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EVALUATION OF ANTI-ULCER POTENTIAL OF THE SIDDHA FORMULATION *PIRANDAI VADAGAM* IN ASPIRIN ULCERATE RATS

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ABSTRACT

In Indian system of traditional medicine siddha system of medicine is considered to be the oldest traditional healing therapies known to the mankind since several centuries. Siddha system of medicine has versatile formulation in curing gastric ulcers as it denoted by Gunmam. The term Gunmam refers to the group of ulcerative disease occurs in the alimentary tract such as like peptic ulcers, dyspepsia, gastritis, GERD etc. According to the ancient vedic siddha physician yugi muni siddhar who was considered as a father of pathology in siddha, he categorized the ulceration in to 8 different types. It is evident that there are some medicinal plants used in siddha have potency of acting as anti-ulcer agents. The novelty of most of the siddha preparations are still not much explored and documented. Hence as a measure of exploring therapeutic potential of the novel siddha formulation *Pirandai Vadagam* (PV) the present study proposed to investigate the anti-ulcer property of the formulation PV in aspirin induced gastric ulcer model in rats. Results of the study has shown that animals treated with 200mg/kg of Aspirin shown increased severity in ulcer score of about 2.667 ± 0.21 and treatment with PV at the dose of 200 and 400 mg/kg significantly reduced the ulcer score and the score was found to be 1.167 ± 0.40 for 200mg/kg and 1± 0.15 for 400g/kg of PV. Further PV at the dose of 200mg/kg offers 58.47 percentage ulcer protection and 66.63% protection at 400mg/kg. It was concluded from the result of the present investigation that the formulation PV has promising anti-ulcer activity against the aspirin ulcerated rats.

KEYWORDS: Siddha system, Pirandai Vadagam, Anti-ulcer, Aspirin, Siddhar, ulcer score.

1. INTRODUCTION

Ulcer has become a global health issue in recent days. Environmental and lifestyle factors contribute more to the prevalence of this issue in developing countries like India. It is now generally agreed that gastric ulcers develop when the delicate balance between some gastro protective and aggressive factors is lost. Major aggressive factors are acid, pepsin, *Helicobacter pylori* and bile salts. Defensive factors mainly involve mucus-bicarbonate secretion and prostaglandins.[1] The modern approach to control gastric ulcer is to inhibit gastric acid secretion, to promote gastro protection, to block apoptosis and to stimulate epithelial cell proliferation for effective healing.[2]

Mucosal defense is a kind of resistance offered by the gastric mucosa towards certain endogenous secretions like acid, pepsin, bile and also toward some injected irritant like alcohols and NSAIDS. The concept of gastro protection offered by siddha formulation against various necrotizing agents has been routinely used to assess the anti-ulcer potential of the preparations.[3] Several scientific studies provided evidence based results on potency and therapeutic efficacy of the siddha system of traditional medicines in treating gastric ulcer in humans and animal *via* divergent mechanisms. The pathogenesis of NSAID-induced gastrointestinal damage may also depend on prostaglandin-independent mechanisms, such as uncoupling of oxidative phosphorylation, alterations of mucosal cell turnover as well as neutrophil activation followed by enhanced endothelial adhesion.[4] These mechanisms, in combination with those related to prostaglandin suppression, lead to micro vessel occlusion and subsequent hyper production of reactive oxygen metabolites. Such substances are then able to induce oxidative tissue injury which seems to play a prominent role in the development of mucosal ulceration caused by NSAIDs.[5]

Numerous formulations indigenous to Indian system of medicine have been reported to be helpful in successfully managing the gastric ulcer condition one among them is been successful in managing ulcer Poora parpam is one among them is *Pirandai Vadagam* (PV). The main aim of the present investigation is to evaluate the anti-ulcer property of the siddha drug PV in aspirin induced gastric ulceration in wistar rats and to document the evidence of the present investigation for future researchers.

2. MATERIALS AND METHODS

2.1. Ingredients

The formulation *Pirandai Vadagam* comprises of the following ingredients

1. Pirandai (*Cissus quadrangularis*)
2. Thalisabathiri (*Taxus baccata*)
3. Inji (*Zingiber officinalis*)
4. Kadukai (*Terminalia chebula*)
5. Nellikai (*Phyllanthus emblica*)
6. Dhandrikai (*Terminalia bellerica*)

2.2. Source of raw drug

Fresh specimen was collected from Siddha medicinal plant garden, Mettur, Salem, Tamil Nadu with concerned of Botanist. Then the raw drugs were authenticated by the concerned Pharmacognosist, SCRI, Chennai.

2.3. Formulation of *Pirandai Vadagam*[6]

The drugs were purified as per Sigichcha Raththa Dheebam and made into coarse powdered *Cissus quadrangularis*, *Zingiber officinalis*, *Phyllanthus emblica* are ground and made in fine paste with double distilled water. To this paste the other ingredients like *Terminalia bellerica*, *Taxus baccata*, *Terminalia chebula* were well grinded and mixed to make in to paste. The mixed content is triturated in the kalvam and made in to pills of 1gm each. The pills were dried in shadow and the stored.

2.4. Drug Storage

The trial drug is stored in clean dry air tight container and it is dispensed to the patients in air tight bottle.

Common Indication : Peptic Ulcer
Dose : 1 pill twice daily (Chewable)
Duration : 48 days.

2.5. Animals

Healthy adult Wistar albino male rats 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 ± 2° C and the relative humidity 50–65%. They were provided with food (Sai feeds, Bangalore, India) 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 University, Chennai, Tamil Nadu, India and the project approval number is SU/CLATR/IAEC/VII/046/2016.

2.6. Aspirin Induced Ulcer[7,8]

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 *Pirandai Vadagam*, 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 *Pirandai Vadagam*, p.o for the period of 07 days 1 hr prior to the administration of aspirin.

2.7. Ulcer Score

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

The scores were:

0 = no ulcer

1 = superficial ulcer

2 = deep ulcer

3 = perforation

2.8. Ulcer Index

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.

2.9. Percentage inhibition of ulceration

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.

2.10. Histological studies

Stomach tissue samples from each group were collected and fixed in 10% formalin for 24 h. The specimens were then embedded in paraffin, sectioned and stained with hematoxylin and eosin, before being evaluated by light microscopy.

2.11. Statistical analysis[9]

The statistical analysis will be carried by one way ANOVA (GRAPH PAD PRISM 5 computer program). Results were expressed as mean ± standard error. A statistical comparison was carried out using the Dunnet's test for the control and treatment group. P-values less than 0.05 were set as the level of significance.

3. RESULTS

3.1. Effect of *Pirandai Vadagam* on Ulcer severity score of Aspirin and drug treated rats

Aspirin being an NSAID widely used for induction of ulcer in rodents. In the present study the animal belongs to group I (Control) shown 0 ulceration which projects the normal mucosal resistance. Animal belongs to group II treated with 200mg/kg of Aspirin shows severe ulceration with the highest score of about 2.667 ± 0.21when compare to that of the control group. Rats belongs to group III treated with 200mg/kg of the formulation PV shown significant reduction in ulcer score of about 1.167± 0.40 whereas rats belongs to group IV treated with 400mg/kg of the formulation PV shown greatest reduction in ulcer severity with score of about 1± 0.51. As shown in Table 1 and figure 1.

Table 1: Effect of *Pirandai Vadagam* on Ulcer severity score of normal, Aspirin and drug treated rats.

Group	Treatment	Ulcer Severity Score
I	Normal Saline	0 ± 0
II	Aspirin,200 mg/kg , p.o	2.667 ± 0.21
III	Aspirin + *Pirandai Vadagam*, 200 mg/kg, p.o	1.167± 0.40
IV	Aspirin + *Pirandai Vadagam*, 400 mg/kg, p.o	1± 0.51

Values are expressed as mean ± S.E.M. (n=6), comparisons were made between: Group I (control) vs. Group II (Disease control), Group III (PV 200mg/kg) vs Group IV (PV 400mg/kg).

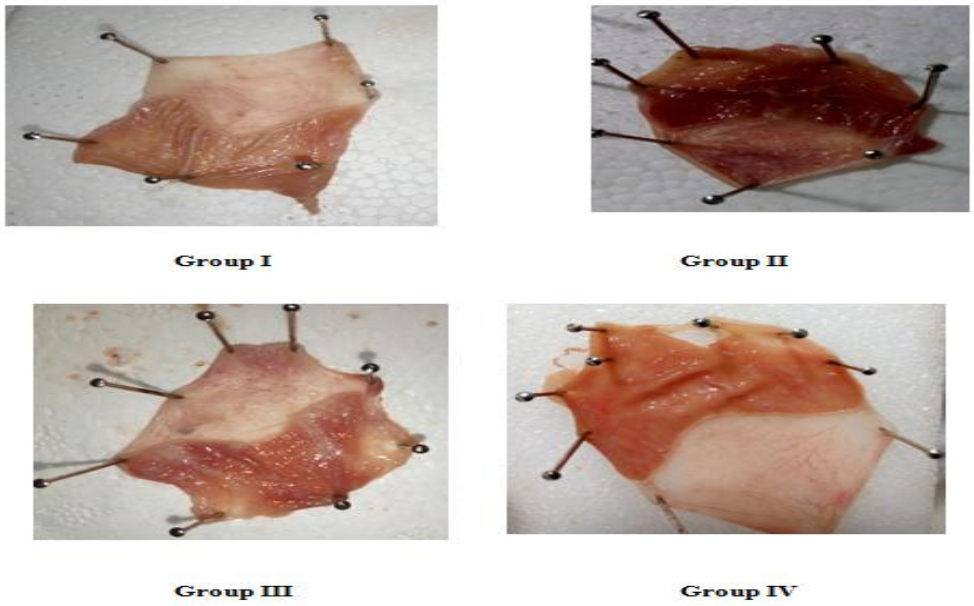


Figure 1: Gross Anatomy of Rat Stomach belongs to Control, Aspirin and *Pirandai Vadagam* Treated Groups.

3.2. Effect of *Pirandai Vadagam* on Ulcer Index of Aspirin and drug treated rats

Ulcer index denotes the degree of percentage protection offered by the test drug *Pirandai Vadagam* in aspirin ulcerated rats. The formulation PV at the dose of 200mg/kg offers the percentage protection of about 58.47% whereas the animals belongs to group IV treated with PV at the dose of 400mg/kg offers the percentage protection of about 66.63%. As shown in Table 2.

Table 2: Effect of *Pirandai Vadagam* on Ulcer Index score of normal, Aspirin and drug treated rats.

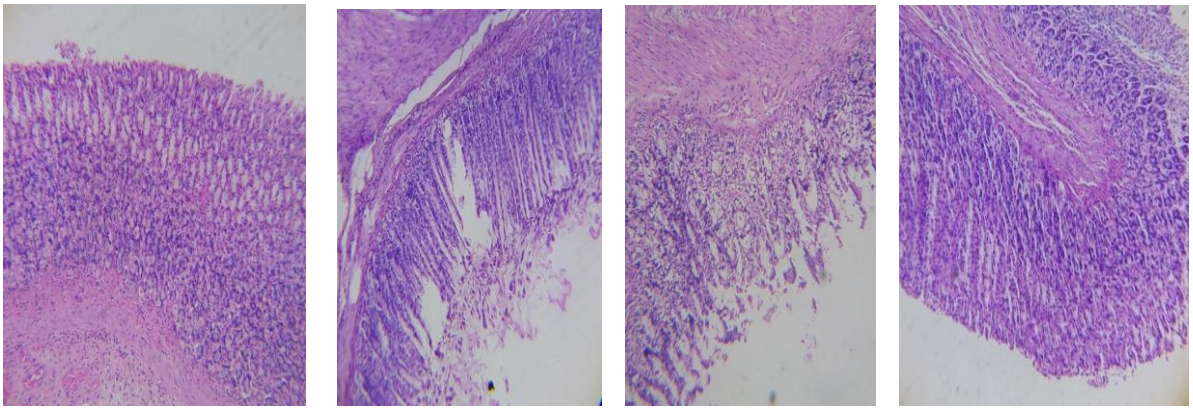
Group	Treatment	Ulcer Index	Percentage of Ulcer Protection
I	Normal Saline	-	100
II	Aspirin,200 mg/kg , p.o	11.15 ± 0.08	-
III	Aspirin + *Pirandai Vadagam*,200 mg/kg, p.o	4.53 ± 0.41	58.47
IV	Aspirin + *Pirandai Vadagam*,400 mg/kg, p.o	3.38 ± 0.42	66.63

Values are expressed as mean ± S.E.M. (n=6), comparisons were made between: Group I (control) vs. Group II (Disease control), Group III (PV 200mg/kg) vs Group IV (PV 400mg/kg).

3.3. Effect of *Pirandai Vadagam* on Histology of rat stomach

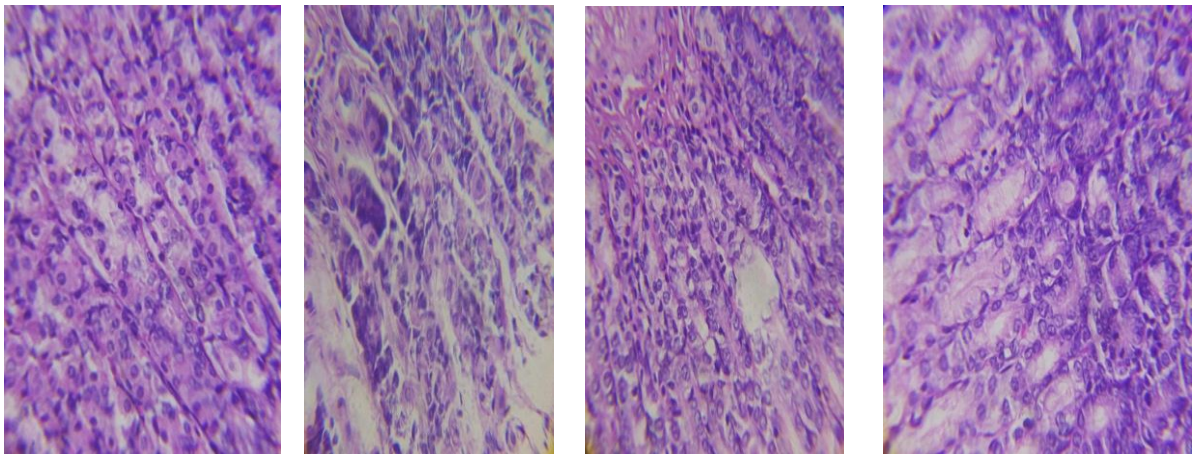
Microscopic image of samples belongs to group I reveals well-arranged and visible as mucosa layer, sub-mucosa layer and muscularis propria layer. The mucosa layer of the stomach of the control rats project normal histology with intact epithelial lining and gastric pits. Sample belongs to group II characterized by increased mucosal lesions with marked degeneration. The mucosa rarely infiltrated by inflammatory cells extended up to the sub mucosa layer.

Low Power Magnification 10 X



Group I **Group II** **Group III** **Group IV**

High Power Magnification 40 X



Group I **Group II** **Group III** **Group IV**

Figure 2: Histology of Rat Stomach (H&E Staining) Treated with Aspirin and *Pirandai Vadagam*.

Sample belongs to group III reveals mild mucosal damage with distorted gastric glands were as decreased perforation was observed as an indication of gastric protection. Sample belongs

to group IV reveals well preserved gastric mucosa with no signs of inflammation and reduced signs of ulceration. Gastric glands and parietal cells appear normal. As shown in figure 2.

4. DISCUSSION

Gastric ulcer is usually due to weakening of the gastric mucosa, and duodenal ulcer due to the dominance of acid and pepsin. Risk of ulcerogenesis is now greatly enhanced due to socio-economic problems and exposure of man to many noxious agents and chemicals.[10] Ulcer is the fourth largest disease in Asia. Many drugs available on the market greatly reduce the morbidity and mortality, but may also produce adverse reactions like gynaecomastia[11] and also suffer from high recurrence rates.

It was reported that phytotherapeutics like flavonoids, tannins, terpenoids and Saponin are found to possess significant anti-ulcer activity in several rodent models. Flavonoids, tannins and triterpenes are the best known bioactive gastroprotectants.[12] Further these phytocompounds will be able to stimulate mucus, bicarbonate and prostaglandin secretion, and counteract with the deteriorating effects of reactive oxidants in gastrointestinal lumen.[13] Tannins may prevent ulcer development due to their protein precipitating and vasoconstriction effects. Their astringent action can help precipitating micro proteins on the ulcer site, thereby forming an impervious layer over the lining that hinders gut secretions and protects the underlying mucosa from toxins and other irritants.[14,17] Treatment with PV at the dose of 200mg/kg offers 58.47 percentage ulcer protection and 66.63% protection at 400mg/kg. It was concluded from the result of the present investigation that the formulation PV has promising anti-ulcer activity against the aspirin ulcerated rats.

Aspirin is a potent nonsteroidal anti-inflammatory drug (NSAID) that is used for the prevention of cardiovascular thrombotic diseases. Gastric ulcer associated with the chronic use of aspirin is a major problem. Many factors such as gastric acid and pepsin secretion, gastric microcirculation, prostaglandin E_2 (PGE_2) content[18], and proinflammatory cytokines interleukin (IL)-1β and tumor necrosis factor (TNF)-α[19,20] play important roles in the genesis of gastric mucosal damage, and its subsequent development.[21] It has been reported that increases in NO synthase (NOS) activity is involved in the gastrointestinal mucosal defense and also in the pathogenesis of mucosal damage.[22,23] Results of the study has shown that animals treated with 200mg/kg of Aspirin shown increased severity in ulcer score of about 2.667 ± 0.21 and treatment with PV at the dose of 200 and 400 mg/kg significantly reduced

the ulcer score and the score was found to be 1.167 ± 0.40 for 200mg/kg and 1± 0.15 for 400g/kg of PV.

One of the mechanisms by which aspirin damages the gastric mucosa is the increased production of NO due to the overexpression of iNOS. NO is a mediator not only of gastrointestinal mucosal defense, but also of its damage. It has been shown that different concentrations of NO have completely opposite effects in the same tissue. In general, the mucosal and endothelial NOS isoforms produce low amounts of NO. However, the high quantity of NO produced by iNOS damages the epithelium. The excessive release of NO from gastric epithelial cells induced by aspirin has been reported to exert detrimental effects. Inhibiting aspirin-induced increases in iNOS expression in the gastric mucosa leads to a reduction in gastric mucosal damage. In the present study, ginger powder reduced iNOS activity and inhibited the production of gastric ulcers, even in the presence of aspirin.[24]

5. CONCLUSION

The present investigation reveals some evidence based data with respect to anti-ulcer potential of the siddha formulation *Pirandai Vadagam*. The investigation drug at both the dose level shown significant reduction in ulcer severity and ulcer index. *Pirandai Vadagam* at both the dose level offers greater percentage of ulcer protection in treated animals. The anti-ulcer potential of the drug may be due to presence of phytocomponents which act by increasing the mucosal resistance and also offers greater cytoprotection in the rats. Further study has to be carried out in molecular level to reveal the exact mechanism of action of the drug in future.

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