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Effects of the stem barks aqueous extract of *Anthocleista schweinfurthii* Gilg (Loganiaceae) on acute and chronic gastric ulcers rats models

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Anthocleista schweinfurthii **is used in the traditional management of gastro-duodenal ulcers; this led us to evaluate the gastro-cytoprotective and healing effects of this plant. Anti-ulcer activity of the stem barks aqueous extract of *A. schweinfurthii* (EAS) was evaluated using five methods: HCl/ethanol; indomethacin-HCl/ethanol; absolute ethanol; pylorus-ligated (acute gastric lesions); and acetic acid-induced chronic ulcers in rats. The parameters assessed were mucus production, gastric ulcer index, pH, acid concentration and volume of gastric contents. Sucralfate, cimetidine and ranitidine were used as the reference anti-ulcer drugs. In all cases, oral administration of EAS (250 and 500 mg/kg), dose-dependently, prevented gastric lesion formation ($p<0.001$). Generally, this cytoprotective action was accompanied by significant increases in gastric mucus production. Intraperitoneal indomethacin (30 mg/kg) significantly reduced mucus production but did not reduce the cytoprotective effect. In pylorus ligation, the extract did not reduce acidity and volume of gastric juice compared to controls. All doses of the extract showed a highly significant ($p<0.001$) reduction of ulceration with a healing rate over 90%. This study indicates that *A. schweinfurthii* possesses significant anti-ulcer activity and these results are substantiated by the histopathological examination of the ulcerated stomachs.**

Key words: Gastric, ulcer, cytoprotection, *Anthocleista schweinfurthii,* Loganiaceae.

INTRODUCTION

Anthocleista schweinfurthii Gilg (Loganiaceae or Gentianaceae) is a tree plant found in tropical Africa and in Madagascar (Bach et al., 1967). In Gabon, *A. schweinfurthii* is used in ethno medicine to treat lactation disorders. In Congo Brazzaville, the stem bark decoction of *A. schweinfurthii* is used to treat fever, stomach ache, ovary infection and sterility in women. In Tanzania, the decoction of *A. schweinfurthii* is used to treat malaria, skin lesions and the juice of the leaves, roots or stem bark is used as cicatrizing agent (Kherharo, 1974). *A.*

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schweinfurthii contains substances that promote vasoconstriction and increase cardiac contraction (Ngombe et al., 2010). The STRC/OAU-Cameroon Government-sponsored ethnobotanical survey did not cite *A. schweinfurthii* for its antiulcer use, but the bark of a sister species, *Anthocleista djalonensis*, is used to treat abdominal pain in Nigeria (Olowokudejo et al., 2008). However, led by reports of the use of *A. schweinfurthii* in the traditional treatment of gastric ulcers in Congo (Kherharo et al., 1974), we have tested the anti-ulcer properties of the aqueous stem bark extract of *A. schweinfurthii* using experimental rat models.

MATERIALS AND METHODS

Plant

The stem barks of *A. schweinfurthii* Gilg (Loganiaceae) were collected in December, 2010 in Yaounde Center region of Cameroon. Botanical identification was done by Pr Jean Michel Onana, botanist, director of the National Herbarium of Cameroon, by comparison with existing herbarium specimen n° HNC 53944. The stem barks of *A. schweinfurthii* were dried at room temperature in the laboratory. The dried stem barks of the plant were powdered and were extracted in distilled water by boiling 700 g in 5 L of distilled water for 30 min. The filtrate was lyophilized and the resulting brownish solid (50 g) was used for the pharmacological tests.

Animal

Male Wistar rats (180±20 g) were used for the experiments. The animals were raised in the animal house of the Higher Teachers Training College, University of Yaounde [1]. They were fed a standard laboratory diet (SPC Ltd, Bafoussam, Cameroon) and given fresh water *ad libitum*. Before the experiments, they were starved for 48 h in wire mesh bottom cages to prevent coprophagy but allowed free access to water. Prior authorization for the use of laboratory animals in this study has been obtained from Cameroon National Ethics Committee (Reg. N. FWA-IRB 00001954). The use, handling and care of animals were done in adherence to the European convention (Strasbourg, 18.III.1986) for the protection of vertebrate animals used for experimental and other purposes (ETS-123), with particular attention to Part III, articles 7, 8 and 9.

Assays

Anti-ulcerogenic tests

HCl/Ethanol-induced gastric lesions: Gastric mucosal lesions were induced by the method describe by Hara and Okabe (1985). The test rats were administered the plant extract (250 and 500 mg/kg) per os while the controls received distilled water (1 ml). Those of the 4th group received by oral route 60 mg/kg of sucralfate (Ulcar®, Laboratoire Adventis 46, quai de la Rapée-75012, Paris, France) (a reference drug). 1 h later, all the animals received the necrotizing HCl/ethanol (1 ml) solution by oral route. After 1 h, under light ether anesthesia, the abdomen of each rat was opened and the stomach removed. The ulcers produced in the glandular region of each stomach were measured and scored as earlier described. The scores were attributed with respect to the ulcerated surface (US) (mm^2): score 0 (US=0); score 1 (0<US≤0.5); score 2 (0.5<US≤2.5); score 3 (2.5<US≤5); score 4 (5<US≤10); score 5 (10<US≤15); score 6 (15<US≤20); score 7 (20<US≤25); score 8 (25<US≤30); score 9 (30<US≤35) and score 10 (35<US).

HCl/Ethanol-induced gastric lesions in rats pre-treated with indomethacin: Indomethacin (Mark Sharp & Dohme, U.K.) was given to the rats (30 mg/kg) by intra peritoneal route. This was followed 1 h later by the HCl/ethanol ulcer procedure as described earlier (Sun et al., 1992).

Absolute ethanol-induced gastric lesions: Absolute ethanol-induced lesions were provoked using the HCl/ethanol-induced gastric lesions method, but instead the absolute ethanol was used. The rats received orally the plant extract or the vehicle followed 1 h later by ethanol. They were also killed using ether and the lesions formed were observed and scored (Robert et al., 1979).

Pylorus-ligated gastric secretion and ulceration: The method described by Shay et al. (1945) was used to study the ability of extract to reduce gastric acid secretion as well as prevent gastric ulceration resulting from auto digestion by stomach secretions. The test rats received the plant extract (250 and 500 mg/kg), controls received the distilled water (1 ml) and those of the 4th group received cimetidine (Tagamet lot 260B, cedex 26-92090 Paris) (200 mg/kg) by oral route, 1 h before the experiment. The pylorus of each rat was tied under light ether anesthesia and the abdominal incisions were closed. The rats were sacrificed 6 h later and the gastric juice produced by each was collected, centrifuged (6000 r/min) and the volume measured. Ulcers produced in the glandular region of the stomachs were measured and scored: score 0 (no ulcer); score 1 (dilation of vessels and small dots of ulcer); score 2.5 (ulcer≤4 mm long) and score 5 (ulcer≥5 mm long).

Measurement of gastric acidity: Samples of gastric contents (1 ml) were analyzed for hydrogen ion concentration by pH-metric titration with 0.1N NaOH solution using a digital pH-meter. The acid content was expressed as mEq/L.

Ulcer healing test

Acetic acid-induced chronic ulcers: The method described by Takagi et al. (1969) was used. Briefly, laparotomy was performed under light ether anaesthesia on experimental rats that were deprived of food during the preceding 24 h. Fifty microliters of 30% glacial acetic acid was injected into the wall of the stomach corpus at the region of the lesser curvature, and the stomach wall wiped using cotton wool soaked in a 0.9% NaCl solution. The abdominal incisions were stitched up and disinfectant (Betadine) applied to the area every day to avoid infection. The animals then continued to receive their regular diet, with free access to water. Four days after the operation, a control group of six rats was killed using ether, and the stomachs were removed and cut open along the greater curvature in order to establish the degree of ulceration prior to the onset of treatment: ulcer area = length × width of ulcer (mm^2). The mucus covering, gastric wall, was measured and the stomachs were stored (in formaldehyde solution) awaiting histological studies. The remaining rats were divided into four groups of six rats each. These rats were treated once a day for two weeks. Group 1 (controls) received 1 ml of distilled water by gavage, while groups 2 and 3 were given 250 and 500 mg/kg of the extract of *A. schweinfurthii*, respectively, dissolved in 1 ml of distilled water. Group 4 rats were given 50 mg/kg of ranitidine (Azantac 300 mg, lot 621, Laboratoire Glaxosmith, Cedex, France). An additional group of 6 healthy non-ulcerated rats (negative control) was subjected to the same experimental conditions and underwent all the experimental manipulations but were given neither the plant extract

Table 1. Effects of stem bark aqueous extract of *A. schweinfurthii* on gastric lesions induced by HCl/ethanol in rats.

Treatment	Dose (mg/kg)	N	Ulcer index (mean ± SEM)	Inhibition (%)	Mucus production (mg)
Control	-	6	5.44 ± 1.53	-	92.50 ± 5.00
A. schweinfurthii	250	6	5.25 ± 2.06	3.49	117.50 ± 5.90*
A. schweinfurthii	500	6	0.88 ± 0.17**	83.82	140.00 ± 6.88*
Sucralfate	60	6	1.78 ± 0.45*	67.27	77.00 ± 1.35

N: Number of rats; *P<0.05 statistically significant relative to control; **P<0.01 statistically highly significant relative to control.

nor ranitidine. Body weight was measured during the remaining length of the experimental period. On the final day of the experiment, all the rats were sacrificed. Ulcer indices and mucus production were evaluated and the healing rates of the ulcers were calculated by comparing the ulcer status of extract and ranitidine-treated rats with those of the ulcerated untreated controls. The degree of auto-healing was evaluated by comparing the untreated control ulcers with those of the rats killed on day 4 post-operation. The stomachs of all the animals were preserved for histological studies.

Measurement of mucus production

After estimating the degree of lesion formation, the gastric mucosa of each rat was immediately scraped gently using a glass slide and the mucus obtained was weighed using a precision electronic balance. The same experimenter performed this operation each time (Djabanguiri, 1969).

Realisation of histological cross-section

The removed organs were fixed in formaldehyde 10% solution. They were later cut into small slices following a well defined plane, and then placed in numbered histological cassettes. The latter was impregnated at room temperature in successive baths of ethylic alcohol at increasing degrees (70°– 80° – 95° – 100°) to dehydrate the organs. Impregnation lasted for an hour in each recipient container of alcohol.

Since paraffin is immiscible with ethylic alcohol, the fragments of the organ were clarified for 2 h in toluene and inclusion was done for 2 h in paraffin heated in an oven at 60°C. After this inclusion, the fragments of the organs were enrobed in paraffin block, thanks to Leuchart's rods. The blocks that were formed were conserved at room temperature for three to four days.

With the help of a microtome, the paraffin blocks that were formed were cut into fine slices of 5 µm thickness permitting the obtention of a band of paraffin on which different levels of cuts were chosen and placed on water baths covered with gelatine for renewal. The cross-sections of the organs were recovered with a slide holder and dried in an oven at 55°C.

Paraffin was removed from the slides that were recovered from the oven in two recipient containers of toluene for 5 min, and then rehydrated by passing the slides successively in five different recipient containers of alcohol of decreasing degrees (100, 100, 95, 80 and 75°) and in distilled water for 2 min.

The cross-sections were later coloured with a mixture of haematoxylin-eosin. The nuclear coloration was done by successively soaking the slides in recipient containers containing Hemalun Mayer (5 min), water acetified at 1% for differentiation (30 s), running water for rinsing (1 min), water containing lithium oxide at saturation point to render the nuclei blue (30 s) and running water for rinsing (2 min). For the coloration of the cytoplasm, the slides were soaked for 15 min in eosin 1% in an aqueous solution and later on rinsed in running water for 1 min. Differentiation and dehydration of cross-sections were done by soaking the slides in alcohol at 80° (1 min) and then in absolute alcohol (Bayelet-Vincent, 2002).

Statistical analysis

Values in tables are given as arithmetic means ± standard error of the mean (SEM). The significance of differences between groups was analyzed by means of analysis of variance (ANOVA), followed by Dunnett's multiple comparison tests using GraphPad InStat. P values less than 0.05 were considered as significant.

RESULTS

HCl/Ethanol-induced gastric lesions

The stem bark aqueous extract of *A. schweinfurthii* (250 and 500 mg/kg) dose-dependently offered significant cytoprotection (3.49 and 83.82% inhibition) to the stomach mucosa of rats against the HCl/ethanol solution compared with the controls. The mean ulcer index score was reduced from 5.44 in controls to 0.88 for the rats receiving 500 mg/kg of extract. Sucralfate (60 mg/kg) also significantly inhibited gastric ulceration compared with controls (Table 1).

HCl/Ethanol-induced gastric lesions in rats pre-treated with indomethacin

The effect of pre-treatment with indomethacin on the protective effect of the stem bark aqueous extract of *A. schweinfurthii* against HCl/ethanol-induced lesions is as shown in Table 2. This procedure had the effect of significantly reducing the protective effect which the extract produced at the dose of 500 mg/kg. Thus, the prevention of lesion formation reduced from 83.32 to 50.70% at 500 mg/kg extract due to indomethacin pre-treatment (Table 2). This was accompanied by a reduction in mucus production for all extract-treated groups. Lesion inhibition was also reduced for control drug, sucralfate.

Absolute ethanol-induced gastric lesions

Table 3 shows the results obtained when the stem bark

Table 2. Effects of pre-treatment with indomethacin on the protective effect of stem bark aqueous extract of *A. schweinfurthii* against gastric lesions induced by HCl/ethanol in rats.

Treatment	Dose (mg/kg)	N	Ulcer index (mean ± SEM)	Inhibition (%)	Mucus production (mg)
Control	-	6	5.64 ± 0.59	-	85.00 ± 4.80
A. schweinfurthii	250	6	5.51 ± 1.05	2.30	75.00 ± 5.35
A. schweinfurthii	500	6	2.78 ± 1.09*	50.70	82.50 ± 4.20
Sucralfate	60	6	4.24 ± 0.65	24.82	76.00 ± 4.41

N: Number of rats; *P<0. 05 statistically significant relative to control.

Table 3. Effects of stem bark aqueous extract of *A. schweinfurthii* on gastric lesions induced by absolute ethanol in rats.

Treatment	Dose (mg/kg)	N	Ulcer index (mean ± SEM)	Inhibition (%)	Mucus production (mg)
Control	-	6	4.03 ± 1.30	-	21.00 ± 5.90
A. schweinfurthii	250	6	3.69 ± 1.48	8.43	29.00 ± 2.50
A. schweinfurthii	500	6	3.66 ± 1.50	9.18	42.40 ± 6.20**
Sucralfate	60	6	4.06 ± 1.04	-	60.13 ± 1.85**

N: Number of rats; **P<0. 01 statistically significant relative to control.

aqueous extract of *A. schweinfurthii* was used to prevent the formation of gastric lesions induced using absolute ethanol. Inhibition of lesion formation was poor (9.18%) at the dose of 500 mg/kg. The aqueous extract of *A. schweinfurthii* and sucralfate (60 mg/kg) both showed significantly low potencies against absolute ethanol-induced gastric lesions.

Pylorus-ligated gastric secretion and ulceration

Table 4 shows the results obtained when the animals were subjected to pylorus ligation. When the extract of *A. schweinfurthii* (500 mg/kg) was administered, ulcer index and ulcerated surface were 3.61 and 14.33 mm^2 compared with 5.00 and 35.7 mm^2 for controls. This significant reduction ($p<0.01$) of the ulcerated surface was accompanied by a significant increase ($p<0.01$) secretion of mucus. For 58.00±4.80 mg in control rats, the amount of mucus was increased to 135.00±1.60 and 141.35±1.42 mg in rats treated with plant extract at doses of 250 and 500 mg/kg, respectively. The plant extract had no significant effect on the volume and gastric acidity.

Acetic acid-induced chronic ulcers

Table 5 shows a dose-dependent enhancement of the healing of acetic acid-induced chronic gastric ulcers following daily treatment with aqueous stem bark extract of *A. schweinfurthii* (EAS). On day 4, ulcer areas reduced from 81.00 to 47.00 mm^2 in control rats. Following two weeks of treatment with EAS, ulcer areas reduced from 47.00 mm^2 in controls to 0.08 and 0.02 mm^2, respectively, for the rats receiving 250 and 500 mg/kg of the extract. A healing rate of 80.42% was recorded for ranitidine (50 mg/kg). Unlike ranitidine, EAS promoted significantly higher levels of mucus production (96.62 and 124.75 mg at 250 and 500 mg/kg) during the treatment period as compared to the controls (58.13 mg/kg).

Histological analysis revealed the presence of a sclerotic block, leukocyte infiltration and edema in rats negative control 1 (sacrificed on day 4 rats). In rats negative control 2, there was presence of fibrillations. Rats treated with aqueous extract of *A. schweinfurthii* showed the normalization of gastric tissue with a well-developed mucosa.

DISCUSSION

The results of this study clearly show that the aqueous stem bark extract of *A. schweinfurthii*, when administered 1 h before injury with HCl/ethanol, reduced significantly ($p<0.01$) the mucosal lesions produced by this ulcerogenic solution. The accompanying significant dose-dependent increases in mucus production suggest that the gastric mucosal strengthening mechanism contributes to the anti-irritant potential of the extract (Table 1).

Treatment with indomethacin reduces prostaglandin and bicarbonate secretion and gastric mucosal blood flow in animals. The inhibition of prostaglandins predisposes the stomach and duodenum to mucosal damage, whereas stimulation of prostaglandins can be protective (Selling et al., 1987). When the cytoprotective effect of an anti-ulcer agent is significantly reduced by pre-treatment with indomethacin, it is usually interpreted that cytoprotection is mediated by endogenous prostaglandins

Table 4. Effects of stem bark aqueous extract of *A. schweinfurthii* on pylorus ligation-induced gastric mucosal ulceration in rats.

Treatment	Dose (mg/kg)	Total ulcer Area (mm^2)	Volume of gastric juice (ml)	Gastric acidity (mEq/L)	Mucus production (mg)	Ulcer index	Inhibition (%)
Control	-	35.75 ± 5.00	5.15 ± 0.40	88.00 ± 8.92	58.00 ± 4.80	5.00 ± 0.00	-
A. schweinfurthii	250	28.33 ± 3.07	5.01 ± 0.42	83.60 ± 5.25	135.00 ± 1.60**	4.29 ± 0.41	14.2
A. schweinfurthii	500	14.33 ± 2.29**	3.86 ± 0.61	85.20 ± 4.81	141.35 ± 1.42**	3.61 ± 0.82	27.8
Cimetidine	200	5.95 ± 0.74**	3.27 ± 0.59*	80.20 ± 2.10	44.23 ± 2.86	1.56 ± 0.20 **	68.8

Each value represents the mean ± SEM of 6 animals; *P<0. 05 statistically significant relative to control; **P<0. 01 statistically highly significant relative to control.

Table 5. Effects of stem bark aqueous extract of *A. schweinfurthii* on the healing rate of chronic acetic acid-induced gastric ulcers in rats.

Treatment	Dose (mg/kg)	N	Ulcer area (mm^2)	Healing rate (%)	Mucus (mg)
Control$^{\alpha}$	-	6	-	-	60.53 ± 3.83
Control$^{\beta}$	-	6	81.00 ±13.37	-	55.26 ± 3.38
Control$^{\gamma}$	-	6	47.00 ± 4.81	41.97	54.25 ± 4.14
A. schweinfurthii	250	6	0.08 ± 0.00**	99.82	96.62±3.40*
A. schweinfurthii	500	6	0.024±0.00**	99.94	124.75±3.41**
Ranitidine	50	6	9.20 ± 2.19**	80.42	58.13 ± 4.39

N: Number of rats; $^{\alpha}$Healthy, non-ulcerated control rats; $^{\beta}$Control rats killed 4 days post operation to establish initial degree of acetic ulceration; $^{\gamma}$Control rats given vehicle for 14 days following ulcer induction; *P<0. 05 statistically significant relative to control; **P<0.01 statistically highly significant relative to control.

(Tan et al., 2002). The results of this study therefore suggest that, in addition to increased mucus production via prostaglandin, the extract may confer direct cytoprotection by effects similar to endogenous prostaglandin.

Absolute ethanol is highly corrosive to the gastric mucosa. Its pathogenic mode of action on gastric mucosa involves, in addition to superficial aggressive cellular necrosis, the release of tissue-derived mediators such as histamine and leucotrine C_4. These mediators act on the gastric micro vasculature, triggering a series of events that result in mucosal and possibly sub mucosal tissue destruction (Oates and Hakkinen, 1988). The results of this study suggest that the aqueous stem bark extract of *A. schweinfurthii* does not prevent the generation or the necrotic action of these mediators on the gastric micro vasculature. These results are similar to those obtained with the leaf methanol extract of *Ocimum suave* (Tan et al., 2002).

Histological analysis revealed the presence of sclerosus block in stomachs, a leukocyte infiltration and oedema in negative control 1 rats (rats sacrificed at day 4), which indicates the presence of inflammation caused by injection of acetic acid in the stomach wall. In the injured area, vasodilatation and increased permeability of the walls of small blood vessels leads to the passage of water and plasma proteins into damaged tissue. Then, leukocytes migrate to the inflamed area where they accumulate (Stevens and Lowe, 1997).

In the negative control rats 2 (rats sacrificed at day 18), the presence of fibrillation showed that ulcer healing was underway. Indeed, fibroblasts and myoblasts migrate and multiply at the injured area. Fibroblasts synthesize collagen, which is the origin of the scar formation (Stevens and Lowe, 1997). The presence of oedema, block leukocyte infiltration and sclerosis in these rats demonstrate the persistence of inflammation; this is explained by the fact that in the absence of treatment, the ulcer healing is slow and incomplete. Normalization of stomach tissue with a fully developed mucosa in rats treated with aqueous extract of *A. schweinfurthii* shows that the extract would accelerate ulcer healing and stimulates the regeneration of the gastric mucosa.

Phytochemical studies of *A. schweinfurthii* have revealed the presence of flavonoids, polyphenols, tannins and leucoanthocyans (Njayou et al., 2000). Polyphenols compounds protect the gastrointestinal mucosa from lesions produced by various experimental ulcer models and against different necrotic agents. Polyphenols have antihistaminic properties, thus, decreases histamine levels, as well as preventing the release of histamine from gastric mast cells and inhibiting the gastric H^+/K^+

proton pump and diminish acid gastric secretion. On the other hand, they possess cytoprotective effects, which increase the mucosal blood flow, stimulate the synthesis of muco-bicarbonate in the gastric mucosa and increase prostaglandins levels. However, the most important mechanism of action responsible for the anti-ulcer activity of flavonoids is their antioxidant properties, which involve free radical scavenging, transition metal ions chelation, inhibition of oxidizing enzymes, increase of proteic and non proteic antioxidants and reduction of lipid peroxidation (Kelly et al., 2009). Flavanoids have also been reported to offer some protection in ulcer development by increasing capillary resistance and improving microcirculation (Sabiha et al., 2011). This extract also has the alkaloids which have gastro-cytoprotective and antiulcer activities (Hashizume et al., 1978). Njayou et al. (2000) revealed the presence of tannin and leucoanthocyans in *A. schweinfurthii*. Tannins are known to protect the outermost layer of mucosa and to render it less permeable and more resistant to chemicals and mechanical injury or irritation and thus prevent ulcer development (Heloina et al., 2008). Others species of Anthocleista have been shown to exhibit gastric cytoprotection effects. The stem barks of *Anthocleista vogelii* possess potent antiulcer properties (Ateufack et al., 2006). The acute toxicity study of the stem barks aqueous extract of *A. schweinfurthii* shows that the lethal dose 50 (LD_{50}) is greater than 2000 mg/kg and the dose of 1000 mg/kg used in subacute toxicity presented no significant toxic effects (Mezui et al., 2015). Therefore, therapeutic doses of extract of *A. schweinfurthii* (250 and 500 mg/kg) used in this study would be non-toxic.

Conclusion

Oral administration of EAS (250 and 500 mg/kg), dose-dependently, prevented gastric lesion formation ($p<0.001$). This cytoprotective action was accompanied by significant increases in gastric mucus production. In pylorus ligation, the extract did not reduce acidity and volume of gastric juice. All doses of the extract showed a highly significant ($p<0.001$) reduction of ulceration with a healing rate over 90%. The results of this work showed that the extract of *A. schweinfurthii* is neither anti-secretory or an antacid. This extract protects the gastric mucosa even when gastric acidity is high and accelerates the healing of chronic gastric ulcers. These experiments confirmed the traditional management of peptic ulcers. Further work is envisaged to evaluate the antioxidant power of the *A. schweinfurthii* extract as well as its possible toxicity.

Conflict of Interest

The authors have not declared any conflict of interest.

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