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PRE-CLINICAL INVESTIGATION OF ANTI-DIARRHEAL POTENTIAL OF NOVEL SIDDHA FORMULATION KAADIKKARA CHENDURAM IN CASTOR OIL AND CHARCOAL MEAL INDUCED PURGATION IN WISTAR RATS

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ABSTRACT

Diarrhea is one of the most common infectious diseases caused by disturbances in secretory and absorptive functions in the intestine, resulting increase in the number (three or more times per Day), flow rate and/or volume of feces. Commonly used anti-diarrheal agents often prone to serious side effects like abdominal pain/discomfort, nausea, vomiting, dry mouth, tiredness, drowsiness, dizziness, constipation, and flatulence etc. Hence the people belief on traditional medicine towards management of diarrhea is increasing in recent times. Kaadikkara Chenduram (KKC) is novel siddha preparation traditionally indicated for the treatment of diarrhea and other gastro intestinal disorders. Still now there is no documentary evidence claiming its efficacy hence the main objective of the present study is to evaluate the anti-diarrheal potential of the formulation KKC against castor oil and charcoal meal induced purgation in wistar rats. Results of the study clearly indicates that treatment with trial drug KKC at both the dose level of 50 and 100 mg/kg has shown significant delay in the onset of defecation time to the maximum of 126 ± 3.15 mins and also offers higher percentage protection of about 52.63% in castor oil induced diarrhea. Further treatment with KKC at both the dose level of 50 and 100 mg/kg exhibit significant reduction in peristalsis index up to 43.24 % in charcoal meal induced peristalsis in rats. From the results it was concluded that the siddha drug KKC possess excellent anti-diarrheal activity and may be recommended for clinical application in patients with gastro intestinal disturbance

KEY WORDS: ***Diarrhea, Siddha drug, Kaadikkara Chenduram, Anti-diarrheal potential, Castor oil, Charcoal, Purgation***

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1. Introduction

Diarrheal disease is one of the leading causes of preventable death in developing countries, and it mainly affects children and infants [1]. According to the WHO and UNICEF reports, there are about 2.5 billion cases of diarrheal disease worldwide every year, and 1.9 million children below 5 years of age die from diarrhea each year, of whom most are from developing countries. Of all child deaths from diarrhea, 78% occur in African and Southeast Asian regions [2].

Diarrhoea remains the second leading cause of mortality among children under five years of age next to respiratory infections and kills more young children than malaria, and measles combined [3]. Diarrhoea is usually a symptom of diseases in the intestinal tract which can be caused by a variety of bacterial (Escherichia coli, Vibrio cholerae, Shigella species etc.), viral (Rota virus, Norovirus, Cytomegalovirus etc.) and parasitic organisms (protozoa and helminths) [4]. Mostly, antidiarrheal agents act by decreasing secretion and/or reducing the propulsive movement of GI smooth muscles.

Populations in socio-economic backwardness, and developing, third-world countries, especially infants and children under the age of 5 years are mainly vulnerable to diarrhea [5]. In spite of advancement in public health and economic wealth, diarrhea still remains an important clinical concern in developed countries. Traditional medicine (also known as indigenous or folk medicine) comprises knowledge that developed over generations within various societies before the era of modern medicine [6]. Historically, these treatments would cure or relieve symptoms.

It is estimated that up to 80% of the population in developing countries depend on traditional medicines for primary healthcare [7]. There are an enormous number of traditional medicines around the world that are claimed to be effective in treating diarrhea [8]. Kaadikkara Chenduram (KKC) is novel siddha preparation traditionally indicated for the treatment of diarrhea and other gastro intestinal disorders. Still now there is no documentary evidence claiming its efficacy hence the main objective of the present study is to evaluate the anti-diarrheal potential of the formulation KKC against castor oil and charcoal meal induced purgation in wistar rats

2.Materials and Methods

2.1. Experimental Animals

Healthy adult Wistar albino rats of either sex weighing between 220-240 g were used for the study. The animals were housed in poly propylene cages and were kept in well ventilated with 100% fresh air by air handling unit. A 12 light / dark cycle were maintained. Room temperature was maintained between 22 ¬+ 2o C and relative humidity 50–65%. They were provided with food and water ad libitum. All the animals were acclimatized to the laboratory for 7 days prior to the start of the study. The experimental protocol was approved by The Institutional Animal Ethics Committee of Sathyabama Institute of science and technology, Chennai, Tamil Nadu, India. The IAEC approval number: SU/CLATR/IAEC/X/096/2018.

2.2. Assessment of Anti-Diarrheal activity by Castor oil induced diarrhea [9,10]

Experimental rats were divided in to four groups of 6 animals each. The first group, which served as control was administered with normal saline. Group II rats received aqueous 1% tragacanth suspension. Group II and IV rats administered with trial drug KKC at the dose of 50 and 100 mg/kg,p.o. After 60 min of drug treatment, the animals of each group received 1ml of castor oil orally and the watery faecal material and number of defecation was noted up to 6 h in the transparent metabolic cages with filter paper at the base. The percentage protection offered by the trial drug will be calculated accordingly.

2.3. Assessment of Gastrointestinal motility by Charcoal meal test [11]

Experimental rats were divided in to three groups of 6 animals each. All the rats were starved for 16hrs prior to the start of the experiment. In which group I served as charcoal meal control was administered with aqueous 1% tragacanth suspension. The second group receives test drug KKC at the dose of 50 mg/kg,p.o. The third group receives test drug KKC at the dose of 100 mg/kg,p.o. 15 min after treatment the animals were given with 1ml of 10% activated charcoal suspended in 10% aqueous tragacanth powder p.o, Animals were euthanized 30 min after charcoal meal administration by high dose of anesthesia. The abdomen was cut off and the small intestine carefully

removed. The distance travelled by charcoal plug from pylorus to caecum was measured, and expressed as percentage of the distance traveled by charcoal plug for each of animal.

2.4. Statistical Method

The statistical analysis was carried by one-way analysis of variance ANOVA (GRAPH PAD PRISM 5 computer program). Results are expressed as ±SEM. The data were statistically analyzed by ONE WAY ANOVA followed by Dunnett's multiple comparison test. Probability P values < 0.05 were considered as significant.

3.Results

3.1. Effect of KKC on castor oil-induced diarrhea in rats

It was observed from the present investigation that onset of defecation was shortly induced in castor oil alone treated group with the mean time of 33.83 ± 2.04 mins. Treatment with trial drug KKC at both the dose level of 50 and 100 mg/kg has shown significant delay in the onset of defecation time to the maximum of 126 ± 3.15 mins. The mean number of wet fecal pellet for the Castrol oil group was 9.5 ±0.76, while in the trial drug -treated group this value was found to be 6.33 ±0.6 and 4.5± 0.34 respectively. The total frequency of defecation observed in the Castrol oil group was 12.5±0.9, when compare to that of the normal control with 2.1 ±0.16, while in the trial drug -treated group this value was found to be 7.6 ±0.71 and 6.1 ± 0.47 respectively. Percentage protection against castor oil induced purgation on KKC 50 mg/kg treated group was found to be 33.68 % whereas treatment with KKC 100 mg/kg offers higher percentage protection of about 52.63%.As shown in table 1

Table 1: Effect of KKC on castor oil-induced diarrhea in rats

Group	Onset of Defecation (min)	No of wet faeces	Number of Defecations	% Inhibition
Normal Control	66.33 ± 2.86	1.333 ± 0.33	2.167 ± 015	0.00
Castor oil - Purgative Control	33.83 ± 2.04*	9.5 ± 0.76**	12.5 ± 0.99*	0.00
Castor oil+ 50 mg/kg of KKC	105.5 ± 4.89**	6.333 ± 0.66*	7.667 ± 0.71*	33.68
Castor oil+ 100 mg/kg of KKC	126.8 ± 3.15**	4.5 ± 0.34*	6.167 ± 0.47*	52.63

Values represent mean ± SEM of 6 experimental animals. * P< 0.05; ** P< 0.01; *** P < 0.001.

3.2. Effect of KKC on Gastrointestinal transit and Peristalsis index (%) in charcoal meal induced purgation in rats

Peristalsis index (%) was measured as mean gastro intestinal motility. PI value of charcoal meal control group was found to be 79.97 %. Further treatment with KKC at both the dose level of 50 and 100 mg/kg exhibit significant reduction in peristalsis index up to 43.24 %. Based on the data's obtained from the present investigation it was concluded that the trial drug KKC exhibited significant anti – diarrheal activity on gastrointestinal transit using charcoal meal and in castor induced purgation model. As shown in table 2.

Table 2: Effect of KKC on Gastrointestinal transit and Peristalsis index (%) in charcoal meal induced purgation in rats

Group	Length of intestine (cm)	Distance travelled by charcoal (cm)	Peristalsis Index (%)
Charcoal meal control	66.33 ± 2.34	52.83 ± 3.08	79.97
Charcoal meal+ 50 mg/kg of KKC	71.67 ± 2.43*	38.5 ± 1.64*	54
Charcoal meal+ 100 mg/kg of KKC	64.33 ± 1.05*	27.83 ± 1.27*	43.24

Values represent mean ± SEM of 6 experimental animals.
* P< 0.05; ** P< 0.01; *** P < 0.001.

4.Discussion

Diarrhoea has long been recognized as one of the most important health problems in developing countries. It is defined as an increase in the frequency, fluidity, or volume of bowel movements and characterized by increased frequency of bowel sound and movement, wet stools, and abdominal pain. In clinical terms, it is used to describe increased liquidity of stools, usually associated with increased stool weight and frequency [12]. WHO has encouraged studies pertaining to the treatment and prevention of diarrheal diseases using traditional medical practices [13]. Currently available drugs are linked with adverse effects and contraindications [14,15]. Drug resistance is another challenge to think about antibiotics used in the treatment of diarrhea [16]. The high incidence of diarrhea in developing countries coupled with limitations of currently available antidiarrheal drugs and poor healthcare coverage may make traditional

medicines good alternative agents for the management of diarrhea.

Castor oil has been widely used for induction of diarrhea in antidiarrheal activity studies because it releases ricinoleic acid, a metabolite that causes diarrhea, upon metabolism in the gut [17]. Ricinoleic acid initiates diarrhea via mechanisms such as irritation of GI mucosa, leading to the release of prostaglandin which stimulates gastrointestinal motility and electrolyte secretion, reducing electrolyte absorption from the intestine and colon; these are similar to the pathophysiologic processes resulting in diarrhea [18].

It was observed from the present investigation that onset of defecation was shortly induced in castor oil alone treated group with the mean time of 33.83 ± 2.04 mins. Treatment with trial drug KKC at both the dose level of 50 and 100 mg/kg has shown significant delay in the onset of defecation time to the maximum of 126 ± 3.15 mins. The mean number of wet fecal pellet for the Castrol oil group was 9.5 ±0.76, while in the trial drug -treated group this value was found to be 6.33 ±0.6 and 4.5± 0.34 respectively. The total frequency of defecation observed in the Castrol oil group was 12.5±0.9, when compare to that of the normal control with 2.1 ±0.16, while in the trial drug -treated group this value was found to be 7.6 ±0.71 and 6.1 ± 0.47 respectively. Percentage protection against castor oil induced purgation on KKC 50 mg/kg treated group was found to be 33.68 % whereas treatment with KKC 100 mg/kg offers higher percentage protection of about 52.63%.

Gastrointestinal motility test with activated charcoal, usually known as charcoal meal test is carried out to determine the effect of test substance on peristaltic movement. Peristalsis index (%) was measured as mean gastro intestinal motility. PI value of charcoal meal control group was found to be 79.97 %. Further treatment with KKC at both the dose level of 50 and 100 mg/kg exhibit significant reduction in peristalsis index up to 43.24 %. Based on the data's obtained from the present investigation it was concluded that the trial drug KKC exhibited significant anti – diarrheal activity on gastrointestinal transit using charcoal meal and in castor induced purgation model.

5.Conclusion

Currently, the treatment for diarrhea is non-specific and is usually aimed at reducing the discomfort and inconvenience of frequent bowel movements. Conventional drugs are often used to treat diarrhea, but adverse effects can be induced by these drugs. Therefore, alternate traditional medicine grabs greater importance. In the present study the antidiarrheal activity of the formulation might be due to the presence of bioactive ingredients that oppose the actions of castor oil for induction of diarrhea. The drug KKC has been shown to decrease the intestinal peristalsis index. This suggests that the formulation may acts as excellent anti-diarrheal activity.

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