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Research Article

Anti-Diarrhoeal Activity Of *Ceratophyllum Submersum* Linn.: Experimental Analysis And Potential Mechanisms

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ABSTRACT

Background: Diarrhoea continues to be a major health concern worldwide, especially in underdeveloped nations, resulting in illness and death. There is a growing interest in investigating the medicinal properties of traditional herbal medicines for the treatment of diarrhoea. The anti-diarrheal effects of *Ceratophyllum submersum*, a plant that grows in water with a history of usage in traditional medicine, were examined.

Objective: The purpose of this study was to assess the effectiveness of both aqueous and methanolic extracts from *Ceratophyllum submersum* in treating diarrhoea in Wistar rats, utilising castor oil as well as magnesium sulfate-induced diarrhoea models.

Methods: Entire specimens of *Ceratophyllum submersum* were gathered, verified and transformed into methanolic as well as aqueous extracts. The efficacy of these extracts in alleviating diarrhoea caused by castor oil along with magnesium sulphate was investigated in male Wistar albino rats. The rats were categorised into different groups and given different quantities of the extracts. Loperamide served as the benchmark reference. The key criteria that were measured included total number of feces, number of wet feces and percentage inhibition of defecation and diarrheic drops.

Results: Both methanolic and aqueous extracts of *Ceratophyllum submersum* significantly reduced the total and wet fecal output in both diarrhoea models compared to the control group. Higher doses (500 mg/kg) demonstrated superior anti-diarrhoeal effects, closely approaching the efficacy of the standard loperamide treatment. The methanolic extract exhibited slightly higher efficacy compared to the aqueous extract across most parameters.

Conclusion: *Ceratophyllum submersum* extracts possess significant anti-diarrhoeal properties, with the methanolic extract showing greater efficacy. These findings support the traditional use of *Ceratophyllum submersum* in managing diarrhoea and suggest its potential as a natural therapeutic agent.

KEYWORDS: *Ceratophyllum submersum*, anti-diarrhoeal activity, methanolic extract, aqueous extract, castor oil-induced diarrhoea, magnesium sulphate-induced diarrhoea, traditional medicine, Wistar rats.

INTRODUCTION

Diarrhoea is a widespread health issue that has a substantial impact on illness and death rates worldwide, especially among children under the age of five in underdeveloped nations.[1] It is characterized by frequent, loose or watery stools, leading to severe dehydration, malnutrition and in many cases, death.[2] The multifactorial etiology of diarrhoea includes infections by viruses, bacteria or parasites, malnutrition and various gastrointestinal disorders.[3] While conventional pharmacological treatments such as loperamide are effective in managing diarrhoea, they are not without side effects and are often less accessible in resource-limited settings.[4] This limitation necessitates the exploration of alternative therapies, including traditional and herbal remedies, which offer a viable solution to enhance treatment accessibility and efficacy.[5]

Ceratophyllum submersum, commonly known as hornwort, is a submerged aquatic plant prevalent in diverse freshwater ecosystems.[6] This plant has a significant historical record of being used in traditional medicine in several cultures to treat gastrointestinal issues, along with other illnesses.[7] Initial phytochemical investigations have detected the existence of bioactive substances, including flavonoids, tannins and saponins, in *Ceratophyllum submersum*.[8] These compounds are recognized for their therapeutic properties, including anti-inflammatory, antimicrobial and anti-diarrhoeal effects.[9] Despite its traditional applications and promising phytochemical profile, there is a paucity of scientific evidence supporting the anti-diarrhoeal efficacy of *Ceratophyllum submersum*. This gap underscores the need for systematic investigations to validate and potentially harness the therapeutic benefits of this plant.[10]

This study seeks to fill this void by conducting a thorough evaluation of the anti-diarrheal properties of methanolic and aqueous extracts from *Ceratophyllum submersum*. This will be accomplished by employing two well-established laboratory models.[11] These models are selected based on their capacity to replicate the pathophysiological mechanisms of diarrhoea, therefore offering a strong framework to evaluate the effectiveness of the extracts. Castor oil-induced diarrhoea is caused by the activation of intestinal movement and secretion due to ricinoleic acid. On the other hand, magnesium sulphate-induced diarrhoea mainly results from a rise in osmotic pressure in the intestines, leading to the accumulation of fluid and subsequent diarrhoea.[12] Together, these models offer a comprehensive evaluation of the anti-diarrhoeal potential of the extracts under different physiological conditions.

By comparing the effects of *Ceratophyllum submersum* extracts with those of loperamide, a widely used standard anti-diarrhoeal drug, this study offers valuable understandings into the probable of these extracts as natural therapeutic agents. Loperamide functions by slowing down gut movement and enhancing water and electrolyte absorption, thus reducing diarrhoeal symptoms.[13] If *Ceratophyllum submersum* extracts demonstrate comparable efficacy, they could serve as a complementary or alternative treatment option, particularly beneficial in regions with limited access to conventional medications. This research also aims to elucidate the underlying mechanisms by which *Ceratophyllum submersum* exerts its effects, which could further enhance the understanding and development of new herbal formulations for diarrhoea management.

The broader implications of this study are significant. With increasing interest in natural and herbal medicines, especially in the context of traditional practices and modern healthcare integration, validating the efficacy of plants like *Ceratophyllum submersum* could contribute to the diversification of therapeutic strategies for diarrhoeal diseases. This aligns with the global health agenda to improve access to safe, effective and affordable healthcare solutions. The findings from this study are anticipated to not only advance the scientific understanding of *Ceratophyllum submersum's* medicinal properties but also potentially lead to the development of new, accessible treatments for diarrhoea, thereby addressing a critical public health issue.

MATERIALS AND METHODS

Plant Material

Ceratophyllum submersum plants were collected in their entirety from the Kolhapur region of Maharashtra state and verified and confirmed by a botanist.

Preparation of Extract

Ceratophyllum submersum plants were initially gathered and thoroughly rinsed with tap water to remove any external impurities. They were then dried in a shaded area to protect their bioactive constituents. Two distinct extraction techniques were employed to isolate the bioactive components:

Soxhlet Extraction with Methanol: 55 grams of the plant powder were extracted using the Soxhlet method with methanol as a solvent. The process involved 50 cycles of continuous solvent vapor circulation, resulting in a dense slurry.

Aqueous Extraction: 100 grams of the plant powder were soaked in 1000 ml of purified water for three days with intermittent stirring. The aqueous extract was filtered to remove insoluble residues and concentrated to a dense slurry.

The extracts were processed to obtain solid forms, yielding 14.70% w/w from the methanolic extract and 17.54% w/w from the aqueous extract. The solid extracts were stored in tightly sealed, light-resistant borosilicate glass containers to maintain their stability and effectiveness.[14]

Animals Used

The study included male albino Wistar rats with a weight range of 150-200 g to assess the effectiveness of the substances in treating diarrhoea. The rats were acclimated for a period of 7 days in laboratory conditions. The subjects were given normal mouse pellets sourced through Gold Mohur Food and Feeds Ltd., located in Vikhroli East, Mumbai. Additionally, they were provided unrestricted access to water.

The experimental techniques rigorously followed the rules specified by the Committee for the Purpose of Control and Supervision of Experiments on Animals.[15]

Pharmacological Evaluation

Anti-Diarrhoeal Activity

Castor Oil-induced Diarrhea Model

Preparation of Animal Model and Grouping:

The anti-diarrhoeal efficacy of *Ceratophyllum submersum* extracts was assessed by utilising the model in Wistar rats. Wistar rats, weighing within 150 to 200 g, were randomly assigned to six distinct groups, including six rats in each group.

Group I functioned as a disease control group and was administered 1 ml of castor oil orally. This group played a vital role in determining the initial response to castor oil-induced diarrhoea without any treatment intervention. Group II was administered a common anti-diarrheal medication, loperamide, at a dosage of 2 mg/kg of body weight, followed by 1 ml of castor oil. Loperamide is a widely recognised medicine utilised for the purpose of controlling diarrhoea. It achieves this by decreasing the movement of the intestines and enhancing the absorption of water and electrolytes. Consequently, it served as the positive control in the present study. Group III and Group IV were administered with extracts made from methanol of *Ceratophyllum submersum* at doses of 250 mg/kg and 500 mg/kg of body weight, respectively, followed by 1 ml of castor oil. Group V and Group VI were administered with aqueous extracts of *Ceratophyllum submersum* at doses of 250 and 500 mg/kg of body weight, respectively, followed by 1 ml of castor oil.

Administration of Treatments:

Prior to delivering the treatments, a 24-hour fasting period was implemented for all animals to establish consistent starting circumstances among all groups and to increase the effectiveness of inducing diarrhoea using castor oil. Following a duration of 1 hour of treatment, all groups with the exception of Group I were administered castor oil orally at a dosage of 1 ml. Castor oil is known to induce diarrhoea primarily through the action of ricinoleic acid, which stimulates intestinal motility and secretion. This step was critical in inducing diarrhoeal symptoms in the rats, thereby allowing the assessment of the anti-diarrhoeal efficacy of the extracts.

Monitoring and Data Collection:

The rats were confined to separate enclosures equipped with sheets of plastic at the bottom and were monitored for a maximum duration of 6 hours and several parameters were evaluated. These included the total number of faeces, the total number of wet faeces and the percentage of protection provided. The diarrhoea score was assessed according to the consistency of the stool: 1 for regular stool, 2 for partially solid stool, and 3 for liquid stool. The percentage of protection against diarrhoea was assessed using the diarrhoea score obtained. To further assess the anti-diarrhoeal efficacy of the extracts, the percentage of protection was calculated for each treatment group. The protection percentage was determined using the formula:

$$\% \text{ Protection of diarrhoea} = \frac{(\text{Diarrhoea score}_{\text{control group}} - \text{Diarrhoea score}_{\text{test group}}) \times 100}{\text{Diarrhoea score}_{\text{control group}}}$$

This calculation compared the reduction in fecal output in the treated groups relative to the disease control group, providing a clear measure of the extent to which each treatment alleviated diarrhoeal symptoms.[16, 17 & 18]

Magnesium Sulphate Induced Diarrhoea Model

Preparation of Animal Models and Grouping:

The anti-diarrhoeal efficacy of *Ceratophyllum submersum* extracts was evaluated utilising a magnesium sulphate-induced diarrhoea model using Wistar rats. This model involved a total of 36 healthy Wistar rats, each weighing between 150 to 200 g. These rats were randomly assigned to six groups, each consisting of six rats, to ensure consistency and reliability in the experimental outcomes.

Group I served as the disease control group and administered with 2 g/kg of magnesium sulphate orally. This group was essential to establish the baseline diarrhoeal response induced by magnesium sulphate without any treatment intervention. Group II received loperamide at a dose of 2 mg/kg body weight, followed by 2 g/kg of magnesium sulphate. Loperamide, known for its effectiveness in reducing diarrhoea by slowing intestinal motility and enhancing fluid absorption, served as the positive control in this experiment. Group III and Group IV were administered with extracts made from methanol of *Ceratophyllum submersum* at doses of 250 mg/kg and 500 mg/kg of body weight, respectively, followed by 2 g/kg of magnesium sulphate. Group V and Group VI were administered with aqueous extracts of *Ceratophyllum submersum* with doses of 250 mg/kg and 500 mg/kg of body weight, respectively, after which they received 2 g/kg of magnesium sulphate. These dosing levels were based on acute oral toxicity study, aimed at evaluating the anti-diarrhoeal potential of both lower and higher doses of the extracts.

Administration of Treatments:

Prior to the administration of treatments, the animals were fasted. Each rat in the standard and test groups (Groups II to VI) received the specified treatments (loperamide or *Ceratophyllum submersum* extracts) orally. This administration was conducted 1 hour before the induction of diarrhoea by magnesium sulphate to ensure the absorption of the treatments and their availability in the system before the diarrhoeal challenge. The respective doses of the methanolic and aqueous extracts, as well as loperamide, were administered. After the 1-hour pre-treatment period, each rat, except those in Group I, received 2 g/kg of magnesium sulphate orally. Magnesium sulphate induces diarrhoea by increasing the osmotic load in the intestine, which leads to increased water retention and intestinal motility, effectively simulating the symptoms of diarrhoea.

Monitoring and Data Collection:
The total fecal output and the number of wet fecal pellets were recorded over a 6-hour observation period. Fecal consistency was evaluated and scored based on a predetermined scoring system: a score of 1 was assigned for formed stools (indicative of normal bowel movement), a score of 2 for semi-formed stools (indicative of mild diarrhoea) and a score of 3 for liquid stools (indicative of severe diarrhoea). This scoring provided a quantitative assessment of the diarrhoeal response in each group.

To further quantify the anti-diarrhoeal efficacy of the treatments, the protection percentage was calculated using the formula:

$$\% \text{ Protection of diarrhoea} = \frac{(\text{Diarrhoea score}_{\text{control group}} - \text{Diarrhoea score}_{\text{test group}}) \times 100}{\text{Diarrhoea score}_{\text{control group}}}$$

This formula allowed for a comparative analysis of the reduction in fecal output between the treated groups and the control group, providing a measure of the protective effect of the treatments against diarrhoea.[19, 20, 21 & 22]

RESULTS

Results of Anti-Diarrhoeal Activity

Castor Oil-Induced Diarrhoea

The effects of *Ceratophyllum submersum* extracts on castor oil induced diarrhoea are summarized in Table 1.

Table 1. Effect of *Ceratophyllum submersum* on Castor Oil Induced Diarrhoea

Parameters	Negative Control	Standard	MECS250	MECS500	AECS250	AECS500
Total No. of Faeces	19.95 ± 1.004	4.56 ± 0.414**	12.54 ± 1.319**	9.88 ± 0.907**	11.60 ± 0.795**	10.26 ± 0.883**
No. of Wet Faeces	16.75 ± 0.768	2.66 ± 0.373**	10.83 ± 0.705**	8.04 ± 0.832**	8.55 ± 0.641**	8.16 ± 0.854**
Percentage Inhibition of Defecation	-	77.14	37.14	50.47	41.85	48.57
Percentage Inhibition of Diarrhoeic Drops	-	84.12	35.34	52	48.96	51.28

The data is displayed as the mean ± standard error of the mean (SEM), using a sample size of 6 in every group. **p-values below 0.01 were deemed highly statistically significant in comparison to the control group. The comparisons were conducted using a one-way analysis of variance (ANOVA) complemented by Dunnett's test.

The table 1 outlines the impact of *Ceratophyllum submersum* (CS) on castor oil-induced diarrhea, measuring parameters like total number of feces, number of wet feces and percentage inhibition of defecation and diarrheic drops. Upon analysis, several significant findings emerge regarding the potential efficacy of CS extracts in mitigating castor oil-induced diarrhea.
In the context of total feces, the negative control group exhibits the highest count, indicating robust induction of diarrhea by castor oil. However, treatment groups administered with CS extracts, including MECS250, MECS500, AECS250 and AECS500, display reduced total feces output compared to the negative control. Notably, the standard treatment group demonstrates the most substantial reduction, suggesting the efficacy of established treatments in alleviating diarrhea symptoms.
Similarly, the number of wet feces, serving as a proxy for the severity of diarrhea, follows a similar trend. The negative control group shows the highest count of wet feces, while treatment groups exhibit significant reductions, indicating the ability of CS extracts to mitigate the severity of diarrhea induced by castor oil.

Further, the percentage inhibition metrics shed light on the comparative efficacy of CS extracts in inhibiting diarrhea. The standard treatment group displays the highest percentage inhibition of both defecation and diarrheic drops, highlighting its superior efficacy in mitigating diarrhea symptoms. However, all treatment groups with CS extracts also demonstrate significant inhibition compared to the negative control, underscoring the potential therapeutic benefit of CS in managing diarrhea.

In conclusion, the findings suggest that *Ceratophyllum submersum* extracts possess notable efficacy in attenuating castor oil-induced diarrhea. The observed reductions in total feces output, wet feces count and percentage inhibition of diarrhea symptoms underscore the potential of CS extracts as a therapeutic intervention for gastrointestinal disorders associated with diarrhea.

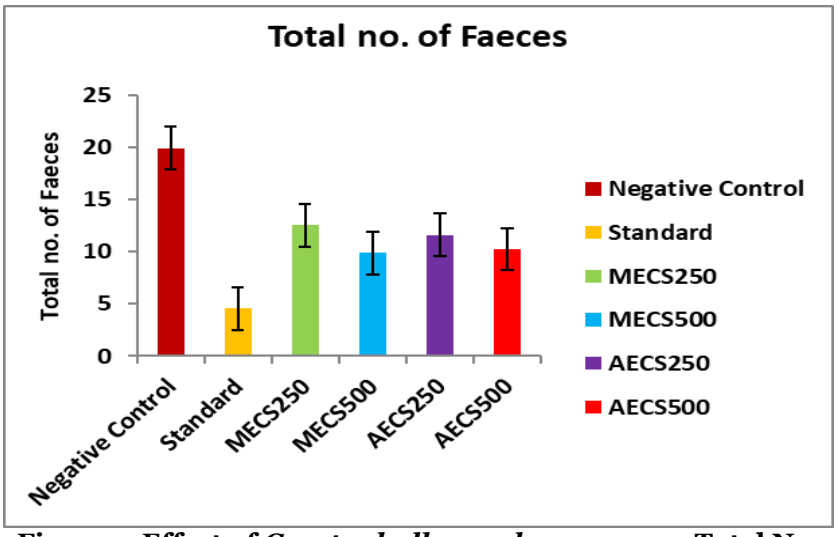

Figure 1. Effect of *Ceratophyllum submersum* on Total No. of Faeces in Castor Oil Induced Diarrhoea

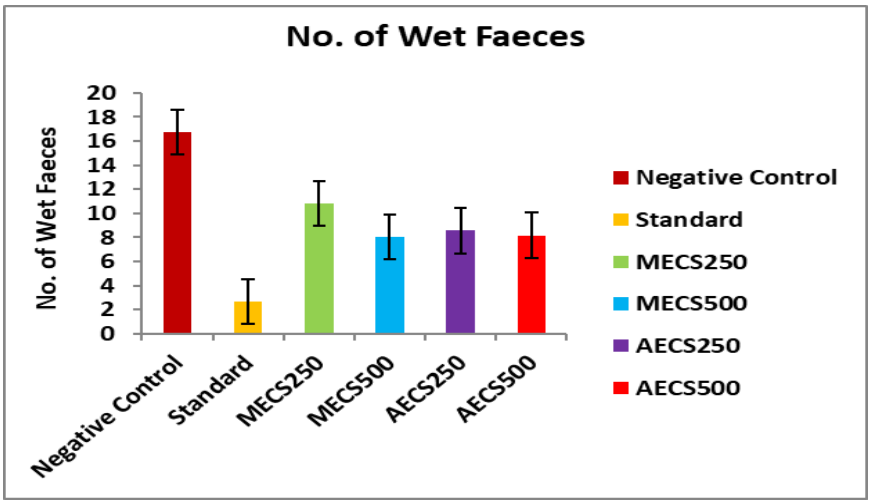

Figure 2. Effect of *Ceratophyllum submersum* on Number of Wet Faeces in Castor Oil Induced Diarrhoea

Magnesium Sulphate-Induced Diarrhoea

The effects of *Ceratophyllum submersum* extracts on magnesium sulphate-induced diarrhoea are summarized in Table 2.

Table 2. Effect of *Ceratophyllum submersum* on Magnesium Sulphate Induced Diarrhoea

Parameters	Negative Control	Standard	MECS250	MECS500	AECS250	AECS500
Total No. of Faeces	12.74 ± 0.920	4.00 ± 0.364**	9.47 ± 0.828*	7.09 ± 0.613**	9.63 ± 0.864*	7.63 ± 0.630**
No. of Wet Faeces	8.18 ± 0.878	2.00 ± 0.592**	5.26 ± 0.952*	4.72 ± 0.828**	5.27 ± 0.335*	4.36 ± 0.398**
Percentage Inhibition of Defecation	-	68.60	25.67	44.35	24.41	40.11
Percentage Inhibition of Diarrhoeic Drops	-	75.55	35.70	42.30	35.57	46.69

The data is displayed as the mean ± standard error of the mean (SEM), using a sample size of 6 in every group. *p-values below 0.05 were deemed statistically significant and **p-values below 0.01 were taken to be highly statistically significant in comparison to the control group. The comparisons were conducted using a one-way analysis of variance (ANOVA) complemented by Dunnett's test.

Table 2 outlines the effects of *Ceratophyllum submersum* (CS) on diarrhoea induced by magnesium sulfate, detailing parameters like the total number of feces, number of wet feces and percentage inhibition of defecation and diarrheic drops. Through analysis, several key findings emerge regarding the potential efficacy of CS extracts in mitigating magnesium sulfate-induced diarrhea. In terms of the total number of feces, the negative control group exposed to magnesium sulfate exhibits a notably higher count, indicating the induction of diarrhea. Conversely, both the standard treatment and various CS extract treatment groups demonstrate significant reductions in total feces output compared to the negative control, suggesting the potential of CS extracts to alleviate diarrhea induced by magnesium sulfate. Similarly, the number of wet feces, serving as an indicator of diarrhea severity, follows a similar trend. The control group displays a higher count of wet feces, while treatment groups administered with CS extracts show significant reductions, indicating the ability of CS extracts to mitigate the severity of diarrhea induced by magnesium sulfate.

Moreover, the percentage inhibition metrics shed light on the comparative efficacy of CS extracts in inhibiting diarrhea symptoms. The standard treatment group exhibits the highest percentage inhibition of both defecation and diarrheic drops, suggesting its superior efficacy in alleviating diarrhea. Notably, all CS extract treatment groups also demonstrate significant inhibition compared to the control, further highlighting the potential therapeutic benefit of CS in managing magnesium sulfate-induced diarrhea.

In conclusion, the findings suggest that *Ceratophyllum submersum* extracts possess notable efficacy in attenuating diarrhea induced by magnesium sulfate. The observed reductions in total feces output, wet feces count and percentage inhibition of diarrhea symptoms underscore the potential of CS extracts as a therapeutic intervention for gastrointestinal disorders associated with magnesium sulfate ingestion. However, further research is warranted to elucidate the underlying mechanisms of action, identify bioactive compounds and optimize treatment protocols for maximal efficacy and safety in clinical applications.

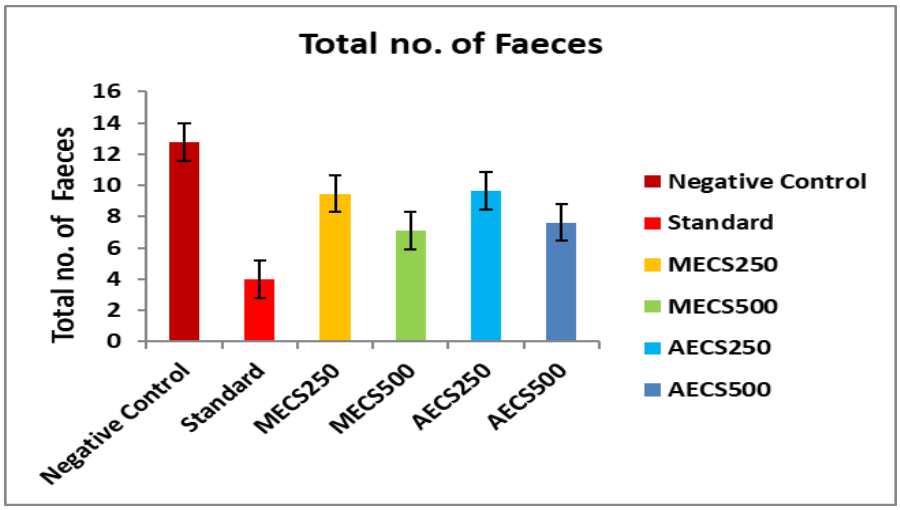

Figure 3. Effect of *Ceratophyllum submersum* on Total Number of Faeces in Magnesium Sulphate Induced Diarrhoea

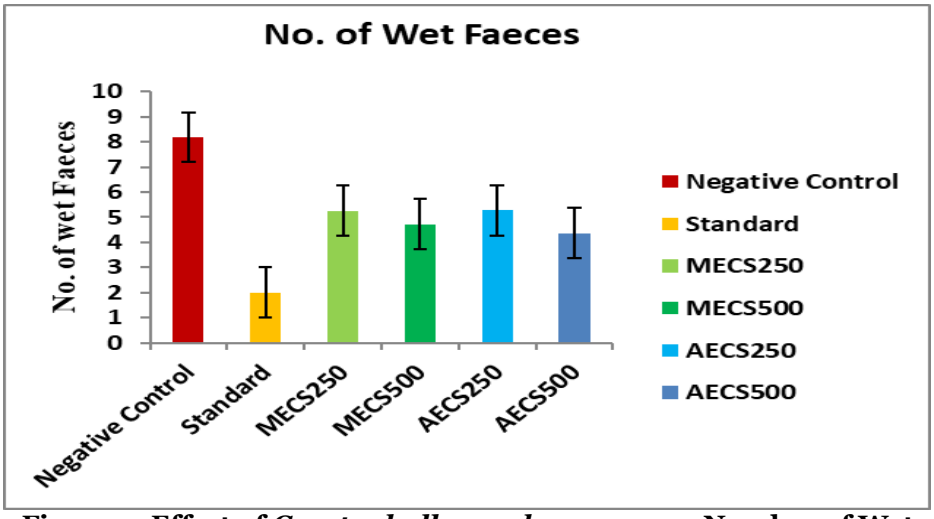

Figure 4. Effect of *Ceratophyllum submersum* on Number of Wet Faeces in Magnesium Sulphate Induced Diarrhoea

DISCUSSION

Diarrhoea, characterized by the frequent discharge of liquid feces, can be attributed to various sources including infections, toxins and psychological stress. Castor oil, rich in ricinoleic acid, induces diarrhea by activating the intestinal lining and promoting the synthesis of prostaglandins. The extracts of *Ceratophyllum submersum* have demonstrated potential as antidiarrheal medications, most likely by inhibiting the generation of prostaglandins and reducing excessive intestinal movement and overactivity. In addition, studies have shown that extracts of *Ceratophyllum submersum* have antidiarrheal characteristics in models induced by magnesium sulfate. This suggests that these extracts have the ability to enhance the absorption of electrolytes and water in the gastrointestinal system. The antidiarrheal features of these effects are attributed to the existence of bioactive components such as the tannins, flavonoids, alkaloid molecules and saponins.[23]
Magnesium sulfate is being demonstrated to induce diarrhea by enhancing the volume of intestinal contents through the inhibition of water reabsorption. Moreover, studies have demonstrated that magnesium sulfate stimulates the excretion of a substance from the duodenal lining, so enhancing secretion and peristalsis in the small intestine, consequently impeding the re-absorption of water and salts. Both the methanolic and aqueous extracts demonstrated efficacy in alleviating diarrhea induced by magnesium sulfate, while also promoting the absorption of electrolytes and water in the gastrointestinal tract.[24]
The therapeutic effects of medicinal plants in treating diarrhea and dysentery are due to a range of bioactive compounds, such as tannins, alkaloid substances, saponins, flavonoids, steroid medication and terpenoids. These chemicals are believed to be responsible for the effectiveness of *Ceratophyllum submersum* extracts in treating diarrhea in living organisms. Flavonoids are known to effectively slow down the movement of the intestines and reduce the emission of fluids and electrolytes, which helps to regulate and alleviate diarrhea. Moreover, it is thought that the presence of tannins and tannic acid in antidiarrheal plants works by altering the structure of proteins in the intestinal lining, resulting in the formation of protein tannates. These tannates make the intestinal lining more resistant to chemical changes and reduce the amount of secretion.[25]

CONCLUSION

The study undertaken reveals that *Ceratophyllum submersum* extracts exhibit significant anti-diarrhoeal activity, highlighting their potential as therapeutic agents in managing diarrhoea. Both methanolic (MECS) and aqueous (AECS) extracts demonstrated a notable capacity to reduce the number and severity of diarrhoeal episodes in castor oil and magnesium sulphate-induced models. The methanolic extract, in particular, displayed superior efficacy, suggesting a more comprehensive extraction of bioactive compounds that contribute to the anti-diarrhoeal effects. This underscores the potential of *Ceratophyllum submersum* as a valuable source of natural remedies for diarrhoeal diseases.
The anti-diarrhoeal properties observed are likely attributed to the presence of key phytochemicals such as flavonoids, tannins and saponins in the extracts. Flavonoids and tannins are known to inhibit intestinal motility and secretion, thereby reducing diarrhoea. Saponins may enhance mucosal barrier integrity, preventing excessive fluid loss. The results align with traditional uses of *Ceratophyllum submersum* in ethnomedicine, validating its historical application and providing a scientific basis for its efficacy in treating gastrointestinal disorders.

Despite the promising results, the efficacy of *Ceratophyllum submersum* extracts did not surpass that of loperamide, a standard anti-diarrhoeal drug used in the study. Loperamide exhibited a more substantial reduction in diarrhoeal symptoms across both models, highlighting its potent pharmacological action. However, the extracts still demonstrated a significant degree of inhibition, suggesting their potential as complementary or alternative treatments for individuals who may prefer or require natural therapeutic options.

Looking forward, several areas require further exploration to fully harness the therapeutic potential of *Ceratophyllum submersum*. Future research should focus on isolating and identifying the active compounds responsible for the anti-diarrhoeal effects to understand their mechanisms of action better. Additionally, dose optimization studies are necessary to determine the most effective and safe dosages for therapeutic use. Comprehensive safety and toxicity assessments will ensure that the extracts are safe for long-term use and clinical trials are essential to validate their efficacy in human subjects.

In conclusion, the study establishes *Ceratophyllum submersum* as a promising natural anti-diarrhoeal agent with significant efficacy in preclinical models. While further research is required to optimize and validate these findings, *Ceratophyllum submersum* has the potential to be developed into a valuable natural treatment for diarrhoea, contributing to the diversification of available therapeutic strategies and offering an alternative for those seeking natural remedies. This research paves the way for *Ceratophyllum submersum* to be integrated into modern medical practices, enhancing the management of diarrhoeal conditions with a focus on safety and efficacy.

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