vitro* experiments and well-designed clinical trials are necessary to substantiate and deepen the understanding of its anti-diarrheal potential.

Conflict of interest

Authors have no conflict of interest.

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CRediT author statement

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas, that is, revising or critically reviewing the article; giving final approval of the version to be published; agreeing on the journal to which the article has been submitted; and confirming to be accountable for all aspects of the work. All authors have read and agreed to the published version of the manuscript.

Data availability

All data contain this manuscript.

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