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Assessing the hypolipidemic and gastro-liver protective activity of herbal combination with emphasis on PPI amid selected multiple antihypertensive drug combination in experimental animal models

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Abstract. – OBJECTIVE: Peptic ulcer (PU) and hypertension are chronic diseases affecting up to 10% and 30% of the adult population worldwide. Most of these patients will require treatment with a combination of antihypertensive medicines, which have adverse effects on the body's different organs. This study specifically focused on antihypertensive multi-drug induced PU disease and disturbance of liver function.

MATERIALS AND METHODS: During a 14-day oral administration of antihypertensive drugs, Cilnidipine (1 mg/kg), Rosuvastatin (1 mg/kg), Bisoprolol (0.52 mg/kg), and Clopidogrel (7.81 mg/kg) were observed for their effects on the stomach lining and liver function in Wister albino rats. This study aimed to assess the potential of an herbal combination of (BO) + (BA) + (ZO) 0.26 mg/kg body weight (b.w.) Powder and water mixture on the ulcer, lipid profile, and liver function for 14 days in the treatment of the indomethacin-induced gastric ulcers in rats at doses of 30 mg/kg b.w. for three days. Esomeprazole (20 mg/kg b.w.) is used as a standard reference to evaluate antiulcer activity in rat models. The experiment suggests that the gastroprotective effect of the herbal combination can be attributed to its reducing effect on the peptic and the Serum Glutamic Pyruvic Transaminase (SGPT) levels and within the normal range of 34.67 ± 0.88 IU/L.

RESULTS: The results for Total Cholesterol (TC), Triglyceride (TG), High density lipoprotein (HDL) and Low density of lipoprotein (LDL) of the herbal combination were 52 ± 9.81495 (mg/dl), 70 ± 12.12435 (mg/dl), 23.33 ± 6.06446 (mg/dl), 14.5 ± 1.32790 (mg/dl), respectively, where the standard group (atorvastatin) 5 mg/kg TC, TG, HDL and LDL were 69.77 ± 9.92 (mg/dl), 47.7 ± 10.35 (mg/dl), 33.43 ± 5.70 (mg/dl), 26.8 ± 3.70 (mg/dl), and control group total cholesterol, triglyceride, HDL and LDL were 68.67 ± 2.20 (mg/dl), 124.07 ± 2.94 (mg/dl), 49.14 ± 1.05 (mg/dl), 54.11 ± 1.15 (mg/dl).

CONCLUSIONS: This investigation reported that antihypertensive drugs did not produce gastrointestinal (GI) toxicity, and the morphological structure of the organ was not changed. So, it could be concluded that the herbal combination used in this experiment has a promising role in controlling lipid profile, liver function, and antiulcer effects. Moreover, multiple drug therapy for hypertension does not cause any harm to the stomach. Further investigations might be carried out on a larger scale to make these statements more valid.

Key Words:
Peptic ulcer, Herbal combination, Gastro-liver and hypolipidemic activity.

Introduction

The gastrointestinal system, also known as the digestive tract or the alimentary canal, is the channel through which food enters the body and is digested. The mouth, pharynx, esophagus, stomach, small intestine, large intestine, and anus are all parts of the gastrointestinal system[1]. Digestion and absorption of ingested food and liquids are handled by the gastrointestinal (GI) system[2]. The esophagus, the tube that joins the mouth and the stomach, is the first section of the GI tract. Before entering the stomach, food goes through the esophagus. As the stomach generates acids for the digestion of food, it can accommodate up to a quarter of the ingest-

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ed food. Food only lingers in your stomach briefly before little muscular contractions drive it into your small intestine. The three portions of the small intestine are the duodenum, jejunum, and ileum. Food is mingled with digestive fluids in these three sections, which break it down and digest it further[3]. The small intestine is also responsible for nutrient absorption into circulation. Bile, intestine-wall fluid, and other pancreatic fluids combine with the foods in the duodenum. This mixture of food and liquids goes into the jejunum, where carbs, lipids, proteins, and other nutrients are broken down. Finally, food enters the ileum, where nutrients and water are absorbed into the bloodstream. Food and fluids that are not absorbed move to the colon until excretion[4].

Peptic ulcer, including both stomach and duodenal ulcers, has posed a severe threat, and during the last couple of years, the morbidity and mortality rate has increased dramatically. Acid and pepsin can cause tissue damage anywhere in the gastrointestinal tract. The duodenal bulb and the antral section of the stomach are the most prevalent sites for ulcers, accounting for nearly 95% of all ulcers. Ulcers can also form in the distal duodenum or jejunum in patients with severe gastric acid hypersecretion in the small intestine at the stomach-jejunum junction[5-7]. However, the current therapeutic options are very limited, and potential therapeutics with lower side effects are highly required. So, this experiment has designed a combination of three readily available vegetables to develop an herbal formulation for treating peptic ulcers.

Materials and Methods

Drug Selection

The study focused on identifying the antihypertensive drugs that are most commonly prescribed, along with their respective dosages. More than 100 prescriptions from hypertensive patients were collected for the study from different hospitals in Dhaka, the capital of Bangladesh. These prescriptions were collected, examined, and concluded with the most often prescribed antihypertensive medicine utilized throughout animal research. These selected drugs were Cilnidipine, Bisoprolol, Rosuvastatin, and Clopidogrel. Indomethacin was used in the non-steroidal anti-inflammatory drugs (NSAID) category.

Herbal / Vegetables Selection and Collection

Brassica oleracea var. capitate, *Basella alba*, and *Zingiber officinale* were collected from the local market of Dhaka, Bangladesh. Details about these plants are given in Table I.

Preparation of Powder

All the vegetables were washed properly.

Brassica Oleracea var. Capitate (BO) Powder

Brassica oleracea var. capitate leaves were harvested, washed, cut, and sun-dried at 26-32°C. After it was properly dried, the powder was created using a blender machine (Figure 1A).

Basella Alba (BA) Powder

Basella alba leaves were harvested, washed, cut, and sun-dried at 26-32°C. After it was properly dried, the powder was created using a blender machine (Figure 1B).

Zingiber Officinale (ZO) Powder

Fresh *Zingiber officinale* was collected, and the pulp was removed. Then, it was washed, cut into small pieces, and dried in the sun at 26-32°C. After it was properly dried, the powder was created using a blender machine (Figure 1c).

Table I. Details about the nomenclature and taxonomy of study plants.

Brassica oleracea	*Basella alba*	*Zingiber officinale*
Scientific Name: *Brassica oleracea var. capitata* Name: *Brassica oleracea* (Capitata Group) Kingdom: Plantae Class: Magnoliopsida Order: Brassicales Family: Genus Brassica Genus: Brassica Species: *B. oleracea*	Scientific Name: *Basella alba* English: Malabar spinach Kingdom: Plantae Unranked: Angiosperms Unranked: Eudicots Unranked: Core eudicots Order: Caryophyllales Family: Basellaceae Genus: Basella Species: Basella alba Linn	Scientific Name: Zingiber officinale English Name: GingerCommon Kingdom: Plantae Order: Zingiberales Family: Zingiberaceae Genus: Zingiber Species: Z. officinale

A B C

Figure 1. **A**, *Brassica oleracea*. **B**, *Basella alba*. **C**, *Zingiber officinale.*

Sample (Herbal Combination) Suspension Preparation

Specific amounts of BO, BA, and ZO powder were mixed, and 1 ml of water was added to make the sample suspension.

Experimental Animal

For this investigation, Wistar Albino rats were collected from the Jahangirnagar University Lab. Female Albino rats, five months old and weighing between 110 g and 230 g, were utilized in the experiments. For five days before the start of the investigation, the rats were kept in colony cages in the department's temperature-controlled animal room (25-30°C). The bedding was changed every day to guarantee cleanliness and hygiene.

Experimental Design

Indomethacin was administered orally at 30 mg/kg body weight for three consecutive days for ulcer induction.

For the study, the rats were divided into four groups, consisting of n = 3 rats. The four groups were:

- Control group
- Standard group
- Group- 1 sample / Herbal combination (BO+BA+ZO) powder
- Group-2 (Antihypertensive drug group)

Medication and Diet

Blood collection

The rats were slaughtered, and blood samples were taken after 14 days of successfully administering the experimental drugs and samples. A 2-3 ml blood sample was obtained using the heart puncture method. After centrifuging the blood, the serum was collected and stored for future research.

Biochemical Test

Two biochemical tests were performed as part of the inquiry. Serum Glutamic Pyruvic Transaminase (SGPT) is the first, while the lipid profile is the second. The lipid profile looked at Total Cholesterol (TC), Triglyceride (TG), High-density lipoprotein (HDL), and Low-density lipoprotein (LDL values. Using spectrophotometry, both tests were performed on a biochemistry analyzer Backman Coulter AU-480 (USA).

Morphological Study

Even though GI toxicity and liver toxicity tests were the key concerns, other major organs were also examined for any physical abnormalities. The rats were slaughtered when the research period finished, and their average body weights were reported. After that, the essential organs (liver, kidney, spleen, and stomach) were removed, and physical appearance changes such as color and size were compared to the control group. The stomach was dissected to look for any symptoms of ulcers or color change in the mucus layer.

Results

Weight Variation Result

Initially, the weight was 156 ± 2.52 gm in the Control group, and the final weight reached 155.47 ± 1.01 gm. In the Standard group, the initial weight was 175.15 ± 3.14 gm, and the final weight was 171 ± 2.52 gm. In the Sample (herbal) group, the initial weight was 129 ± 2.08 gm, and the final weight was 126 ± 3.17, where the antihypertensive drug, the initial weight was 195 ± 7.21 gm and final weight was 183 ± 7.02 gm. The experiment measured the initial and final body weight of the

Table II. Medication and diet performed throughout the study.

Group	Medication, Dose, and Manufacturer	Duration	Observation
Control Group	Normal water	14 days	Prevent hypotension in the antihypertensive drug group frequently, and salt was used by checking blood pressure.
Standard Group	Esomeprazole (20 mg/kg)		
Antihypertensive drugs Group	Cilinidipine (1 mg/kg) (Opsonin Pharmaceuticals),		
	Rosuvastatin (1 mg/kg) (Square Pharmaceuticals),		
	Bisoprolol (0.52 mg/kg) (Radiant Pharmaceuticals),		
	Clopidogrel (7.81 mg/kg) (Square Pharmaceuticals)		
Sample group (Herbal)	(BO) powder (0.26 g/kg) + (BA) powder (0.26 g/kg) + (ZO) powder (0.26 g/kg) + Water		

experimental animals. Here, the weight loss in the control group was minimal, 0.86 gm loss only, and the standard group weight loss was 4.15 gm. The weight of the sample group was 3 gm, and the antihypertensive group's weight loss was 12 gm.

Maintaining a regular, healthy diet throughout the study had no noticeable effects on the weight variation of the control group. In the sample (herbal), weight loss occurs due to the presence of fiber. The sample group contains ginger and cabbage, which can decrease body weight. The use of antihypertensive drugs caused weight loss in some groups. This is because the group included Rosuvastatin which is known to lead to weight loss. Therefore, it can be inferred that the antihypertensive medications along with Esomeprazole played a significant role in reducing weight. However, when the herbal sample was applied, it had very little impact on weight loss as shown in Table III.

Biochemical Test Result

Based on the results shown in Table IV, it is clear that the SGPT levels of the standard control, sample (herbal), and antihypertensive drug groups were significantly different. The normal range for SGPT is between 10-40 (IU/L). The control group had an SGPT level of 40.33 ± 1.76 (IU/L), while the sample (herbal) group had an SGPT level of 34.67 ± 0.88 (IU/L). Comparing the SGPT values with the control group, it was found that the sample group's SGPT level decreased by 5.66 (IU/L). This suggests that the sample (herbal) group has the potential to reduce SGPT levels.

Table V illustrates the lipid profile in the control, standard, and sample groups. For the standard group, atorvastatin (5 mg/kg) was orally administered as an anti-hyperlipidemia drug. The total cholesterol level of the sample group was 46.67 mg/dl, compared to 68.67 mg/dl in the control group and 42 ± 9.92 mg/dl in the standard groups. Consequently, it is assumed that the sample treatment caused the total cholesterol level to drop compared with the control. The triglyceride value in the sample group was 60 mg/dl, compared to 124.07 mg/dl in the control group, and 47.7 ± 10.35 mg/dl in the standard

Table III. Effects on body weight of the sample and conventional drugs.

Group Name	Body weight variation in gm			
	Medication and Dose	Initial weight (gm)	Final weight (gm)	Weight variations (gm)
Normal control	Normal Water	156 ± 2.52	155.47 ± 1.01	0.86 gm loss
Standard	Esomeprazole (20 mg/kg)	175.15 ± 3.14	171 ± 2.52	4.15 gm loss
Sample (Herbal)	(BO) powder (0.26 g/kg) + (BA) powder (0.26 g/kg) + (ZO) Powder (0.26 g/kg) + Water	129 ± 2.08	126 ± 3.17	3 gm loss
Antihypertensive drug	Cilinidipine 1 mg/kg	195 ± 7.21	183 ± 7.02	12 gm loss
	Rosuvastatin 1 mg/kg			
	Bisoprolol 0.52 mg/kg			
	Clopidogrel 7.81 mg/kg			

[Data were expressed as mean ± SEM (Standard Error Mean) where n = 3 for the single group].

Table IV. Effects of the sample (herbal combination) on SGPT (ALT), a biomarker for liver function.

	Liver marker SGPT (ALT)		
Group	**Medication and Dose**	**SGPT (ALT) level (IU/ L)**	**Normal range of SGPT**
Control	Normal Water	40.33 ± 1.76	10-40 (IU/L)
Sample (Herbal)	(BO) powder (0.26 g/kg) + (BA) powder (0.26 g/kg) + (ZO) powder (0.26 g/kg) + Water	34.67 ± 0.88	

group. That made a significant impact on sample results. There was an issue with the HDL value since the herbal combination also lowered the value of HDL compared to the control and standard groups. HDL value was 49.14 ± 1.05 mg/dl in the control group, 41 ± 5.70 mg/dl in the standard group, and 42.33 ± 6.06446 mg/dl in the sample group. However, there was a remarkable change in LDL, where the sample group's value was 14.5 mg/dl, the control group's value was 54.11 mg/dl, and the standard group value was 26.8 ± 3.70 mg/dl, with a decrease in LDL of 39.61 mg/dl. Additionally, compared to the control, all total cholesterol, triglycerides, HDL, and LDL measurements were significantly lower (Table V).

Morphological Investigation of Stomach

The purple circle indicates ulcer formation, whereas the black indicates inflammation in control group animals (Figure 2).

Inflamed tissues were spotted in the standard group animal's stomach; in antihypertensive multi-drug therapy and herbal combination, no evidence was found that indicates any toxic effects on the stomach layer of the experimental animals (Figure 3 A-C).

Morphological Study of the Stomach of the Sample (Herbal) Group with the Standard Group

Appearance and color of the stomach were normal, and no abnormalities were found in Figure 3C. It was treated with herbal combination (BO) powder (0.26 g/kg) + (BA) powder (0.26 g/kg) + (ZO) powder (0.26 g/kg) + water. It was discovered that herbal combination has antiulcer activity. The herbal combination helped to reduce stomach ulcers.

Morphological Study of the Stomach of the Antihypertensive Group with the Standard Group

Appearance and color of the stomach were normal, and no abnormalities were found in Figure 3C. The exterior layer of the stomach showed no morphological alterations, while the interior layer developed a red color in both the control and standard groups. However, no discoloration or perforation was identified in the antihypertensive drug groups.

Table V. Effects on body weight of the sample and conventional drugs.

		Serum lipid profiles (mg/dl)			
Group	**Medication and Dose**	**Total Cholesterol**	**Tri-glycerides**	**HDL cholesterol**	**LDL cholesterol**
Control	Normal water	68.67 ± 2.20	124.07 ± 2.94	49.14 ± 1.05	54.11 ± 1.15
Standard	Atorvastatin (5 mg/kg)	42 ± 9.92	47.7 ± 10.35	41 ± 5.70	26.8 ± 3.70
Sample (Herbal)	(BO) powder (0.26 g/kg) + (BA) powder (0.26 g/kg) + (ZO) Powder (0.26 g/kg) + Water	46.67 ± 9.81495	60 ± 12.12435	42.33 ± 6.06446	14.5 ± 1.32790

[Data were expressed as mean ± SEM (Standard Error Mean) where n = 3 for a single group]. Total Cholesterol (TC) Triglyceride (TG), High density lipoprotein (HDL), Low density of lipoprotein (LDL). All data presented as mg/dl.

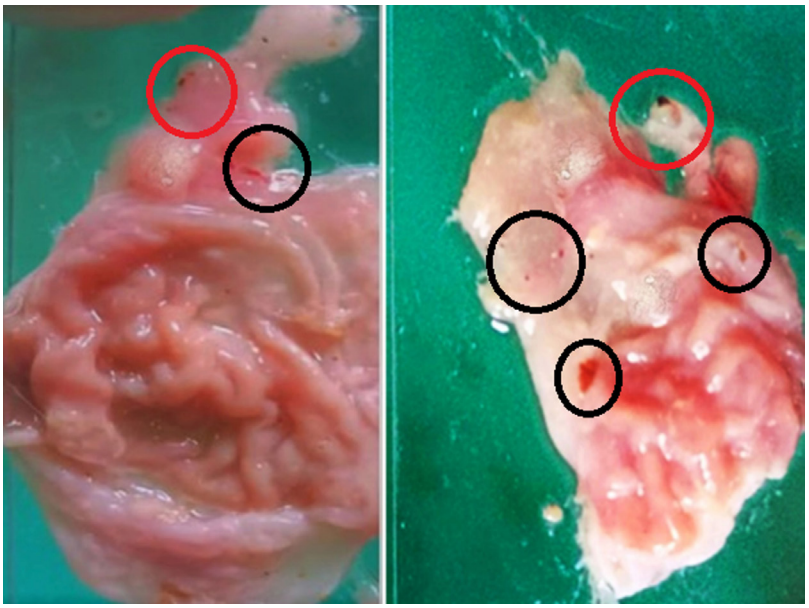

Figure 2. In the image of control group red circled portion indicates slightly inflamation and black circled parts indicate severe inflammation and ulcer.

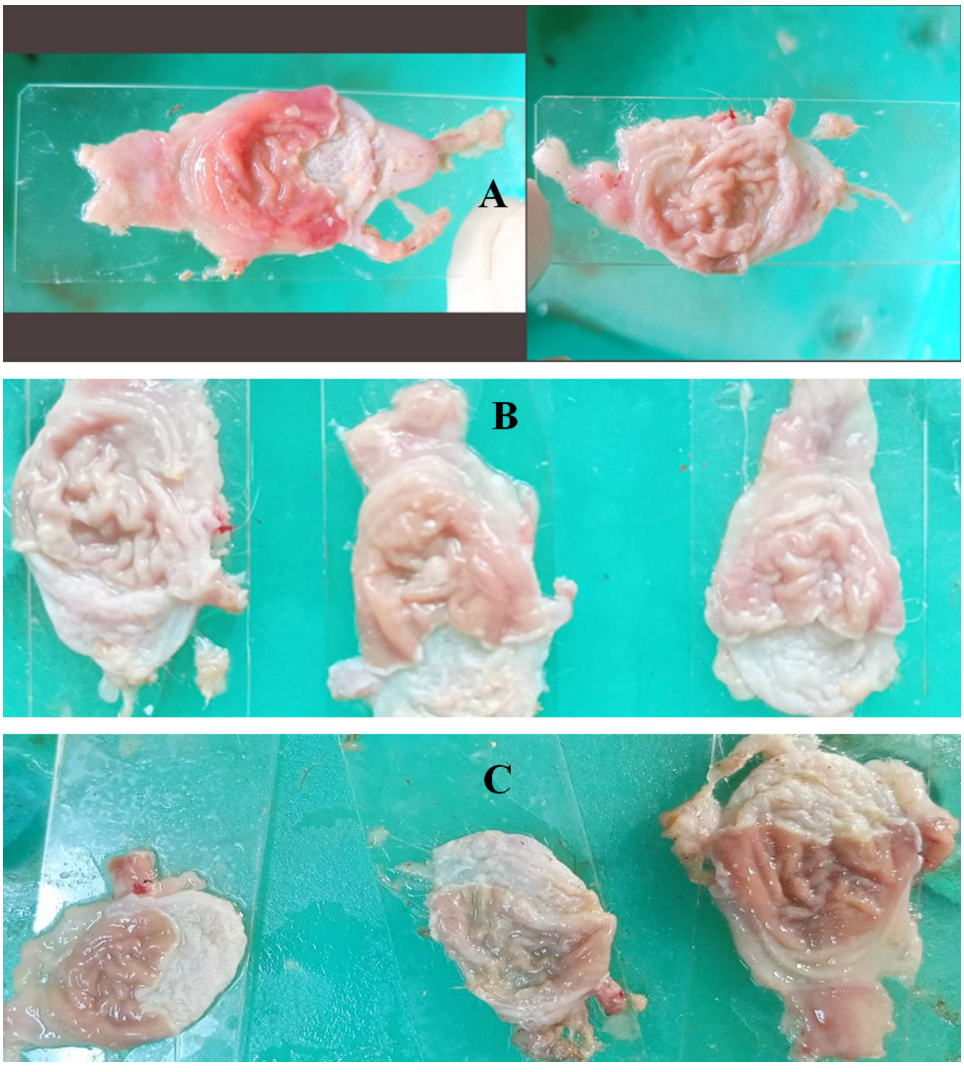

Figure 3. The stomach of the standard group (**A**), the stomach of the antihypertensive Drug group (**B**), and the stomach of the sample (Herbal) group rat (**C**).

Discussion

Peptic ulcer is a gastrointestinal disorder due to an imbalance between aggressive factors like acid, pepsin, and *Helicobacter pylori* and defensive factors like bicarbonate secretion, prostaglandins, gastric mucus, and innate resistance of the mucosal cell factors. Due to lower side effects, the herbal combination is an important choice to treat peptic ulcers. So, this experiment has been carried out and observed biochemical and morphological parameters.

There are several treatments for peptic ulcers, including antibiotics and proton pump inhibitors. The bacteria H. pylori may cause stomach ulcers[8]. Currently, several antibiotics are prescribed for treating stomach ulcers, such as amoxicillin, clarithromycin, metronidazole, tinidazole, tetracycline, and levofloxacin[9].

Proton-pump inhibitors (PPIs) have fundamentally altered how peptic ulcer disease is managed since they were first used in medicine in the late 1980s. PPIs continue to be the cornerstone of medical treatment for gastrointestinal bleeding brought on by peptic ulcers. Although a definite mortality advantage has not been shown, well-conducted systematic reviews recommend using PPIs before endoscopic assessment for acute upper gastrointestinal bleeding[10,11]. Following a peptic ulcer diagnosis, the period of PPI medication varies on the underlying cause, location, and complications of the ulcer. The ultimate objective of PPI therapy is to facilitate ulcer healing while addressing the underlying causes of the ulcer(s) through acid suppression. Patients with NSAID-induced ulcers are advised to avoid aggravating medications, while positive *H. pylori* tests urge treatment of the illness[12,13]. Besides, several different medications are used to treat peptic ulcers, such as H2 receptor antagonists[14]. Details are given in Figure 1 and Table I.

Plants' Distribution, Traditional Uses, and Pharmacological Uses

Basella alba[15]

Distribution: Cabbage is classified as a cool-season crop. It is cultivated in various countries including China, India, Russia, Bangladesh, Japan, Ukraine, South Korea, and others. Most cabbage production occurs in the southern states during the fall, winter, and spring months and in the northern states during the summer[16-19].

Traditional uses*:* Cabbage treats stomach pain, excess stomach acid, stomach, and intestinal ulcers, and Roemheld syndrome. Cabbage can also help with asthma and morning sickness. It is also used to prevent osteoporosis and lung, stomach, colon, breast, and other types of cancer. Breastfeeding mothers may apply cabbage leaves or cabbage leaf extracts to their breasts to reduce swelling and pain[20,21].

Pharmacological uses: Cabbage is low in calories and vitamins, minerals, and antioxidants. Cabbage is high in vitamin C, a potent antioxidant that may aid in preventing heart disease, certain cancers, and vision loss. Cabbage contains over 36 different types of anthocyanins, making it an excellent choice for heart health. Eating more potassium-rich cabbage is a tasty way to lower high blood pressure and keep it within a healthy range. Cabbage is high in soluble fiber and plant sterols. These compounds have been shown to lower LDL cholesterol. Cabbage is a fantastic source of vitamin K, which is essential for blood clotting[22-24].

Basella alba species[16]

Distribution: Bangladesh, India, China, Japan, the Philippines, Borneo, Fiji, Hawaii, the West Indies, Brazil, Guyana, and Central America are home to a large population of this *Basella alba* species.

Traditional Uses: The herb is renowned for having demulcent, diuretic, and emollient properties. Chinese medicine claims to alleviate fever and neutralize toxins using the entire plant. The pulped or crushed leaves are used topically to treat ulcers and expedite the maturity of abscesses. It treats constipation in children and pregnant women and is thought to have laxative qualities. Pregnant women are given the extract as a safe aperient when combined with *Hibiscus rosa-sinensis.* The plant's juice is used as food coloring, a facial rouge, and a dye for official seals. The plant is used to treat aphthae in southern India[16,20,25,26].

Pharmacological uses: *B. alba* has androgenic activity, anti-inflammatory activity, wound healing activity, central nervous system (CNS) depressant activity, nephroprotective effect, cytotoxic and antibacterial activity, and antioxidant activity. Including *B. alba* leaves in patients' diets may help them remain healthy and lessen anemia. Antiulcer activity parameters have been studied, including ulcer index, percentage of ulcer inhibition, gastric pH, pepsin content, lipid hydroperoxides, superoxide dismutase (SOD), glutathione peroxidases (GPx), catalase, glutathione (GSH), vitamin C, and vitamin E[20,21,27].

Zingiber officinale[17]

Distribution: Ginger is cultivated globally with India, China, Indonesia, Nepal, Thailand, Nigeria, Bangladesh, Japan, and the Philippines being the top producers. India and China are the two that predominately supply the global market[28].

Traditional uses: Ginger has a long history of usage in Ayurvedic and herbal therapy. Specifically, motion sickness and hyperemesis gravidarum symptoms can be treated with it. In Southeast Asia, ginger has been widely used as a food and medicinal ingredient for millennia. It is essential to many traditional medical systems worldwide, including Chinese, Ayurvedic, Unani, Tibetan, Sri Lankan, Korean, Arabic, and Greek. It also has several uses in other conventional and folk medical systems. As a carminative and digestive, as well as a treatment for nausea and vomiting, motion sickness, stomach aches, stomach ulcers, bacterial dysentery, and dyspepsia, ginger has long been a key component in the management of digestive diseases[29-32].

Pharmacological uses: It has been demonstrated that ginger has protective benefits against ulcerogenic. Ginger's impact on stomach dysrhythmias brought on by hyperglycemia. Free radicals are scavenged by ginger. It shields lipids from oxidative damage. Detoxifying enzymes are modulated. Ginger possesses antimicrobial and antimutagenic properties. The gentamycin toxin's harmful effects on the reproductive system were inhibited by ginger extract, which also reduced testicular apoptosis. The gastrointestinal system is where ginger's effects are most noticeable. The reproductive system was inhibited by ginger extract, which also reduced testicular apoptosis. The gastrointestinal system is where ginger's effects are most noticeable because it seems to increase gastric motility. Ginger has been shown to offer antiulcer properties and reduce mucosal damage[33-41].

After this investigation, it was reported that the weight of the sample group was 3 gm, and the antihypertensive group's weight loss was 12 gm. The control group's SGPT level was 40.33 ± 1.76 (IU/L), whereas the sample (Herbal formulation) group's SGPT was 34.67 ± 0.88 (IU/L). Comparing SGPT values with the control group, it was found that the sample group's SGPT decreased by 5.66 (IU/L). This sample (Herbal) group can reduce SGPT levels. The sample group's total cholesterol level was 52 mg/dl, triglyceride value was 70 mg/dl, HDL value was 32.33 mg/dl, and LDL value was 14.5 mg/dl. Compared to the control, all total cholesterol, triglycerides, HDL, and LDL measurements were significantly lower. In another investigation[42], it was discovered that antihypertensive medication has no harmful effects on GI. Also, see PPI or antiulcer drugs are not required, along with several antihypertensive medications.

Conclusions

In this study, herbal combinations have significant antiulcer activity, liver function, and lipid profile in animal models. The findings of this study support the view that herbal combinations have antiulcer activity and lipid profile and are beneficial for liver function.

Ethics Approval

Ethical Approval for this study was granted by the Department of Pharmacy, Faculty of Allied Health Sciences, Daffodil International University Dhaka under Ref No. ETH/PHRM/23-101.

Informed Consent

Not applicable.

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Conflicts of Interest

The authors declare no conflict of interest.

Authors' Contribution

Conceptualization, R.P. Monisa.; methodology, A.K. Azad.; software, I. Rahman.; validation, J.T. Israt.; formal analysis, A. Shopnil.; investigation, T. Aziz.; resources, A. Metab.; data curation, F.A. Abdullah; writing-original draft preparation, A.K. Azad.; writing-review and editing, H.A. Thamer.; visualization, A. Metab.; supervision, T. Aziz.; project administration, T. Aziz; funding acquisition, T. Aziz.

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