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Poly-Herbal Extract: A Promising Approach for Mitigating Gastric Ulcers in Rat Models

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ABSTRACT

A prevalent condition that affects humans is stomach ulcers. The constraints and rapid expansion of civilization, particularly a stressful lifestyle, are contributing to an increase in the occurrence of ulcers. New synthetic pharmaceuticals and herbal drugs must fulfil global quality, safety, and efficacy criteria as Western medicine progresses. The stomach mucosa breaks down into gastric ulcers, which have a diameter greater than 5 mm and extend into the muscularis mucosa. Changes in the stomach's defence mechanisms may alter the gastric mucosa, resulting in erosion and ultimately ulceration. This study aims to explore the potential of tamarind seed and aloe vera extracts in mitigating gastric ulcers, presenting a natural alternative to NSAID-induced ulcer treatment. The herbal extract's effectiveness in reducing oxidative stress and gastric mucosal damage was assessed in comparison to omeprazole. The anti-ulcer activity was assessed using approximated biochemical parameters, and in a dose-dependent manner, the outcomes were statistically noteworthy in contrast to the rats in the ulcer group.

Keywords: Gastric ulcer; Aloevera; Tamarind seeds; Indomethacin; Omeprazole

NOMENCLATURE

CAT : Catalase
CCSEA : Committee for control and supervision of experiments on animals
GI : Gastrointestinal
GPx : Glutathione peroxidase
IAEC : Institutional animal ethics committee
MDA : Malondialdehyde
MPx : Myeloperoxidase
NSAIDs : Nonsteroidal anti-inflammatory drugs
PG : Prostaglandin
PPIs : Proton pump inhibitors
SOD : Superoxide dismutase

1. INTRODUCTION

Peptic ulcers, characterized by disruptions in the mucosal integrity of the stomach, duodenum, or esophagus, present a significant health challenge[1]. While conventional treatments such as Proton Pump Inhibitors (PPIs) like omeprazole are effective in reducing gastric acid secretion, they come with their own set of drawbacks, including long-term dependence, potential drug interactions, and side effects like nutrient malabsorption and an increased risk of gastrointestinal infections[2]. Moreover, patients on chronic Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) therapy, such as aspirin and indomethacin, face a heightened risk of developing ulcers due to the suppression of mucosal prostaglandin synthesis, leading to weakened mucosal defenses[3].

The use of NSAIDs remains essential for managing pain and inflammation, but their associated Gastrointestinal (GI) complications significantly limit their therapeutic scope[4]. The primary concern with NSAIDs is their ability to cause erosive and ulcerative lesions in the gastric lining, particularly in chronic users. This has led to the search for safer, natural alternatives that can address both the root cause of ulcer formation and the side effects caused by NSAIDs.

In this context, the exploration of traditional medicinal plants like *Tamarindus indica* (tamarind) and *Aloe barbadensis* (aloe vera) offers a promising avenue[2]. Both tamarind seeds and aloe vera have long been recognised for their anti-inflammatory, antioxidant, and wound-healing properties. Tamarind seeds, commonly used in traditional medicine across Asia and Africa, have been reported to alleviate gastric discomfort and provide protective effects against mucosal damage[5,6]. Aloe vera, known for its soothing and tissue-repairing properties, has demonstrated the potential to reduce inflammation and promote ulcer healing[7].

This study aims to assess the anti-ulcerogenic potential of tamarind seeds and aloe vera in mitigating NSAID-induced gastric ulcers. By focusing on these natural

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alternatives, we seek to address the gaps in conventional therapies, particularly the limitations and side effects associated with synthetic drugs like omeprazole.

2. MATERIALS AND METHODS

2.1 Drugs and Chemicals

The local farmers of Mallapurain Chitradurga, and Hullekere in Tumkur, India, provided the Tamarind Seeds (*Tamarindus indica Linn.*).Aloe Vera powder purchased from Patanjali Ayurveda store, Bagalagunte, Bangalore-560073. We obtained the medications indomethacin and omeprazole from Bharani Medicals, located at Bhuvenshwari Nagar, Bagalagunte, Bangalore-560057.Normal saline, Methanol, Petroleum ether, and Hydrogen peroxide 100V 30 % Solution w/v, were procured from KFC, Sigma-Aldrich, Bengaluru.

2.2 Animals

The experiment was approved by the Acharya & BM Reddy College of Pharmacy's institutional animal ethics committee (Approved IAEC no: 997/PO/Re/S/06/ CPCSEA) and carried out in compliance with CCSEA, New Delhi, India norms. Wistar albino rats weighing 150-200g were chosen for in vivo studies. Normal environmental conditions were maintained for the animals, including a 12-hour light/dark cycle, a controlled humidity level, and normal feed pellets and water available for consumption.

2.3 Authentication of Seeds

The indigenous farmers of Mallapura, Chitradurga, and Hullekere, Tumkur, India, provided the dried seeds of *Tamandus indica Linn*, which were verified for authenticity by Dr. Kanupriya, Senior Scientist at the Indian Institute of Horticultural Research, Bengaluru-560089, Division of Fruit Crops.

2.4 Extraction of Seeds for Crude Drug

To detach their outer brown covering, the dried *Tamarindus indica* seeds were roasted to 140 °C in a hot air oven for 45 minutes, cooled, and then cracked. The only seed coat to be gathered and pulverized into a fine powder was the brown-red one. Petroleum ether was then used to defeat them. Following a 48-hour methanol extraction and defatting process using petroleum ether, the powdered seed coat was filtered with filter paper (Whatman No. 4). A second extraction of the residues using 100 milliliters of methanol was performed. The solvent in the combined extract was taken out with less force (34–36 kPa) by employing a rotating vacuum heater set at 40 °C. Subsequently, the contents underwent air drying[2].

2.5 Indomethacin-Induced Ulcer Model

The animals were fasted for 18-24 hours before the experiment, with access to water only, to ensure empty stomachs and enhance ulcer induction sensitivity. Following the fasting period, indomethacin, an ulcerogenic agent, was administered orally via gavage at a dose of 20 mg/kg, suspended in saline. The animals were then kept in their cages for 4-6 hours, during which gastric ulcers developed as a result of indomethacin-induced inhibition of prostaglandin synthesis, leading to gastric mucosal damage.

After ulcer induction, the combination of *Tamarindus indica Linn* and *Aloe Vera* was administered orally at two different dose levels: a low dose of 200 mg/kg and a high dose of 400 mg/kg. The standard drug, omeprazole, was administered at a dose of 20 mg/kg. These treatments were given daily for 15 consecutive days to evaluate their therapeutic effects on the indomethacin-induced ulcers.

The animals were grouped according to Table 1, which categorized them based on different treatment regimens. This allowed for a clear assessment of the efficacy of the treatments across different groups.

At the end of the treatment period, the animals were sacrificed humanely using an overdose of CO_2 asphyxiation. A midline incision was made, and the stomachs were carefully dissected out and opened along the greater curvature to expose the gastric mucosa for ulcer assessment and further analysis[7,12].

Table 1. Grouping of experimental animals (n=6)

Group	Treatment(Dose and route of administration)
Normal control	Normal Saline (2 ml/kg, p.o.)
Positivecontrol	Indomethacin[3] (20 mg/kg, p.o.)
Standard treatment	Omeprazole[2] (20 mg/kg, p.o.)
Treatment low dose	Methanolic extract of Tamarind Seeds + Aloe Vera (200 mg/ kg, p.o.)
Treatment high dose	Methanolic extract of Tamarind Seeds + Aloe Vera (400 mg/ kg, p.o.)

2.6 Parameters

2.6.1 Estimation of Gastric Juice

The measuring cylinder was used to determine the total volume of the stomach content[15].

2.6.2 Total Acidity Estimation

A 1-milliliter sample of gastric juice, diluted with an equal amount of distilled water, was introduced into a conical flask with a 50-milliliter capacity. Add two drops of phenolphthalein indicator, and titrate the liquid using 0.01N NaOH until a consistent pink hue appears. Note the quantity of 0.01N NaOH utilized and indicate the overall acidity in milliequivalents per liter (mEq/L)[16,17].

The formula for estimation of Total acidity:

$$\text{Acidity} = \text{NaOH volume} \times N \times 100$$

2.6.3 Free Acidity Estimation

Topfer's reagent replaced phenolphthalein as the indicator in the titration of a sample of stomach juice mixed with 0.01N NaOH. There was a noticeable canary

yellow coloring, and the quantity of 0.01N NaOH used was recorded. The free acidity was computed with the same procedure that was used to determine the total acidity in an ulcer caused by ethanol[18].

2.6.4 Catalase (CAT) Estimation

To prepare a 10 % w/v homogenate, stomach tissue underwent homogenization using a homogenizer in ice-cold Tri's buffer. Following homogenization, the resultant mixture was centrifuged for 15 minutes at 4 °C at 10,000 rpm. Next, 1.9 ml of 50 mM phosphate buffer and 0.1 ml of the supernatant were mixed in a cuvette. One milliliter of recently made 30-millimeter hydrogen peroxide was added to this mixture. Utilizing anultraviolet spectrophotometer, the alteration in absorbency was measured over three minutes at 240 nm, with 30-second intervals. The blank value was determined using 0.1 ml of supernatant-free distilled water. The catalyst concentration required to maintain a 50 % change in absorbance for the control sample within one minute is defined as one unit of enzyme activity. Units of enzyme activity per milligram of protein are used to express catalase activity[19].

The formula for estimation of CAT

Catalase = (Absorbance×Volume of reaction mixture)/(43.6 ×Volume of sample)×1/(mg protein)

2.6.5 Superoxide Dismutase (SOD)Estimation

To prepare a 10 % weight/volume homogenate, stomach tissue underwent homogenization using a homogenizer in a Tris buffer that was frozen. After that, the homogenate was centrifuged for 30 minutes at 4 °C at 5000 rpm. After adding 0.1 ml of stomach supernate, 0.1 ml of phenazine methosulphate, 0.3 ml of nitroblue tetrazolium, 0.2 ml of 0.052 M sodium pyrophosphate buffer (pH 8.3), and 0.2 ml of NADH, the reaction was stopped with 1 milliliter of glacial acetic acid and heating the mixture for 90 minutes at 300 degrees Celsius. Following stirring, 4 ml of n-butanol was added before centrifuging for 10 minutes at 4000 rpm. Using the blank value, the organic layer's absorbance at 550 nm was calculated.Determined with 0.1 ml of tissue supernatant-free distilled water. Enzyme activity was quantified based on the quantity of enzyme required to reduce the chromogen absorbance in the control sample by 50 % during testing[20].

The formula for estimation of SOD:

SOD = (Control absorbance-Sample absorbance)/(Control absorbance/2)×1/(mg protein)

2.6.6 Estimation of Malondialdehyde (MDA)

To prepare a 10 % w/v homogenate, stomach tissue underwent homogenisation with a homogenizer in an ice-cold Tris buffer. The combination was composed of 0.1 ml of homogenate, 1.5 ml of 0.8 % thiobarbituric acid solution, 0.2 ml of 0.1% sodium dodecyl sulfate, and 1.5 ml of 20 % acetic acid solution. After adding distilled water to make a total volume of 5 mL, the mixture was heated to 95 °C for 60 minutes, utilizing a condenser made of glass,following cooling under running tap water, 5 ml of a 15:1 n-butanol and pyridine combination were added, followed by vigorous shaking. After a 10-minute after 4000 rpm of centrifugation, the organic layer was separated, then the intensity of absorption at 532 nm was determined compared to a reference blank. Using the standard curve, the tissue MDA level was determined and interpreted as nmol/g wet tissue[21].

The formula for estimation of MDA:

x = y-0.0162⁄0.0654

Where, y = absorbance of the sample

2.6.7 Estimation of Glutathione peroxidase (GPx)

To create a 10 % w/v homogenate, stomach tissues were uniformized using a polytron homogenizer in a cold phosphate buffer. The resulting homogenate was centrifuged for 15 minutes at 4 °C and 5,000 rpm, after which the supernatant was collected. For GPx estimation. For the preparation of a 0.4 M phosphate buffer solution (pH 7), test tubes were loaded with 0.2 M EDTA, 0.1 M sodium azide, 0.1 M GSH, 0.1 M H2O2 solution, and 0.2 M tissue supernatant, followed by incubation for ten minutes at 37 °C. The tubes were then heated to ambient temperature, and before centrifugation at 2000 rpm for 10 minutes, 0.5ml of 10 % TCA was added. After centrifugation, 0.1 milliliters of 0.04 % DTNB solution was introduced to the supernatant, and the solution's absorbance at 420 nm was calculated in comparison to the blank. A blank reaction mixture was created by omitting the tissue supernatant. Theμ moles of GSH oxidized/min/mg protein was the expression for the GPx activity[22].

The formula for estimation of GPx:

GPx = ((change in absorbance/min×GSH std×volume of total mixture))/((absorbance of sample×307.32×volume of sample source)×protein(mg/ml))

2.6.8 Estimation of Myeloperoxidase (MPx)

Using a homogenizer with a volume of 1/10 of the stomach weight stomach tissue was homogenized in ice-cold phosphate buffer containing 0.5 % hexadecyl trimethyl ammoniumbromide. The homogenate was centrifuged for 30 minutes at 4ºC at 15000 rpm. After adding 40 µl of the supernatant to 960 µl of phosphate buffer that contained hydrogen peroxide (0.0005%) and o-dianisidine dihydrochloride (0.167 mg/ml), the concoction was intensely agitated. For three minutes, every 60 seconds, the absorbance at 460 nm was measured. An activity's single unit of measurement was the quantity of MPx needed to cause a change in absorbance measured at 460 nm for three minutes. The units/ml for MPx activity statistics are displayed[23].

The formula for estimation of MPx:

$MPX = (\Delta A \times Vt \times 4)/(E \times \Delta t \times Vs)$

Where, Vt = Total volume (ml)
Vs = Sample volume (ml)
Δ A = Change in absorption
E = Extinction coefficient
Δ t = Measuring time

2.6.9 Evaluation of gastric mucosal injury (Ulcer index)

Ulcer indexing was completed using the following modified Adami et al. (1997) grading system: Lesions are represented by the numbers 0 = no lesions, 1 = hemorrhagic suffusions, 2 = small ulcers up to 3 mm in size ranging from 1 to 5, 3 = 5 numerous small ulcers exceeding 5 or 1 ulcer exceeding 3 mm, 4 = many numerous ulcers exceeding 3 mm, and 5 = perforated ulcers. The results were analyzed after the mean score for each group was calculated[24].

2.6.10 Statistical Analysis

The mean ± SEM was employed to showthe values (n = 6). ANOVA was used forthe data analysis, and a statisticallysignificance level of P≤0.05 for the Dunnett test indicates a notable variation between the treatment and disease groups.

3. RESULTS

3.1 Effects of Tamarind and Aloe Vera Extracts on Gastric Volume and Acidity Levels - Free and Total

When indomethacin was given to ulcerated rats, there was a statistically significant rise in gastric volume compared to normal controls as shown in Table 2. However, in rats treated with 200 mg/kg and 400 mg/kg b.w. of polyherbal extracts of methanolic extract of tamarindseeds combined with aloe vera, the observed increases in gastric volume were significantly decreased to 1.06±0.04 and 0.85±0.05, respectively.

Regarding acidity levels, the estimated levels of free and total acidity in the group treated with indomethacin (disease control) were 87±1.155 mEq/L and 14±1.155 mEq/L, respectively. Pre-treatment with 200 mg/kg b.w. and 400 mg/kg b.w. of the polyherbal extracts significantly reduced free acidity to 56±2.309 and 45.67±1.202, respectively, and total acidity to 8±0.5774 and 6.333±0.8819, respectively (p≤0.001). These reductions were comparable to the standard treatment with omeprazole.

3.2 Impact of Tamarind and Aloe Vera Extracts on Tissue Antioxidants - MDA, SOD, CAT, GPx, and MPx Levels

The combined results of the effects of polyherbal extracts of tamarind seed methanolic extract and aloe vera on tissue antioxidants in an indomethacin-induced model are as follows:

The ulcerated group (disease control) exhibited significantly higher levels of MDA (P≤0.001), while rats given indomethacin showed a substantial Decrease in CAT and SOD activities (P≤0.001) as shown in Table 3. However, the polyherbal extracts of tamarind seed and aloe vera, administered in a dose-dependent manner, significantly improved the parameters of ratstomach mucosa lipid peroxidation, SOD, and CAT activity with Indomethacin ulcers. These effects were comparable to those of the standard drug, Omeprazole, and the normal control group. Additionally, in the ulcerated group, the GPx level was considerably lower, while there was a significant increase in MPx activity in rats given indomethacin. Impressively, the polyherbal extracts of tamarind seed methanolic extract and aloe vera significantly improved the GPx and MPx activity of the gastric mucosa in rats with Indomethacin ulcers. These effects also compared favorably with the standard drug (omeprazole) used in the study and the normal control.

Table 2. Gastric volume and acidity levels-free and total

Parameters	Normal control	Disease control (Indomethacin20mg/kg)	Treatment low dose (Tamarind Extract + Aloe vera Extract-200mg/kg)	Treatment high dose (Tamarind Extract + Aloe vera Extract400mg/kg)	Standard treatment (Omeprazole 20mg/kg)
Gastric volume	0.45±0.05	1.75±0.05	1.06±0.04***	0.85±0.05***	0.65±0.05***
Free acidity	32.67±1.453	87±1.155	56±2.309***	45.67±1.202***	50.67±1.453***
Total acidity	6±0.5774	14±1.155	8±0.5774***	6.333±0.8819***	10.33±0.8819***

The values for n=6was expressed as Mean ± SEM. Statistical analysis included ANOVA, and significance, denoted by *, was determined through the Dunnett test when comparing treatment groups with the disease group.**

Table 3.Tissue antioxidant parameters

Parameters	Normal control	Disease control (Indomethacin 20 mg/kg)	Treatment low dose (Tamarind Extract + Aloe vera Extract 200 mg/kg)	Treatment high dose (Tamarind Extract + Aloe vera Extract 400 mg/kg)	Standard treatment (Omeprazole 20 mg/kg)
MDA	2.446±0.381	12.2±0.6612	7.997±0.5012***	5.953±0.5506 ***	4.037±0.1846***
SOD	42.35±1.272	25.75±0.3252	32.93±0.6944***	36.69±0.6458***	41.59±1.366***
CAT	24.75±0.7491	13.18±0.6412	18.67±0.3782***	20.81±0.332***	23.22±0.5969***
GPx	57.62±1.054	26.27±0.944	33.5±1.181***	41.81±0.7102***	55.02±0.5173***
MPx	16.01±0.8285	36.88±0.9135	22.31±0.6536***	19.63±0.5259***	17.35±0.3018***

The values for n=6was expressed as Mean ± SEM. Statistical analysis included ANOVA, and significance, denoted by ***P<0.001, was determined through the Dunnett test when comparing treatment groups with the disease group.

3.3 Ulcer Index and % Ulcer Inhibition

The effects of the extract on the percent inhibition against ulcer and ulcer index in experimental animals are shown in Table 4 and Fig. 1, respectively.

The ulcer index, which measures the degree of ulceration increased significantly in rats treated orally with indomethacin at a dose of 20 mg/kg b.w. The animals treated with aloe vera and tamarind seed methanolic extract polyherbal extracts showeda notable increase in the degree of inhibition against ulcer formation. Taking 200 mg/kg b.w., the extract compared favorably with the usual medication (omeprazole) used and provided superior protection against ulcers.

Table 4. Ulcer index and % ulcer inhibition

Parameters	Normal control	Disease control (Indomethacin 20 mg/kg)	Treatment low dose (Tamarind Extract + Aloe vera Extract 200 mg/kg)	Treatment high dose (Tamarind Extract + Aloe vera Extract 400 mg/kg)	Standard treatment (Omeprazole 20 mg/kg)
Ulcer index	0	1.887±0.1145	0.6367±0.0120***	0.5367±0.01453***	0.51±0.02082***
% Ulcer inhibition	0	107%	50%	62%	66%

The values for n=6was expressed as Mean ± SEM. Statistical analysis included ANOVA, and significance, denoted by *, was determined through the Dunnett test when comparing treatmentgroups with the disease group.**

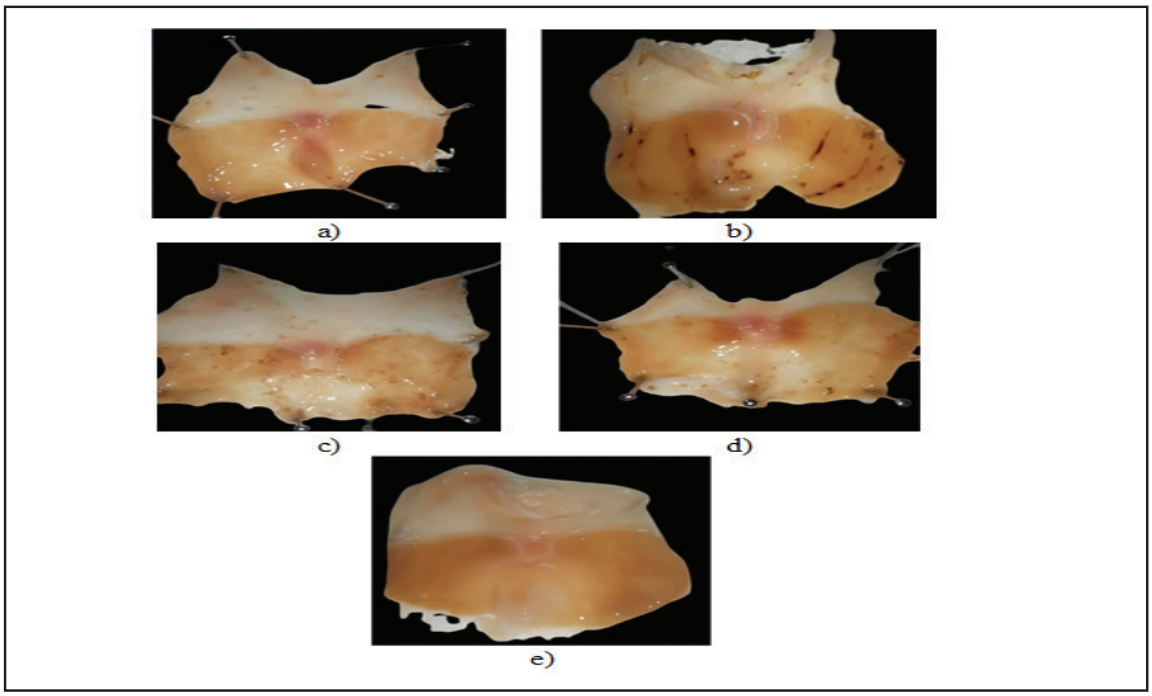

Figure 1. Open stomach of Indomethacin-induced gastric ulcer rat model, a) Normal control, b) Disease control (Indomethacin 20 mg/kg), c) Treatment low dose (Tamarind Extract + Aloe vera Extract 200 mg/kg), d) Treatment high dose (Tamarind Extract + Aloe vera Extract 400 mg/kg), e) Standard treatment (Omeprazole 20 mg/kg).

4. DISCUSSION

An ulcer is described as active inflammation that results in a local defect or excavation by disrupting the mucosal integrity of the stomach and/or duodenum. Ulcers in the stomach or duodenum are common and often chronic. Stomach and duodenal ulcers are frequent and frequently chronic. Gastric ulcers are the result of an imbalance between the destructive forceand the gastro-duodenal mucosal defence mechanism[2].

It is widely acknowledged that an imbalance between aggressive forces and endogenous defence mechanisms that maintain mucosal integrity leads to stomach ulcers. Prostaglandin (PG)-induced excess stomach acid production is accompanied by a reduction in aggressive components, mainly pepsin and acid, as well as an increase in mucosal resistance[25].

Because of their analgesic, antipyretic, and anti-inflammatory properties, NSAIDs are frequently utilised. The bulk of side effects from NSAID medication are associated with the digestive system. The primary limitation on the use of NSAIDs as anti-inflammatory drugs is ulcerative lesions, which include bleeding, perforation, and stomach ulcers[4].

Consequently, the current investigation examined the anti-ulcer effect of polyherbal extract on rat models of stomach ulcers caused by indomethacin[26].

The study's findings indicate the potential of polyherbal extracts, specifically a combination of tamarind extract and aloe vera extract, in reducing gastric volume and acidity in rat models of stomach ulcers caused by indomethacin. This suggests a promising anti-ulcer effect of these extracts, which may be related to their capacity as antioxidants. The study also emphasizes how crucial oxidative stress is to the pathophysiology of indomethacin-induced gastric lesions and the potential role of Myeloperoxidase (MPx) in this process.

The findings regarding the effects of Tamarind extract and Aloe vera extract on the activities of Superoxide Dismutase (SOD) and Catalase (CAT) in the stomach mucosa of rats with indomethacin-induced ulcers are particularly noteworthy. These extracts were found to significantly enhance the activities of these antioxidant enzymes, which could contribute to their anti-ulcer effects. Additionally, the study suggests that the combination of tartar extract and aloe vera extract may have a greater impact on ulceration compared to the individual extracts alone.

Overall, the findings of this study underscore the significance of oxidative stress in the pathogenesis of stomach ulcers and offer insightful information on the possible processes underpinning the anti-ulcer benefits of polyherbal extracts. To completely comprehend the medicinal potential of these extracts and their modes of action in the management of stomach ulcers, more investigation is required.

5. CONCLUSION

The study demonstrated that a combination of tamarind and aloe vera extracts significantly reduced the likelihood of stomach ulcers induced by indomethacin. The treatment also led to a notable reduction in stomach capacity, particularly at 200 mg/kg and 400 mg/kg body weight dosages. The combination of tamarind and aloe vera resulted in a significant decrease in Malondialdehyde (MDA) levels and a significant increase in Glutathione Peroxidase (GPx) and Metalloproteinase (MPx) activities.

Moreover, the combination significantly reduced the ulcer index, indicating its potential as a preventive measure against stomach ulcers. The anti-inflammatory, antioxidant, anti-infective, laxative, anthelmintic, anti-microbial, anti-bacterial, anti-diabetic, and wound-healing properties of tamarind and aloe vera further support their efficacy in treating stomach ulcers.

The methanolic extract of tamarind and aloe vera at a dose of 400 mg/kg showed noteworthy anti-ulcer efficacy in contrast to the pharmaceutical Omeprazole, suggesting its potential as a natural alternative for ulcer treatment.

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