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A STUDY ON FORMULATION OF A NOVEL HERBAL TREATMENT FOR PEPTIC ULCER

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ABSTRACT
It has been demonstrated that extracts of Curcuma longa, Piper nigrum, and Berberis aristata are effective in treating stomach disorders and exhibit antiulcer properties. Since treatment for peptic ulceration involves the ingestion of multiple herbs, their effects are synergistic compared to those of a single herb. This project's objective was to keep herbal extract-based gastroretentive formulations in the stomach for improved antiulcer activity. Therefore, formulation and evaluation of a spray-dried extract of Curcuma longa, Piper nigrum, and Berberis aristata floating tablet were conducted. In most instances, gastric lesions that develop in the upper portion of the gastrointestinal tract and are characterized by an imbalance between acid and mucin, characterize peptic ulcer. The purpose of this study is to develop and evaluate herbal formulations containing Curcuma longa, Berberis aristata, and Piper nigrum. As a single drug or in combination with other drugs, these are reported to be effective in treating peptic ulcer. Curcumin extracted from Curcuma longa has gastroprotective and antiulcerogenic properties. Piperine, an active component of Piper nigrum, has bioenhancer and antiulcer properties. Berberine from Berberis aristata inhibited the growth of H. pylori and the N-acetyltransferase activity of H. pylori.

KEY WORDS: Formulation, Herbal Treatment, Peptic Ulcer, Stomach.

1. INTRODUCTION
Today, natural medicines are becoming an integral element of the health care system for humans. Presently, natural pharmaceuticals are in high demand, and their prevalence is steadily increasing. India has a rich history of herbal medicines and satisfies the global demand for numerous herbal-based drugs. Major health care systems, including Ayurveda, Naturopathy, Unani, and Siddha, rely solely on herbal-based treatments.

Herbal medications play a significant role in the development of potential therapeutic agents and in the maintenance of human health. Traditional medicines provide symptomatic relief at a lower cost and with fewer side effects than allopathic medicines. As a result, people prefer to use traditional medicines. Because phytomedicine is safe, readily accessible, has fewer side effects, and is compatible with the human body, the majority of people today rely on it for the treatment of various diseases. There is an urgent need to develop safer medications for the treatment of inflammatory disorders, diabetes, liver diseases, and gastrointestinal conditions. There are a variety of herbal supplements and plant-based remedies used to treat gastric and peptic ulcers.

1.1 Peptic ulcer
The term peptic is derived from the Greek word peptikos, which means conducive to digestion3. Peptic ulcer is defined as mucosal erosions in the gastrointestinal tract that are acidic, excruciating, and at least 0.5 cm in diameter. Acid peptic ulcers are caused by a number of factors, most notably the effects of gastric acid on stomach and duodenal mucosa and the failure of mucosal barrier mechanisms to oppose these effects.

The two types of peptic ulcers are acute (stress) and chronic. In accordance with their anatomical locations, gastric and duodenal ulcers are chronic ulcers. Ulcers develop in the region of the digestive tract exposed to acidic gastric fluid. Typically, ulcers occur on the minor curvature of the stomach and duodenum, where they are referred to as gastric ulcers and duodenal ulcers, respectively. Ulcer formation is accompanied by disruption of the mucosal layer and a decrease in prostaglandin (PG) release, which promotes the corrosive action of acid and pepsin on the stomach lining.

1.2 Causes of peptic ulcer

1.2.1 Gastric acid secretion

The inability of the stomach to protect itself from hydrochloric acid, digestive fluids, and pepsin leads to ulcer formation. In particular instances, the stomach can defend itself against these fluids via a variety of mechanisms. Bicarbonate neutralizes digestive fluids, and mucus coats the interior lining of the stomach.

1.2.2 The presence of Helicobacter pylori infection

Research indicates that Helicobacter pylorus (H. Pylori) is the primary organism responsible for the formation of peptic ulcers. Corkscrew-shaped H. Pylori adhere to the mucous membrane of the stomach or duodenum lining. By releasing urease, an enzyme that generates ammonia and neutralizes the acid8, they can survive in severe acidic environments. The bacteria produce substances that impair the mucus barrier of the stomach, making it more susceptible to the effects of acid and pepsin, and also stimulate the production of more acid. Ultimately, the acid and bacteria irritate the lining and create an ulcer.

1.2.3 Utilization of Nonsteroidal Anti-Inflammatory Drugs

Long-term use of NSAIDs, such as aspirin, is associated with gastrointestinal disease. Today, twenty-five percent of the population suffers from ulcers caused by nonsteroidal anti-inflammatory drugs (NSAIDs), and this percentage continues to rise. NSAIDs drugs impact the epithelial, intraepithelial, and subepithelial layers of the stomach. Local means topical effects on the epithelium layer of the stomach and systemic impacts of systemic damage to the gastrointestinal lining that reduces mucosal prostaglandin synthesis are the two mechanisms implicated in NSAIDS-induced ulcer. It decreases the production and secretion of mucus at the epithelial level and increases the activity of pepsin. Intraepithelial penetration of ionized NSAIDs into the gastric wall results in cellular injury. It causes thrombosis in the microcirculation and vasoconstriction of the submucosal arterioles at the subepithelial level. NSAIDs inhibit the COX-1 and COX-2 enzymes, which are responsible for PGE synthesis. The NSAIDs decreased prostaglandin-E2, which inhibits acid secretion and increases mucus secretion. By inhibiting COX-1, NSAIDs release Endothelin-1, which damages mucous membranes. NSAIDs promote TNF-, which causes mucosal injury, blood flow reduction, and ulcer formation.

1.2.4 Physiological stress

Stress contributes to the etiology of peptic ulcer infection. It is a risk factor for patients with severe injuries or who are undergoing surgery. In stress-induced patients, the rate of ulcer hemorrhage is reduced. The increased gastric acid secretion caused by stress aggravates the ulcer. Stress reduces mucin secretion, cell renewal, prostaglandin production, and blood flow to the mucosa.

1.2.5 Cigarette smoking

The principal cause of gastric ulcers is smoking. It causes the recurrence of gastric ulcers and delays the ulcer's ability to heal. It has a direct impact on acid secretion, slows the production of prostaglandin and bicarbonate, and reduces the blood flow to the mucosa. It may provide an environment more conducive to H. pylori infection.

1.2.6 Liquor

Alcohol damages the mucosal lining of the stomach and stimulates acid secretion. People with ulcers should avoid alcoholic beverages that irritate their existing ulcers.

1.2.7 Food

Caffeine-containing products and acidic fruits (which contain citric acid) increase acid production and vulnerability to Helicobacter pylori infection, aggravating ulcer symptoms. Generally, milk is used to reduce ulcer symptoms, but it can sometimes stimulate acid secretion in the stomach. Vegetables rich in fiber reduce the risk of developing an ulcer. The stomach is irritated by spices.

1.2.8 Over production of histamine and gastrin

Histamine (H2) receptor in gastric parietal cells initiates the release of acid into the stomach lumen via a c-AMP, protein kinase A, or proton pump pathway. The primary cause of the production of histamine and gastrin, which promote ulceration, is the Zollinger-Ellison syndrome. Additionally, pancreatic and duodenal tumors (gastrinomas) produce excess gastrin, a hormone that produces gastric acid. These malignancies are typically life-threatening and must be removed. In conclusion, surgery is effective for decreasing acid production and ulcer recurrence in gastrinomas.

1.3 Symptoms of peptic ulcer

Ulcers that cause no adverse effects are sometimes referred to as "silent ulcers." Typical symptoms of ulcer include abdominal discomfort. The discomfort results from tissue ulceration that exposes nerve fibers. The discomfort is located in the upper abdomen and has a burning sensation. Several hours after a meal or when the stomach is vacant, pain is at its worst. Bleeding is a secondary sign of ulcers that cause foul-smelling feces (known as melena) due to the presence of hemoglobin's oxidized iron. Vomiting is another indicator of an ulcer patient. In severe conditions, blood in vomit is the result of bleeding from the upper portion of the intestines. Heartburn, indigestion, burping, weight loss and loss of appetite, bleaching, and vertigo are among the various adverse effects. Gastric ulcers induced by H. pylori infection are more likely to lead to stomach cancer. Untreated peptic ulcers can cause anemia, infection, and scar tissue that can obstruct food passage.

1.4 Treatment of Peptic Ulcer with Herbal Medicine

The medical superintendent determines the specific

treatment for peptic ulcers based on the patient's medical history and the severity of the pathogenesis. Historically, reducing gastric acid secretion was regarded the primary therapeutic approach. Currently, the treatment strategy entails enhancing mucosal resistance and reducing acid output. A peptic ulcer is frequently treated with single or combination medications. The routinely available synthetic antiulcer drugs are associated with dose and days of therapy. Nitric Oxide-NSAIDs and H2S-NSAIDs are being investigated as potential alternatives to NSAIDs. These novel classes of substances reduce gastrointestinal toxicity and inhibit enzyme activity. In various studies, single or combination pharmaceuticals have demonstrated advantages in the treatment of peptic ulcer disease, but they are not without side effects. At present, standard open surgery is the only treatment option for extremely severe conditions. In this fashion, the search for suitable medications derived from nature is an area of study for the treatment of peptic ulcers.

2. RESEARCH METHODOLOGY

2.1 Collection and authentication of crude drugs

Rhizomes of *Curcuma longa*, fruits of *Piper nigrum*, and roots of *Berberis aristata* were collected from local market. All the crude drugs materials were authenticated. Crude drugs and their powder photos were shown in figure 1 and 2.

a b c

Figure 1: Crude drugs of a. rhizome of Curcuma longa, b. fruit of Piper nigrum, c. root of Berberis aristata.

a b c

Figure 2: Powder photos of a. Curcuma longa, b. Piper nigrum and c. Berberis aristate.

2.2 Evaluation of crude medicines using parameters for quality control

2.3 Physical-chemical analysis

It is necessary to evaluate crude pharmaceuticals in order to determine the quality and purity of herbal raw materials. Loss on drying, extractive values (alcohol and water soluble extractive values), total and acid insoluble ash values were determined for a selection of pulverized pharmaceuticals. Adoption of the WHO recommendation for determining the physicochemical constants of three pulverized samples1. The mean values and standard error of the mean (SEM) were calculated for each parameter that was measured in triplicate.

2.4 Chemical evaluation - Initial Phytochemical Investigation

Various chemical analyses were performed on the pulverized materials in order to identify various phytoconstituents. Powdered substances underwent qualitative evaluations using chemical analyses. The 50 g of powdered samples of each substance were percolated for two days with intermittent stirring in 200 ml of methanol. Each extraction was filtered with whatman

filter paper. Analyses of the phytochemistry of concentrated extracts were performed. Hydrodistillation is applied to pulverized substances for volatile hydrocarbon analysis.

2.5 Procurement of standardized herbal extracts

In order to compare the quality of laboratory extracts, standardized herbal extracts of the investigated pharmaceuticals were sought on the market. NJP Healthcare Private Ltd of Vapi contributed Piper nigrum, Curcuma longa, and Berberis aristata standard extracts. The active constituents of extracts were analyzed qualitatively and quantitatively using thin-layer chromatography, ultraviolet light, and high-performance liquid chromatography. After comparing laboratory and commercial extracts, it will be determined which extracts warrant further investigation.

3. RESULTS AND DISCUSSION

3.1 Antiulcer activities of combined herbal extracts

Ethanol induced ulcer

In all rodents, ethanol caused severe gastric ulcers. The majority of ulcers were superficial (Figure -3). Initially, treatment with an aqueous suspension of methanolic extracts of Curcuma longa, Berberis aristata, and Piper nigrum (250 mg/kg) did not provide a significantly higher percentage of protection than ranitidine. Therefore, the decision was made to create a mixture of combined extract. In addition, the order of dose of combined drug extracts was investigated, and the protection percentage was calculated. In comparison to ranitidine (65.27 7.73%), a mixture of methanolic extracts of Curcuma longa (250 mg/kg), Piper nigrum (125 mg/kg), and Berberis aristata (125 mg/kg) significantly protected the gastric mucosa from ethanol-induced ulceration (Table-1).

Table -1: Effect of combined herbal extracts on ethanol induced ulcers.

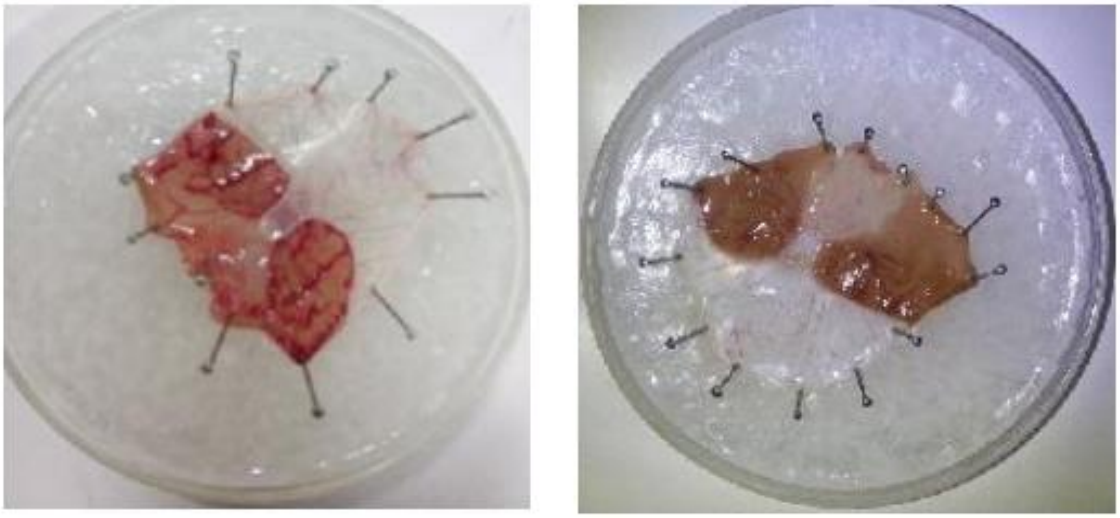
Groups	Ulcer Index	Mean % Protection
Disease Control (Normal saline)	12 ± 1.80	0.0 ± 0.0
Standard (Ranitidine)	4.16 ± 0.92***	65.27 ± 7..73 ***
ACL (250 mg/kg) + APN (125 mg/kg) + ABA (125 mg/kg)	2.0 ± 0.28 ***	83.33 ± 2.40***
APN (250 mg/kg) + ABA (125 mg/kg) + ACL (125 mg/kg)	7.0 ± 1.04 *	41.66 ± 8.67 ***
ABA (250 mg/kg) + ACL (125 mg/kg) + APN (125 mg/kg)	5.66 ± 0.44 **	52.77 ± 3.67 ***
ACL (250 mg/kg)	7.0 ± 0.63 *	41.66 ± 3.8 ***
APN (250 mg/kg)	10.0 ± 1.19	16.66 ± 1.7
ABA (250 mg/kg)	8.5 ± 0.92	29.16 ± 4.0 **

Where,

ACL: Aqueous methanolic extract of *Curcuma longa*

APN: Aqueous methanolic extract of *Piper nigrum*

ABA: Aqueous methanolic extract of *Berberis aristate*



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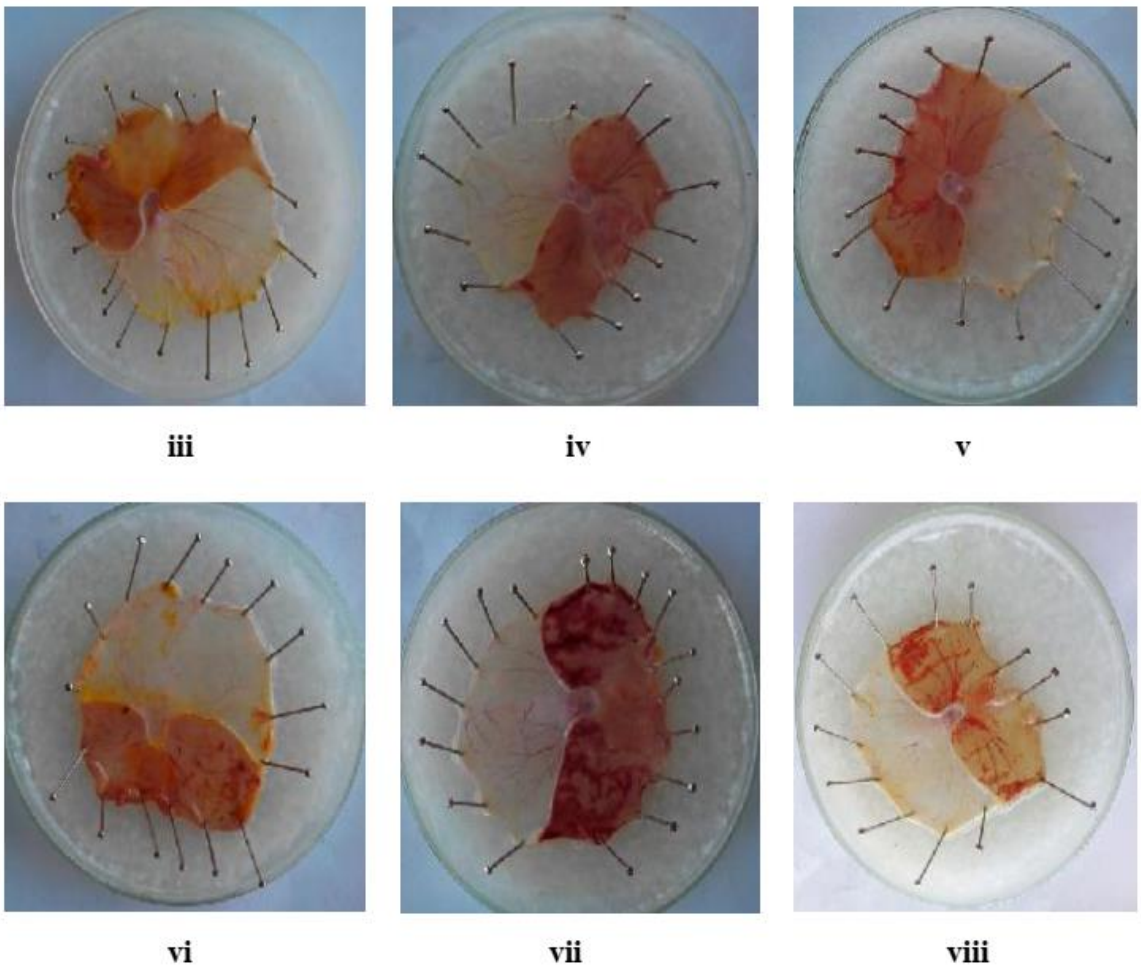

Figure -3: Effect of herbal extracts in ethanol induced ulcer in rats.

i - Disease Control group, **ii**- Ranitidine treated group, **iii -** ACL (250 mg/kg) + APN (125 mg/kg) + ABA (125 mg/kg) treated group, **iv** - APN (250 mg/kg) + ABA (125 mg/kg) + ACL (125 mg/kg) treated group, **v** - ABA (250 mg/kg) + ACL (125 mg/kg) + APN (125 mg/kg) treated group, **vi** - ACL (250 mg/kg) treated group, **vii** - APN (250 mg/kg) treated group, **viii** - ABA (250 mg/kg) treated group.

Pylorus ligation induced ulcer

Aqueous suspension of methanolic extracts of *Curcuma longa* (250mg/kg), *Berberis aristata* (125mg/kg) and *Piper nigrum* (125 mg/kg) were tested. The results obtained from the effect of combined methanolic herbal extracts in pylorus ligation were shown in Table-2 and Figure-4. In control animals, without any drug pH was 1.93±0.17. Combined methanolic extract shown significant rise in pH 4.73±0.52 as compared to control. Ranitidine (20mg/kg), standard drug was shown pH to 5.1 ± 0.17. This was more potent than the extracts used. The gastric volume has been decreased 3.23±0.49 and 2.86 ± 0.17 in methanolic extracts and ranitidine compared to control (6.73 ± 0.67). Gastric free acidity was found 24.66±3.8, 7.6±1.20 and 8.66±2.02 mEq/liter in control, standard and extracts treated animals respectively. Combined methanolic extract shown significantly reduced free acidity as compared to control, whereas similar potency with ranitidine in decreasing gastric acidity. Ranitidine (29.00±5.50 mEq/L) and combined methanolic extract (33.66±6.56 mEq/L) shown significant reduction in total acidity compared to control (62.33±3.93 mEq/L). In measurement of ulcer index, combined methanolic extract (2.5±1.25) shown significant lower ulcer index compare to control (14.66±0.60) and ranitidine (3.0±0.57). Percentage Inhibition of ulcer formation by methanolic extract (82.94±8.58%) was more significant compared to control (0.0%) and ranitidine (79.53 ± 3.93%).

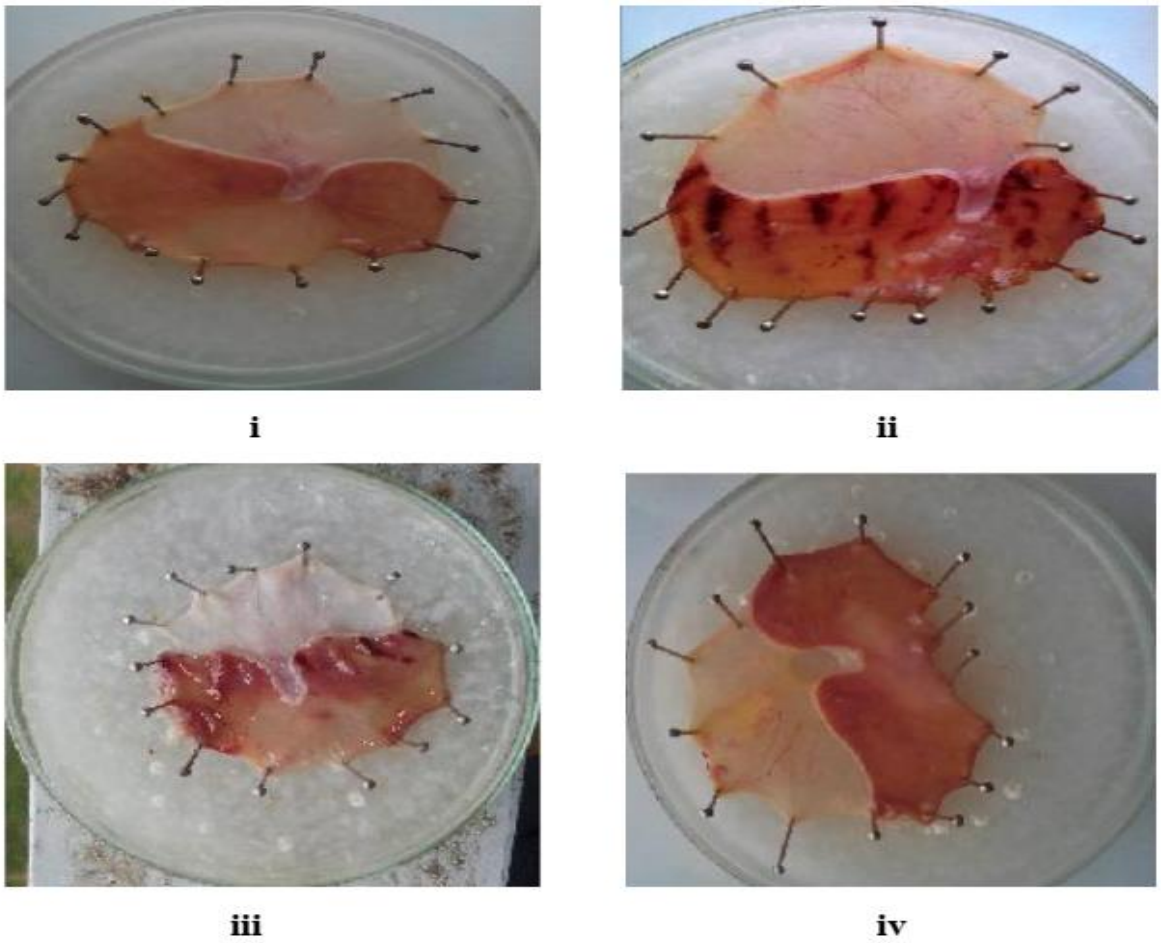

Figure -4: Effect of herbal extracts in Pylorus ligation induced ulcer.

(i - Normal Control group, **ii**- Disease Control group, **iii** - Ranitidine treated group,
iv - ACL (250 mg/kg) + APN (125 mg/kg) + ABA (125 mg/kg) treated group**)**

Table-2: Effect of combined herbal extracts on ulcer induced by pyloric ligation.

Treatment	Dose (mg/kg) p.o	Volume of gastricjuice (ml/4h)	pH	Free Acidity (mEq/L)	Total Acidity (mEq/L)	UlcerIndex	%Inhibitionof ulcer
Control (Normal saline)	2 ml/kg	6.73±0.67	1.93±0.17	24.66±3.8	62.33±3.93	14. 66±0.60	0.0±0.00
Standard (Ranitidine)	20 mg/kg	2.86±0.17**	5.1±0.17***	7.6±1.20**	29.00±5.50**	3.0±0.57***	79.53±3.93***
ACL (250 mg/kg) + APN (125 mg/kg) + ABA(125 mg/kg)		3.23±0.49**	4.73±0.52**	8.66±2.02**	33.66±6.56*	2.5±1.25***	82.94±8.58***

Where,
ACL = Aqueous methanolic extract of *Curcuma Longa*,
APN = Aqueous methanolic extract of *Piper Nigrum*,
ABA = Aqueous methanolic extract of *Berberis Aristata*
Values are mean ±SD, n = 6 in each group
*p<0.05; ** p<0.01; ***p<0.001 when compared with control group.

4. CONCLUSION

Today, numerous herbal medications and phytoconstituents are used to treat peptic ulcer. As a result of scientific research and traditional wisdom, we have a plethora of natural remedies with great potential as disease treatments. Based on ethnopharmacological research, carbenoxolone was the first gastric ulcer drug to be isolated from a plant. In addition, Gefarnate is derived from cabbage, which has been used in traditional medicine as an antiulcer agent. In recent years, a great deal of research has been conducted on herbal medicines to determine their potential efficacy in the treatment of peptic ulcers.

In a variety of animal models, such as aspirin, ethanol, pylorus ligation, etc., a number of herbal medicines have been found to be experimentally beneficial for peptic ulcer. Flavonoids (quercetin, rutin, and naringin), saponins (Araloside), tannins, resins and adhesives, alkaloids, and terpenoids are anti-ulcer herbal constituents. Turmeric, glycyrrhiza, and aloe gel have been widely utilized and their clinical efficacy documented as homegrown medicines.

Spices and botanicals have antioxidant properties that reduce superoxide formation, oxygen level, lipid peroxidation, and free radicals, and are therefore used to treat a variety of diseases. Herbal drugs and phytoconstituents exhibit antiulcer activity through various mechanisms, including decreased acid and pepsin secretion, increased mucosal content in the mucosa, antioxidant action, stimulation of mucosal cell proliferation, inhibition of H. pylori activity, cytoprotective action, inhibition of leukotriene and endothelin release, and reduction in inflammation. Herbs can protect the stomach mucosa by increasing the bioavailability of arachidonic acid, which leads to the biosynthesis of cytoprotective prostaglandins in the stomach.

To combat more severe diseases, it is essential to coordinate floating drug delivery system and herbal medications. It penetrates the gastric mucus layer and aids in providing a concentration sufficient for antibacterial activity in herbal medications. To improve the retention of an oral dosage form in the stomach, numerous methods, including high-density systems, expandable systems, unfolding systems, ballooning systems, and floating delivery systems, have been investigated.

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