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Gastroprotective and Antiulcer Potential of Aerial Part Extract of Gaertnera Phanerophlebia Baker (Rubiaceae)

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Abstract: Gastric ulcers are a growing public health problem worldwide. It is crucial to find new anti-ulcerogenic substances that have few or no side effects. Medicinal plants are a primary source of therapeutic potential for treating gastric ulcers. However, available data show that consuming plant products can significantly alter the body. Therefore, an acute toxicity study was conducted on the aqueous extract of the aerial parts of *G. phanerophlebia* before testing its anti-ulcer activity. The results showed no signs of toxicity or mortality in mice tested at a maximum oral dose of 5,000 mg/kg. According to the toxicity scale, this aqueous extract is considered to have the lowest toxicity and is classified as safe for the human body. Anti-ulcer tests carried out *in vivo* using the stress-induced ulcer method demonstrated the extract's dose-dependent gastroprotective and healing capacity on the gastric mucosa. Compared to omeprazole (100 mg/kg) and the ulcerated control group, the aqueous extract (300 mg/kg) exhibited significant gastroprotective and curative effects. The reduction in ulcer index associated with increased gastric pH observed in groups treated with 100-300 mg/kg doses of the aqueous extract indicates that *G. phanerophlebia* possesses antiulcer, gastroprotective, and gastric mucosal healing properties. Additionally, recently identified phytoconstituents highlight potential bioactive compounds related to its pharmacological effects. *G. phanerophlebia* extract is a promising natural therapeutic approach for preventing and treating gastic ulcers.

Keywords: *Gaertnera Phanerophlebia, Aerial Part, Toxicity, Gastroprotective, Healing.*

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I. INTRODUCTION

Nowadays, nearly one in five people suffers from digestive diseases such as gastric hyperacidity, gastrointestinal inflammation, and ulcers. Though little known, these diseases are becoming a major public health problem, especially as they are experiencing an unexplained increase. According to statistics, approximately 10 % of people will develop a gastric ulcer at some point of their lives [1,2]. Treating and preventing peptic ulcers has become one of the challenges facing medicine today. These ulcers are certainly becoming a major human disease, affecting nearly 8 to 10 % of the world's population, 5 % of whom suffer from gastric ulcers [3]. According to statistical data on non-communicable diseases in Madagascar, gastric ulcers are relatively common, particularly duodenal ulcers. This condition presents a significant public health and therapeutic challenge due to the associated treatment costs [4].

A gastric ulcer is one of the major gastrointestinal disorders. It occurs due to an imbalance between offensive factors, such as increased gastric acid secretion, and defensive factors, such as gastric mucosal integrity [5]. It manifests as an erosion of the stomach lining, which corresponds to an inflamed rupture of the digestive mucosa. Peptic ulcers are caused by emotional stress and anxiety, a *Helicobacter pylori* infection (present in approximately 80-95 % of cases), prolonged use of nonsteroidal anti-inflammatory drugs (NSAIDs), alcohol consumption, smoking, and defensive factors such as prostaglandins, mucus, and bicarbonate [6,7,8]. It has also been suggested that reactive oxygen species (ROS), including superoxide anions, hydroxyl radicals, and lipid peroxides, are harmful and cause gastric ulcers [9].

Despite the availability of numerous antiulcer medications, most of them are expensive and often cause serious side effects, including gastrointestinal issues (bloating, diarrhea, and nausea), general effects (fatigue), and organ toxicity (hepatotoxicity and nephrotoxicity) [10]. Consequently, there is an urgent need to search for safer, more effective, and less toxic medicines to replace or complement the existing ones.

Since the time of our ancestors, traditional medicine has been an alternative to modern medicine due to its lower cost. Medicinal plants are a valuable resource for humanity, particularly for poor communities in developing countries, as they ensure primary healthcare and subsistence [11].

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For the Malagasy people, nearly all plant species have medicinal properties, which is why traditional medicine is used by more than 80 % of the population, particularly those in remote areas.

Madagascar is a biodiversity hotspot with singularly rich and varied flora [12]. It is a true paradise for medicinal plants, with species found nowhere else that possess exceptional virtues unique to the island [13]. Of the 3,245 medicinal plants recorded in Madagascar, 60 % are endemic.

The FABACEAE, ASTERACEAE, and RUBIACEAE families are among the top thirty richest in medicinal species in Madagascar, with each containing over 200 species [14]. Knowledge of the use of flora in traditional medicine remains insufficient because the list of medicinal plants is far from exhaustive [15]. Many species listed in traditional Malagasy pharmacopoeias have not yet been marketed as sources of medicines or molecules with therapeutic properties.

The genus Gaertnera is among the medicinal plant's endemic to the Malagasy vegetation cover. There are few studies on the chemical composition of this genus in the literature so far. Some Gaertnera species are known to contain rare and specific lactones with interesting cytotoxic properties [16]. They are regional endemics and the center of its diversity is in Madagascar and the Mascarene Islands [17]. The Big island is home to 61.76 % of Gaertnera species worldwide, with 42 confirmed species, including 16 that have been newly described. They are found along the eastern coast, through the central-eastern highlands, and westward through the northern highlands [17]. As with other RUBIACEAE, many Gaertnera species are geographically restricted and/or poorly understood. Some of them are considered extinct, including *G. calyciana* Bojer and *G. crassifolia* Bojer from the Mascarene Islands [18].

The aim of this study is to evaluate the antiulcer and gastroprotective properties of *Gaertnera phanerophlebia* Baker (RUBIACEAE). This plant is endemic and one of the lesser-known medicinal plant belonging to the Gaertnera genus of Madagascar. There is little data on the importance of this plant, except for a few studies. The main objective of this study is to analyze the antiulcer properties of the plant extract. Chemical and biological investigations of *G. phanerophlebia* have revealed the presence of secondary metabolites, such as sterols, flavonoids, and coumarins, as well as the antioxydant potential of the crude extract [19]. Recently, Rakotoarisoa *et al.* (2025) revealed its potential to accelerate the healing of external wounds [20]. A potent anti-ulcer drug must possess anti-ulcerogenic and wound-healing properties.

Therefore, extracts from this plant could provide an effective, natural alternative for preventing and treating gastric ulcers and associated inflammation. This study enhances and verifies the plant's pharmacological activities and preserves it for long-term use.

II. MATERIALS AND METHODS

➢ *Plant Collection*

The aerial parts of *Gaertnera phanerophlebia* Baker were collected in December 2019 from the Alaotra Mangoro region of Madagascar, Commune d'Ambohibary, Fokontany Ampitambe Ambatomainty (Fig 1). Botanists at the National Center for Pharmaceutical Research Applications (CNARP) identified and authenticated the plant. A voucher specimen was archived in the CNARP Department of Botany herbarium under the registration number ST380.

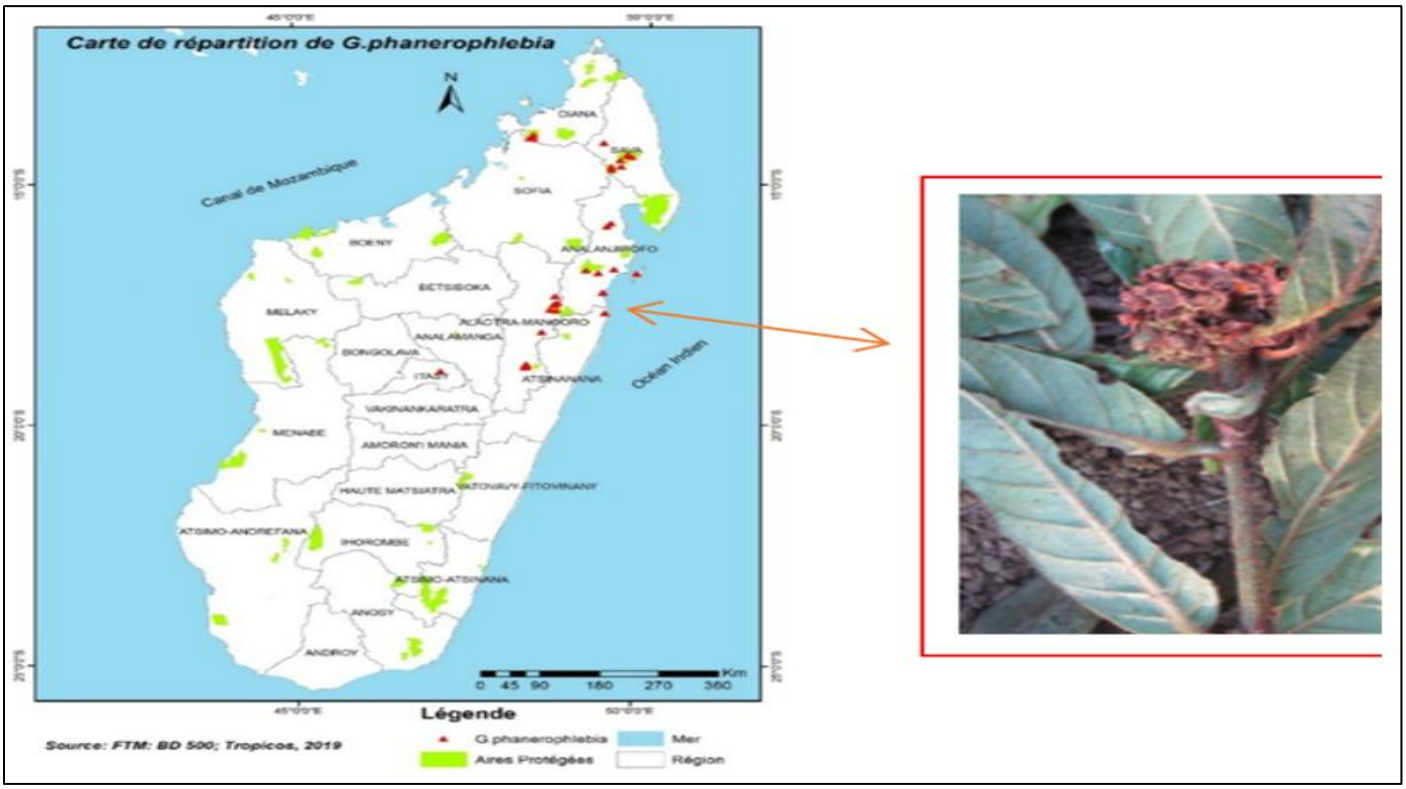

Fig 1 Distribution Map of G.Phanerophlebia in Madagascar (Rakotoarisoa F.M)

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➢ *Animals*

Male Wistar rats (150–200 g) and male Swiss mice (25 – 30 g) were used. The rats were obtained from the Institut Malgache des Vaccins Vétérinaires (IMVAVET), and both species were kept in a separate room under a 12-hour light/dark cycle at room temperature with free access to water prior to the experiment.

All animal experiments were performed in accordance with Organization for Economic Cooperation and Development guidelines [21]. All experimentation on animals was approved by the Pasteur Institute of Madagascar (IPM) Ethics Committee and aligned with the established standards.

➢ *Extract Preparation*

According to the literature on *G. phanerophlebia*, the plant is extracted by decoction using the powdered, dried aerial parts. For this study, 100 g of powder were treated at reflux in distilled water at a ratio of 1/10 (M/V) for 10 minutes. After standing for four hours, the resulting aqueous solution was filtered using a Büchner funnel. Then, it was centrifuged for ten minutes at 500 rpm and evaporated to obtain the aqueous extract. The aqueous extract (ST380) was labeled and stored in a refrigerator until ready for use.

➢ *Oral Acute Toxicity*

Despite the apparent safety of the traditional use of *G. Phanerophlebia*, as describe in the litterature, it is essential to determine this plant's possible toxicity and side effects. The test was performed using an established protocol described by Rakotoarisoa *et al*. (2021) [22].

An acute toxicity study of the aqueous extract (ST380) was conducted according to Organization for Economic Cooperation and Development guidelines (423, 425). Twenty-one male Swiss mice were randomly divided into four groups (*n=3*) and allowed to acclimate for seven days before the experiment. After an 18-hour fast with free access to water, the test group received the aqueous extract (1 mL/100 g) at doses of 250, 500, 1,000, 2,000, 2,500, and 5,000 mg/kg orally, while the control group received distilled water.

The animals were observed at 10, 30, and 60 minutes, as well as at 2, 4, 6, 12, and 24 hours after the administration of the test substance. The animals were deprived of food and water during this time. Mortality and findings, including variations in the color of the skin, membranes, and pupils of the eyes, were recorded for 24 hours and then daily for three days. After this period, the animals were given access to food and water. Main observations, such as body posture, movement, rearing, tremors, and absorbance, were recorded, as well as the results of the dose on pain response, touch response, and righting reflex.

The median lethal dose (LD_{50}) of extract was calculated as the geometric mean of the dose that did not produce mortality and the highest dose that produced mortality. If no mortality was recorded, the dose was estimated to be above the highest exposure. Changes in body weight monitored during the experiment were also used as an index of toxicity.

➢ *Anti-Ulcer And Gastro-Protective Test*

The antiulcer and gastroprotective activity of the aqueous extract of *G. phanerophlebia* was evaluated using Gairard *et al*. (1967) stress method on rats with stress-induced ulcers [23]. This method involves verifying the potential of the plant extract to affect the formation of experimental ulcers. The animals were weighed, marked, and randomly divided into five groups (G1, G2, G3, G4, and G5), with three animals in each group. All treatments were administered intragastrically via oral gavage.

- The Treatment Groups and Experimental Protocol Are Detailed Below:

✓ Group G1- control group : received only distilled water as a vehicule (0.5 ml/100 g body weight).
✓ Group G2- positive control group : received omeprazol (100 mg/kg).
✓ Group G3, G4, G5- test groups : treated respectively with the aqueous extract doses (100, 200, and 300 mg/kg).

The pharmacological capacity was investigated in two steps. The effectiveness and therapeutic potential of the aqueous extract were established by comparing both preventive and anti-ulcer tests to omeprazole, a known anti-ulcer drug.

▪ *Preventive Ulcer Test (Pre-Treatment)*:

The procedure involves administering the plant extract orally one hour before inducing a gastric ulcer using the stress method. Eighteen hours later, the degree to which the gastric mucosa is protected by the plant extract is evaluated. This process highlights the extract's potential to prevent ulcer formation.

▪ *Curative Ulcer Test (Post-Treatment)*:

This study involved inducing gastric ulcers in rats using the contraint method for 24 hours. Then, the rats were treated with the plant extract orally. This approach evaluates the extract's ability to heal existing ulcers.

▪ *Ulcer Induction Method*:

The method described by Shay *et al*. (1945) was used with modifications to induce a gastric ulcer via contraint [24]. After 24 hours of fasting (withdrawal of food and water), each animal was tied by its legs and positioned horizontally on a wire mesh support with all four legs extended [25].

▪ *Gastric pH Measurement*:

Eighteen hours after drug administration, the animals were euthanized with deep anesthesia induced by intraperitoneal injection of thiopental (100 mg/kg body weight). Then, the abdomens were opened and the stomachs were removed [26]. The excised stomachs were thoroughly washed with 10 ml of normal saline solution in plain test tubes. The tubes and their contents were then centrifuged at 400 rpm for 10 minutes. The pH of the supernatant was subsequently measured using a digital pH meter.

▪ *Ulcer Index Determination*:

For the macroscopic examination, the stomach of each animal was excised, opened along the greater curvature,

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washed, and spread on white paper. The entire stomach surface was observed for ulceration, looking for lesions, hemorrhages, erosions, and thickening of the gastric epithelium. Then, ulcers in the stomach mucosa were counted. The ulcer index (UI) was determined using the previously described scoring criteria [27].

Table 1 Method of Ulcer Index Determination

Score	Observation	Score	Observation
0	No lesion	3	1–3 thickened lesions
0.5	Hemorrhage	4	more than 3 small lesions
1	1–3 small lesions < 10 mm length	5	more than 3 large lesions
2	1–3 large lesions > 10 mm length	6	more than 3 thickened lesions

- *Ulceration Percentage:*

The percentage of ulceration (% Ulceration) is calculated using the following formula: when the sum of the UI scores is 15, there is 100 % ulceration.

$$\% \text{ Ulceration} = (\text{UI} \times 100)/3$$

- *Protection Percentage:*

To estimate the degree of mucosal protection (or inhibition), the percentage of protection was calculated using the values obtained from the ulcer index (UI). Percentage protection was calculated as follows :

$$\% \text{ Protection} = (\text{mean UI (ulcerated)} - \text{mean UI(treated)})/(\text{mean UI (ulcerated)) x 100}$$

The values obtained with different doses of the aqueous extract of *G. phanerophlebia* were compared with those obtained with omeprazole.

➢ *Statistical Analysis*

The results are expressed as the mean ± standard error of the mean. The significance of the mean differences was evaluated using the Student's T-test with the R Studio software. Values of p lower than 0.05 were considered statistically significant.

III. RESULTS AND DISCUSSIONS

➢ *Extraction Yield*

The powdered aerial parts of *G. phanerophlebia* produced 10.86 g of aqueous extract (ST380), yielding 10.86 % after decoction.

➢ *Behavioural Toxicity Assessment*

All animals treated with doses ranging from 250 to 5,000 mg/kg of ST380 survived the three-day observation period. Again, no signs of drug-related toxicity or major behavioral changes were observed in the tested animals. Since no mortality was observed at this dose rate, the median lethal dose of the aqueoux extract via the oral route is greater than 5,000 mg/kg.

Plant extract concentrations were found to be safe and non-toxic in an acute toxicity study. According to Hodge and Sterner's (1943) comparative scale of toxicity of chemical substances and the OECD's (2008) guidance, this aqueous extract of G. phanerophlebia's aerial parts may be classified as having the lowest toxicity, class 5 (LD_{50} > 2,000mg/kg) [28,29].

➢ *Gastroprotective Effect*

Forced immobilization of the animals resulted in stomach ulceration accompanied by inflammation of the gastric mucosa. Black or red spots with smooth edges ranging from 0.5 to 6 mm in diameter were observed along the entire body of the stomach in untreated batches. The results reporting gastric pH and ulcer inhibition as a function of the tested products' dose are presented in Fig 2

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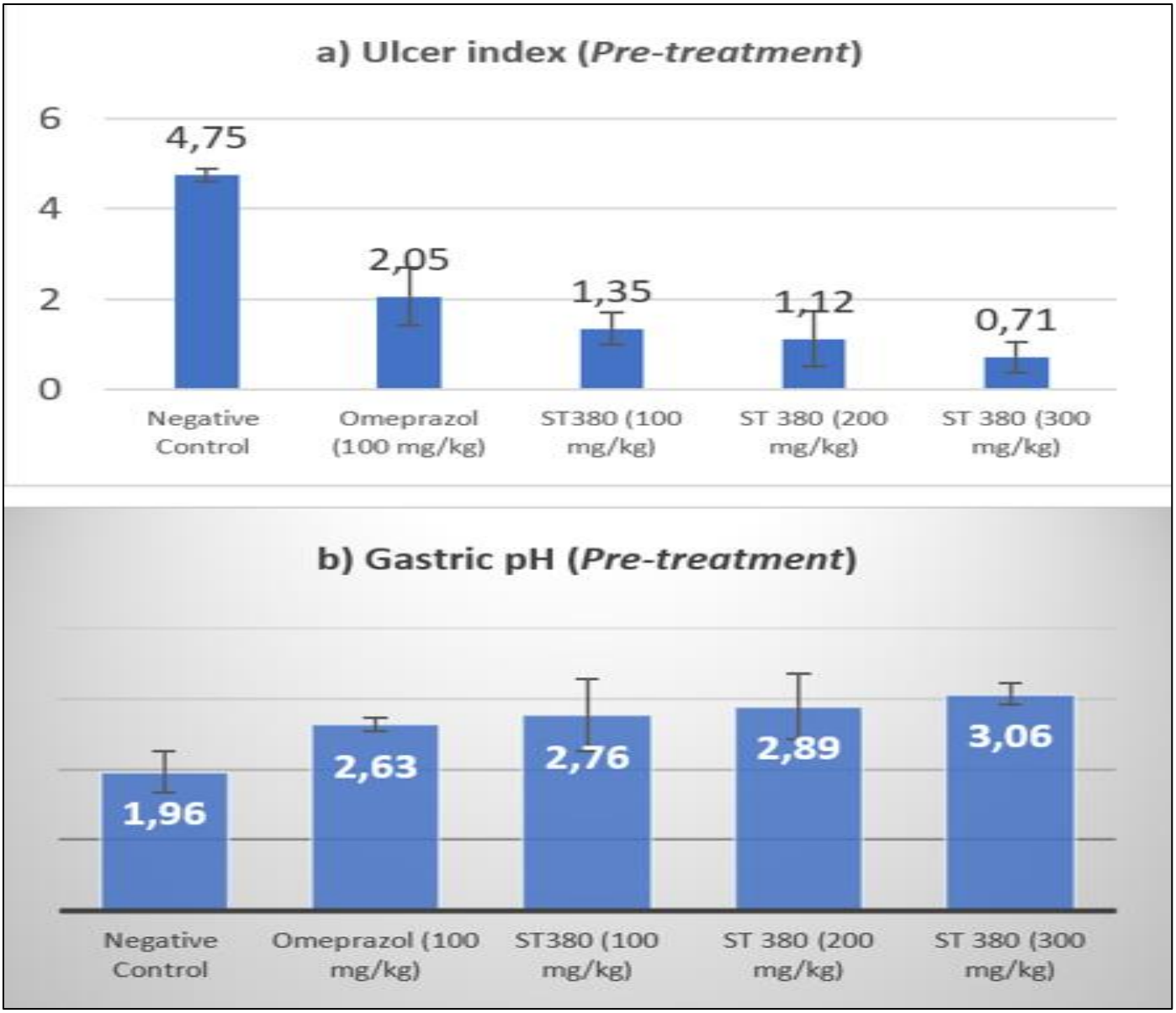

Fig 2 Gastric Ulcer Parameters of The Gastroprotective Effect of The Aqueous Extract (ST380)

The average ulcer indices for pre-treatment with 100, 200, and 300 mg/kg of ST380, as well as for omeprazole (100 mg/kg), were 2.5 ± 0.64, 1.35 ± 0.35, 1.12 ± 0.62, and 0.71 ± 0.35, respectively, compared to a mean ulcer index of 4.75 ± 0.14 for the ulcerated group. The mean % inhibitions of ulcer values were 56.84 %, 71.57 %, 71.42 % and 85.73 %, respectively, for 100, 200, and 300 mg/kg of the aqueous extraxt and omeprazole (100 mg/kg).

Furthermore, the mean pH of the ulcerated group (negative control) was 1.96 ± 0.29, whereas the mean pH of the group that received the highest dose of ST380 (300 mg/kg) increased significantly to 3.06 ± 0.15 ($p < 0.05$), which was higher than the value obtained with 100 mg/kg omeprazole (2.63 ± 0.10), as shown in Fig 2.

These experiments demonstrate that treatment with the oral administration of different doses (25, 50, 100, 200, 300 mg/kg) of the aqueous extract (ST380) or omeprazole (100 mg/kg) decreases the ulcer index in a dose- dependent manner compared to the control group. The ulcer index was only 0.71 ± 0.35 (85.73 %) at the dose of 300 mg/kg, which is comparable to the effect of omeprazole tested at 100 mg/kg (Fig. 3).

These values confirm that the aqueous extract of *G. phanerophlebia* exhibits antiulcer activity against restraint-induced ulcers in rats.

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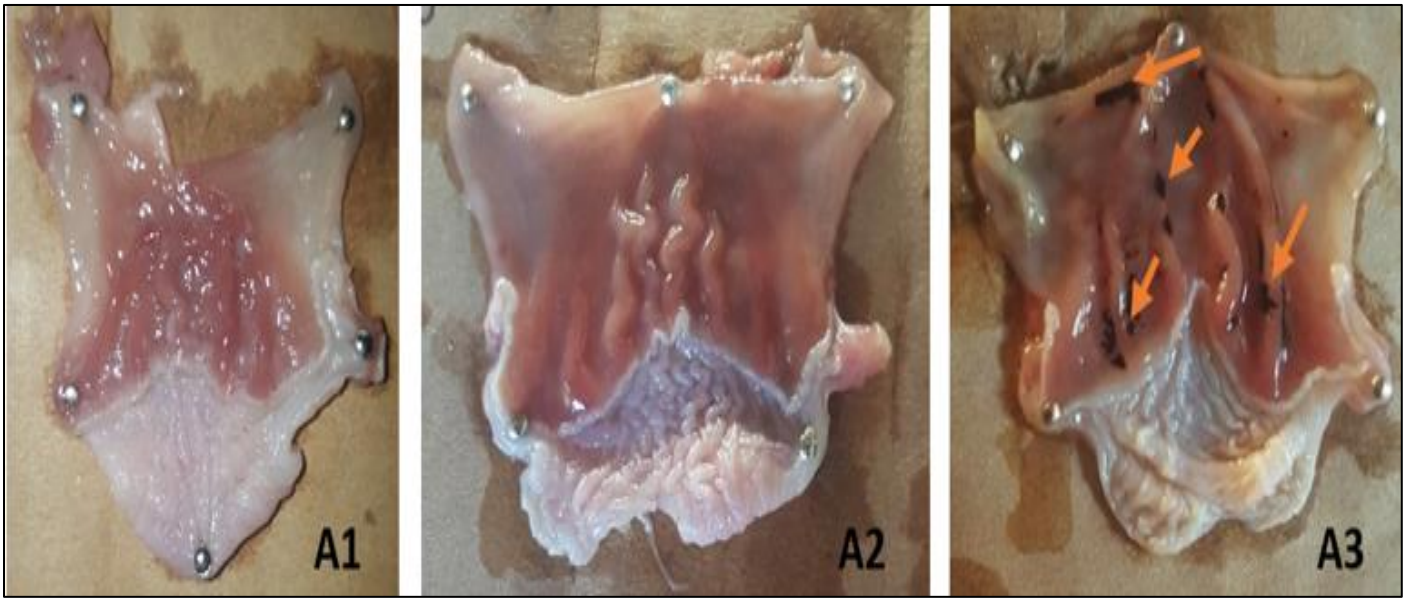

Fig 3 Demonstrative Images of Stomachs Pre-Treated From All Experimental Groups (A1-Omeprazol Group (100 Mg/Kg), A2- ST 380 (300 Mg/Kg), A3- Non-Treated Group)

➢ *Curative Activity of Gastric Ulceration*

All animals in the negative control group (non-treated) developed significant macroscopic lesions evidenced by hemorrhagic ulcerations (Fig. 4).

Gastric ulceration was attenuated after treatment with ST380 (300 mg/kg) compared to the effect of omeprazole (100 mg/kg). The *G. phanerophlebia* extract restored stress-induced gastric mucosal lesions in a dose-dependent manner. Furthermore, the aerial plant extract exhibited no macroscopic toxicity and preserved the morphological integrity of the gastric mucosa, as compared to the untreated control group. Stress significantly increased the ulceration index compared to control animals (10.85 ± 0.14).

However, groups treated with ST380 at doses of 100, 200, or 300 mg/kg, as well as omeprazole at a dose of 100 mg/kg, exhibited a notable reduction in ulcer index and an increase in gastric pH, as illustrated in Fig. 5, compared to untreated animals. Additionally, the group treated with ST380 (300 mg/kg) was able to heal lesions caused by gastric ulceration.

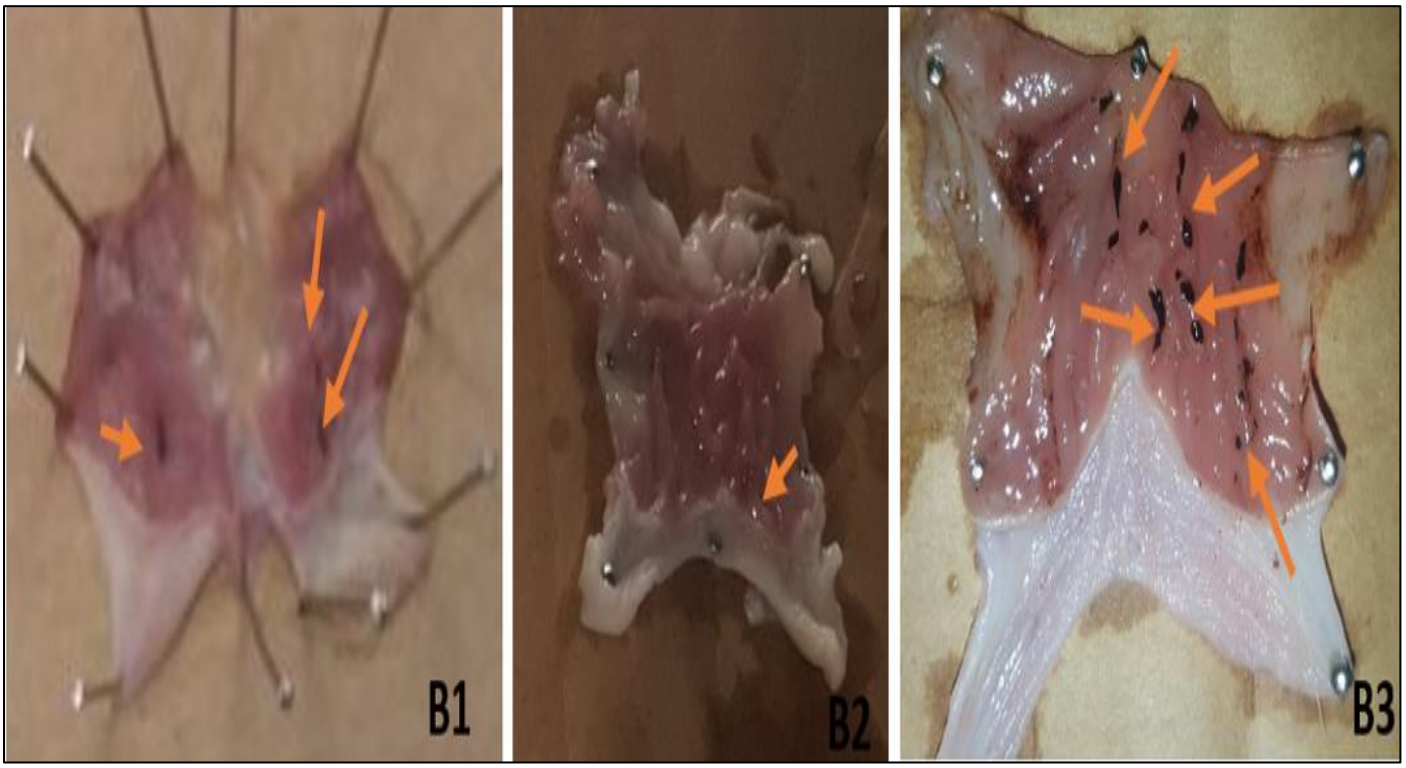

Fig 4 Demonstrative Images of Ulcers in the Stomachs of the Experimental Groups (B1-Omeprazol Group (100 Mg/Kg), B2- ST 380 (300 Mg/Kg), and B3- Non-Treated Group)

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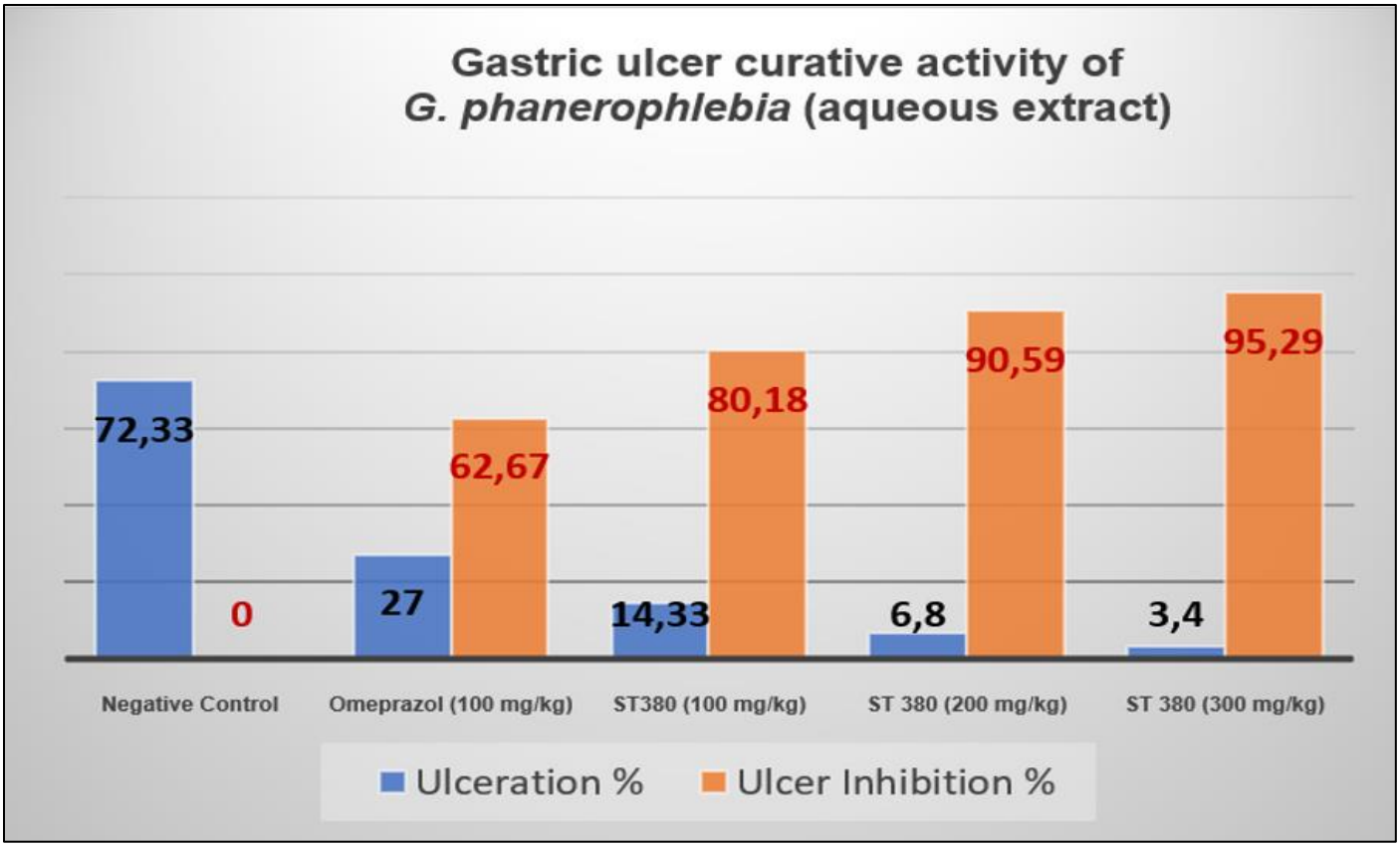

Fig 5 Curative and Healing Capacity Parameters of the Aqueous Extract (ST380)

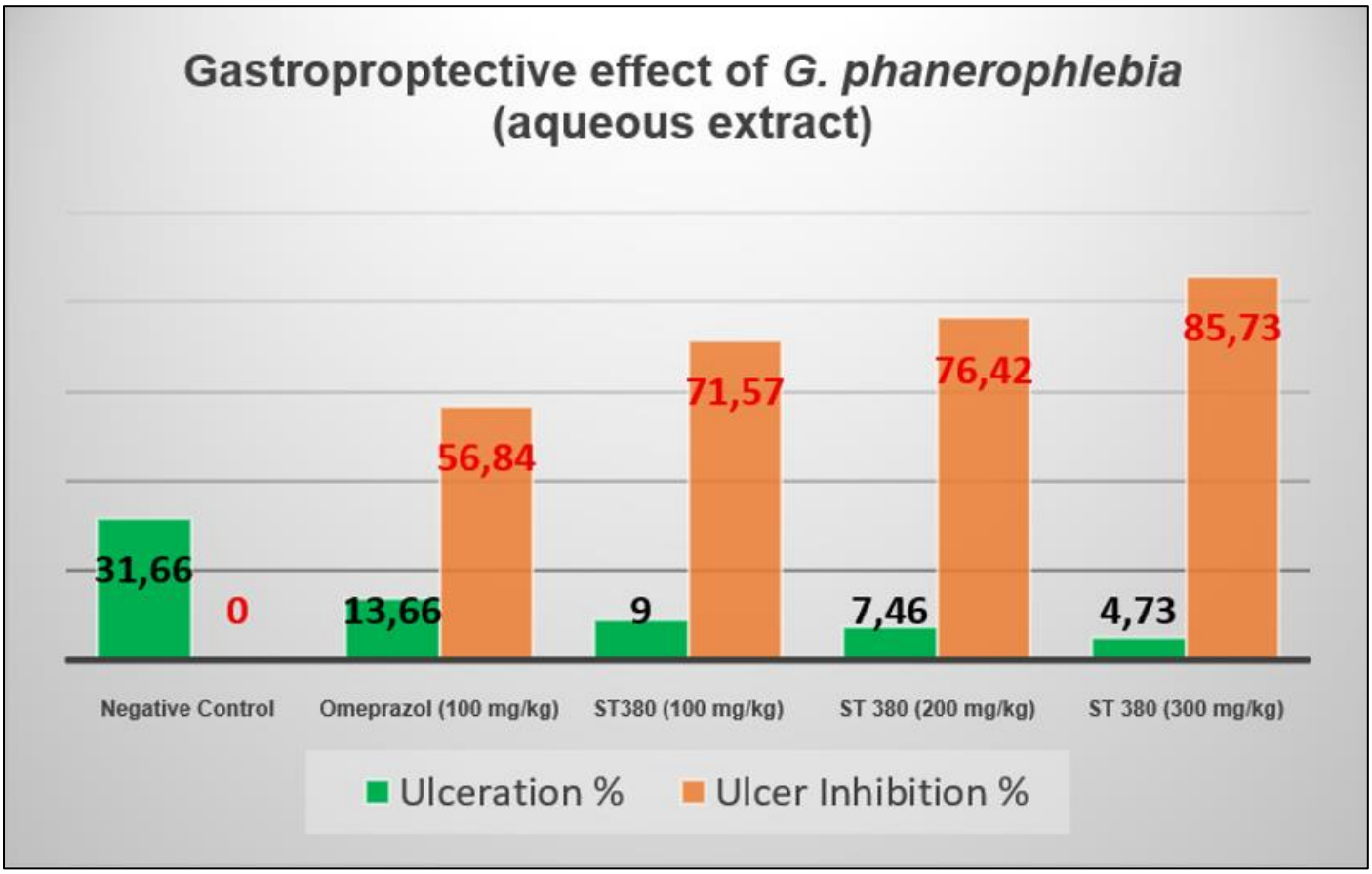

Fig 6 Gastroprotective Effet with Aqueous Extract of G. Phanerophlebia

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Investigations of the curative and gastric healing activities demonstrated the effectiveness of *G. Phanerophlebia* aerial part in promoting internal healing, especially of the gastric mucosa (Fig. 5).

➢ *Antiulcer Activity of The Aqueous Extract*

The obtained results (Fig. 6) showed that the aqueous extract of the aerial parts of *G. phanerophlebia* (ST380) exhibited antiulcer activity in a dose-dependent manner in gastroprotection and curative tests.

The best gastric protection were obtained with a 300 mg/kg/day oral dose. At this dosage, the ulceration index (0.71 ± 0.35) and percentage of ulceration (3.4 %) were significantly lower than omeprazole's (100 mg/kg). The aqueous extract resulted in almost complete healing with an inhibition rate of 95.29 % (Fig. 7).

Previous studies carried out *in vivo* with the leafy branches of *G. phanerophlebia* have already proven its healing potential for external wounds [30]. This study confirms that *G. phanerophlebia* has healing properties for both external and internal injuries, such as gastric ulcers.

When compared to results obtained with other plants, it appears that *G. phanerophlebia* exhibits gastroprotective capacity.

The aqueous extract of its aerial parts was found to be an effective gastroprotective agent that is potentially superior to omeprazole. It also demonstrated a promising anti-ulcer effect.

The mechanism of action of this plant could potentially be linked to its antioxidant, anti-inflammatory and pro-angiogenic properties [31].

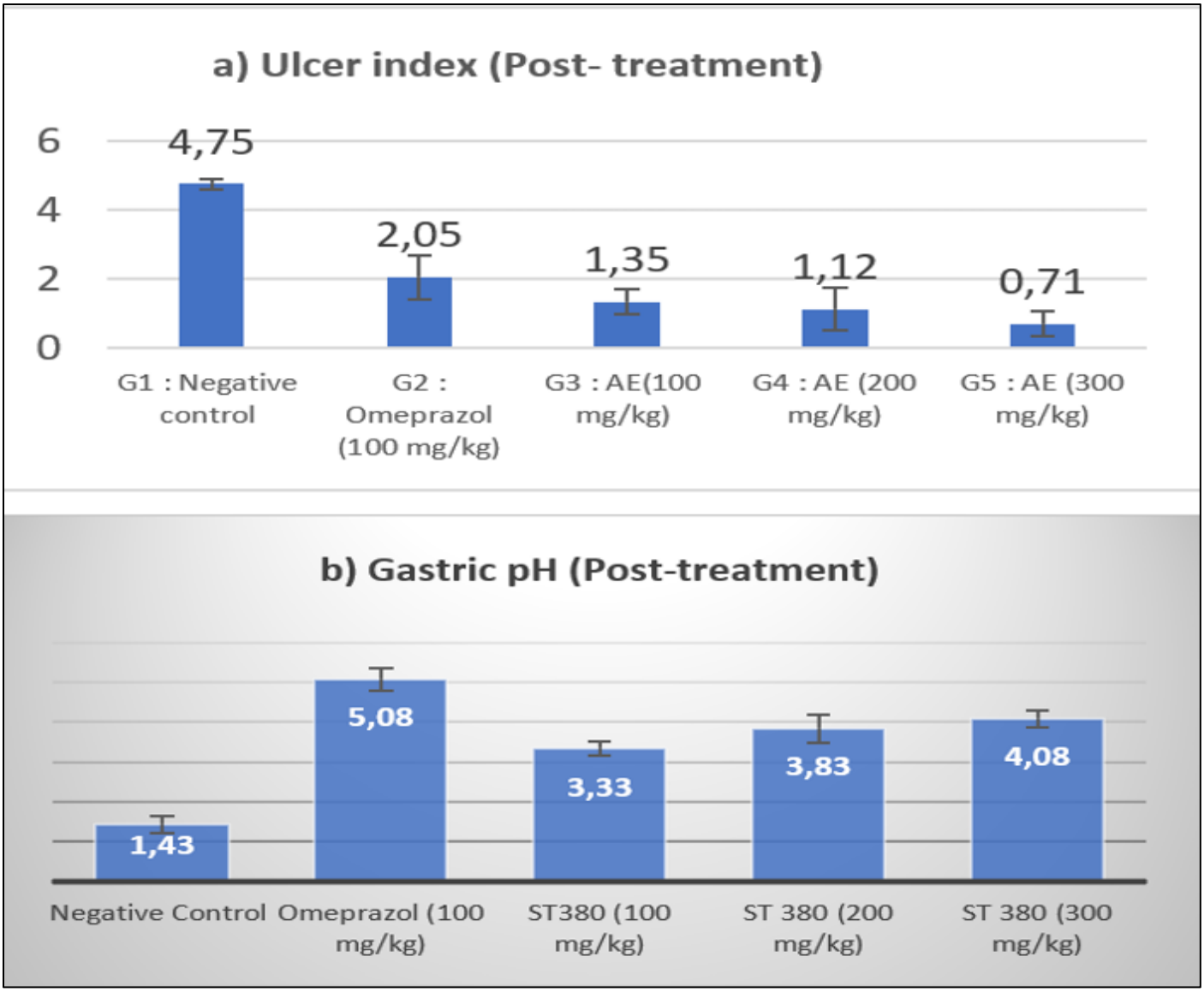

Fig 7 Gastric Ulcer Healing and Curative Properties of G. Phanerophlebia

Despite the efficacy of the aqueous extract of *G. phanerophlebia* for internal wound healing and gastric protection, the precise mechanism of action for re-epithelialization and healing of ulcerative lesions remains unclear. Earlier phytochemical tests by Rakotoarisoa *et al.* (2016) revealed secondary metabolites, including tannins, saponins, and phenolic compounds, in the methanolic extract of the plant. Several studies have linked gastric ulcer protection

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to the presence of phenolic acids and flavonoids in plant extracts [32, 33].

Accordingly, the presence of these phytochemicals strongly suggests that *G. phanerophlebia* primarily acts through direct wound healing and mucosal protection mechanisms. These substances act synergistically to promote re-epithelialization and repair. Additional studies have demonstrated that the antiulcer and gastroprotective effects of certain saponins are mediated by mucus formation on the gastric mucosa and inhibition of acid secretion [34, 35]. Further studies aimed at isolating the active secondary metabolites and testing their antiulcer properties and mechanism(s) of action are recommended.

IV. CONCLUSION

In summary, the aqueous extract of *G. phanerophlebia* was found to be non-toxic and exhibit interesting anti-ulcerogenic and gastric mucosal healing properties. This plant could be a potent therapeutic agent against peptic ulcers. Further experiments are recommended to replicate the results in other ulcer models, elucidate the mechanisms of action of the extract, and isolate the specific phytocompounds responsible for the observed gastroprotective effect. This study contributes to the promotion of traditional medicine using *G. phanerophlebia* to develop accessible, effective remedies for gastric ulcers.

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