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Cytoprotective Activity of a Herbal Formulation on Induced Gastric Ulcers in *Wistar* Rats

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Abstract *Macaranga barteri* and *Terminalia superba* are two plants from the Ivorian flora used in traditional medicine to treat gastric disorders. This study aims to evaluate the cyprotective effect of a herbal formulation based on these herbs (AEMbTs) against induced ulcers in rats. The cytoprotective effect of AEMbTs was carried out on HCl/Ethanol and ibuprofen rats' models. For each model, nine groups of six rats each were formed. The rats were orally pretreated with distilled water (Groups I and II), those of groups III and IV received Cimetidine (12 mg/kg bw) and Maalox (50 mg/kg bw) respectively in HCl/Ethanol model while Misoprostol (0,012 mg/kg bw) and Ranitidine (50 mg/kg bw) were respectively used as standard drugs in ibuprofen model. The rats in groups V to IX received AEMbTs at the respective doses of 31.25; 62.50; 125; 250 and 500 mg/kg bw. In the HCl/ethanol model, one hour after administration of the various treatments, all groups except group I received HCl/Ethanol orally at 1 ml/150 g bw. All the animals were sacrificed one hour later. As for the ibuprofen model, thirty (30) minutes after the treatments, all the animals except those of group 1 received orally a first dose of ibuprofen (500 mg/kg bw). Fifteen hours after the first dose, a second dose of ibuprofen was administered. Six (6) hours later, all the animals were sacrificed, the mucus was collected and weighed, the ulcerations were measured, the ulceration index and the inhibition percentage of the ulcerations were calculated. The results showed that the doses of AEMbTs induced significant decrease ($p<0.05$) of the ulceration areas. The inhibition values were 99.29 and 100%, respectively for the ibuprofen and HCl/ethanol models at the extract dose of 500 mg/kg bw. AEMbTs, also, significantly ($p<0.001$) increased mucus production. These results suggest that the herbal formulation has cytoprotective effects on the rat stomach and could justify the use of these plants by traditional healers to treat gastric disorders.

Keywords: *Macaranga barteri, Terminalia superba, HCl/Ethanol, ibuprofen, gastric ulcer*

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1. Introduction

Gastric ulcers result from an imbalance between the aggression factors and the defense factors of the gastric mucosa [1]. Two main etiological factors associated with gastric ulcers are alcohol and nonsteroidal anti-inflammatory drugs (NSAIDs) abuse [2,3]. They work by causing destruction of the protective mucosal barrier [4]. This disease affects 5 to 10% of the world's population and therefore represents a major health problem [5]. In Côte d'Ivoire, studies carried out in a hospital setting on peptic ulcers showed a prevalence of 26.9% [6]. The therapeutic regimen of anti-ulcer treatment consists either of intensifying the protective barriers and/or reducing the invasive factors of the gastric mucosa. For this, modern medicine offers a wide range of cytoprotective drugs sometimes associated with antibiotics which are not without health consequences. In addition, health centers and specialized structures for the treatment of ulcers are sometimes inaccessible for most populations in developing countries. All these factors have pushed urban and rural populations to use medicinal plants for their health care. These populations are estimated to more than 80%, according to the World Health Organization. Faced with this observation, the WHO recommends developing countries to undertake studies on medicinal plants in order to establish scientific proof of their therapeutic efficacy [7]. It is in this perspective that *Terminalia superba* and *Macaranga barteri* have aroused interest. Indeed, people use the decoctions of these two plants to treat gastric ulcers [8,9]. Moreover, the work carried out by Ehilé *et al.* and Goze *et al.* showed that the aqueous extracts of these two plants are endowed with a cytoprotective potential for extract doses between 125 and 500 mg/kg bw in the HCl/Ethanol and ibuprofen models [10,11].

The objective of this work is to evaluate the cytoprotective effect of this recipe composed of leaves of *M. barteri* and stem barks of *T. superba* (AEMbTs) on gastric ulcers induced by HCl/Ethanol and ibuprofen in rats.

2. Material and Methods

2.1. Material

2.1.1. Plant

The herbal formulation consisted of the barks of *Terminalia superba* and the leaves of *Macaranga barteri*. These samples were identified by botanists from NANGUI ABROGOUA University and authenticated at the National Floristic Center (CNF) of the Félix Houphouët Boigny University (Abidjan, Côte d'Ivoire). The samples were kept under the voucher number 10477 of february 26, 1969 for the trunk bark of *T. superba* and 14735 of april 6, 1979 for *M. barteri.*

2.1.2. Animal

Rattus norvegicus species rats of the *Wistar* strain aged 12 to 16 weeks with body weights varying between 180 to 200 g were used. They were bred in the animal facility of the Laboratory of Physiology, Pharmacology and Pharmacopoeia of the NANGUI ABROGOUA University (Abidjan, Côte d'Ivoire). They were fed with IVOGRAIN® brand pellets and water *ad libitum*. The various experimental protocols were followed in accordance with the protocols for the protection of experimental animals [12].

2.1.3. Chemical and Drugs

The chemicals used in this study were aluminum hydroxide (Maalox®, Sanofi Aventis, France), Cimetidine (Saint Louis, MO, USA), Ibuprofen (ibuprofen®, Sanofi Aventis, France), Misoprostol (Cytotec®, Pfizer, Germany), ethanol (Saint Louis, MO, USA), and hydrochloric acid (Saint Louis, MO, USA), ether (VWR International Geldenaakfebaan 464-B-3001, Leuven, Belgium).

2.2. Methods

2.2.1. Preparation of Herbal Formulation

Terminalia superba stem bark and *Macaranga barteri* leaves were harvested and dried at 25°C for one week. Once they were dried, these leaves and barks were separately powdered using a RETSH brand electric grinder, type SM 100 (Haan, Germany). The aqueous extracts of the leaves of *M. barteri* and the barks of *T. superba* were separately prepared according to the methods described by Ehilé *et al*. and Kouakou *et al.* respectively [10-13]. Thus, hundred (100) g of each powder was boiled for 15 minutes in one liter distilled water. The decocted was, thereafter, filtered on absorbent cotton and on Whatman No.1 filter paper. The filtrates were dried in an oven (Friucell, Germany) at 45°C for 48 hours. At the end of the process, a crystalline, very friable black powder of 12.14 g for the trunk bark of *T. superba* and a powder of 17 g of very aromatic brown color for the leaves of *M. barteri* were obtained. The different doses of the herbal formulation were prepared extemporaneously by dissolving the same amount of both extracts into distilled water.

2.2.2. Model of Induction of Gastric Lesions with the Necrotizing Solution HCl/Ethanol in the Rat

The gastric lesions were induced by following the method described by Hara and Okabe [14]. Fifty-four rats were fasted for 24 hours before the the experiment day. They were divided into nine batches of six rats each. The rats of group I and II, received orally distilled water (1 ml/100 g bw.)

Those of groups III and IV received cimetidine (12 mg/kg bw) and maalox (50 mg/kg bw) by oral route, respectively. As for the rats of groups V, VI, VII, VIII and IX, they were gavaged with 31.25; 62.50; 125; 250 and 500 mg/kg bw of AEMbTs respective. One hour after the administration of the various treatments, all the rats' group except group I, received orally a solution of HCl/Ethanol (150 mM of HCl in Ethanol 60% v/v). One hour later, all the animals were sacrificed by an overdose of ether. The stomach was removed and opened along the longest axis (cardia-pylorus) and its contents were collected. The mucus were we, the surface area was measured and ulceration index were calculated as described by Robert *et al.* [15].

0: normal mucosa; 1: hyperemic mucosa or up to 3 small patches of ulceration; 2: 4 to 10 small patches of ulceration; 3: more than 10 small or up to 3 patches of medium-sized ulcers; 4: 4 to 6 patches of medium-sized ulcerations; 5: more than 6 medium or up to 3 large patches of ulceration; 6: from large ulceration plaques 4 to 6 mm in diameter; 7: 7 to 10 large patches of ulceration and 8: more than 10 large or extensive necrotic areas.

Once the measurements were done, the ulceration index and the inhibition percentage of ulcerations were calculated using the formulas described by Nguelefack *et al.* [16].

$$DUG = Score / NUG$$

With:
DUG: degree of ulceration of the group
Sore: sum of points assigned to gastric lesions (score)
NUG: number of ulcerative rats in the group

$$UI = DUG\ X\ \frac{PUG}{100}$$

With:
UI: group ulceration index
PUG: percentage of ulcerated rats in the group

$$\%\ I = SUt\ X\ \frac{100}{(SUt - SUe)}$$

With:
% I = ulceration inhibition percentage of the treated rats
SU_t = Ulceration surface of the group II (ulcerative non-treated rats)
SU_e= Ulceration surface of the treated groups

2.2.3. Induction Model of Gastric Lesions with Ibuprofen

The model was that described by Parmar and Desai [17]. It was usedto evaluate the cytoprotective effect of AEMbTs

in the presence of a nonsteroidal anti-inflammatory drug. In this model, fifty- four rats were fasted for 24 hours and then divided into nine groups of six rats each. The rats of group I and those of group II, received orally distilled water (1 ml/100 gbw). Groups III and IV were treated respectively with misoprostol (0.012 mg/kg bw) and maalox (50 mg/kg bw). As for groups V to IX were treated with AEMbTs at doses between 31.25 to 500 mg/kg bw. Thirty (30) minutes after the various treatments, all the animals orally received a first dose of ibuprofen at 500 mg/kg bw. Fifteen (15) hours thereafter a second same dose of ibuprofen were administered. Six (6) hours later, the animals were sacrificed by an overdose of Ether. The stomachs were removed and opened along the greater curvature. The mucus was collected and weighed. The different stomachs were examined for ulceration and severity of intraluminal hemorrhage according to the classification scale of gastric lesions described by Kulkarni [18].

0: No ulcer (normal mucosa); 0.5: Dilation of blood vessels (presence of redness); 1: Small ulcer marks; 1.5: Dilation of blood vessels and presence of ulcer marks; 2: Ulcers ≥ 3 mm long ≤ 5 mm long; 3: Ulcers >5 mm long.

The ulceration index and the inhibition percentage of ulcerations were calculated by the formulas described by Nguelefack *et al.* [16].

2.2.4. Statistical Analysis

The data recorded during the different tests were classified and performed using Graph Pad Prism 7.01 software (San Diego, California, USA). The results were expressed as means ± standard error on the mean (M ± SEM). The Student's t-test and the one-factor analysis of variance (ANOVA 1) were used to compare treated and control rats' batches. When significant differences were revealed, One-way ANOVA was completed by the Tukey-Kramer test as a post-test. The significance level was set at $p<0.05$.

3. Results

3.1. Effects of AEMbTs on HCl/ethanol Solution-induced Gastric Ulcers

Figure 1 and Table 1 show the effect of the different treatments on the macroscopic parameters. The non-ulcerated rats (group I) presented zero score, index and ulceration area and a quantity of 128.2±3.35 mg of mucus.

However, the rats in group II, pre-administered with distilled water and received the HCl/ethanol solution later one, showed significant increase ($p<0.001$) in the score, index and ulceration surface area and a significant decrease ($p<0.001$) of the mucus was observed compared to the rats in group I. The group II, also, showed an ulceration index of 4.67±0.42 and a quantity of 45.70±6.22 mg of mucus produced.

Furthermore, the pretreatment of the rats with AEMbTs showed that the score, the surface area and the ulceration index were significantly decreased ($p<0.05$) compared to the rats with no pretreatment (Group II). The score dropped from 3.97±0.47 to 00.00 ± 00.0 and the percentage inhibition of the gastric ulcerations increased from 33.67 to 100% for extract doses ranging between 31.25 to 500 mg/kg bw. AEMbTs induced a significant dose-dependent increase ($p<0.05$) in secreted mucus from 66.7± 6.67 to 119.6± 7.74 mg compared to group II where this quantity was 45.7 ± 6.22 mg.

As for the rats of groups III and IV pretreated respectively with cimetidine and maalox, significant reductions ($p<0.001$) in the score, the index and the ulceration surface were observed compared to group II. In fact, the ulceration area of 5.20±0.58 and 7.22±0.86 mm^2 respectively in the groups III and IV, with ulceration index of 0.58± 0.08 (Group III) and 0.64±0.16 (Group IV) which corresponds to inhibition percentages of 96.72% (Group III) and 95.45% (Group IV). significant increases ($p<0.001$) in secreted mucus of 106.2 and 97.8 mg was recorded respectively for the groups III and IV compared to the group II.

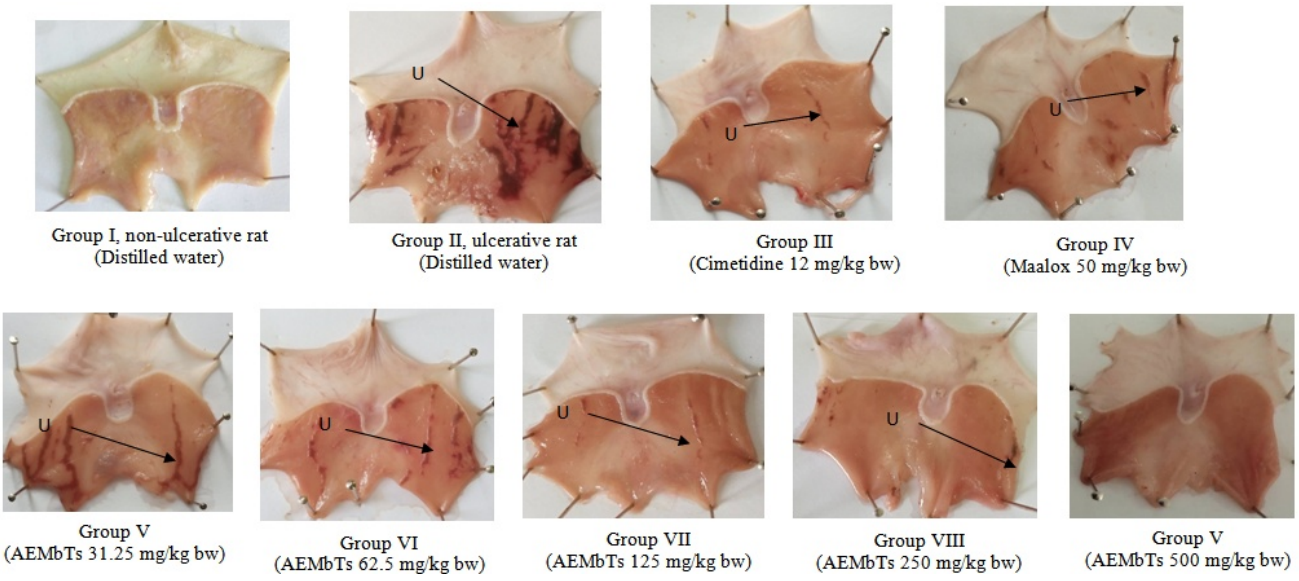

Figure 1. Photographs of stomachs after different treatments in the HCl/ethanol model (**AEMbTs**: Aqueous extract of *Macaranga barteri* leaves and *Terminalia superba* stem bark; **U**: ulceration)

Table 1. Macroscopic parameters of gastric lesions induced by HCl/Ethanol

Groups	US (mm^2)	UI	Score	% I	Mucus (mg)
Group I, non-ulcerative rats (distilled water)	00 ± 00	00 ± 00	00 ± 00		128.2 ± 3.35
Group II, ulcerative rats (distilled water)	159 ± 15.70$^{###}$	4.67 ± 0.42$^{###}$	6.67 ± 0.42$^{###}$		45.7 ± 6.22$^{###}$
Group III (Cimetidine 12 mg/kg bw)	5.20 ± 0.58***	0.58 ± 0.08***	0.40 ± 0.40***	96.72	106.2 ± 11,20***
Group IV (Maalox 50 mg/kg bw)	7.22 ± 0.86***	0.64 ± 0.16***	0.80 ± 0.20***	95.45	97.8 ± 10.71***
Group V (AEMbTs 31.25 mg/kg bw)	69 ± 9.77***	2.17 ± 0.47***	3.97 ± 0.47***	56.60	66.7 ± 6.67***
Group VI (AEMbTs 62.5 mg/kg bw)	57.3 ± 12.4***	1.75 ± 0.75***	3.20 ± 0.74***	63.96	78. 7 ± 9.42***
Group VII (AEMbTs 125 mg/kg bw)	19.8 ± 9.29***	0.80 ± 0.25***	1.00 ± 0.32***	87.54	92.3 ± 6.57***
Group VIII (AEMbTs 250 mg/kg bw)	3.17 ± 3.97***	0.54 ± 0.30***	0.33 ± 0.21***	96.11	107.2 ± 9.79***
Group IX (AEMbTs 500 mg/kg bw)	00.00 ± 00***	0.00 ± 0.00***	00.00 ± 00.0***	100	119.6 ± 7.74***

###p<0.001: Comparison between group I (non-ulcerative rats) and group II (ulcerative rat) for the same parameter.
**p<0.01; ***p<0.001: Significant difference between the values of the same column and those of group II (ulcerative rats); US: ulceration surface; UI: ulcer index; I: inhibition percentage; AEMbTs: Aqueous Extract of *Macaranga barteri* leaves and stem bark of *Terminalia superba*; n=6 rats/group.

3.2. Effects of EAMbTs on Gastric Lesions Induced by Ibuprofen

The results of the effect of EAMbTs on gastric lesions induced by Ibuprofen were shown in Figure 2 and Table 2. The score, the ulceration area and the ulceration index in the non-ulcerated rats (control group I) are zero, while the quantity of mucus produced was 128.2±3.35 mg. On the other hand, the administration of the HCl/ethanol increased significantly (p<0.001) the score, the ulceration area and the ulceration index of rats in group II compared to those of control group I. The score, the ulceration area and the ulceration index were respectively 2.75±0.25; 35.25±6.41 mm^2 and 2.04±0.12 in group of rats without no pretreatment (Group II). As for the mucus collected, it decreased significantly (p<0.001) compared to its value in the control group (Group I) and reached 65.63±3.69 mg (Table 2).

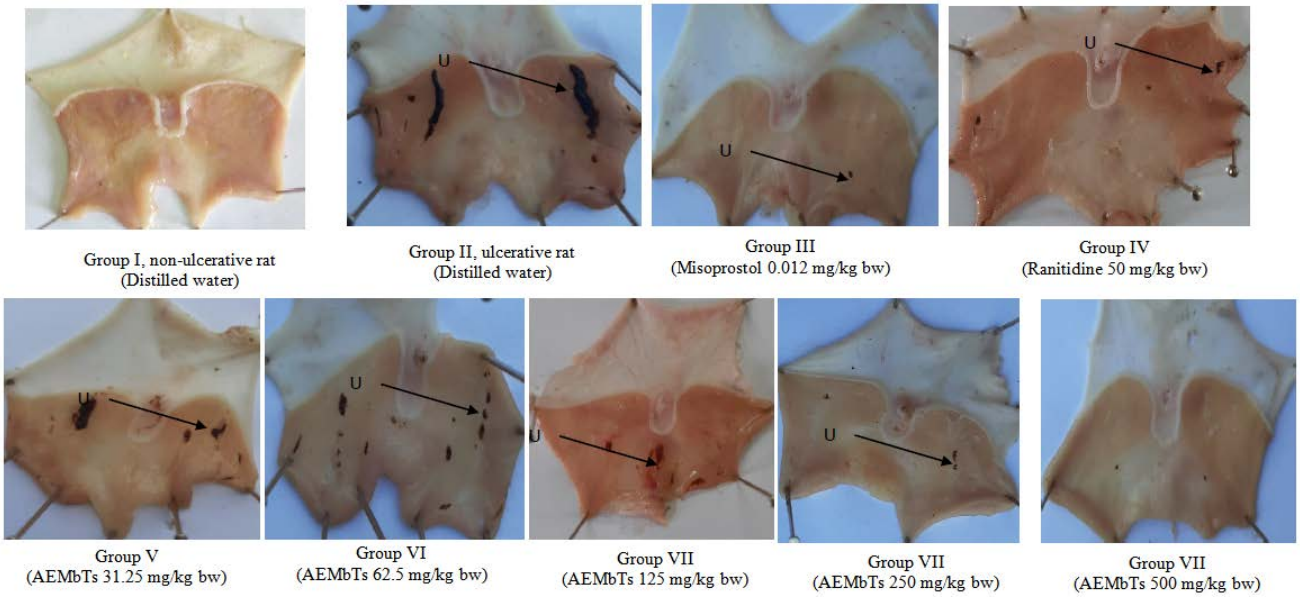

Figure 2. Photographs of stomachs after different treatments in the ibuprofen model (**AEMbTs:** Aqueous extract of *Macaranga barteri* leaves and *Terminalia superba* stem bark**; U:** ulceration)

Table 2. Macroscopic parameters of gastric lesions induced by ibuprofen

Groups	US (mm^2)	UI	Score	% I	Mucus (mg)
Group I, non-ulcerative rats (distilled water)	00 ± 00	00 ± 00	00 ± 00	-	128.2 ± 3.35
Group II, ulcerative rats (distilled water)	35.25 ± 6.41$^{###}$	2.04 ± 0.12$^{###}$	2.75 ± 0.25$^{###}$	-	65.63 ± 3.69 $^{###}$
Group III (Misoprostol 0.012 mg/kg bw)	3.20 ± 1.65***	0.10 ± 0.01***	0.70 ± 0.00***	90.92	94.2 ± 6.20***
Group IV (Ranitidine 50 mg/kg bw)	2.93 ± 0.047***	0.17 ± 0.02***	0.50 ± 0.28***	91.68	81.71 ± 3.71***
Group V (AEMbTs 31.25 mg/kg bw)	15.67 ± 0.155***	1.55 ± 0.31***	2.15 ± 0.04*	55.54	74.23 ± 4.67***
Group VI (AEMbTs 62.5 mg/kg bw)	10.68 ± 0.239***	1.07 ± 0.10***	2.01 ± 0.11*	69.70	83.10 ± 0.42***
Group VII (AEMbTs 125 mg/kg bw)	6.40 ± 0.227***	0.90 ± 0.20***	1.75 ± 0.25**	81.84	96.80 ± 0.57***
Group VIII (AEMbTs 250 mg/kg bw)	1.92 ± 0.103***	0.66 ± 0.12***	0.85 ± 0.47***	94.55	103. 20 ± 4.79***
Group IX (AEMbTs 500 mg/kg bw)	0.25 ± 0.144***	0.12 ± 0.01***	0.30 ± 0.25***	99.29	116.2 ± 6.74***

###p < 0.001: Comparison between group I (non-ulcerative rats) and those of group II (ulcerative rat).
p < 0.01; ***p < 0.001: Significant difference between the values of the same column and those of group II (ulcerative rats); **US: ulceration surface; **UI**: ulcer index; **I**: inhibition percentage; **AEMbTs**: Aqueous extract of *Macaranga barteri* leaves and trunk bark of *Terminalia superba*; n=6 rats/group.

The pretreatment of group III rats with misoprostol (0.012 mg/kg bw) and those of group IV with ranitidine (50 mg/kg bw) induced a significant decrease ($p<0.001$) in ulceration parameters mentioned earlier compared to control II (rats with no pretreatment). Misoprostol and ranitidine inhibited the ulcerations induced by HCl/ethanol from 90.92% and 91.68% respectively. The rats of group V to IX pretreated with the herbal formulation (AEMbTs) doses (from 31.25 to 500 mg/kg bw) showed significant decrease ($p<0.001$) in ulceration parameters compared to those of group II. The inhibition percentages of AEMbTs varied significantly ($p<0.001$) from 55.54% (31.25 mg/kg bw) to 99.29% (500 mg/kg bw) compared to group II. The amount of mucus produced increased significantly ($p<0.001$) and reached 116.2± 6.74 mg at 500 mg/kg bw compared to the rats of group II.

4. Discussion

The results of the cytoprotective activity of the herbal formulation (AEMbTs)against induced ulcers in rats revealed that this extract has a real antiulcerogenic potential. This extract at doses between 31.25 and 500 mg/kg bw exerts cytoprotective effects against gastric lesions induced with HCl/ethanol. Indeed, the HCl/ethanol solution is considered as a "gastro-toxic" agent which causes a decrease in gastric mucus which considerably damages the cell membrane of the stomach [19]. Ethanol penetrates the mucosal layer down to the submucosa, causing lesions such as erosion, hemorrhage and ulcers [20,21]. This is what could be the cause of the very large area of ulceration observed in the control rats which received the necrotizing solution of HCl/ethanol. However, the pretreatment of rats with AEMbTs significantly decreased ulceration surfaces while increasing the inhibition percentages of ulceration and the mucus quantity. The production of mucus could testify the cytoprotective activity of this herbal formulation Several classes of phytochemicals such as phenolic compounds (flavonoids, tannins) and saponins have been isolated from the aqueous extract of *Macaranga barteri* leaves and trunk bark of *Terminalia superba* [8,10,11]. According to Gadekar *et al*. and Sharifi-Rad *et al.* [22,23] the anti-ulcer activity of certain plants may be due to the presence of saponins, flavonoids and tannins. Indeed, flavonoids reduce histamine secretion from mast cells by inhibiting histidine decarboxylase**.** These effects of flavonoids enhance the secretion of mucus and prostaglandins which are involved in the regulation of mucus, which would have resulted in protection of the gastric mucosa in pretreated rats. These results are similar to those obtained by Pious *et al.* [25] with the mixture of extracts made of *Aristolochia krisagathra* and *Aristolochia bracteata* in the gastric ulcer model induced with HCl/ethanol in rats. In order to understand the effect of AEMbTs on cyclo-oxygenase, an enzyme that activates the secretion of gastroduodenal bicarbonate and the biosynthesis of endogenous prostaglandins, the effect of EAMbTs were studied on models of ulcers induced by ibuprofen, a specific inhibitor of this enzyme. The results of this study indicated that AEMbTs reduces the index and the ulceration surface and also increases the secretion of mucus in the pretreated groups compared to the control in this model. This suggests that AEMbTs could somehow influence the activity of this enzyme to induce anti-inflammatory activity. According to Beck *et al.* and Wallace *et al.*, ibuprofen is a nonsteroidal anti-inflammatory drug that suppresses gastroduodenal bicarbonate secretion and reduces endogenous prostaglandin biosynthesis and disrupts blood circulation in the gastric mucosa [26,27]. This leads to ulcers. However, the results of this study showed that AEMbTs, misoprostol and ranitidine reduce the ulceration area while increasing the inhibition percentage of ulcerations. The protective effect observed in rats that received the herbal formulation is similar to those pretreated with ranitidine and misoprostol. AEMbTs could therefore act like ranitidine and misoprostol. Indeed, ranitidine is a histamine H_2 receptor antagonist. It inhibits gastric acid secretion caused not only by histamine, but also by pentagastrin, insulin, caffeine or food [28]. As for misoprostol, it is effective in healing ulcers and preventing gastric damage induced by NSAIDs. Its physiological action on the gastric mucosa is twofold. It blocks the action of the H^+/K^+-ATPase, proton pump, final effector of the secretion of H^+ ions from the intraductal medium towards the gastric lumen in exchange for K^+ ions and it stimulates the production of mucus and ion HCO_3^- by the parietal cell [29,30]. The effect of AEMbTs could also be attributed to the presence in the different extracts of compounds such as flavonoids and tannins**.** These results corroborate those obtained by Tejasvi *et al*. with the aqueous extracts *Aloe Vera* and Liquorice in rats [31]. The results of this study imply that AEMbTs is a good candidate for the treatment of gastric ulcers in view of its pharmacological effects. Also, the mechanisms of action of these extracts must be researched to avoid any drug interaction.

5. Conclusion

The herbal formulation (AEMbTs) revealed that this extract significantly decreases gastric ulcerations. The inhibition values are 100% and 99.29 respectively in the HCl/ethanol and ibuprofen models at the dose of 500 mg/kg bw. EAMbTs significantly increased mucus production. This extract is, therefore, endowed with cytoprotective activity in the HCl/ethanol and ibuprofen models. This could explain the use of the leaves of *Macaranga barteri* and the trunk bark of *Terminalia superba* in traditional medicine for the management of gastric ulcers.

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