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GASTRO PROTECTIVE POTENTIAL OF SIDDHA FORMULATION MULLANGI CHOORANAM ON ASPIRIN INDUCED ULCER IN WISTAR RATS

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ABSTRACT

Peptic ulcer disease includes both gastric and duodenal ulcers which posed a major threat to the world's population over the past two centuries with a high morbidity and mortality. The evolution of knowledge regarding etiopathogenesis of peptic acid disease from acid-driven disease to an infectious disease has opened up this topic for various studies to find the best possible options for management of this disease. Clinical evaluation of synthetic drugs show that there are incidences of relapses and danger of drug interactions during ulcer therapy. Hence, the search for new and ideal antiulcer drug continues and has also been extended to herbal in search for new and novel molecules, which afford better protection and decrease the incidence of relapse. Treatments for gastric ulcers include proton pump inhibitors, which reduce the production of stomach acid. Although these inhibitors help to decrease mortality and morbidity rates, these pharmaceutical products are costly and may cause adverse effects. Traditional siddha medicine offers potential comfort in managing gastro intestinal disorders like gastric and duodenal ulcers. Hence the main aim of the present study is to evaluate the anti-ulcer potential of the siddha drug Mullangi Chooranam (MC) in aspirin ulcerated rats. Results of the study clearly indicates that ulcerative score of the rats belongs to aspirin group has shown the increased intensity and severity of the ulcer induction. There was significant decrease in the ulcerative score observed in trial drug MC treated rats at both the dose level of 200 and 400 mg/kg which reveals the anti-ulcer potential of the formulation. It was concluded from the outcome of the present investigation that traditional formulations like MC offers better therapeutic outcome in ulcer patients upon clinical usage.

KEY WORDS: ***Peptic ulcer, Siddha drug, Mullangi Chooranam, Anti-ulcer potential, Aspirin, Ulcerative score***

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1. Introduction

Gastric ulcers result from damage to the mucosal lining of the stomach due to an increase in aggressive factors such as reactive oxygen species (ROS) and gastric acid, and a decrease in protective factors such as prostaglandins and mucus [1]. The most common symptom is upper abdominal pain, which occurs at night and is relieved by food intake [2]. Gastric ulcers are very painful and lower the quality of life of those who suffer from them [3].

Peptic ulcer disease and its complications remain the cause of significant morbidity worldwide, representing a major burden for health care resources [4].Although potent anti-ulcer drugs are available, most of them produce several toxicities, thus emphasizing the need to search for new alternatives [5]. As high as 80% of the world population depends on plant-derived medicines for the first line of primary health care [6], reinforcing the theory that plant extracts can be good sources of new drug

In spite of the domination of synthetic drugs in managing most of human diseases including gastric ulcer, extensive proportion worldwide now directed to traditional medicine [7]. This may be, in part, due to considerable incidence of side effects, drug interactions, microbial resistance and high cost during chemical therapy [8]. Hence, natural products with wide biological activities, better effectiveness and safe profiles are needed to substitute chemical medications [9]. Consequently, there is extensive require for scientific analysis of herbal products with pharmacological effects to discover alternative bioactive phytocompounds [10].

Herbal medicines have been used to treat human gastric ulcer for several centuries. Several controlled clinical studies have demonstrated that herbal medicines are effective in treating human gastric ulcer .The link of oxidative stress and gastric ulcer is well recognized [11]. That some herbal medicines benefit gastric ulcer is likely due to their antioxidant properties.

The development of new anti-ulcer drugs from medicinal plants is an attractive proposition, because diverse chemical compounds with anti-ulcer activities have been isolated from these plants,[12] and they have shown to produce promising results in the treatment of gastric ulcers.[13] The bioactive molecules (generally alkaloids, glycosides, lupeols, essential oils, e.t.c) isolated from crude extracts have been used directly as therapeutic agents or as starting materials for the synthesis of useful drugs or serve as a model for pharmacologically active compounds in the process of drugs in synthesis [14].The main objective of the present investigation is to evaluate the anti-ulcer potential of the siddha formulation Mullangi Chooranam (MC) on aspirin induced gastric ulcer model in rats.

2. Materials and Methods

2.1. Experimental Animals

Healthy adult Wistar albino rats of either sex weighing between 200-220 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±2ºC 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/XIII/130/2019.

2.2. Animal grouping and Methodology [15]

The animals were grouped into four groups of 6 animals each. Group I (Control group) -received normal saline, Group II – Ulcer control rats received 200mg/kg of Aspirin, p.o for the period of 7 days (Day 1 to 7). Group III (Low dose treated group): Aspirin ulcerated rats was treated with 200mg/kg of MC,p.o for the period of 07 days 1 hr prior to the administration of aspirin. Group IV (High dose treated group): Aspirin ulcerated rats was treated with 400mg/kg of MC,p.o for the period of 07 days 1 hr prior to the administration of aspirin.

2.3. Sample Collection [16,17]

At the end of the study, before sacrifice, the animals were fasted for overnight with free access to water. Animals were sacrificed with excess anesthesia. The stomach was removed and opened along the greater curvature. The stomach was gently rinsed with water to remove the gastric contents and blood clots. The inner surface of free stomach was examined for gastric lesions. The number of ulcers was counted. Ulcer

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scoring was carried out according to the method by as given below.

The scores were:

0 = no ulcer, 1 = superficial ulcer, 2 = deep ulcer and 3 = perforation

2.3.1.Ulcer score

Ulcer index was measured by using the following formula

$$UI = U_N + U_S + U_P \times 10^{-1}$$

Where UI is the ulcer index; U_N is the average number of ulcers per animal; U_S is the average number of severity score and U_P is the percentage of animals with ulcers.

2.3.2. Percentage inhibition of ulceration

Ovaries from the experimental rats were dissected out Percentage inhibition of ulceration was calculated as follows:

$$\%\ \text{inhibition of ulceration} = \frac{\text{UI of Control} - \text{UI of Test}}{\text{UI of Control}} \times 100$$

There was a low percentage of ulcer in the study drug treated animals.

2.4. Histopathology [18]

Sample obtained from the study were immersed in 10% formalin for 24 h-48h for histopathological examination. After standard processing, the cut tissue was embedded in paraffin (Leica TP1020 tissue processor) and cut into 5 µm thick sections in a rotary microtome (Leica RM2255 - Fully Automated Rotary Microtome). The sections were stained with haematoxylin-eosin (Merck). Histological measurement and photographs were taken with Olympus CX31, Trinocular Biological Microscope (magnification 10x & 40 x).

2.5. 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 MC on ulcer severity score on aspirin ulcerated rats

Results of present investigational analysis clearly reflects that ulcerative score of the rats belongs to group II rats has shown the intensity and severity of the ulcer induction by aspirin in the experimental animals (2.66 ± 0.21). There was significant decrease in the ulcerative score observed in MC drug treated rats which reveals the anti-ulcer potential of the formulation. It was further observed that there was a significant increase in the percentage protection offered by the trial drug MC at both the dose of 200 and 400 mg/kg. As shown in table 1 and figure 1.

Table 1: Effect of SC on Ulcer Index of Aspirin ulcerated rats

Group	Treatment and Dose	Aspirin Induced Ulceration		Percentage of Ulcer Protection
		Ulcer Severity Score	Ulcer Index	
I	Normal Saline	0.0 ± 0.0	-	100
II	Aspirin 200mg/kg	2.66 ± 0.21	11.53 ± 0.17	-
III	Aspirin + 200 mg/kg of MC	1.83 ± 0.40*	9.43 ± 0.14*	18.21*
IV	Aspirin + 400 mg/kg of MC	1.16 ± 0.4*	5.9 ± 0.50*	48.82*

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

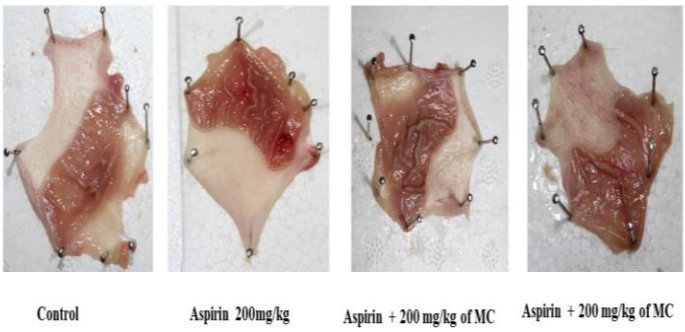

Figure 1: Effect of MC on gross anatomy of rat stomach aspirin ulcerated rats

3.2.Effect of MC on Histopathology of aspirin ulcerated rats under low and high power magnification

Microscopic examination of the tissue samples reveals that normal appearance of glandular lumen, Intra cytoplasmic zone of mucosa appears normal in sample belongs to group I rats. Sever ulceration with glandular degeneration were observed in sample belongs to group II rats. The continuity of mucosa was marginally improved with mild evidence of ulceration in sample belong to group III animals. Regular arrangement of muscularis externa and outer longitudinal muscle were observed in group IV samples. As shown in figure 2.

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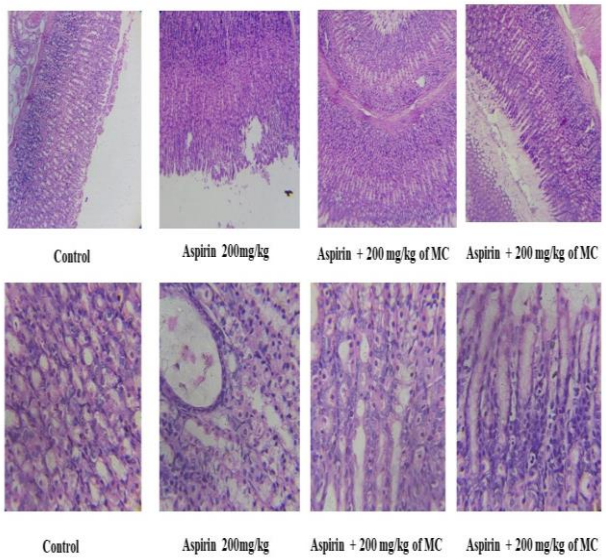

Figure 2: Histopathology of rat stomach belongs to control, aspirin ulcerated and treatment group rats under low and high power magnification

4.Discussion

Peptic ulceration is one of the common disease affecting millions of people. It is now considered to be one of the modern age epidemics affecting nearly 10% of world population [19]. Research advances during last decade have offered new insights in the therapy and prevention of peptic ulceration. Although drug treatment for peptic ulceration has improved in the recent past, the need for better therapy is still prevailing. Herbs provide an alternative strategy in search for new drugs. There is a rich abundance of plants reputed in traditional medicine to possess anti-ulcer properties [20]. It is likely that traditional herbs will continue to be a valuable source of new molecules which may, after possible chemical manipulation, provide new and improved anti-ulcer drugs.

Typical treatments for gastric ulcers are acid suppressant drugs, such as type-2 histamine receptor antagonists and proton pump inhibitors [21], but they have some adverse effects. Long-term use of acid suppressants can lead to gynecomastia, impotence, osteoporotic bone fracture, and deficiencies of iron and magnesium, as well as vitamin B12 hypergastrinemia after discontinuation [22].

Peptic ulcer is one of the major gastrointestinal disorders, which occur due to an imbalance between the offensive (gastric acid secretion) and defensive (gastric mucosal integrity) factors [23]. Consequently, reduction of gastric acid production as well as reinforcement of gastric mucosal production has been the major approaches for therapy of peptic ulcer disease. Prostaglandins are synthesized by the gastric mucosa and are known to inhibit the secretion of gastric acid and stimulate the secretion of mucus and bicarbonate. Also, there is evidence concerning the participation of reactive oxygen species in the etiology and pathophysiology of ulcer [24].

Aspirin causes mucosal damage by interfering with prostaglandin synthesis. Disturbances in gastric secretion, damage to gastric mucosa, alteration in permeability, gastric mucus depletion, increase in the pepsin and protein content, and generation of free radical production are reported to be the pathogenic effects of aspirin

Results of present investigational analysis clearly reflects that ulcerative score of the rats belongs to group II rats has shown the intensity and severity of the ulcer induction by aspirin in the experimental animals. There was significant decrease in the ulcerative score observed in MC drug treated rats which reveals the anti-ulcer potential of the formulation. It was further observed that there was a significant increase in the percentage protection offered by the trial drug MC at both the dose of 200 and 400 mg/kg.

The main mechanism of NSAID-associated damage of the gastroduodenal mucosa is the systemic inhibition of constitutively expressed cyclooxygenase-1 (COX-1), which is responsible for prostaglandin synthesis, and is associated with decreased mucosal blood flow, low mucus and bicarbonate secretion, and the inhibition of cell proliferation. NSAIDs inhibit the enzyme reversibly in a concentration-dependent manner [25].

Microscopic examination of the tissue samples reveals that normal appearance of glandular lumen, Intra cytoplasmic zone of mucosa appears normal in sample belongs to group I rats. Sever ulceration with glandular degeneration were observed in sample belongs to group II rats. The continuity of mucosa was marginally improved with mild evidence of ulceration in sample belong to group III animals. Regular arrangement of muscularis externa and outer longitudinal muscle were observed in group IV samples.

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5. Conclusion

Siddha system of medicines are effective in treating gastric ulcer with minimal adverse effects and lower recurrence rates. Combination of herbal medicines and conventional anti-gastric ulcer drugs may reveal a synergistic effect against gastric ulcer. Thus, polyherbal preparations like Mullangi Chooranam either alone or in combination with conventional drugs could be used as an alternative for treating certain gastric ulcers and preventing recurrence.

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