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ACUTE ORAL TOXICITY OF ANACID SYRUP (HERBO-MINERAL FORMULATION) WITH ITS ULCER PROTECTIVE AND ANTI OXIDANT ACTIVITIES IN PYLORUS LEGATED INDUCED PEPTIC ULCER

Nilesh Patel[1], Janmejay Patel[2], Achal Patel[3] and Upendra U. Zala[4]*

[1]Associate Professor & Head, Department of Pharmacology, Shree S K Patel College of P'ceutical Education & Research, Ganpat University, At. Kherva – 382711, Dist. Mehsana Gujarat, India.
[2]CEO, Petlad Mahal Arogya Mandal Pharmacy, At. Pipalata -387355, Dist. Kheda, Gujarat, India.
[3]MBBS Student, Pramukh Swami Medical College, Karamsad -388325, Dist. Anand, Gujarat, India.
[4]Professor & Head, Postgraduate Department of Rasashastra Evam Bhaishajya Kalpana, J. S. Ayurved Mahavidyalaya, Nadiad - 387001, Gujarat, India.

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***Corresponding Author**
Dr. Upendra U. Zala
Professor & Head,
Postgraduate Department of Rasashastra Evam Bhaishajya Kalpana, J. S. Ayurved Mahavidyalaya, Nadiad - 387001, Gujarat, India.

ABSTRACT

Aim: To evaluate acute oral toxicity of Anacid syrup (Herbo-mineral formulation) on swiss albino mice and to evaluate ulcer protective and antioxidant effect of Anacid syrup against peptic ulcer in pylorus ligation induced ulcer model. **Method:** The present study was conducted according to OECD guideline AOT-425 to know single dose toxicity of Anacid syrup (Herbo-mineral formulation) on swiss albino mice. The IAEC no. for the study is SKPCPER/IAEC/2016-02/01. The study was conducted using 5 swiss albino mice. The male and female animals were selected for study of 8 - 12 weeks old with weight range of within ± 20 % of mean body weight at the time of randomization. A limit dose of 2000 mg/kg of extract was used involving five mice. Each mouse was treated with a single oral dose of 2000 mg/kg of extract in sequence at 48 h intervals. Animals were observed individually at least once during the first 30 min after dosing, periodically during the first 24 h and daily thereafter, for a total of 14 days for any clinical signs of toxicity or mortality. Body weight of all animals was recorded once in a week. The ulcer protective effect of test drug was performed in Pylorus ligation induced ulcer model in Albino Wister Rats. The anti oxidant activities of Anacid syrup was carried out by its effect on various

oxidative stress markers i.e. Superoxide dismutase (SOD), Catalase and Lipid peroxidation (LPO-MDA). **Results:** There were no physical and behavioral changes observed in swiss albino mice during 14 days. Body weight of all animals did not reveal any significant change as compared to vehicle control group. Mortality was not observed in any animal of a group. The statistically significant increase in pH and decrease in gastric volume, total acidity, free acidity and ulcer index was found in Anacid syrup treated group in compression to various control and standard drug treated group which proves potential ulcer protective and antacid effect of this combination. The results of test drug on oxidative stress markers favor its anti oxidant properties. **Conclusion:** This study reveals that Anacid syrup (Herbo-mineral formulation) does not have any toxic effect at dose of 2000 mg/kg. So No-Observed-Adverse-Effect-Level (NOAEL) of Anacid syrup is 2000 mg/kg. The obtained results suggest that, tested Herbo-mineral formulation (Anacid syrup) has anti ulcer and anti oxidant effect without any major side effects or mortality.

KEYWORDS: Herbo-Mineral formulation, Anacid syrup, OECD Guideline, Mortality, NOAEL Peptic ulcer, Antioxidant.

INTRODUCTION

Herbal medicine or phyto-medicine is recognized as the most common form of alternative medicine. The World Health Organization (WHO) estimates that 80 % of the world's population relies on these “alternative” plant-based medicines as their primary medical intervention especially in the developing and in the developed countries.

These drugs are either single plant extracts or mixtures of extracts derived from different plants. These plant extracts are standardized for their safety and efficacy.[1]

Herbo-mineral formulations bring to improved convenience for patients by eliminating the need of taking more than one different single herbal formulation at a time which indirectly leads to better compliance and therapeutic effect. In preparation of Herbo-mineral formulations, it is crucial to note that herbs are sometimes considered to be incompatible therefore evaluation of toxicity is necessary.[2]

Open sores or break in inner lining of stomach, duodenum or esophagus is called peptic ulcers.[3] They are different from erosion due to its extend in inner lining of stomach, duodenum or esophagus and also causes more inflammatory reactions compare to other

erosion. Peptic ulcers occurrence is estimated and according to study 10 % people from total population have it and also annual increase rate in this category of patient is 0.3%. Majority of them have duodenal ulcers. So its occurrence ratio is higher compare to other types of peptic ulcers. Sometimes this ulcer converts in tumor due to environmental and diet changes.[4] The main cause of peptic ulcer is H.pylori infection (80%).[5] Other causes are NSAIDS, stress, alcohol, smoking and genetic factors.[6] Occurrence of disease in male is three times higher than female. Treatment cost of peptic ulcer is higher due to requirement of preventive therapy for reoccurrence but now a day's advances in this field expanded other treatment options.[7] Herbal drugs are comparatively safer and treat the disease without or with least side effect or adverse effect.[8]

The present study has been conducted to develop NOAEL and evaluate ulcer protective and antioxidant effect of Anacid syrup (a newly developed Herbo-mineral formulation).

AIM AND OBJECTIVES

- To evaluate acute oral toxicity of Anacid syrup (Herbo-mineral formulation) on swiss albino mice.
- To evaluate ulcer protective and antioxidant effect of Anacid syrup against peptic ulcer in pylorus ligation induced ulcer model.

MATERIALS AND METHODS

Test Material: The test drug (Anacid syrup) was manufactured at Petlad Mahal Arogya Mandal Pharmacy, At & Po. Pipalata, Dist. Kheda, Gujarat, India. All the GMP standards were followed during manufacturing. The detail of Anacid syrup is mentioned below.

Table 1: Ingredients of anacid syrup.

Sl. no.	Name of ingredient	Each 5 ml contains
1	Ext. Asparagus racemosus	60 mg
2	Ext. Hedychium spicatum	50 mg
3	Ext. Glycyrrhiza glabra	20 mg
4	Kamdudha Ras	60 mg
5	Shankha Bhasma	60 mg
6	Kapardika Bhasma	50 mg
7	Sodium methyl paraben (IP)	0.5 mg
8	Sodium propyl paraben (IP)	0.25 mg
9	Flavor rose white	Q.S.

Method: The present study was performed after obtained permission from IAEC (SKPCPER/IAEC/2016-02/01) as per the CPCSEA, Ministry of Environment, Forest and Climate Change (MoFCC), Government of India.

(A) Acute oral toxicity:[9] It was conducted according to OECD guideline AOT-425 to know single dose toxicity of Anacid syrup on swiss albino mice. All the Animals were kept in standard condition mentioned in guideline. They were randomized in different groups without irrespective of their gender and acclimatized prior to dosing. Each mouse was treated with limit single oral dose of extract (2000 mg/kg) in sequence at 48 h intervals. Animals were observed individually at least once during the first 30 min after dosing, periodically during first 24 h and daily thereafter for a total of 14 days for any clinical signs of toxicity or mortality. Body weight of all animals was recorded once in a week. The dosing detail is mentioned below;

Table 2: Individual animal dosing record of test drug.

Animal no.	Gender	Experiment Day	Dose (ml)
H	M	1st day	1
B	M	3rd day	1
T	F	5th day	1
HT	F	7th day	1
UM	F	9th day	1

H: Head, B: Body, T: Tail, HT: Head & Tail, UM: Unmarked, M: Male, F: Female

(B) Effect on Peptic ulcer: This study was performed in Pylorus ligation induced ulcer model in Albino Wister Rats. Animals assigned for study were maintained in standard condition. They were acclimatized for a minimum period of five days prior to dosing and subjected to randomization.

Table 3: Grouping of animals.

Group no.	Group Name	Dose (Oral)	No. of animals
I	Normal control (NC)	Normal saline	6
II	Disease control (DC)	Normal saline	6
III	Sham operated control (Sham)	Normal saline	6
IV	Standard drug (Ranitidine) treated (Std.)	27 mg/kg	6
V	Anacid syrup(AS)	25 mg/kg	6

One day before surgery, animals were divided in six different groups. Formulation or standard drug dose was given according weight of animal and interpretation of toxicological data. Animals were kept fasted for 24 h and after that, group IV & V were administered

orally with standard drug (Ranitidine – 27mg/kg) and Test drug (Anacid Syrup – 25mg/kg) respectively before 1 h of surgery. First animal was anaesthetized then tied on surgical board. Hairs below xiphoid process were removed and midline incision was made. Then pylorus portion was legated by lifting it out without damaging any blood supply of stomach. The incision was closed by interrupted suture. Animals were kept for recovery in individual cage. After 24 h, animals were sacrificed by cervical dislocation method. Stomach of animal was isolated and parameters were analyzed.

Evaluation of gastric parameters

Volume of Gastric juice: The gastric juice was centrifuged at 3000 rpm for 15 min and then it was read from calibration on the centrifuge tubes.

pH: After centrifugation, pH of withdrawn liquid from centrifuge tubes was measured by pH strip.

Free acidity and Total acidity:[10] 1 ml of collected supernant liquid was taken and diluted up to 10 ml by distilled water. Resulting mixture was titrated using 0.01N NaOH, phenolphthalein and methyl red (2-3 drops of both) as indicator. First end point was taken when yellow color solution turned in orange. The volume of titrant was noted, which gives amount of NaOH required to measure free acidity. Now same solution was kept titrated until pink color obtained and it persisted for more than 30 sec. At end point amount of titrant was noted down which indicate amount of NaOH required to measure total acidity.

Ulcer Index:[11] Calculation and representation of ulcer index is highly complicated and controversial process. Bonny castle (1964) and Robert et al (1968) suggested a method in which the stomach was given grades (0 to 4) as follows:

0. Normal swelling & white spots
1. Red hemorrhagic spots ulcers,
2. Deeper hemorrhagic spots & white spot like ulcers,
3. Hemorrhagic ulcers & other type of ulcers,
4. Perforated stomach due to ulcers.

Ulcer index = % of animals having ulcers × average severity of ulcer (from scale 0 to 4) /Average number of ulcers per stomach.

(C) Evaluation of oxidative stress markers

Superoxide dismutase (SOD) activity[12]

Reagents: 0.0001 M EDTA, 0.003 M Epinephrine, Carbonate buffer (pH 9.7)

The SOD calibration curve was prepared by taking 0.01, 0.1, 1 & 10 U/ml concentration of standard solution. Then solution of 1 ml carbonate buffer, 0.2 ml EDTA, 2 ml epinephrine and 0.5 ml supernant liquid were mixed. Absorbance of resulting solution was taken at 480 nm in spectrophotometer taking solution mixture without supernant as blank. Reading was taken at 30 sec interval for 3 min.

Catalase activity[13]

Reagents: 50 mm Potassium phosphate buffer (pH 7), 30 mM H_2O_2

Solution of 1 ml potassium phosphate buffer, 1 ml hydrogen peroxide and 50 µl samples (supernant) was prepared and absorbance of resulting mixture was taken at 240 nm by UV Visible Spectrophotometer taking solution mixture without supernant as blank solution. Reading was taken at 15 sec interval for 2.5 min.

Lipid peroxidation (LPO-MDA)[14]

Reagents: 0.8 % TBA, 20 % CH_3COOH in 0.27 M HCL (pH 3.5), 4 % W/V SLS, Distilled water

In 1 ml of supernant liquid, 0.2 ml of SLS, 1.5 ml 20% CH3COOH in 0.27 M HCl & 0.8% 1.5 ml of thiobarbituric acid (TBA) solution was added. Obtained mixture was heated at 85° C for 15 min and centrifuged at 1000 rpm for 15 min. After separation, upper organic layer was taken and its absorbance was taken in spectrophotometer at 532 nm against blank prepared by omitting sample solution.

Estimation of total protein[15]

Reagents: (A) NaOH 2 gm, $NaHCO_3$ 10 g, Sodium potassium tartrate 0.1 gm

All above reagent added and 500 ml volume was made up with distilled water.

(B) 5%CuSO4 in dis.H2O.

(C) 10 ml and 0.2 ml of solution A & B taken respectively.

In 0.2 ml of sample, 4 ml of solution C and 0.6 ml distilled water were added and kept aside for 15 min at 37° C. 0.4 ml of Folin-phenol reagent was added in that mixture after 15 min and resulting solution was again incubated for 30 min. After that, absorbances of prepared

solutions were taken at 540 nm in spectrophotometer by taking solution without sample as blank. Total protein was obtained in mg/ml of sample from standard albumin calibration curve.

Statistical analysis: Graph Pad Prism computer software was used.[16] Result was expressed as Mean ± S.E.M, numbers of rats represented by n. Statistical significance between two means are determined by performing one way analysis of variance (ANOVA) followed by Dunnett's post hoc-test. P value <0.05 was considered significant.

OBSERVATIONS AND RESULT

(A) Acute oral toxicity: The animals were observed continuously for behavioural changes, autonomic profiles and other signs of toxicity or mortality up to period of 14 days. The body weight, food intake and water intake were also observed on 1st, 7th and 14th day. There were no physical and behavioural changes observed in swiss albino mice during observation period. Body weight of all animals did not reveal any significant change as compared to vehicle control group and mortality was Nil.

Table 04: Individual animal weekly body weight, dose & Mortality record.

Animal no.	Gender	Given Dose (mg/kg)	Experiment Day, Unit : gm			Mortality
			1st	7th	14th	
H	M	2000	22	23	24	NIL
B	M		23	24	24	NIL
T	F		24	25	26	NIL
HT	F		29	30	30	NIL
UM	F		21	22	23	NIL

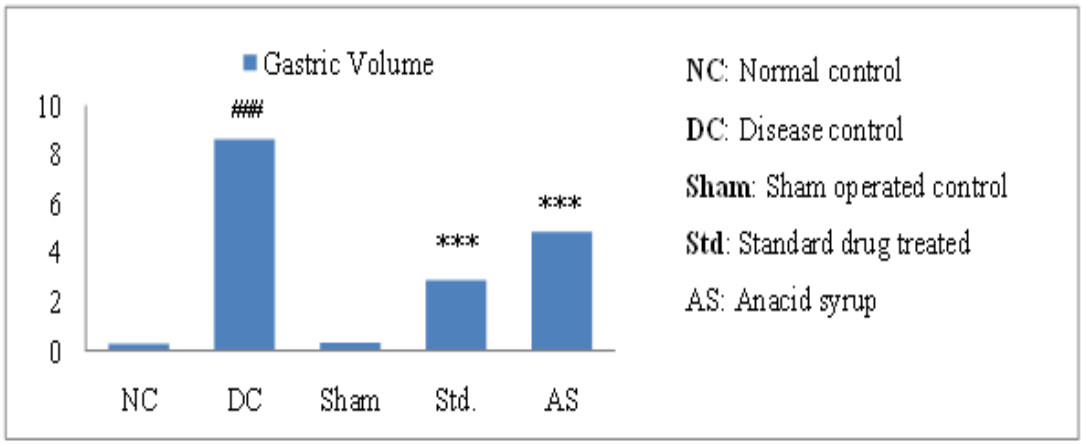
H: Head, B: Body, T: Tail, HT: Head & Tail, UM: Unmarked, M: Male, F: Female

(B) Effect on Peptic ulcer: The results of Anacid syrup on Pylorus Ligation Induced Gastric Ulcer Model are as mentioned below.

Table 05: Effect of test drug on various gastric parameters.

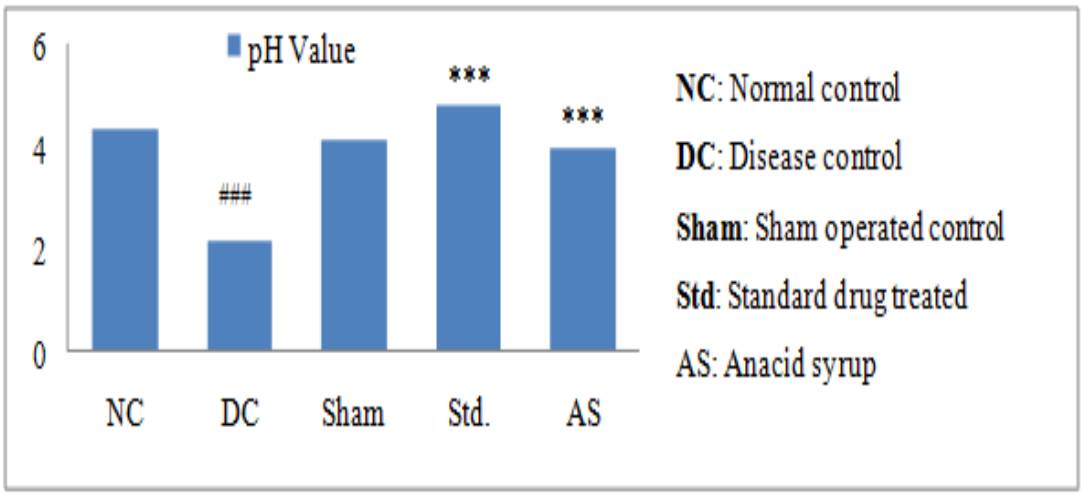
Group	Dose (Oral)	Gastric volume	pH	Free acidity	Total acidity	Ulcer Index
I (NC)	Normal saline	0.3±0.0707	4.333±0.1667	--	--	0.0
II (DC)		8.625±0.4250###	2.167±0.1667###	31.33±3.75###	135.7±8.686###	213.8±23.75###
III (Sham)		0.3250±0.0853	4.167±0.0.1667	--	--	0.0
IV (Std.)	27 mg/kg	2.875±0.3683***	4.833±0.1667***	7.00±1.00***	48.00±7.234**	16.25±3.75***
V (AS)	25 mg/kg	4.850±0.4735***	4.00±0.00***	9.00±1.732***	66.67±16.05***	37.50±2.50***

###p < 0.001 Vs Normal control, ***p <0.001, **p <0.01, *p <0.05 Vs Disease control.



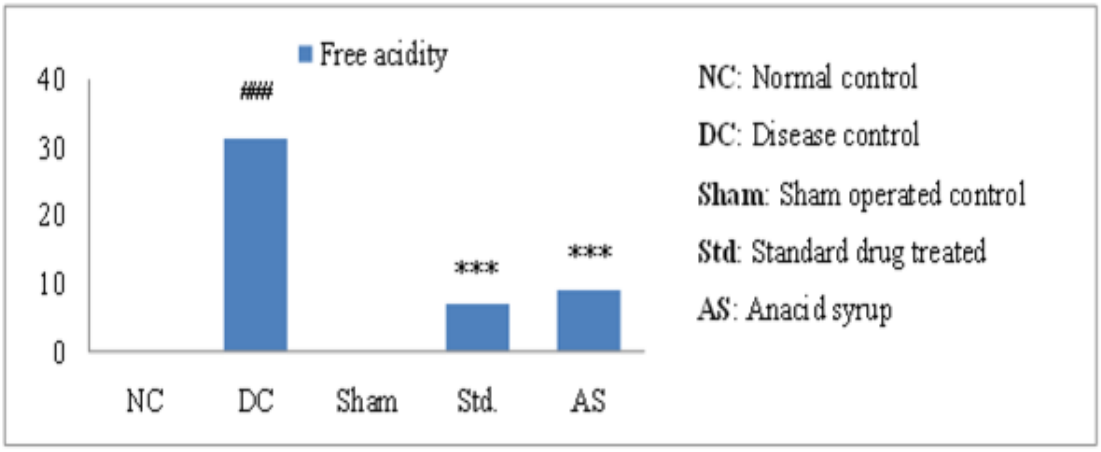
###p < 0.001 Vs Normal control, ***p < 0.001 Vs Disease control.

Graph no.1: Gastric Volume (Values are expressed as mean ± S.E.M., n=6).



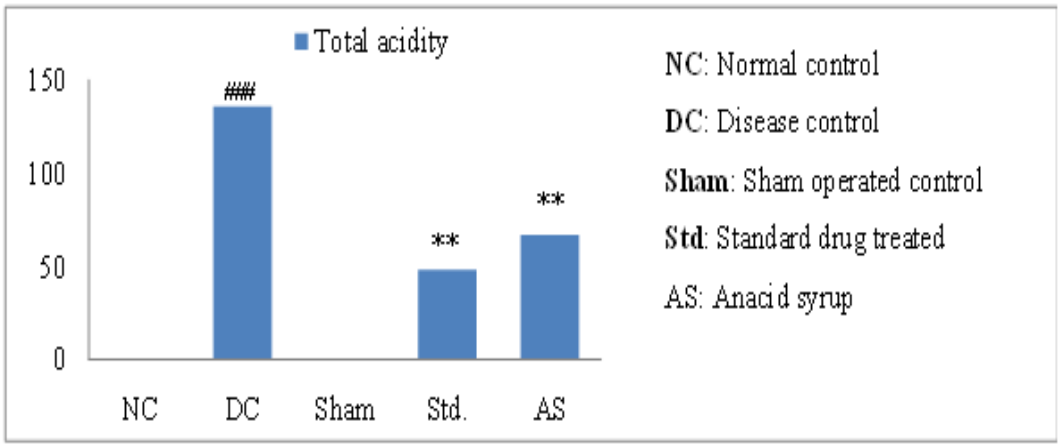
###p < 0.001 Vs Normal control, ***p <0.001 Vs Disease control.

Graph no. 2: pH of gastric juice (Values are expressed as mean ± S.E.M., n=6).



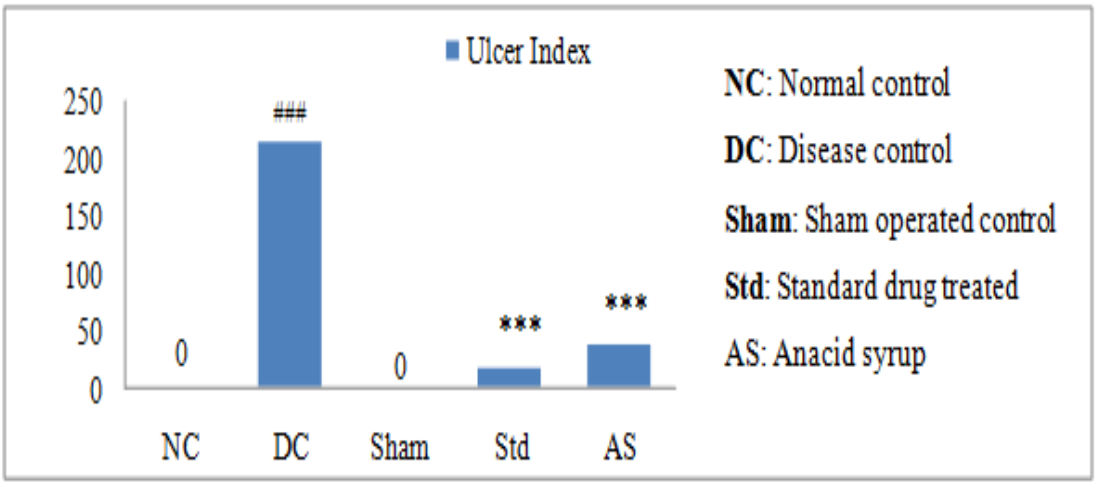
###p < 0.001 Vs Normal control, ***p <0.001 Vs Disease control

Graph no. 3: Free acidity (Values are expressed as mean ± S.E.M., n=6).



###p < 0.001 Vs Normal control, ***p <0.001 Vs Disease control

Graph No. 4: Total acidity (Values are expressed as mean ± S.E.M., n=6).



###p < 0.001 Vs Normal control, ***p <0.001 Vs Disease control.

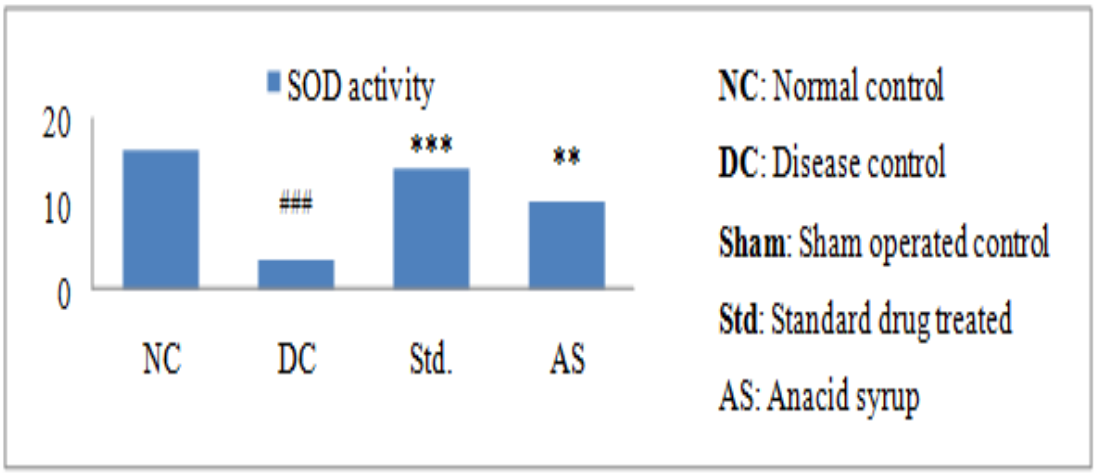
Graph no. 5: Ulcer Index (Values are expressed as mean ± S.E.M., n=6).

(C) Effect on oxidative stress markers: The results of Anacid syrup on various oxidative stress markers are as mentioned below;

Table 06: Effect of test drug on oxidative stress markers.

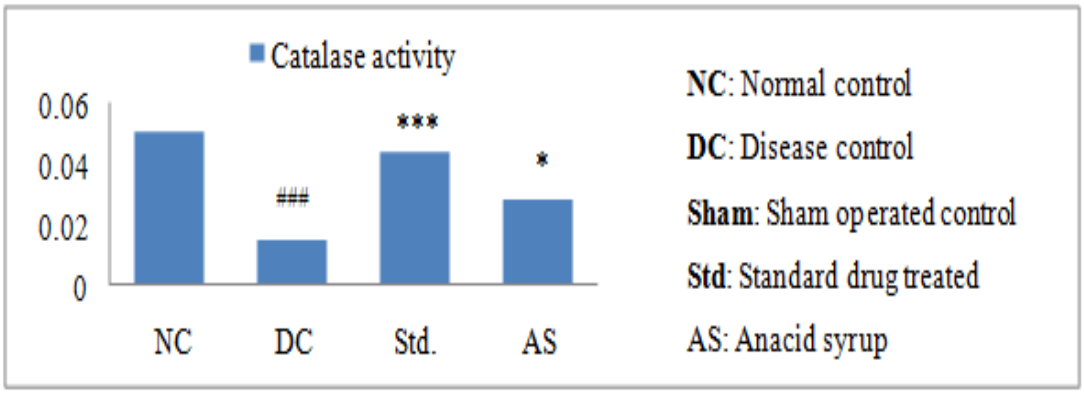
Group	Dose (Oral)	SOD activity Units/mg protein	Catalase activity Unit/min/mg tissue protein	LPO MDA mmoles/mg tissue protein
I (NC)	Normal saline	16.28±1.071	0.04983±0.0008	17.55±1.360
II (DC)		3.724±0.3645###	0.0146±0.0011###	59.41±2.883###
IV (Std.)	27 mg/kg	14.37±0.2256***	0.04361±0.00063***	19.04±0.7666***
V (AS)	25 mg/kg	10.48±1.316**	0.02784±0.0023*	27.51±2.885***

###p < 0.001 Vs Normal control, ***p < 0.001, **p < 0.01, *p < 0.05 Vs Disease control.



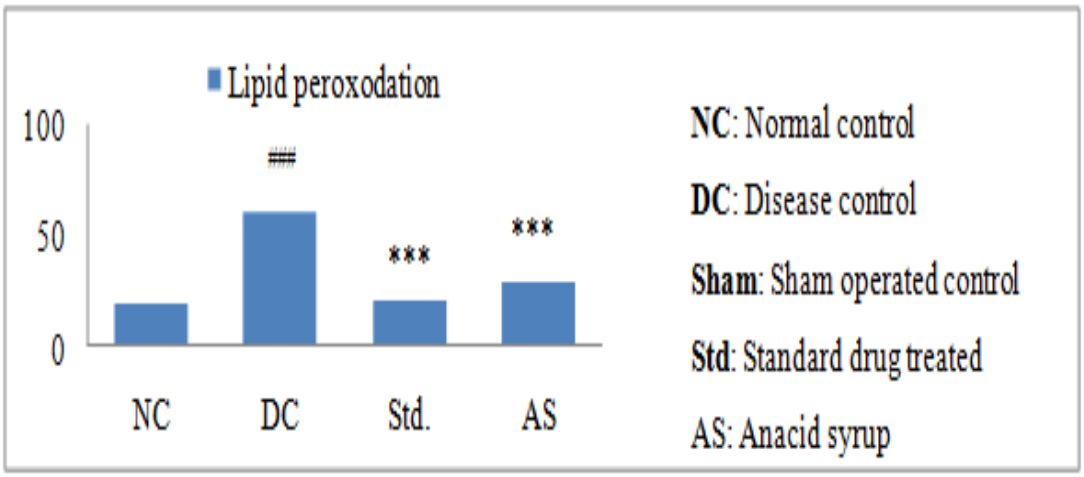
###p < 0.001 Vs Normal control, ***p < 0.001, **p < 0.01 Vs Disease control.

Graph No. 6 SOD activity (Values are expressed as Mean ± S.E.M.).



###p < 0.001 Vs Normal control, ***p < 0.001, *p < 0.05 Vs Disease control.

Graph no. 7: Catalase activity (Values are expressed as Mean ± S.E.M.)



###p < 0.001 Vs Normal control, ***p < 0.001 Vs Disease control.

Graph no. 8: LPO-MDA (Values are expressed as Mean ± S.E.M.).

DISCUSSION

The toxicity screening of newly developed formulation is essential to assure its safety and effectiveness. This study can consider as a pioneer step for the establishment of safety profile and efficacy of Anacid syrup.

The study was done on Swiss Albino Mice of both the sex for 14 days to rule out any toxic effect of Anacid syrup at the single dose of 2000 mg/kg. Individual animal weekly body weight was recorded and found to be increasing during the observation period. Animal daily observation was recorded and found to be same and mortality rate was Nil [Table 4]. There were no physical and behavioral changes observed in animals during the observation period. This study reveals that Anacid syrup which is indicated as antacid have no oral toxicity effect on Swiss albino mice. Hence, this can be used safely for therapeutic purposes.

The ulcer protective effect of test drug was performed in Pylorus ligation induced ulcer model in Albino Wister Rats. The statistically significant increase in pH and decrease in gastric volume, total acidity, free acidity and ulcer index was found in Anacid syrup treated group in compression to various control and standard drug treated group [Table 5] which proves potential ulcer protective and antacid effect of this combination.

During normal metabolic process reactive oxygen species are generated and its accumulation is controlled by specific enzymes like superoxide dismutase, catalase and glutathione peroxidase. Any disturbance in enzyme activity leads to accumulation of free radicals which can cause peptic ulcer.[22] The antiulcer and healing mechanism can be obtained by antioxidant activity of any medicinal plant or herbal formulation. The results of test drug on oxidative stress markers favors its anti oxidant properties [Table 6].

The Anacid syrup contains various ingredients along with aqueous base, preservatives and flavoring agents. Among them *Shatavari* (*Asparagus racemosus*).[17] and *Yastimadhu* (*Glycyrrhiza glabra*) are proven to have anti secretory and anti ulcerative activity.[18] *Shati* (*Hedychium spicatum*) showed protection against histamine-induced gastric ulcer.[19]

Shankha Bhasma is alkaline in nature and has been proved for its anti ulcer effect.[20] It is indicated in various pathological conditions like Hyper acidity (*Amlapitta*), Loss of appetite (*Agnimandhya*), Dysentery (*Grahani*) and Duodenal ulcer (*Parinama Shula*).[21] Its acid neutralizing capacity, speed of antacid action and prolonged buffering action are excellent.

Kamadudha Rasa is a proven formulation for having antacid properties.[22] Evidences of antacid property of *Kapardika Bhasma* is also available as well.[23]

Oral route of drug administration is perhaps the most appealing route for the delivery of drugs. The syrup is advantageous dosage form among the various dosage forms administered orally because of having more flexibility in achieving the proper dosage of the medicines and helping in faster absorption.

CONCLUSION

This study reveals that Anacid syrup (Herbo-mineral formulation) does not have any toxic effect at dose of 2000 mg/kg. So No-Observed-Adverse-Effect-Level (NOAEL) of Anacid syrup is 2000 mg/kg. The obtained results suggest that, tested Herb formulation (Anacid Syrup) has antiulcer and anti oxidant effect without any major side effects or mortality.

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1. Petlad Mahala Arogya Mandal Pharmacy, At.Po. Pipalata, Dist. Kheda, Gujarat, India.
2. Shree S.K. Patel College of Pharmaceutical Education and Research, Ganpat University, Ganpat Vidyanagar-384012, Gujarat, India.
3. J. S. Ayurved Mahavidyalaya, College Road, Nadiad - 387001, Gujarat, India.

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